Chapter 1:

Introduction and Review of Literature

1.1 Neurodegenerative Diseases

With the rise in life expectancy over the years, there has been an unanticipated increase in the frequency of age-related illnesses, particularly neurodegenerative diseases. Neurological disorders constitute a significant contributor to premature mortality and transient or permanent disability among those who survive. As per the World Health Organization (WHO), in 2006, neurological disorders were recognized as a substantial public health challenge, representing 6.3% of the overall disability-adjusted life-years (DALYs) [1]. Furthermore, a World Health Organization report projects that neurodegenerative diseases are anticipated to surpass cancer, emerging as the second leading cause of mortality by 2040 due to the synergistic effects of aging and inadequate treatment options [2].

Neurodegenerative diseases (NDDs) represent a diverse array of neurological disorders that significantly impact millions globally. These diseases involve the gradual degeneration of neurons in either the central nervous system (CNS) or peripheral nervous system (PNS). The deterioration of neural networks and the irreversible loss of neurons, hindered by their terminally differentiated state, lead to the disruption of fundamental communicative circuitry. This cascade results in compromised memory, cognition, behaviour, and impaired sensory and/or motoric function. DM Wilson *et al*. posits that a distinct set of hallmarks serves as defining features for Neurodegenerative Diseases (NDDs). These include pathological protein aggregation, dysfunction in synaptic and neuronal networks, disruptions in proteostasis, abnormalities in the cytoskeleton, altered energy metabolism, defects in DNA and RNA, inflammatory responses, and eventual neuronal cell death (**Fig. 1.1.1**) [3]. This underscores the urgent need for a deeper comprehension of protein accumulation and aggregate formation, potentially offering avenues for the development of effective therapeutic approaches for these debilitating conditions.

Mechanistic insights reveal a commonality among these diseases, characterized by the accumulation of mutant proteins and the formation of visible microscopic aggregates in the brain [4,5]. Mutated proteins adopt abnormal conformations, generating small peptides upon proteolytic processing and accumulating in cells as soluble oligomers and insoluble aggregates. Aggregate formation constitutes the "pathological hallmark" of these diseases and is extensively studied for its role in disease pathogenesis. It is posited that defective proteins impact multiple cellular pathways, leading to neuronal cell demise through transcriptional dysregulation, disintegration of

Ca^{2+} homeostasis, mitochondrial dysfunction, oxidative stress, synaptic abnormalities, impaired intracellular transport, vesicular trafficking, axonal blockage, and compromised ubiquitin-proteasome system [6].

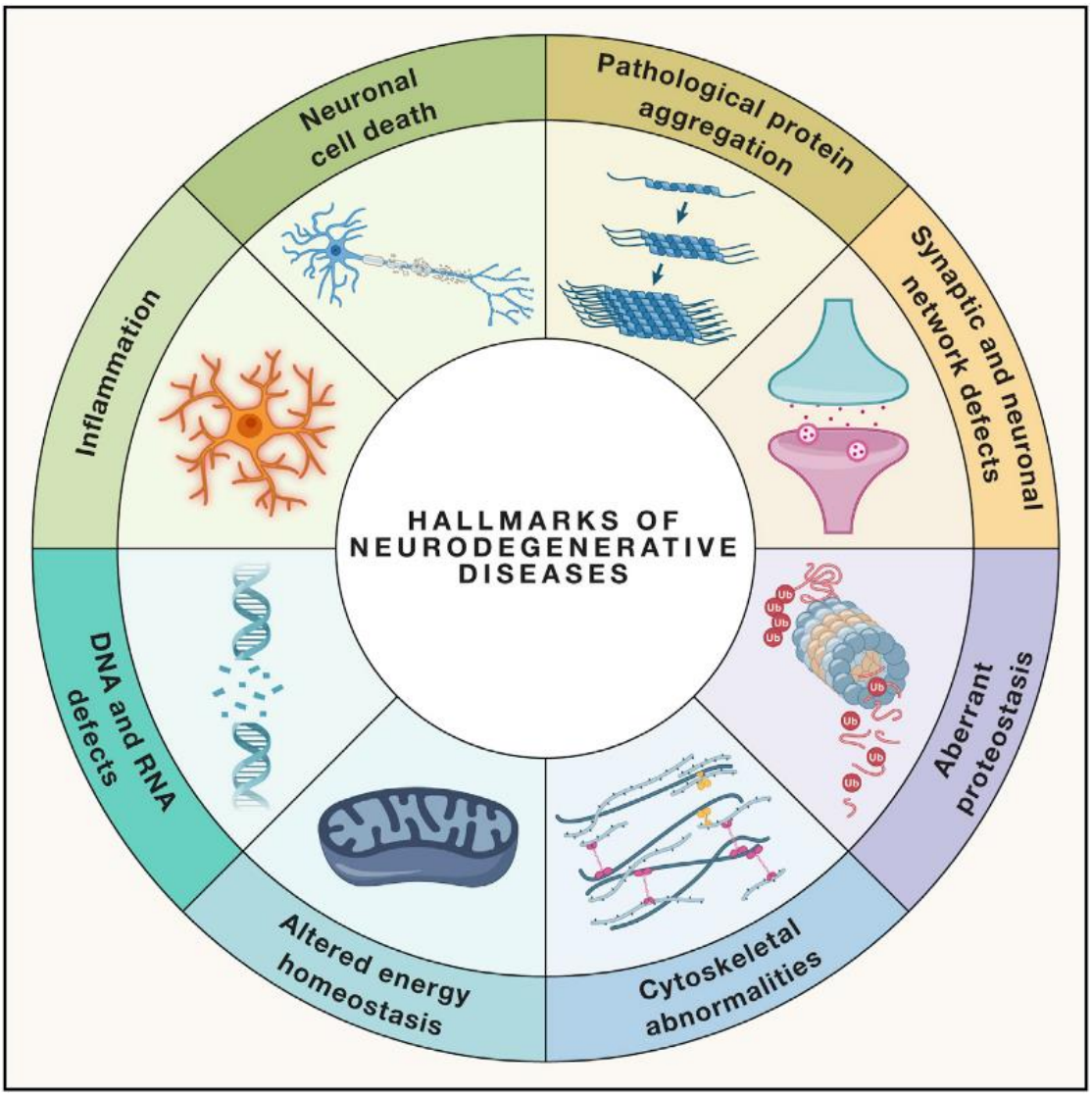

Figure 1.1.1: Hallmarks of neurodegenerative diseases [3].

Furthermore, neurodegeneration is linked to the impairment of synaptic function, neural network dysfunction, and the accumulation of physiochemically modified protein variants within the brain (**Fig. 1.1.2**). Predominant neurodegenerative disorders encompass Alzheimer's disease, Parkinson's disease, Huntington's disease, prion disease, Amyotrophic lateral sclerosis (ALS), motor neuron disease, spinal muscular atrophy, and spinocerebellar ataxia [7].

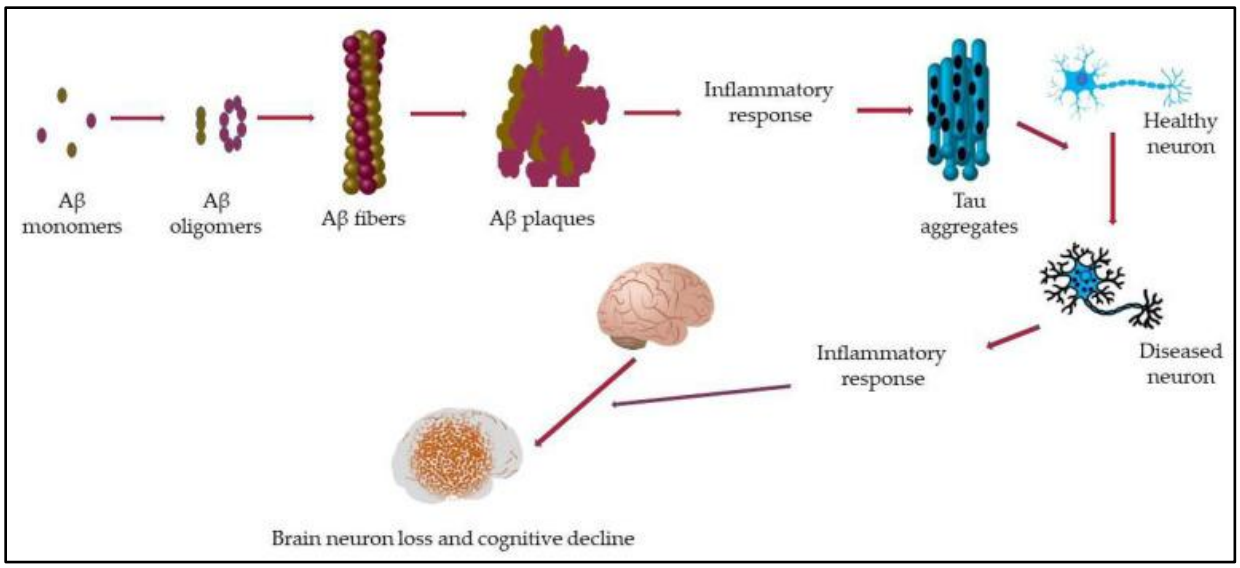

Figure 1.1.2: Path to cognitive decline in neurodegeneration [7].

Several prominent neurodegenerative diseases demanding attention include:

1.1.1 Alzheimer's disease

Alzheimer's disease (AD), the most prevalent neurodegenerative disorder impacting millions with a substantial mortality rate, involves familial and sporadic mutations. These mutations trigger excessive beta-amyloid (Aβ) production and aggregation in the central nervous system, forming insoluble plaques and toxic soluble oligomers [6]. Sporadic AD typically occurs after 65, while early-onset cases follow autosomal dominant inheritance, often linked to mutations in the apolipoprotein E (APOE) gene [8]. APOE's role in cholesterol transport and CNS repair implicates it in AD pathogenesis, particularly in increased β-amyloid deposition. Early-onset familial AD involves mutations in the amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) genes [6].

Accumulated Aβ induces tau protein deposition, impacting kinases and phosphatases like glycogen synthase kinase 3 (GSK3), leading to abnormal tau phosphorylation [9,10]. This disrupts microtubule stabilization, causing the formation of neurofibrillary tangles. AD is characterized by senile β-amyloid plaques and neurofibrillary tangles, causing significant neuronal loss in critical brain regions. Neurodegeneration results from Aβ and tau aggregate formation, with early soluble species being highly cytotoxic. Mutant protein accumulation leads to various cellular dysfunctions, including mitochondrial dysfunction, oxidative stress, altered signal transduction, lysosomal

dysfunction, and glutamate receptor alterations. These processes contribute to synaptic plasticity loss, disrupted synaptic connections, and cognitive and behavioral abnormalities in AD [6].

1.1.2 Parkinson's disease

Parkinson's disease (PD), the second most prevalent neurodegenerative disorder after Alzheimer's disease, displays genetic complexity and heterogeneity. Both sporadic and familial mutations, distributed across approximately 28 chromosomal locations involving nine genes, contribute to PD pathogenesis [11,12]. Dominant forms, arising from mutations in the α-synuclein (SNCA) gene, result in elevated cytoplasmic SNCA levels [13], while autosomal dominant PD is associated with leucine-rich repeat kinase 2 (LRRK2) gene mutations. Autosomal recessive early-onset PD is linked to loss-of-function mutations in Parkin, PINK1, DJ-1, and ATP13A2 [11,5]. Susceptibility variants involve polymorphisms in SNCA and LRRK2 genes, and heterozygous mutations in the β-glucocerebrosidase (BGA) gene [11].

Late-onset PD typically emerges in individuals aged 50 or older, involving progressive dopaminergic neuron loss in the substantia nigra and other brainstem monoaminergic neurons [14]. Clinical features encompass resting tremor, rigidity, bradykinesia, and postural and autonomic instability. A key pathological hallmark is the formation of Lewy bodies, abnormal protein aggregates in cytoplasmic regions and neurites. These bodies, immunopositive for α-synuclein, ubiquitin, synphilin-1, proteasome proteins, and cytoskeletal proteins, play a crucial role in neural degeneration and are extensively studied in the context of PD pathology [5].

1.1.3 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease, is a severe neurodegenerative disorder marked by the progressive denervation of voluntary muscles due to the degeneration of upper motor neurons in the motor cortex and lower motor neurons in the brainstem and spinal cord. The global incidence is estimated at approximately 2 cases per 100,000 person-years, boasting a prevalence ranging from 6 to 9 cases per 100,000 individuals, with a lifetime risk approximating 1 in 350 [15]. Genetic heterogeneity is a notable feature of ALS, with familial cases displaying autosomal dominant inheritance in 5–10% of affected individuals. The complexity of the disorder is further compounded by the identification of diverse genetic determinants through systematic genetic testing [16].

Pathologically, ALS manifests distinctive features, including the loss of upper and lower motor neurons, degeneration of neural tracts, and proteinopathy, predominantly involving TAR DNA-binding protein 43 (TDP-43) in approximately 97% of cases [17]. Diagnosis of ALS necessitates the exclusion of mimic disorders, employing criteria such as the revised El Escorial criteria [18]. FDA-approved therapeutic options, such as riluzole, edaravone, and AMX0035, are formulated to address disease symptoms and modify its progression, although their success is circumscribed [19]. Symptomatic management of the disease entails both pharmacological and non-pharmacological interventions, with non-invasive ventilation emerging as a pivotal element significantly enhancing the life expectancy and quality of life for the majority of ALS patients [20]. Despite the expansive clinical trial landscape, ALS confronts a considerable unmet need for efficacious therapies, underscoring the urgency to surmount challenges in the development of novel treatment modalities.

1.1.4 Huntington's disease

My thesis work is focused on Huntington's disease (HD) which is one of the most extensively studied fatal autosomal dominant neurodegenerative disease arising from the expansion of polymorphic CAG triplet repeats in the exon 1 of the huntingtin (*HTT*) gene on chromosome 4. This expansion translates into an elongated abnormal polyglutamine (polyQ) tract in the huntingtin (HTT) protein. The symptoms differ between individuals but are usually characterized by progressive motor dysfunction, cognitive impairment and behavioral abnormalities. Other than neuronal symptoms, patients with HD have been also reported to exhibit peripheral symptoms such as muscle atrophy, osteoporosis, difficulty in swallowing, weight loss, compromised immune system, slurred speech, heart failure, testicular atrophy, and so on [21]. Typically, the onset of the disease manifests between the ages of 35 to 50, and patients commonly die within a span of 10 to 20 years.

1.2 Huntington's disease

1.2.1 Historical perspective

Huntington's disease (HD) was meticulously elucidated for the first time by a 22-year-old American physician, Dr. George Huntington. In 1872, Dr. Huntington authored a paper titled "On Chorea," which was published in the Medical and Surgical Reporter of Philadelphia. The term "chorea," derived from Latin and Greek, denotes the rhythmic and dance-like movements observed

in the hands, feet, and faces, which constitute the distinctive features of this disorder. Huntington's seminal report, titled "On Chorea," delineated the condition as an autosomal dominant, hereditary, adult-onset ailment characterized by emotional, cognitive, and motor symptoms. The disease exhibits a progressive nature and culminates in fatality [22]. For numerous decades, the nomenclature persisted as "Huntington's chorea," reflecting the universal acknowledgment of choreic movements as a cardinal manifestation. However, in the 1980s, with the comprehensive delineation of its non-motor symptoms, the nomenclature underwent a transition to "Huntington's disease" (HD).

1.2.2 Epidemiology

Huntington's disease (HD), a rare genetic disorder, exhibits notable global variability in prevalence rates. Populations in America, Europe, the United Kingdom, and Canada show a higher prevalence (10.6-13.7 individuals per 100,000) [23,24], while Japan, Hong Kong, and Taiwan demonstrate a considerably lower prevalence (1-7 per million) [25]. This geographical divergence corresponds to significant genetic variations in the mean number of CAG repeats in the *HTT* gene, with higher prevalence groups displaying an elevated average of CAG repeats. The clinical diagnosis of HD involves genetic testing, especially in individuals with a family history and discernible motor signs. Epidemiological studies integrate genetic testing and neurological examinations [25,26]. The consistent increase in HD prevalence over decades is attributed to the broader availability of genetic testing, enabling the identification of sporadic and late-onset cases [24,25]. Previously estimated at 4-10/100,000 in Western populations, HD prevalence may have been underestimated due to societal stigma, hindering accurate diagnosis. Global prevalence variation is influenced by genetic differences in the *HTT* gene, with populations of European ancestry having longer average CAG repeats [27,28]. The estimated incidence of HD is 4.7-6.9 new cases per million per year in Western populations, potentially rising with improved case ascertainment and increased longevity. Ancestry-specific prevalence rates reveal higher frequencies in individuals of European descent [25]. The genetic bias towards longer CAG repeats in high-prevalence populations implies repeated expansion events, contributing to global variations in HD prevalence [25,26,29].

Additionally, the prevalence of HD varies with ethnic origin, particularly in Caucasian populations of North America and Western Europe, where 5-10 individuals per 100,000 are affected. The prevalence is on the rise with the increasing prevalence of genetic testing. Juvenile forms are rare,

accounting for 5% of cases [30]. About 90% of HD cases are inherited, with 10% resulting from new mutations and transmitted in an autosomal dominant fashion [31]. The prevalence in the Indian population is not well-established due to a lack of large-scale population studies, with only a few studies conducted to determine HD prevalence in India [32,33].

1.2.3 The Genetic Basis of Huntington's Disease

1.2.3.1 Early Discoveries and the *HTT* Gene

The initial description of the genetic underpinnings of HD dates back to 1872, with George Huntington's seminal work [22]. However, the precise genetic locus on chromosome 4 remained elusive until 1983, when Gusella *et al.* identified an expanded CAG repeat within the Huntingtin (*HTT*) gene as the culprit for HD [34]. Subsequent investigations by The Huntington's Disease Collaborative Research Group [21] further characterized this gene, revealing its large size (180 kilobases) and extensive exon structure (67 exons).

1.2.3.2 *HTT* Gene Structure and Expression

Interestingly, the *HTT* gene demonstrates a consistent expression pattern across various tissues, despite being regulated by a housekeeping promoter [35]. This ubiquitous expression hints at a fundamental role for this protein in cellular function.

1.2.3.3 The CAG Repeat and HD Onset

The length of the CAG repeat within the *HTT* gene plays a pivotal role in HD development. While the general population exhibits a highly variable CAG repeat length (ranging from ten to twenty-six repeats) [36], individuals with forty or more repeats inevitably develop HD [37]. Moreover, a fascinating correlation exists between the CAG repeat length and the age at onset (AAO) of HD (**Fig. 1.2.1**). Notably, longer CAG repeats are associated with earlier disease onset [25], with repeats exceeding sixty even leading to juvenile HD, characterized by symptom manifestation in young adulthood or childhood [38].

1.2.3.4 Meiotic Instability and Anticipation

The relationship between CAG repeat length and disease progression is further complicated by a phenomenon known as meiotic instability [39]. During meiosis, the process of cell division that leads to sperm and egg formation, the CAG repeat can undergo expansion or contraction. This instability, particularly prevalent in paternal inheritance, can result in anticipation [40], where

successive generations experience progressively earlier disease onset due to increasing CAG repeat lengths.

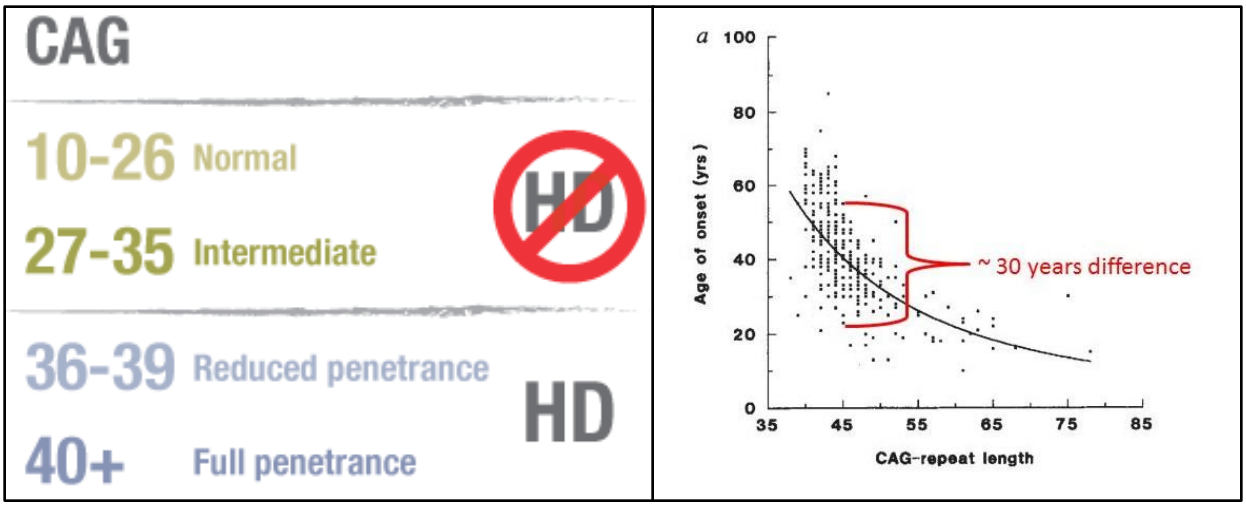

Figure 1.2.1: Correlation between the length of polyQ and the age at onset. Figures adapted from HDBUZZ (https://en.hdbuzz.net/222) and Andrew S. E. *et al.* [41].

1.2.3.5 Dominant Role of CAG Repeat Length

Studies have highlighted the crucial role of CAG repeat length in determining AAO for HD [42]. Approximately 59-71% of AAO variability is attributed to the length of the CAG repeat expansion [43], emphasizing its dominant influence on the disease. However, it is important to note that while the CAG repeat length plays a significant role in AAO, it shows a poor correlation with disease progression [44]. This suggests the involvement of other genetic and environmental factors in shaping the overall course of HD.

1.2.3.6 Inheritance Patterns and Sporadic Cases

HD follows an autosomal dominant inheritance pattern, meaning that a single mutated copy of the *HTT* gene is sufficient to cause the disease. However, penetrance, the likelihood of developing HD given the presence of the mutation, varies depending on the CAG repeat length (**Fig. 1.2.1**):

- Full penetrance: 40 or more repeats [37]
- Reduced penetrance: 36-39 repeats [36]
- Intermediate alleles: 27-35 repeats [36]

While intermediate alleles are not typically associated with HD, they can expand during meiosis, increasing the risk of offspring inheriting the disease gene with 36 or more repeats. Additionally, inheritance through the paternal bloodline is associated with a higher likelihood of anticipation [39].

Despite the importance of detailed family history in diagnosing HD, approximately 6-8% of newly diagnosed patients lack a family history [36]. This is often attributed to *de novo* mutations arising from intermediate length alleles, leading to sporadic cases of HD [40].

1.2.3.7 The Huntingtin Protein and Polyglutamine Stretch

The HD mutation itself comprises an expanded CAG triplet repeat located near exon 1 of the *HTT* gene. This translates into a polyglutamine stretch within the Huntingtin protein, which is believed to contribute to the disease's pathology [37].

1.2.4 Clinical features of Huntington's disease

The clinical manifestations of Huntington's disease stem predominantly from central nervous system (CNS) degeneration, encompassing a spectrum of symptoms such as motor dysfunction, cognitive decline, and psychiatric disorders [37]. The extent to which each symptom type affects individuals varies considerably, although most patients experience a combination of these symptoms. A formal clinical diagnosis of HD is established when an unexplained extrapyramidal movement disorder (e.g., chorea or dystonia) is observed in an individual with a genetically confirmed CAG repeat expansion [45]. However, the cognitive and psychiatric aspects of HD may develop many years before motor symptoms.

Motor dysfunction in HD is categorized into worsening involuntary movements and impaired voluntary movements [45]. Early indicators include restlessness and loss of fine motor control, progressing to chorea (involuntary, dance-like movements) [46]. As the disease advances, it assumes a more Parkinsonian profile, characterized by increased rigidity and reduced chorea [47]. Additional motor impairments encompass dystonia, bradykinesia, akinesia, and compromised coordination, notably impacting speech, gait, and postural reflexes, thereby elevating the risk of falls and injuries [45].

Cognitive symptoms in HD exhibit considerable variability but often involve deficits in executive function and impulsivity [47]. Initial cognitive impairments manifest as difficulties in executing

complex tasks, memory loss, and diminished learning capacity [25]. These deficits progressively worse, leading to significant impairments in comprehension, judgment, reasoning, and memory [45]. Cognitive decline can commence prior to the onset of motor symptoms and deteriorates gradually [48,49].

Psychiatric disturbances are prevalent in HD, with approximately 40-50% of patients experiencing depression [50]. The incidence of suicide attempts is markedly higher in HD patients compared to the general population [51]. Other psychiatric manifestations include apathy, aggression, psychosis, irritability, obsessive behaviours, and social difficulties [47]. Depression and apathy are particularly debilitating, often emerging in the pre-manifest stage and progressively worsening over time [52].

1.2.4.1 Disease Progression

The clinical progression of HD is categorized into two primary phases: pre-manifest and manifest disease [45]. The pre-manifest phase includes a prodromal period characterized by subtle abnormalities that can precede formal diagnosis by up to fifteen years [25]. During this period, individuals may exhibit subclinical features such as weight loss, cognitive decline, and structural brain changes without prominent motor symptoms [53,47]. This phase can be further subdivided into a pre-symptomatic period, where genetic carriers are clinically indistinguishable from healthy individuals, and a prodromal period, where subtle motor, cognitive, and functional declines become apparent [45].

The manifest phase begins with the formal onset of clinically diagnosable symptoms, which progress inexorably over 15-20 years until death [54,55,45]. The manifest phase is often divided into early, middle, and late stages based on symptom severity [45]. The early stage is marked by the onset of diagnosable motor symptoms, while the middle stage is characterized by worsening motor and cognitive functions [45]. The late stage is distinguished by severe motor impairments, profound dementia, and significant psychiatric symptoms [45].

1.2.4.2 Clinical Assessment and Predictive Models

Clinical assessment of HD progression utilizes tools such as the Unified Huntington's Disease Rating Scale (UHDRS) and the Total Functional Capacity (TFC) scores [56,57]. These instruments evaluate motor features, emotional and behavioral functions, cognitive abilities, and functional

capacity. Efforts to develop detailed predictive models of HD progression aim to enhance disease management and understanding of its trajectory [58].

1.2.4.3 Metabolic Disturbances

HD is associated with a broad spectrum of metabolic disturbances, including unintentional weight loss, severe dysphagia, hepatic and gastrointestinal abnormalities, pancreatic defects, sleep disturbances, skeletal muscle wasting, endocrine dysfunction, and cardiovascular issues [59-61]. These disturbances may arise in the early stages of the disease and sometimes even in preclinical subjects, indicating that HD impacts both the CNS and peripheral organs [45].

1.2.5 Pathophysiology of Huntington's Disease

Huntington's disease is a devastating neurodegenerative disorder characterized by progressive motor dysfunction, cognitive decline, and behavioral disturbances [3]. It is caused by an abnormal expansion of a CAG trinucleotide repeat in the Huntingtin (*HTT*) gene, resulting in the production of a mutant huntingtin protein (mHTT) with an expanded polyglutamine (polyQ) tract [62,63]. This pathological protein aggregates intracellularly, disrupting normal cellular function and ultimately causing neuronal death in specific brain regions [3].

At a cellular level, the neuropathology of Huntington's Disease is characterized by the preferential degeneration and death of predominantly striatal medium spiny neurons (MSNs) as well as cortical pyramidal neurons [64]. A pathological hallmark of HD is the accumulation of nuclear and cytoplasmic protein aggregates containing mutant huntingtin N-terminal polyQ fragments in the cortex and striatum [65]. The very N-terminal region of HTT contains the expandable polyQ stretch, which induces conformational changes in the protein, leading to the formation of intracellular aggregates that manifest as nuclear inclusions or form outside the nucleus [30,66].

The core neuropathological feature of HD is the selective neurodegeneration within the striatum, a basal ganglia structure critical for motor control. The mHTT protein accumulates predominantly in medium spiny neurons (MSNs) of the striatum, leading to their dysfunction and loss [67]. This degeneration disrupts the balance between excitatory and inhibitory signaling within the basal ganglia circuitry, resulting in movement abnormalities such as chorea, rigidity, and akinesia [67].

Beyond the striatum, HD pathology also extends to other brain regions, including the cerebral cortex, hippocampus, and amygdala, contributing to cognitive decline, emotional disturbances,

and psychiatric symptoms frequently associated with the disease [68,69]. The precise mechanisms by which mHTT exerts its toxic effects remain under investigation, but several key pathways are implicated, including mitochondrial dysfunction, oxidative stress, impaired protein degradation, and dysregulation of transcriptional programs [67].

The mutant huntingtin protein triggers a cascade of molecular events, such as excitotoxicity, transcriptional dysregulation, mitochondrial dysfunction, impaired proteostasis, altered axonal trafficking, and reduced trophic factor availability [67]. HD is also associated with DNA damage, reduced PARP1/2 activity, and altered poly ADP-ribose (PAR) levels, indicating a connection between DNA repair pathways and disease progression. These molecular events collectively lead to progressive neuronal loss, particularly in the MSNs of the striatum [3].

Huntingtin has been shown to interact with polycomb repressive complex -2 (PRC2) and facilitates its activity [70]. PRC2 complex plays a vital role as transcriptional regulator and mediates gene silencing by Histone H3-Lysine-27-tri-methylation. Mutant huntingtin facilitates PRC2 activity significantly higher compared to the normal Huntingtin, contributing to the complex interplay of molecular factors driving HD pathogenesis [70].

HD manifests with a range of symptoms, including motor abnormalities like chorea and parkinsonism, cognitive decline, depression, and psychosis [71]. Despite extensive research, no curative therapy is currently available. Understanding the multifaceted molecular mechanisms underlying HD is crucial for identifying therapeutic targets to delay disease onset and progression [67].

1.2.6 Peripheral Pathology in Huntington's Disease

Huntington's disease is increasingly recognized as a multi-system disorder affecting both the Central nervous system (CNS) and peripheral tissues. Research has revealed that the mutant huntingtin protein causes similar molecular dysfunctions in peripheral tissues as in the brain, including protein aggregation, metabolic impairment, and cell death mechanisms [72]. HD also involves non-neurological symptoms like immune system activation, severe weight loss, endocrine deficiencies, and skeletal muscle wasting [73,74].

Peripheral pathology in HD includes mitochondrial defects in lymphocytes and increased inflammation markers in blood samples [75,76]. Studies in mouse models suggest that mHTT

affects metabolic functions, revealing that HD is not solely a brain disease [77]. Immune activation is evident from gene expression alterations in blood samples and microglia activation in both pre-manifest and manifest HD [78,79]. Recent research has identified numerous inflammatory biomarkers linked to HD. Notably, plasma levels of IL-6, VEGF, and TGF-β1 are significantly elevated in HD patients, whereas IL-18 levels are decreased [80]. A meta-analysis further validated that plasma levels of IL-6 and IL-10 are higher in HD patients compared to controls [81]. These findings indicate that certain inflammatory markers may serve as potential biomarkers for the onset, progression, and clinical severity of HD (**Fig. 1.2.2**), underscoring the need for further research into their role in tracking disease progression and developing targeted therapies.

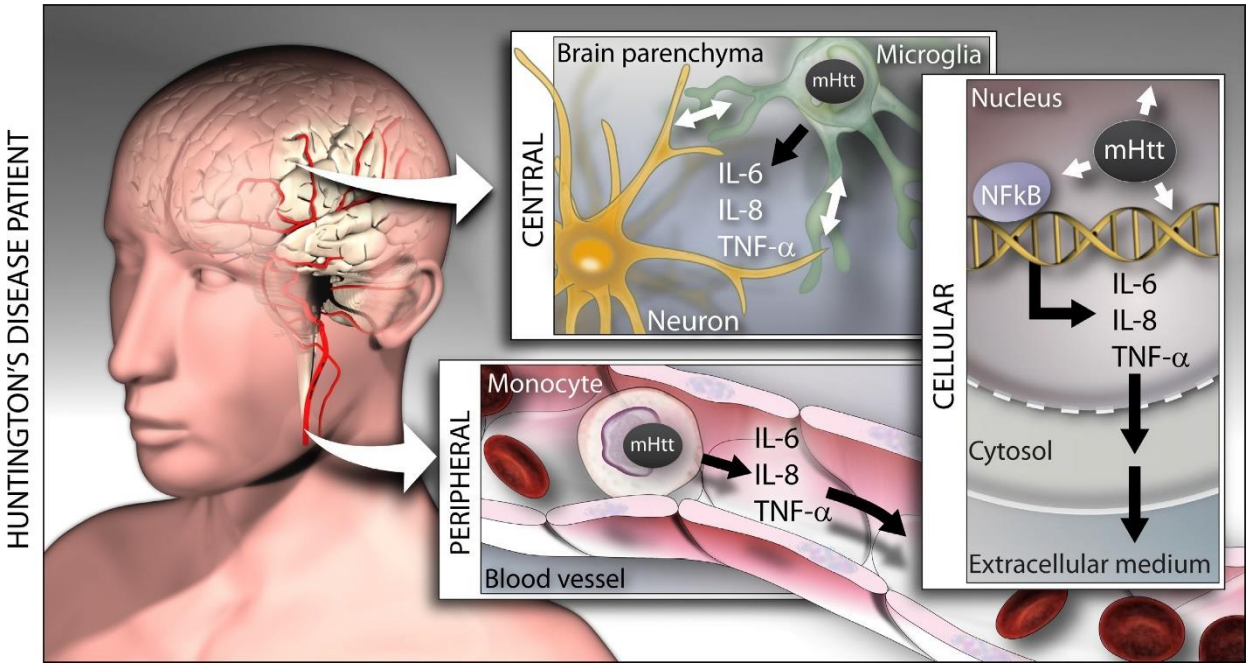

Figure 1.2.2: Immune activation, induced by mutant huntingtin, occurs both peripherally and centrally in HD [79].

Weight loss in HD results from an increased metabolic rate, with higher body mass index correlating with slower disease progression [82,83]. Pancreatic impairments, including decreased insulin sensitivity, contribute to weight loss, along with swallowing defects, chewing difficulties, and adipocyte dysfunction [83,84].

Skeletal muscle wasting involves significant muscle atrophy, with mHTT disrupting gene expression in myocytes [85]. Mitochondrial dysfunction in skeletal muscles is linked to reduced *PGC-1α* expression, and apoptosis in muscle cells further supports muscle wasting [85-87].

Cardiomyocytes are affected, with cardiac failure being a leading cause of death in HD patients, highlighting the cardiac implications of mHTT [88,89].

HD is now recognized as a systemic disease, with mHTT affecting diverse tissues beyond the CNS. Peripheral changes include endocrine dysfunction, osteoporosis, and testicular atrophy. These findings underscore the widespread impact of mHTT and suggest that addressing peripheral symptoms is crucial for comprehensive HD treatment strategies [60,72]. The peripheral tissue alterations not only contribute to disease symptoms but also offer potential avenues for identifying biomarkers and developing new therapeutic approaches. Understanding the interplay between the brain and peripheral tissues in HD may lead to more comprehensive treatment strategies targeting multiple affected systems.

1.2.7 The diagnosis of Huntington's Disease

The diagnosis of HD primarily depends on clinical manifestations and genetic testing to identify CAG repeat expansions in the huntingtin gene [90]. Although the diagnostic process is generally straightforward, atypical presentations and conditions that mimic HD can pose challenges [90]. Genetic testing has facilitated the identification of premanifest individuals and a prodromal phase prior to the onset of manifest disease. Several molecular diagnostic techniques, including PCR and Southern blot, are employed to detect the CAG expansion [91]. However, the unstable nature of the HD mutation, the lack of effective treatments, and the mid-adulthood onset of symptoms complicate diagnostic testing [92]. Accurate laboratory procedures, proper interpretation of genetic test results, and thorough pre- and post-test counselling are essential components of HD diagnosis [92]. Optimal management of HD patients is achieved in specialized multidisciplinary clinics, particularly when genetic testing is involved [90].

1.3 The Huntingtin (HTT) protein

1.3.1 Wild-type Huntingtin structure

HTT gene was originally called Interesting Transcript 15 (IT15) gene that is a 169279-bp gene that is found on chromosome 4 at 4p16.3 [21]. It has 3142 amino acids in total, resulting in a 348-kDa protein (UniProt P42858). There are 67 exons in this gene. The CAG repeats codes for a polymorphic polyglutamine stretch (polyQ) and is found in the exon 1 region of the huntingtin gene [93]. The *HTT* gene encodes a 348-kDa huntingtin (HTT) protein, highly conserved from

flies to mammals, exhibiting the greatest sequence identity among mammals. Huntingtin is ubiquitously expressed in mammalian cells, with the highest concentrations observed in the brain and testes, and moderate levels detected in the liver, heart, and lungs [30,94]. Since the discovery of the HD mutation, researchers have concentrated on elucidating the structure and function of normal huntingtin protein to better understanding the mechanisms driving HD pathology and to develop effective treatments for the disease.

Huntingtin protein is ubiquitously distributed in the nucleus, endoplasmic reticulum, Golgi complex, neurites, and synapses [95,96,39]. The huntingtin gene comprises 67 exons, with exon 1 being the most extensively studied. Structurally, the protein features an N17 domain at its N-terminus, characterized by an alpha-helical configuration[97]. This domain undergoes various post-translational modifications, including acetylation, phosphorylation, and palmitoylation. The polyQ stretch, starting at the 18th amino acid, is believed to adopt a polar zipper structure. Typically, the polyQ repeats range from 7 to 35, serving the function of binding transcription factors containing polyQ regions [98]. Adjacent to the polyQ stretch is the polyproline region, forming a polyproline helix structure that may stabilize the polyQ stretch and influence the aggregation propensity of mutant huntingtin [97]. Downstream of these regions, HEAT repeats are found, which are crucial for protein-protein interactions [99,100]. Bioinformatic analyses suggest the presence of approximately 37 putative HEAT repeats within this region [101].

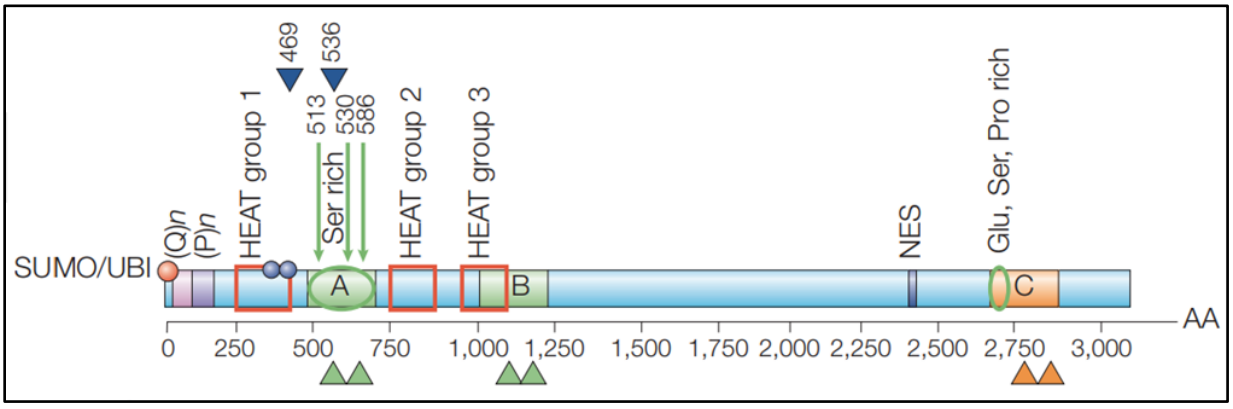

Figure 1.3.1: Schematic diagram of huntingtin amino acid sequence [102].

The C-terminal of huntingtin includes an active Nuclear Export Signal (NES) and a less active Nuclear Localization Signal (NLS), which predominantly localize the wild-type huntingtin protein to the cytoplasm. Removal of these signals can result in nuclear accumulation of huntingtin

[103,104]. Huntingtin is cleaved by caspase 3, caspase 6, and calpains, contributing to its pathophysiology. The green arrow in the **Fig. 1.3.1** depicts caspase sites, while the blue arrowhead represents calpain sites on huntingtin. Notably, neuronal dysfunction and degeneration necessitate cleavage of mutant huntingtin at the caspase 6 site [105].

1.3.2 Wild-type Huntingtin function

Huntingtin is found in all body tissues and is important for many cellular processes. It plays key roles in embryonic development, neurogenesis, gene regulation, synaptic activity, intracellular transport, and preventing cell death [102]. Its structure allows it to interact with various cellular components, especially through tandem HEAT repeats that help in protein interactions [106]. Despite its many functions, the exact way *HTT* works is still not fully understood, likely due to its complex structure [102].

During embryonic development, mice lacking *HTT* due to disruption of exon 5 in the Hdh gene die before day E8.5 because of failed organogenesis, underscoring huntingtin's vital role [107]. Heterozygous knockout mice live but show HD-like symptoms [108]. Similar embryonic lethality occurs with deletions in exon 4 and 5, or the promoter and exon 1 [109]. Introducing wild-type or mutant human *HTT* into these knockout mice prevents embryonic lethality, proving huntingtin's essential role in early development regardless of polyQ length [110]. High levels of nuclear *HTT* in early development and its link to mitotic spindles suggest roles in gene regulation, mitosis, and cell differentiation [111].

HTT is crucial for neurogenesis and neuron survival, particularly in the forebrain [112]. Reduced HTT levels lead to abnormal brain development and perinatal death, while normal HTT levels with expanded polyQ do not impact CNS development [108]. Conditional Hdh knockout in mouse forebrain regions causes progressive degeneration, highlighting huntingtin's role in forebrain neuron survival [110]. Chimeric mice studies show limited distribution of HTT-null cells in specific brain areas like the thalamus and cortex, emphasizing huntingtin's importance in these regions [113]. HTT also regulates hippocampal neurogenesis and affects anxiety/depression-related behaviours [114]. It controls mitosis by interacting with proteins such as p150Glued and NuMA [115].

HTT influences transcriptional regulation by interacting with various transcription factors and complexes, including Sp1, TAFII130, and REST/NRSF, affecting gene activation and repression

[116,106]. HTT is known to upregulate the expression of Brain Derived Neurotrophic Factor (BDNF) at the transcription level, a vital protein for neuron survival [117,65,118]. Huntingtin also influences gene transcription, such as by sequestering REST to indirectly increase the expression of BDNF [116]. It also modulates the activity of nuclear receptor co-repressor 1 (N-CoR) and the Sin3A complex, repressing gene activity [119].

HTT plays a role in intracellular transport by participating in axonal transport, exo- and endocytosis, and endosomal movements, interacting with motor proteins such as kinesin and dynactin, and the actin-based motor myosin VI through optineurin [118]. HTT depletion leads to defects in protein secretion and recycling endosome trafficking, impacting cellular functions like haemoglobin production [120]. The interaction between HTT and HAP40 regulates vesicle affinity for cytoskeletal tracks, affecting vesicular trafficking in HD [120].

HTT has an anti-apoptotic function by inhibiting apoptotic pathways downstream of Bcl-2 and upstream of caspase-3 activation [121]. It prevents caspase-9 and caspase-3 activation by interacting with procaspase-9, caspase-3, and HIP1, protecting against HIP1-mediated cell death [121]. HTT also regulates survival genes like Bcl-xL and BDNF while repressing death genes such as BAX and Bcl-2 [121,106]. Additionally, HTT inhibits p21-activated kinase 2 (Pak-2) activation, further promoting cell survival [122].

HTT is also essential for the maintenance of tissues beyond the central nervous system, as conditional *HTT* knockout in mice results in death from acute pancreatitis [123]. The localization of HTT to the mitochondrial membrane further indicates its role in regulating energy metabolism [124]. Interestingly, a recent study suggested that wild-type HTT might have a novel role in immune cell function, as lowering HTT significantly reduced cytokine production by control cells following stimulation with lipopolysaccharide (LPS) and interferon-gamma (IFNγ) [125]. These findings demonstrate that wild-type HTT is a multifunctional protein with diverse effects in both neuronal and non-neuronal cells.

1.3.3 Mutant Huntingtin protein (mHTT)

When the polyQ tract in huntingtin expands, it induces significant structural and conformational changes in the mutant HTT protein, which are crucial for HD development [37,126]. Wild-type HTT is primarily α-helical, but toxic mHTT fragments form a compact β-sheet structure, which aggregates similarly to other protein misfolding diseases [37]. The formation of these aggregates

involves a complex process where mHTT transitions from monomers to various intermediate structures before forming insoluble aggregates [127,5,128]. These aggregates are commonly found at sites of neuronal degeneration in the brains of HD patients and various model systems, making them the pathological hallmark of the disease [4,129-132]. The length of the CAG repeat highly influences the efficiency of these aggregates' formation [133].

Although the exact toxic species of mHTT remain unidentified, N-terminal fragments with the polyQ tract are necessary for the disease [105]. The location of mHTT in cells differs from wild-type HTT; wild-type HTT is mostly in the cytoplasm, whereas mHTT forms nuclear inclusions primarily composed of N-terminal fragments [4]. Analyses of post-mortem tissues and mHTT aggregates from HD patients reveal that both soluble and insoluble forms predominantly consist of N-terminal fragments of mHTT [4,134,135]. In HD mouse models expressing the full-length mHTT, intranuclear aggregates also show these N-terminal fragments [136]. This suggests that producing N-terminal fragments is a key step in mHTT aggregation and HD development.

The predominant theory is that HD pathogenesis is driven by a toxic gain of function in mHTT rather than a loss of function in wild-type HTT. Studies have shown that mHTT aggregates are toxic and lead to cell death, though the exact mechanism is still unclear. Interestingly, recent research suggests that soluble mHTT, rather than aggregates, may be the most harmful form in HD [137,138]. This has led to debates about which form of mHTT is the most toxic. For instance, HD mouse models with two mutant alleles, such as the $Hdh^{150Q/150Q}$ mouse, are viable [139], unlike HTT knockout mice, which die during embryonic development [107]. This suggests that mHTT can partially substitute for wild-type HTT function. This idea is further supported by the observation that homozygous mutant HD patients do not exhibit more severe disease than those with one mutant allele [140]. However, mHTT-related pathogenesis begins early, with functional issues detectable in cultured cells from HD patients up to fifteen years before symptoms appear [48].

Research indicates that these N-terminal fragments of mHTT are more toxic and form aggregates faster than the full-length protein in both *in vitro* and *in vivo* conditions. Various disease models have demonstrated that expressing only the N-terminal fragment of mHTT is sufficient to cause aggregation and HD symptoms [141,129,142-145]. Together, these evidences suggest that the

production of mHTT fragments and mHTT aggregation are strongly linked and play an important role in HD pathology.

1.3.4 N-terminal huntingtin

The initial 17 amino acids (N17) of the huntingtin protein are crucial for its localization and aggregation [146,147]. This N17 sequence, which is directly followed by the polyQ domain and a proline-rich region, is highly conserved across different species, indicating its essential role in the HTT protein. In experiments, HTT tagged with GFP at the C-terminus remains mostly in the cytoplasm, whereas mutant HTT lacking the N17 sequence tends to accumulate in the nucleus, suggesting that N17 functions as a cytoplasmic retention signal [146].

Supporting the idea that HTT has a membrane association signal directing it to the endoplasmic reticulum (ER) and vesicles [148], Rockabrand *et al.* found that both normal and mutant HTT co-localize with the ER. However, non-expanded HTT interacts more strongly with the ER membrane compared to the polyQ-expanded HTT [146]. This weaker association in mutant HTT could allow more of it to move to the nucleus, disrupt cellular functions, and form aggregates. The membrane-associated signal is located in the N17 region, as a mutation disrupting the N17 helical structure causes significant nuclear accumulation of HTT [148]. The N17 domain is also necessary for HTT aggregation; its deletion or structural disruption reduces aggregation [146]. Additionally, the chaperonin TRiC, which decreases HTT aggregation and toxicity in cell culture, binds specifically to the N17 domain [149]. It was also noted that N17 interacts with itself and the polyQ tract to initiate aggregation.

The mechanism by which HTT enters the nucleus remains unclear since a classical nuclear localization signal (NLS) has not been identified in HTT [103]. While an NES has been identified at the protein's C-terminus, it is not part of the N-terminal region of HTT that accumulates in the nucleus. Nuclear aggregates consist of N-terminal HTT fragments already localized to the nucleus [103]. Both expanded and non-expanded N-terminal HTT fragments can enter the nucleus, but only the expanded protein becomes trapped there, indicating that nuclear export, rather than import, is affected by the polyQ tract. This is supported by studies showing that HTT interacts with the nuclear pore protein Tpr via the N17 domain, and this interaction is inhibited by the polyQ expansion in mutant HTT [104]. Consequently, the mutant N-terminal protein gets trapped in the nucleus, while the wild-type can be exported. This is further supported by observations in PC12

cells, where HTT exon-1 with 20Q is primarily cytoplasmic, whereas HTT with 150Q is mostly nuclear [150].

1.4 Misfolding and Aggregation of mHTT in Huntington's Disease

Misfolding of N-terminal fragments of huntingtin and other polyQ proteins is a well-known phenomenon. Proper protein folding is essential for their normal function, and misfolding leads to altered functionality, interactions, aggregation, and toxicity [151]. Molecular chaperones play a key role in maintaining proper protein folding within cells [151]. In Huntington's Disease, chaperone levels are crucial for regulating HTT aggregation and the associated symptoms. For instance, in the R6/2 mouse model of HD, chaperones like hsp70 and hsp40 are found to be downregulated [152]. Interestingly, overexpressing hsp40, but not hsp70, reduces polyQ protein aggregation and toxicity in cell cultures [153,154]. Overexpressing either hsp40 or hsp70 also prevents neurodegeneration and aggregation in *Drosophila* models expressing expanded HTT or ataxin-3 [155,156]. Similar results were observed in mouse models for SCA1 and SBMA [157]. However, findings in HD mice have been inconsistent. An earlier study indicated that overexpression of exogenous Hsp70 in R6/2 HD mice did not significantly change the phenotype [152], while a later study showed that knocking out endogenous hsp70 in the same mouse model led to a significant decline in motor abilities, survival, and other physical phenotypes [158]. This suggests that the source of hsp70 (endogenous vs. exogenous) may impact HD symptoms differently.

Many researchers believe that chaperones reduce HTT-induced toxicity by reducing polyQ protein aggregation. First, chaperones like hsp40 and hsp70 co-localize with nuclear inclusions formed by misfolded polyQ proteins [157,152-154]. Second, overexpressing these chaperones in various polyQ disease models suppresses aggregation, indicating that aggregates might be the toxic element.

However, the role of aggregates in HD pathogenesis remains a topic of intense debate. Emerging evidence indicates that soluble HTT, rather than aggregated HTT, constitutes the toxic species within the nucleus. For example, studies have demonstrated that while hsp40 reduces HTT aggregation in HEK 293 cells, it concurrently decreases caspase activity, suggesting a reduction in apoptosis [159]. In our previous study, we demonstrated that treatment with Decanoic acid, 2-butyloctanoic acid, and Glyceryl triacetate significantly reduced mHTT aggregation in HD150Q

cells, highlighting the potential neuroprotective effects of these medium chain fatty acids in HD [160]. Furthermore, hsp40, but not hsp70, reduced aggregation, yet both chaperones significantly decreased caspase activity, indicating that chaperones may mitigate neurodegeneration by preventing apoptosis. Another study demonstrated that hsp40 reduces the aberrant interaction between soluble mutant HTT and Sp1 caused by HTT misfolding, suggesting that polyQ-mediated toxicity might not be attributable to nuclear aggregation [104]. Other studies also support the notion that nuclear aggregates are either protective or neutral, showing no correlation with cell death [161,162]. In fact, some data suggest a protective role for aggregates, as neurons with earlier inclusion formation survived longer [137]. However, this study did not specify the localization of the aggregates, leaving open the possibility that their role might vary based on location.

To mitigate the harmful effects of misfolded proteins, cells rely on two primary systems: the ubiquitin proteasome system (UPS) and autophagy. UPS tags misfolded proteins for degradation, while autophagy engulfs proteins in autophagosomes, which fuse with lysosomes for degradation. Although some initial studies suggested that mutant HTT impairs the UPS globally [163,164], more recent evidence indicates that the UPS is not globally impaired in HD animal models. For example, no significant decrease in UPS activity was observed in R6/2 HD mice compared to wild-type controls [165]. Crossbreeding transgenic models of SCA7 or HD with a ubiquitin-GFP reporter mouse also showed no global UPS impairment [166,167]. However, localized UPS impairment in specific neuronal regions like synapses has been noted [168], suggesting that UPS function may depend on subcellular localization. An age-dependent decrease in proteasome activity has been observed, which might explain the late-onset of the disease and progressive accumulation of mutant polyQ proteins that increase inclusion body size with age [169-171].

The role of autophagy in polyQ repeat disorders remains to be fully elucidated. Significant evidence suggests that autophagy can clear mutant HTT and that its activation can improve the HD phenotype. Early experiments treating HD-N171-82Q mice and a *Drosophila* HD model with rapamycin, an autophagy activator, showed reduced neurodegeneration in flies and improved motor deficits in mice [172]. Rapamycin treatment also decreased aggregation in the mouse striatum. Later studies found that inhibiting autophagy increased toxicity in cell and *Drosophila* HD models, while enhancing autophagy reduced neurodegeneration in flies [173]. Generally, autophagy clears large cytoplasmic protein complexes or damaged organelles, so cytoplasmic aggregates are more prone to degradation by autophagy than nuclear aggregates [174]. However,

recent evidence challenges this idea, showing that rapamycin inhibits HTT aggregation in both autophagy-deficient and proficient cells [175]. Moreover, the presence of mutant HTT in the brains of HD mice does not significantly change LC3-I to LC3-II conversion, a marker of autophagy activation [176]. Similar to UPS, there might be an age-related decline in autophagy activity. For instance, Beclin 1, necessary for autophagosome formation, co-localizes with HTT aggregates in HD R6/2 mice, and its expression levels decrease over time in both HD and control human brains [177]. This suggests that, like UPS, the autophagy system becomes less active with age, making HD patients' brains more vulnerable to mutant HTT accumulation later in life. Overall, it is clear that the systems responsible for clearing misfolded proteins like mutant HTT become dysregulated, leading to the accumulation of these proteins in neuronal cells over time.

1.5 Role of PRC2 Complex in HD pathology

The Polycomb Repressive Complex 2 (PRC2) plays a crucial role in various pathological processes, including Huntington's disease pathology [178]. The PRC2 is a crucial molecular structure involved in epigenetic regulation across eukaryotic cells [179]. PRC2 consists of four core proteins: EZH2, EED, SUZ12, and RbAp46/RbAp48 (**Fig. 1.5.1**) [180]. EZH2 catalyses the trimethylation of histone H3 at lysine 27 (H3K27me3), a repressive marker ultimately resulting in transcriptional silencing through chromatin compaction (**Fig. 1.5.2**) [181]. EED binding of H3K27me3 allosterically activates EZH2 [182,183]. PRC2 influences over 2000 genes on 10 chromosomes [184-187]. Experimental studies involving mice have demonstrated that deletion of these core proteins leads to morphological defects and premature death, underscoring PRC2's pivotal role in cell development and differentiation [188]. Evolutionary conservation underscores its significance in maintaining specific gene expression states [184,189]. PRC2 ensures the maintenance of histone modifications, particularly trimethylation of lysine 27 on histone 3, throughout the cell cycle, crucial for preventing erroneous transcriptional activity that could prove fatal [190]. This modification affects nucleosome organization and gene activity by altering chromatin compaction, impacting cellular proliferation, differentiation, and identity [190,178]. The PRC2 complex, along with accessory proteins, mediates mono-, di-, and trimethylation states of H3K27 (H3K27me1, H3K27me2, and H3K27me3), influencing approximately 70% of the genome and thereby playing a pivotal role in transcriptional regulation and gene silencing across diverse cellular contexts [191-193].

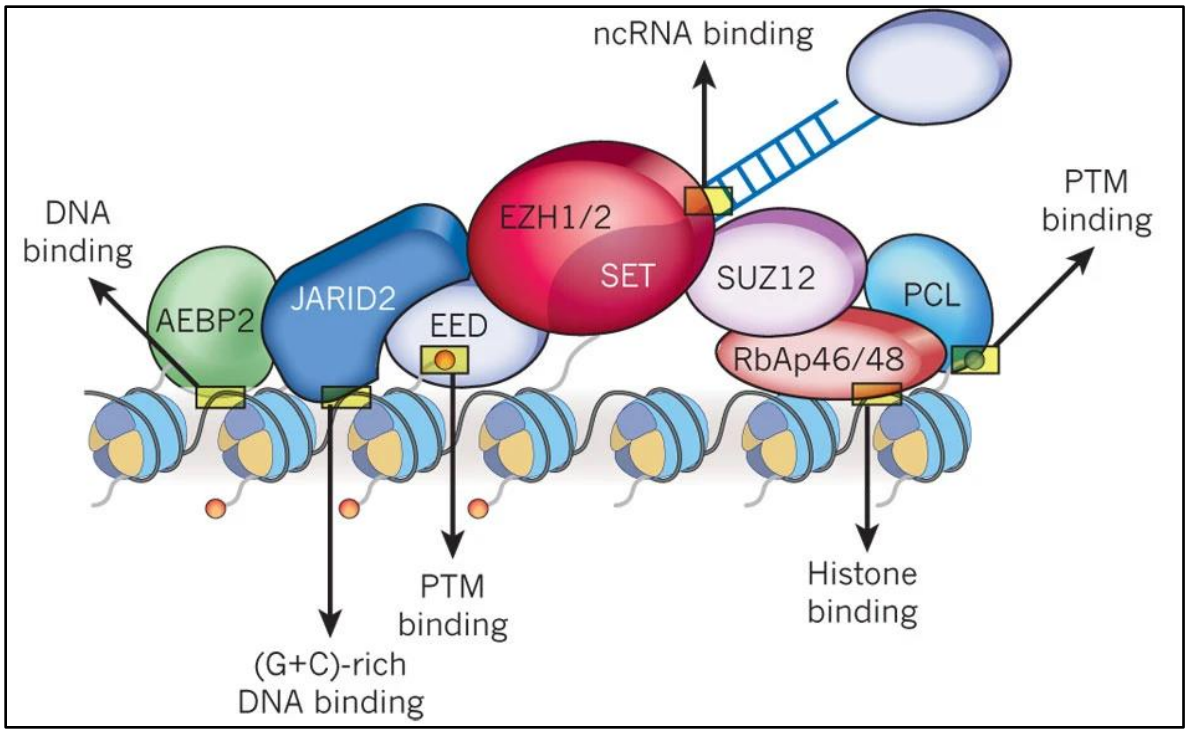

Figure 1.5.2: The schematic representation of Polycomb repressive complex 2 (PRC2) suppression of neurodegenerative transcription process in neurons [190].

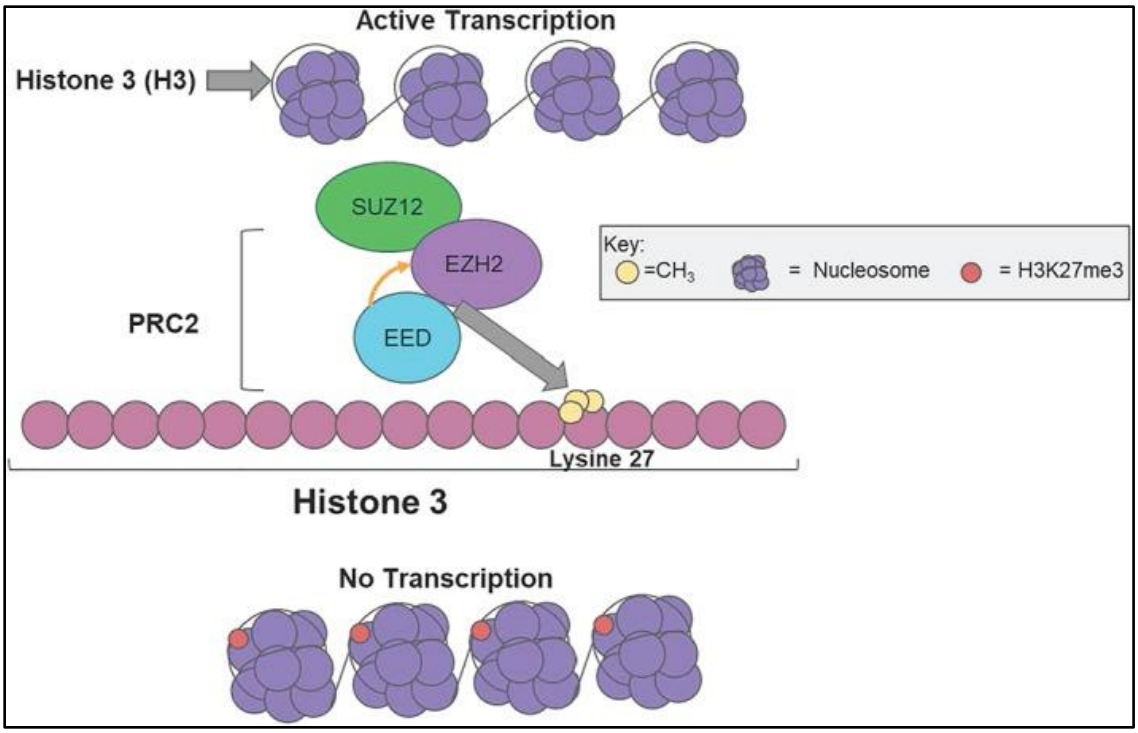

Figure 1.5.1: The schematic representation showing interactions of PRC2 with chromatin [180].

In the context of HD, PRC2's dysregulation can contribute to neurological diseases, as mutations or dysfunctions in PRC2 subunits are linked to neurodegenerative conditions [178]. Additionally, PRC2's intricate regulatory networks in the central nervous system (CNS) are vital for neuronal identity, neural stem cell differentiation, and gliogenesis, highlighting its significance in understanding and potentially targeting HD pathology for therapeutic interventions [178]. Huntingtin has been shown to interact with PRC2 and facilitate its activity [70]. Mutant huntingtin facilitates this activity significantly more than the normal huntingtin [70]. Mutant huntingtin also disrupts PRC2 regulation, leading to impaired Hox gene expression and histone H3K27 tri-methylation [70]. PRC2 recruitment and H3K27 methylation patterns are influenced by various factors, including chromatin residence time and catalytic activity [193]. Furthermore, mutant huntingtin alters histone monoubiquitylation by disrupting its interaction with Bmi-1, a component of the hPRC1L E3 ubiquitin ligase complex. This leads to changes in uH2A and uH2B levels at gene promoters, affecting transcriptional regulation and histone methylation patterns [194]. Therefore, exploring PRC2's role in HD pathology could provide valuable insights into the disease mechanisms and aid in the development of novel treatment strategies. Based on these observations, it is imperative that any intervention that can abrogate mutant huntingtin mediated hyper-activation of PRC2 can be of potential therapeutic interest.

1.6 Consequences of expansion of polyQ length in mutant huntingtin protein

The exact molecular mechanisms and pathways that lead to Huntington's Disease are not yet fully understood. However, it is known that a variety of cellular processes are disrupted by the expansion of the polyglutamine (polyQ) tract within the huntingtin protein [30]. Research indicates that this expansion in the amino-terminal region of huntingtin not only causes the protein to gain toxic functions but also results in the loss of normal huntingtin functions and affects many other cellular proteins [30]. This dual impact disrupts numerous cellular processes. The toxic gain-of-function of mutant huntingtin leads to the formation of various oligomeric species and inclusion bodies, which abnormally interact with multiple cellular proteins, thereby disrupting several cellular pathways [195]. Concurrently, the loss of function of wild-type huntingtin hampers cellular operations due to its reduced interaction with proteins crucial for development, transcription, cell cycle regulation, intracellular transport, and cell survival [196].

1.6.1 Cell-autonomous pathogenesis

Since the discovery of the HD gene, significant strides have been made in understanding the biology of Huntington's Disease. Research involving cellular models, transgenic animal models, and post-mortem HD brain samples has revealed numerous cellular dysfunctions that contribute to the progression of HD (**Fig. 1.6.1**). These cell-autonomous pathogenesis include abnormal protein interactions, transcriptional dysregulation [197], mitochondrial dysfunction, oxidative stress [198,199], impaired clearance of mutant huntingtin, defects in protein quality control [200-202], and issues with axonal transport [199,203].

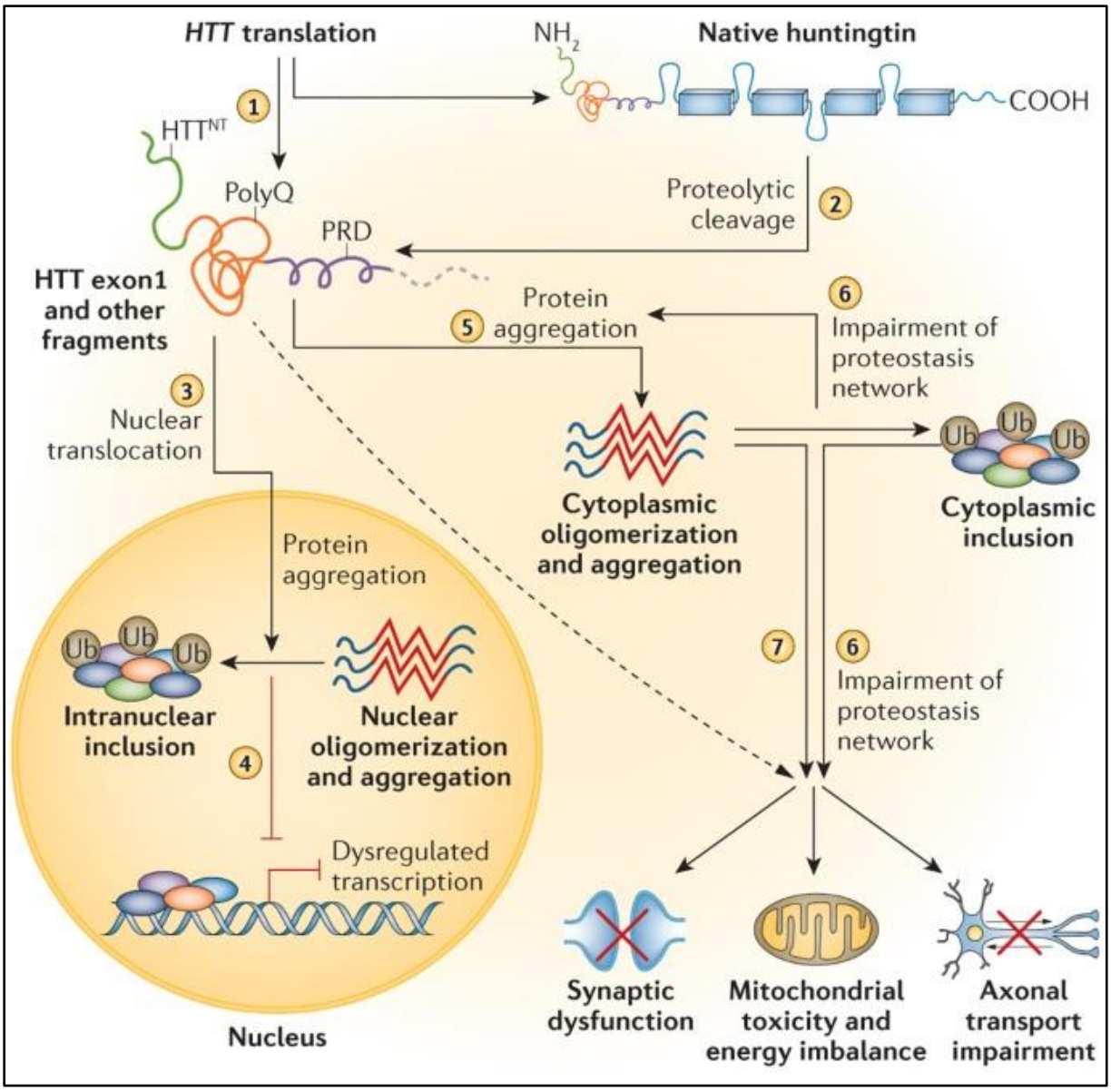

Figure 1.6.1: Pathogenetic cellular mechanisms in Huntington's disease [25].

1.6.1.1 Excitotoxicity

Overactivation of ionotropic glutamate receptors, whether from increased glutamate release, reduced glutamate uptake, or heightened receptor sensitivity, can lead to neuronal stress and death through excessive calcium influx [204]. Ionotropic glutamate receptors are categorized into three types based on their pharmacological and physiological properties: AMPA, kainate, and NMDA receptors. Particularly, excessive stimulation of NMDA receptors is playing a significant role in HD pathogenesis [205].

The first evidence linking excitotoxicity to HD pathogenesis came from studies where direct injections of glutamate receptor agonists, such as kainic acid, into rat striata caused striatal neuron death [206,207]. Later, it was shown that NMDA agonists selectively induce the loss of GABAergic medium spiny neurons (MSNs) [208]. In R6/2 mice, striatal neurons are vulnerable to NMDA receptor-induced excitotoxicity even before motor deficits appear [209]. Intra-striatal injections of the NMDA receptor agonist quinolinic acid in the YAC72 mouse model lead to larger lesions and MSN apoptosis [210].

NMDA receptors interact with PSD95, which localizes the receptors with various intracellular signaling enzymes, including NOS [211]. Huntingtin also interacts with PSD-95, and this interaction diminishes as the polyglutamine length increases, potentially contributing to enhanced NMDA receptor activity and toxicity [212]. Mutant HTT affects neurotransmitter release by disrupting glutamatergic signaling and causing excessive mitochondrial depolarization, which exposes neurons to prolonged Ca^{2+} influx and makes them more susceptible to excitotoxic damage [213]. The NMDA receptor antagonist Memantine has been shown to mitigate excitotoxicity by blocking extrasynaptic NMDA receptors [214].

1.6.1.2 Mitochondrial dysfunction and impaired energy metabolism

Mitochondria are dynamic organelles that play a critical role in dendritic spine formation and synaptic activity by regulating intracellular calcium levels [215-217]. In HD, mutant huntingtin disrupts mitochondrial structure and function, leading to impairments in the electron transport chain and cellular respiration [218,219]. Studies have shown a progressive decrease in the number and size of mitochondria in the striatal neurons of HD patients, and mitochondrial PCR array profiling in the caudate nucleus of HD patients has revealed increased mRNA and protein

expression involved in mitochondrial localization, membrane translocation, and polarization [220].

Signs of energy deficits in the brains of HD patients include reduced glucose consumption [221], elevated lactate levels, and ATP depletion [222]. These bioenergetic changes are linked to various factors such as oxidative stress [223], impaired calcium regulation [224], abnormal mitochondrial movement [225], and decreased glycolysis [226]. Our previous research revealed that treatment with Decanoic acid, 2-butyloctanoic acid, and Glyceryl triacetate mitigated mitochondrial dysfunction and oxidative stress, as well as restored ATP levels in HD150Q cells, indicating their potential to alleviate energy metabolism impairments associated with Huntington's Disease [160]. Earlier studies have suggested that alterations in mitochondrial function are crucial in the pathogenic processes in HD, with the net result being compromised energy metabolism and enhanced oxidative damage [227-234]. This is due to either obstructing transcription of nuclear-encoded mitochondrial proteins or directly interacting with the organelle and modulating respiration, membrane potential, and Ca2+ buffering, resulting in neuronal dysfunction and death [228,229].

The length of the huntingtin polyQ region has been found to be significantly associated with a decline in the cellular ATP/ADP ratio [227]. NMDA receptor-mediated excitotoxicity in medium spiny neurons (MSNs) can exacerbate cell death by increasing energy demand [235]. Deficiencies in mitochondrial complex II and III subunits have been detected in the basal ganglia of symptomatic patients [236]. Additionally, polymorphisms in mitochondrial DNA and PGC-1α have also been reported as genetic modifiers for the age at onset of HD in genetic association studies, supporting the hypothesis that energy metabolism dysregulation is a crucial component of HD pathogenesis [237,238].

PGC-1α, a transcriptional co-activator critical for mitochondrial energy production and defense against reactive oxygen species (ROS), has been implicated in neurological dysfunction and HD pathogenesis [239,240]. Various antioxidants and energy-related supplements, such as ethyl-EPA, coenzyme Q10, and creatine, are being tested in clinical trials to address mitochondrial defects in HD patients [241].

1.6.1.3 Neuroinflammation

Inflammation is a key early mechanism in the development of many neurodegenerative diseases, including Huntington's Disease. This process significantly impacts neuronal survival during pathological conditions. In HD patients, inflammatory proteins, such as complement proteins, are elevated in both the peripheral and central nervous systems [242]. Microglia, the central nervous system's resident immune cells, are primary mediators of inflammation. Their activation in the brains of HD patients is closely linked to striatal neuron loss and disease severity [243,244].

The kynurenine pathway in microglia produces metabolites that increase reactive oxygen species (ROS), contributing to non-cell autonomous degeneration in HD. The enzyme kynurenine 3-monooxygenase (KMO) in microglia regulates the toxic effects of mutant huntingtin in yeast models of HD [245]. Mouse models of HD, either crossed with KMO knock-out mice or treated with KMO inhibitors, show extended survival, highlighting the significant role of microglia in HD progression [246].

Recently, increased activation of nuclear factor-κB (NF-κB) has been observed in astrocytes in both mouse models and human patients with HD. NF-κB, a key transcriptional mediator of the inflammatory response, may play a crucial role in accelerating HD progression through astrocyte-mediated, NF-κB-dependent inflammation [247].

1.6.1.4 Autophagy

Autophagy is the process where lysosomes degrade unnecessary cytoplasmic material [248,249]. This requires a dynamic interaction between autophagic and endocytic pathways to fully break down unwanted components. Normally, wild-type and mutant huntingtin in the nucleus are degraded by the proteasome, but toxic forms of cytosolic mutant HTT are primarily processed by the lysosomal system through autophagy. This process serves as a compensatory mechanism to deal with polyglutamine toxicity [250], but the buildup of mutant HTT suggests impaired autophagic clearance [251]. Autophagosomes, which are double-membrane vesicles, are involved in this process by fusing with lysosomes for degradation [252], and they help clear both soluble and insoluble forms of HTT [253]. An increased number of autophagosomes has been observed in the striatal neurons of mice expressing mutant HTT and in the brains of HD patients [254].

When macroautophagy is blocked, many cell types respond by increasing chaperone-mediated autophagy (CMA) [255]. CMA degrades cytosolic proteins with the aid of molecular chaperones in the cytosol and lysosomal lumen [256]. This upregulation has also been observed in various

cellular and mouse models of HD. Components of CMA, such as lysosome-associated membrane protein type 2A (LAMP-2A) and lysosomal-Hsc70, are significantly increased in HD models. This increased activity is thought to compensate for macroautophagic dysfunction in the early stages of HD, but its effectiveness may diminish with age, contributing to the disease's pathology [257,258]. Pharmacologically boosting the autophagic pathway has been shown to alleviate polyglutamine-induced symptoms. Inhibiting the mammalian target of rapamycin (mTOR) induces autophagy and reduces polyglutamine toxicity in fly and mouse models of HD [172,259]. Aggregation-prone pathogenic proteins are also known to disrupt autophagic activity by sequestering and inhibiting its regulators. The abnormal interaction of mutant polyglutamine with autophagic vesicles can interfere with their ability to recognize cytosolic cargos, leading to further accumulation of the mutant protein [260].

1.6.1.5 ER stress and axonal trafficking

Proteins with the correct conformation are transported through the endoplasmic reticulum (ER) to their target organelles. When ER function is disrupted, abnormally folded proteins can accumulate, causing significant ER stress [261]. This stress activates a signal transduction cascade known as the unfolded protein response (UPR), which monitors protein folding and up-regulates ER chaperones and ER-associated degradation (ERAD) genes (**Fig. 1.6.2**) [262]. Prolonged ER stress can lead to cell death via various pro-apoptotic factors [263]. Under stress, ASK1 and its downstream target JNK trigger mitochondria-mediated apoptosis [264]. Increased levels of ASK1 and ER stress markers have been observed in HD transgenic mouse models [265]. Injecting the ER stress agent tunicamycin into the striatum has been shown to enhance mutant HTT aggregation [266]. Additionally, the ER protein quality control system, ERAD, is found to be defective in HD models, with essential ERAD proteins being sequestered by mutant HTT [267].

In both *in vitro* and *in vivo* settings, HTT aggregates in axons disrupt axonal transport [268,269]. HTT can bind directly to dynein intermediate chains to facilitate vesicle movement [270]. In the brains of HD patients, tubulin acetylation, which helps kinesin dock onto microtubules, is reduced [271]. Polyglutamine also affects microtubules via JNK3, which phosphorylates the kinesin-1 motor domain, reducing its binding affinity for microtubules. Neuronal JNK3 levels are affected in HD mouse models [272]. The expression of mutant HTT disrupts vesicular trafficking and axonal transport, causing cargo vesicle accumulation through interactions with HAP1, HAP40,

and dynein [273]. The transport of type-A GABA receptors to synapses, mediated by HTT, HAP1, and kinesin, is defective in HD [274]. Furthermore, the retrograde transport of BDNF is compromised due to the loss of wild-type HTT expression [275].

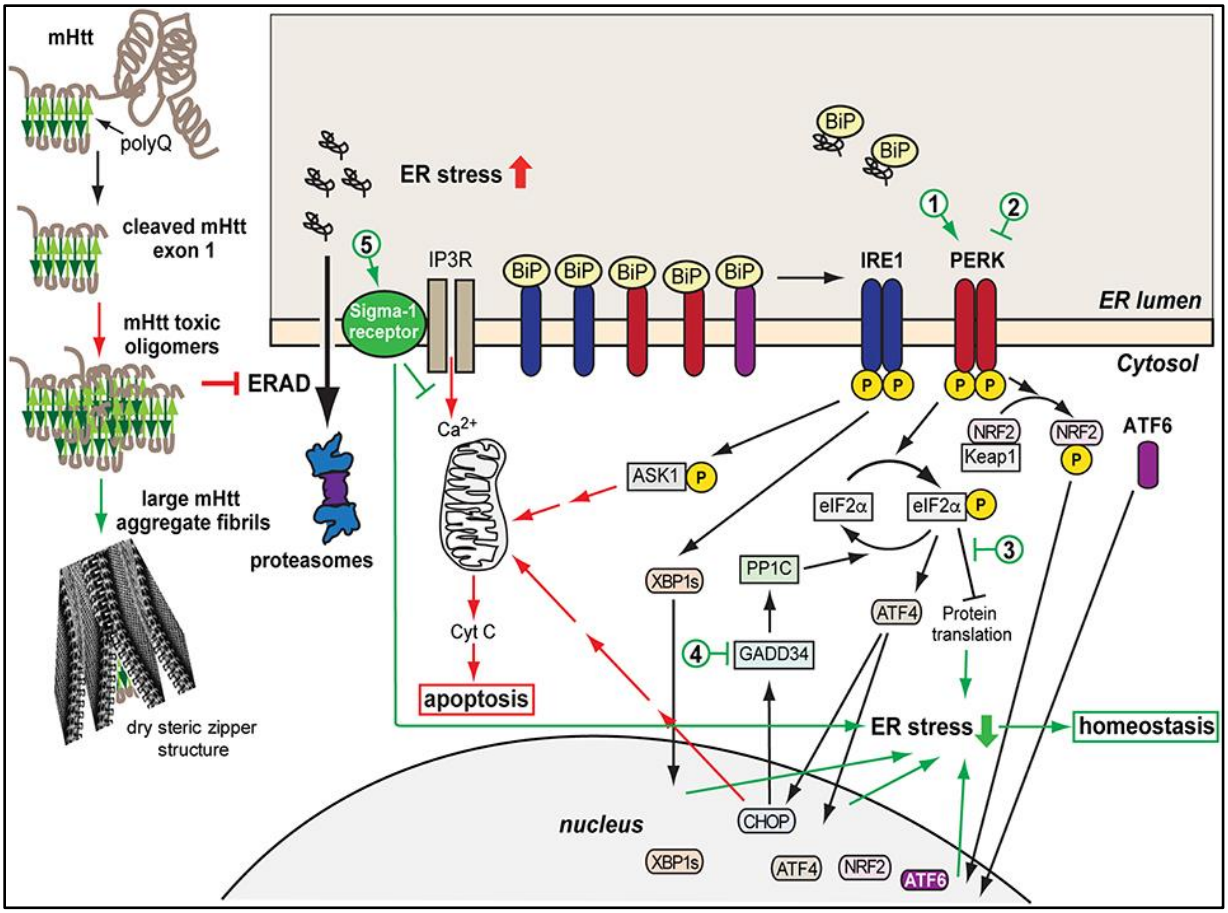

Figure 1.6.2: Model of mHTT aggregation, generation of ER stress and the consequent UPR protective and later pro-apoptotic responses [151].

1.6.1.6 Impairment of ubiquitin-proteasome system (UPS)

The ubiquitin-proteasome system (UPS) is a tightly regulated mechanism responsible for degrading and removing potentially toxic proteins, such as those that are misfolded, improperly assembled, or damaged [276]. In this system, defective proteins are tagged with ubiquitin and then broken down by proteasomes at their hydrophobic, acidic, and basic residues [277]. However, if the proteasome system malfunctions, these misfolded or damaged proteins can accumulate and form aggregates [277]. In Huntington's Disease, the impairment of UPS was first suggested by the presence of ubiquitin in mutant huntingtin aggregates [278]. Components of the UPS, including

ubiquitin and proteasome subunits, have been found sequestered in mHTT aggregates in brain tissues from HD patients and animal models [278].

The exact reason for UPS impairment is not fully understood. Some evidence indicates that this impairment may be due to the irreversible sequestration of proteasomes into aggregates [278]. Additionally, the UPS might be overwhelmed by the increased amount of mHTT as the disease progresses. For example, studies with conditional HD mouse models have shown that silencing mHTT expression leads to aggregate degradation by proteasomes, whereas using proteasome inhibitors prevents aggregate clearance [279]. This suggests that aggregate formation is a balance between the synthesis rate of the mutant protein and its degradation by the proteasome [279].

1.6.2 Non-cell-autonomous pathogenesis

Non-cell-autonomous mechanisms are increasingly recognized as significant contributors to HD pathogenesis alongside cell-autonomous factors. Glial cells, particularly astrocytes expressing mutant huntingtin, play a pivotal role in this process, inducing a neurological phenotype in mice and causing neuronal death in co-culture models [280,281]. Additionally, mHTT aggregates may propagate in a prion-like manner and affect neural transplants within HD brains, although the widespread expression of mHTT potentially limits the pathological relevance of this spread [282,283,35]. Impaired trafficking of brain-derived neurotrophic factor (BDNF) and reduced BDNF expression in HD patient brains contribute to heightened striatal susceptibility, as medium spiny neurons (MSNs) rely on cortical BDNF supply [118,116,37]. Excitotoxicity, mediated by excessive activation of AMPA and NMDA glutamate receptors predominantly expressed on MSNs, leads to neuronal apoptosis in HD. This is supported by elevated levels of excitotoxic KMO metabolites and compromised synaptic glutamate clearance, highlighting potential therapeutic targets to mitigate excitotoxic damage [284-287].

Peripheral immune abnormalities are prevalent in HD, extending beyond the central nervous system (CNS). HD patients and animal models exhibit elevated levels of proinflammatory cytokines such as IL-6 and TNFα in plasma, with correlations observed between these markers and disease progression, as well as microglial activation [288,79,289,290]. Myeloid cells from HD patients express mutant huntingtin and demonstrate heightened reactivity, characterized by increased cytokine production following stimulation, a response that can be reversed by lowering HTT levels [291,125,292]. Functional deficits in migration and phagocytosis have also been

observed in HD myeloid cells, indicating potential abnormalities in basal immune function beyond stimulated conditions [292,77]. While adaptive immune responses in HD are less studied, T and B lymphocytes from patients express mHTT, with altered cytokine profiles noted but no significant changes in circulating immunoglobulin levels[291,79,293]. Therapeutically, modulation of peripheral immune responses through CB2 receptor and KMO inhibition has shown promise in HD models, reducing CNS inflammation, extending lifespan, and improving motor deficits [294-297]. Additionally, bone marrow transplantation has demonstrated modest benefits, underscoring the potential of peripheral immune mechanisms in modifying HD progression [298].

These findings underscore the complex interplay between cell-autonomous and non-cell-autonomous factors in HD pathogenesis, highlighting the intricate involvement of peripheral immune dysregulation and suggesting avenues for multifaceted therapeutic interventions targeting both neuronal and glial dysfunction to potentially mitigate disease progression.

1.6.3 Transcriptional dysregulation in HD

Both wild-type and mutant huntingtin proteins are known to interact with various transcription factors. Microarray analyses have shown that numerous transcriptional pathways are disrupted in Huntington's Disease. However, the exact role of transcriptional deregulation in HD pathogenesis remains unclear, with several hypotheses proposed to explain how mutant huntingtin might cause these disturbances [197,299,300]:

1) The gain-of-function property of the polyglutamine stretch may lead to abnormal binding to DNA.

2) Mutant huntingtin might form inactive transcriptional complexes with other factors, functioning as a repressor.

3) By forming complexes with co-repressors, it might activate genes that are usually silent.

4) Mutant huntingtin may sequester transcription factors, reducing their cellular levels.

Microarray studies have identified more than 10,000 functional classes of genes whose expression is affected in polyglutamine diseases [301-305]. A common finding in various polyglutamine transgenic mice is the altered expression of neuropeptides, such as enkephalin, and proteins involved in signal transduction. The cAMP-responsive element (CRE) pathway regulates genes essential for neuronal survival, and down-regulation of CRE-mediated genes is a hallmark of pre-

symptomatic HD [306]. Polyglutamine protein expression is known to influence CRE-mediated transcription, and deletion of CREB results in an HD-like phenotype in mouse models [307]. Expanded polyglutamine interacts with the co-activator CREB-binding protein (CBP) and can sequester it into aggregates, as observed in HD, SBMA, and SCA-3 models [308]. Other genes that interact with soluble huntingtin and are similarly recruited include SP-1, TBP, and CA-150 [309,310].

The disruption of Sp1 occurs early in HD pathogenesis. Mutant huntingtin with expanded polyglutamine disrupts the association of TAFII130 with Sp1, interfering directly with its DNA binding, thereby down-regulating gene promoters of dopamine D2 receptors and nerve growth factor receptor [310,311]. Huntingtin also interacts with several transcriptional repressor proteins. The N-terminus of HTT-171 interacts in a repeat-length-dependent manner with nuclear receptor co-repressor (N-CoR) to re-localize its repressor protein [312]. Mutant huntingtin has been shown to repress PGC-1α transcription by associating with the promoter and interfering with the CREB/TAF4-dependent transcriptional pathway crucial for its expression. The absence of PGC-1α can lead to increased degeneration of striatal neurons and motor abnormalities in HD mice [313].

Wild-type huntingtin modulates the activity of neuron-restrictive silencer elements (NRSE)-containing genes, including brain-derived neurotrophic factor (BDNF), a crucial pro-survival factor for striatal neurons. Mutant huntingtin suppresses the transcription of NRSE-regulated genes, resulting in a reduction of BDNF levels and subsequently leading to the death of striatal neurons due to insufficient trophic support [116,121]. Furthermore, PRC2, an epigenetic silencing complex, plays a crucial role in Huntington's disease pathophysiology. Dysregulation of PRC2 can contribute to the disease, as mutations or malfunctions in its subunits are associated with HD pathology [178]. Huntingtin has been demonstrated to interact with PRC2 and enhance its activity [70], with mutant huntingtin significantly amplifying this effect compared to its normal counterpart [70]. Additionally, mutant huntingtin disrupts PRC2 regulation, resulting in aberrant Hox gene expression and impaired histone H3K27 trimethylation [70].

1.7 Huntington's Disease Therapeutics

Currently, there is no effective treatment for HD. However, various strategies such as silencing the mutant allele using siRNA, RNAi [314], Zinc-finger nucleases [315], DNA Aptamers [316] and

targeting huntingtin post-translational modifications are being employed in animal models of HD [317], with limited success. Recently, a human trial involving HD patients used the mutant huntingtin-specific antisense oligonucleotide Tominersen (previously known as IONIS-HTTRx and RG6042), which showed a significant reduction in mutant huntingtin protein expression [318], Unfortunately, the trial was halted after interim data from the Phase 3 GENERATION HD1 clinical trial indicated that the therapy was not benefiting participants. A detailed description of HD treatments and ongoing clinical trials of HD therapeutics is provided below.

1.7.1 Current therapeutics for HD

As previously mentioned, there are currently no treatments available to slow the progression of Huntington's disease, so management focuses on symptomatic relief [47]. Tetrabenazine is the first drug specifically approved for treating HD-related chorea, though neuroleptics like haloperidol can also be used for chorea and are helpful in managing non-motor symptoms such as psychosis and irritability. Psychiatric symptoms are treated with conventional methods, such as selective serotonin reuptake inhibitors for depression. Other treatment strategies include dietary supplements and physiotherapy for cachexia, while social care often proves more effective than pharmacological interventions in addressing behavioral issues [45]. Unfortunately, recent clinical trials have mostly resulted in disappointing outcomes [25]

1.7.2 Experimental therapeutics for HD

Experimental therapeutics for HD have focused on targeting specific pathogenic mechanisms to mitigate cellular deficits associated with the disease. Enhancing cellular degradation pathways, such as mTOR-dependent autophagy, has shown potential in clearing mutant huntingtin aggregates in fly and mouse models of HD [260]. Strategies involving the overexpression of molecular chaperones and administration of small molecule aggregation inhibitors have also been explored, although concerns regarding off-target effects may limit their clinical application [319,320]. Another approach aims at supporting neuronal function through interventions like increasing brain-derived neurotrophic factor (BDNF) levels, which have demonstrated improvements in motor performance and synaptic plasticity in HD models [321,322]. Conversely, attempts to mitigate excitotoxicity, a significant contributor to neuronal damage in HD, using agents like riluzole have not yielded disease-modifying effects in clinical trials [323]. Neuronal replacement strategies through grafting neurons in animal models initially showed promise but faced challenges

in clinical trials, including potential mHTT spread and graft degeneration [324-326,283]. Additionally, targeting transcriptional dysregulation via histone deacetylase inhibition and genetic knockdown has shown efficacy in improving motor function in preclinical studies, yet these approaches address only specific facets of HD's complex pathogenesis [327,328]. These therapeutic strategies underscore the multifaceted nature of HD pathophysiology and highlight the need for comprehensive approaches in developing effective treatments.

1.7.3 Post-transcriptional gene silencing

Recent interest has focused on post-transcriptional gene silencing (PTGS) as a therapeutic approach for genetic disorders, aiming to interrupt mRNA translation and mitigate disease progression. Initial clinical trials, particularly in Duchenne's muscular dystrophy, have shown promising results [329]. PTGS methods primarily utilize small interfering RNA (siRNA), double-stranded oligonucleotides approximately 20-25 bp in length. These molecules interact with the RNA-induced silencing complex (RISC) upon cytoplasmic delivery, where the guide strand directs RISC to target complementary mRNA sequences for degradation, facilitated by Argonaute enzymes [330]. In contrast, antisense oligonucleotides (ASOs), single-stranded molecules of 15-25 bp, mediate PTGS by promoting mRNA degradation via ribonuclease H (RNase H) or physically blocking translation [331].

Delivery mechanisms differ between siRNAs and ASOs; ASOs can penetrate cells, including neurons, directly, whereas siRNAs require efficient transfection protocols for delivery and target mRNA exclusively in the cytoplasm [332]. Additionally, siRNAs are generally considered more robust and stable due to their double-stranded structure, which avoids the extensive chemical modifications often needed to enhance ASO potency [333].

1.7.4 HTT-lowering in HD

Recent research has focused on using post-transcriptional gene silencing (PTGS) techniques to target Huntington's disease, a monogenic disorder primarily caused by mHTT. Experimental approaches have demonstrated the efficacy of reducing mHTT levels as a therapeutic strategy. Initial studies employing doxycycline-induced conditional knockout of mHTT in HD mouse models showed significant reductions in brain pathology, supporting the hypothesis that lowering cellular mHTT levels can beneficially impact disease progression and survival [334]. Subsequent investigations have utilized small interfering RNAs (siRNAs) and antisense oligonucleotides

(ASOs) with promising outcomes. Lentiviral vector-mediated delivery of anti-HTT siRNA effectively mitigated neuropathology in HD mice [335], while intracerebroventricular infusion of ASOs delayed disease progression and prolonged symptom improvement, even beyond the period of HTT mRNA reduction, suggesting potential long-lasting therapeutic benefits [336]. However, the clinical translation of PTGS therapies for HD faces significant challenges in effective drug delivery to the brain. Traditional peripheral administration methods are inadequate due to poor blood-brain barrier penetration, necessitating invasive techniques such as implantable infusion systems for direct brain delivery. Initial studies investigating direct CSF infusion of ASOs are underway to explore their feasibility and efficacy in clinical settings [337].

1.7.5 Allele-selective HTT-lowering

Therapeutic strategies for Huntington's Disease encompass two main approaches: total HTT-lowering therapies utilizing siRNAs and ASOs, and allele-selective methods aimed at targeting mutant HTT while sparing wild-type expression [338]. Studies in animal models, including mice and non-human primates, have demonstrated the tolerability of non-specific HTT-lowering treatments over extended periods, albeit with unresolved concerns regarding potential long-term effects in human patients [336,339,340,123]. Allele-selective strategies primarily focus on targeting expanded CAG repeats or single nucleotide polymorphisms (SNPs), which pose challenges such as off-target effects and reduced efficacy with normal-range CAG repeats [341-343]. SNP-based targeting approaches consider the variability in SNP heterozygosity among different populations, suggesting the potential for achieving selective knockdown using a limited number of SNPs [344,332,345]. Experimental validation includes studies utilizing siRNAs and ASOs directed against specific SNPs (e.g., rs363125, rs7685686), demonstrating varying degrees of allele-selectivity and efficacy in cellular and animal models [346-349]. Despite progress, significant technical challenges remain in achieving robust allele-selective suppression across both alleles in human cells, underscoring the imperative for further research and clinical validation [350,335,339].

1.7.6 Protein Clearance Approaches to Lowering Mutant Huntingtin

Huntington's Disease involves impaired proteostasis, affecting the degradation of mutant huntingtin through the ubiquitin-proteasome system (UPS) and autophagy pathways [351]. Therapeutic strategies targeting mHTT proteostasis pathways aim to enhance protein clearance

mechanisms, showing promise in HD models but currently lacking clinical trials [352]. There is significant interest in orally bioavailable small molecules for lowering mHTT levels, offering simplified administration, good systemic distribution, and potential cost-effectiveness compared to other therapies [352]. Additionally, PROTAC-based approaches have emerged as a novel strategy to selectively target mHTT for UPS degradation, demonstrating efficacy in HD patient-derived cells [353,354]. However, these approaches require further development and validation before advancing to clinical trials, particularly in terms of delivery to the central nervous system (CNS). These findings underscore ongoing efforts to develop effective therapeutic agents for Huntington's Disease by exploiting cellular protein quality control mechanisms.

1.8 Huntingtin Post-translational Modifications

As previously discussed, proper protein folding is essential for protein functionality. Post-translational modifications are crucial in this process, and any alterations can lead to misfolding and potential toxicity [355]. Several modifications of huntingtin occur within the highly conserved N-terminal 17 amino acids. Ubiquitination was the first identified modification, occurring after HTT interacts with the ubiquitin-conjugating enzyme E2-25K, which is significantly enriched in the striatum and cortex—the brain regions most impacted by Huntington's disease [356]. In a *Drosophila* model of Huntington's disease, inhibiting huntingtin (HTT) ubiquitination exacerbated neurodegeneration. The same study revealed that lysines 6 and 9 of the HTT N-terminus were SUMOylated, and increased SUMOylation in HD flies further intensified neurodegeneration [147]. These findings imply that N-terminal ubiquitination of HTT serves a protective role, whereas SUMOylation contributes to toxicity, indicating a competitive interaction between these modifications in mitigating cell degeneration. More recently, it was discovered that Rhes (Ras Homolog Enriched in Striatum), which is specifically localized to the striatum, interacts with mutant HTT, induces its SUMOylation, decreases aggregation, and enhances cytotoxicity [357]. This supports the idea that large aggregates may not be the toxic elements in HD pathology.

1.8.1 Phosphorylation of HTT

Another significant post-translational modification of huntingtin, including phosphorylation, have been shown to regulate its function and toxicity [358]. Phosphorylation of many proteins, at serine (S), threonine (T) or tyrosine (Y) residues, regulates their functional activities, turnover [359] and nuclear transport [360]. Huntingtin is heavily phosphorylated and several phosphorylation sites

have been reported. Phosphorylation at several sites including Ser421, Ser434, Ser513, Ser536, Ser1181 and Ser1201 were shown to be protective in nature and reduce the aggregation and toxicity of the mutant protein [361-367]. Several other phosphorylation sites have also been predicted in huntingtin and some sites have been confirmed; Thr3 and Ser13 and Ser16 [368,369], as well as Ser421, which is phosphorylated by AKT [370]. Some of these sites have been implicated in toxicity of mutant huntingtin while others are demonstrated to be of protective nature.

Initially, a mass spectrometry screen identified several phosphorylation sites in both mutant and wild-type full-length HTT, with the most N-terminal site being amino acid 421, which is crucial for axonal transport [365,371,362]. As noted earlier, the nuclear accumulation predominantly involves small N-terminal fragments, indicating that if phosphorylation influences the localization of N-terminal mutant HTT, phosphorylated sites are likely situated near the N-terminus. Recent research employing mass spectrometry has identified phosphorylation sites within exon 1 (the N-terminal 67 amino acids of HTT), with threonine 3 (T3) emerging as the most frequently phosphorylated site [368]. In cell culture and an HD *Drosophila* model, phosphorylation of T3 is essential for aggregation. Notably, T3 appears to contribute to toxicity not through its phosphorylation, but rather due to its critical role in maintaining the tertiary structure of the N-terminus. Another notable recent study by Lee Y *et al.* demonstrated that phosphorylation of Ser2550 by cAMP-dependent protein kinase A (PKA) modulates huntingtin degradation, subsequently affecting the steady-state levels of huntingtin in HD cells [372].

1.8.2 Ser13/Ser16 Phosphorylation

Within the first 17 amino acids of huntingtin are two serine residues, S13 and S16, which are also subject to phosphorylation. The role of these phosphorylations in HD pathogenesis remains debated. Two research groups investigated these residues by mutating S13 and S16 to either alanine (to create a non-phosphorylatable mutant) or aspartic acid (to create a phosphomimetic mutant). One group performed these mutations in cell culture [369], while the other generated a BACHD mouse model with these point mutations [65]. Thompson *et al.* reported that phosphorylation of both residues enhances the nuclear localization of N-terminal huntingtin and promotes its targeting to lysosomes or the proteasome for degradation [369]. Conversely, Gu *et al.* found that phosphorylation of these residues reduces aggregation and toxicity of mutant huntingtin [65].

However, some of the most compelling evidence for the protective nature of huntingtin phosphorylation comes from the study in which constitutive phosphorylation at Ser13 and Ser16 was shown to revert the toxic phenotype of mutant huntingtin in a BAC mouse model [65]. Expression of phosphomimetic huntingtin, where serine was changed to aspartate (SD) or, alternatively, expression of nonphosphorylatable alanine (SA) residues-huntingtin, demonstrated that while, both SA and SD mutant huntingtin proteins retained essential huntingtin function in rescuing Hdh knockout mouse phenotypes, only the SD mutant protein was associated with a striking absence of the motor, psychiatric and neuropathological phenotypes and decrease in mutant huntingtin aggregates [65]. This result strongly predicts that huntingtin phosphorylation at Ser13/Ser16 can directly or indirectly prevents the toxic consequences associated with expanded polyQ huntingtin. Although the precise mechanism remains unclear and requires further investigation.

1.9 Kinase and Phosphatase Inhibitors as Huntington's Disease Therapeutics

Kinase and phosphatase inhibitors are pivotal in modulating huntingtin phosphorylation in HD, impacting the protein's subcellular localization and toxicity [373]. The phosphorylation of huntingtin at Ser13 and Ser16, which enhances its clearance by proteasomes and lysosomes, can be altered by small-molecule kinase inhibitors such as casein kinase-2 (CK2) inhibitors [373]. CK2 and the inflammatory kinase IKK catalyse the addition of phosphate groups to these sites, with IKK-induced phosphorylation activating other post-translational modifications (PTMs) of nearby lysine residues, including acetylation, ubiquitination, and SUMOylation, promoting huntingtin clearance by lysosomes and proteasomes [369]. Interestingly, inhibiting IKKβ kinase can paradoxically increase N17 phosphorylation, further influencing huntingtin localization within cells [373]. These findings suggest that targeting kinase and phosphatase activity could provide therapeutic benefits by modifying the molecular mechanisms underlying HD progression.

In preclinical development, Protein Kinase CK2 has emerged as a promising kinase target for HD therapeutic intervention. Studies have shown that inhibition of CK2 reduces HTT phosphorylation but increases toxicity [374]. Genetic approaches in mouse models have demonstrated beneficial effects of targeting CK2, highlighting its potential [374]. In addition, research by Randy Singh Atwal and colleagues examined 80 compounds, with BMS 345541 and Bay 11-7082 showing enhanced N17 phosphorylation [373]. These two drugs demonstrated the ability to influence the

subcellular localization of huntingtin, with CK2 inhibitors reducing N17 phosphorylation and nuclear translocation, while IKK kinase inhibitors boosted N17 phosphorylation and p-N17 huntingtin nuclear localization [373]. Kinetin (N6-furfuryladenine), a plant cytokine, aids N17 phosphorylation by substituting ATP as a substrate for CK2, thereby enhancing the clearance of mHTT inclusions in the context of decreased ATP levels in HD [375].

Additionally, inhibition of phosphatase and tensin homolog (PTEN) has led to significant improvements in morphological phenotypes, functional vision, and climbing ability in transgenic flies and mouse neuronal models of HD [376]. Bay 11-7082 and BMS-345541, which inhibit IKK phosphorylation through different pathways, further underscore the potential of kinase inhibitors in HD treatment [373]. BMS-345541 is a selective inhibitor of the catalytic subunit of IKK beta kinase. IKK beta kinase mediated phosphorylation leads to the activation of Protein phosphatase 2A (PP2A) and Serine/threonine-protein phosphatase 2B (PP2B), which are responsible for dephosphorylation at the N17 domain of the HTT protein [373]. In presence of BMS-345541, the N17 phosphorylation is preserved.

Despite these promising findings, several challenges remain in translating this research into clinical trials. There is a need for further validation of the efficacy and long-term safety of kinase inhibitors, and the availability of FDA-approved drugs for neurological treatments is limited compared to cancer therapies [377,378]. The concept of "Aberrant Cell Cycle Diseases" proposes that kinase inhibitors approved for cancer treatment could also benefit neurological disorders like HD, where kinase activation contributes to neuronal death [378]. These challenges underscore the importance of rigorous preclinical testing and regulatory approval processes to ensure that kinase inhibitors successfully transition from preclinical development to clinical trials for HD treatment.

1.10 References

1. Deuschl G, Beghi E, Fazekas F, Varga T, Christoforidi KA, Sipido E, Bassetti CL, Vos T, Feigin VL (2020) The burden of neurological diseases in Europe: an analysis for the Global Burden of Disease Study 2017. The Lancet Public health 5 (10):e551-e567. doi:10.1016/s2468-2667(20)30190-0

2. Chang CJ, Cravatt BF, Johnson DS, Lim MH (2014) Molecular medicine and neurodegenerative diseases. Chemical Society Reviews 43 (19):6668-6671. doi:10.1039/C4CS90065K

3. Wilson DM, 3rd, Cookson MR, Van Den Bosch L, Zetterberg H, Holtzman DM, Dewachter I (2023) Hallmarks of neurodegenerative diseases. Cell 186 (4):693-714. doi:10.1016/j.cell.2022.12.032

4. DiFiglia M, Sapp E, Chase KO, Davies SW, Bates GP, Vonsattel JP, Aronin N (1997) Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. Science (New York, NY) 277 (5334):1990-1993. doi:10.1126/science.277.5334.1990

5. Ross CA, Poirier MA (2004) Protein aggregation and neurodegenerative disease. Nature medicine 10 Suppl:S10-17. doi:10.1038/nm1066

6. Bossy-Wetzel E, Schwarzenbacher R, Lipton SA (2004) Molecular pathways to neurodegeneration. Nature medicine 10 Suppl:S2-9. doi:10.1038/nm1067

7. Lamptey RNL, Chaulagain B, Trivedi R, Gothwal A, Layek B, Singh J (2022) A Review of the Common Neurodegenerative Disorders: Current Therapeutic Approaches and the Potential Role of Nanotherapeutics. International journal of molecular sciences 23 (3). doi:10.3390/ijms23031851

8. Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G (2013) Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nature reviews Neurology 9 (2):106-118. doi:10.1038/nrneurol.2012.263

9. Hooper C, Killick R, Lovestone S (2008) The GSK3 hypothesis of Alzheimer's disease. Journal of neurochemistry 104 (6):1433-1439. doi:10.1111/j.1471-4159.2007.05194.x

10. Gong CX, Iqbal K (2008) Hyperphosphorylation of microtubule-associated protein tau: a promising therapeutic target for Alzheimer disease. Current medicinal chemistry 15 (23):2321-2328. doi:10.2174/092986708785909111

11. Lesage S, Brice A (2009) Parkinson's disease: from monogenic forms to genetic susceptibility factors. Human molecular genetics 18 (R1):R48-59. doi:10.1093/hmg/ddp012

12. Klein C, Westenberger A (2012) Genetics of Parkinson's disease. Cold Spring Harbor perspectives in medicine 2 (1):a008888. doi:10.1101/cshperspect.a008888

13. Olanow CW, Brundin P (2013) Parkinson's disease and alpha synuclein: is Parkinson's disease a prion-like disorder? Movement disorders : official journal of the Movement Disorder Society 28 (1):31-40. doi:10.1002/mds.25373

14. Forno LS (1996) Neuropathology of Parkinson's disease. Journal of neuropathology and experimental neurology 55 (3):259-272. doi:10.1097/00005072-199603000-00001

15. Mead RJ, Shan N, Reiser HJ, Marshall F, Shaw PJ (2023) Amyotrophic lateral sclerosis: a neurodegenerative disorder poised for successful therapeutic translation. Nature reviews Drug discovery 22 (3):185-212. doi:10.1038/s41573-022-00612-2

16. Masrori P, Van Damme P (2020) Amyotrophic lateral sclerosis: a clinical review. European journal of neurology 27 (10):1918-1929. doi:10.1111/ene.14393

17. Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, Bruce J, Schuck T, Grossman M, Clark CM, McCluskey LF, Miller BL, Masliah E, Mackenzie IR, Feldman H, Feiden W, Kretzschmar HA, Trojanowski JQ, Lee VM (2006) Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science (New York, NY) 314 (5796):130-133. doi:10.1126/science.1134108

18. Brooks BR, Miller RG, Swash M, Munsat TL (2000) El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders 1 (5):293-299. doi:10.1080/146608200300079536

19. Petrov D, Mansfield C, Moussy A, Hermine O (2017) ALS Clinical Trials Review: 20 Years of Failure. Are We Any Closer to Registering a New Treatment? Frontiers in aging neuroscience 9:68. doi:10.3389/fnagi.2017.00068

20. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ (2006) Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. The Lancet Neurology 5 (2):140-147. doi:10.1016/s1474-4422(05)70326-4

21. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group (1993). Cell 72

(6):971-983. doi:10.1016/0092-8674(93)90585-e

22. Huntington G (2003) On chorea. George Huntington, M.D. The Journal of neuropsychiatry and clinical neurosciences 15 (1):109-112. doi:10.1176/jnp.15.1.109

23. Fisher ER, Hayden MR (2014) Multisource ascertainment of Huntington disease in Canada: prevalence and population at risk. Movement disorders : official journal of the Movement Disorder Society 29 (1):105-114. doi:10.1002/mds.25717

24. Rawlins MD, Wexler NS, Wexler AR, Tabrizi SJ, Douglas I, Evans SJ, Smeeth L (2016) The Prevalence of Huntington's Disease. Neuroepidemiology 46 (2):144-153. doi:10.1159/000443738

25. Bates GP, Dorsey R, Gusella JF, Hayden MR, Kay C, Leavitt BR, Nance M, Ross CA, Scahill RI, Wetzel R, Wild EJ, Tabrizi SJ (2015) Huntington disease. Nature reviews Disease primers 1:15005. doi:10.1038/nrdp.2015.5

26. Kay C, Hayden MR, Leavitt BR (2017) Epidemiology of Huntington disease. Handbook of clinical neurology 144:31-46. doi:10.1016/b978-0-12-801893-4.00003-1

27. Baig SS, Strong M, Quarrell OW (2016) The global prevalence of Huntington's disease: a systematic review and discussion. Neurodegenerative disease management 6 (4):331-343. doi:10.2217/nmt-2016-0008

28. Roos RAC (2010) Huntington's disease: a clinical review. Orphanet Journal of Rare Diseases 5 (1):40. doi:10.1186/1750-1172-5-40

29. Medina A, Mahjoub Y, Shaver L, Pringsheim T (2022) Prevalence and Incidence of Huntington's Disease: An Updated Systematic Review and Meta-Analysis. Movement disorders : official journal of the Movement Disorder Society 37 (12):2327-2335. doi:10.1002/mds.29228

30. Saudou F, Humbert S (2016) The Biology of Huntingtin. Neuron 89 (5):910-926. doi:10.1016/j.neuron.2016.02.003

31. Bertram L, Tanzi RE (2005) The genetic epidemiology of neurodegenerative disease. The Journal of clinical investigation 115 (6):1449-1457. doi:10.1172/jci24761

32. Pramanik S, Basu P, Gangopadhaya PK, Sinha KK, Jha DK, Sinha S, Das SK, Maity BK, Mukherjee SC, Roychoudhuri S, Majumder PP, Bhattacharyya NP (2000) Analysis of CAG and CCG repeats in Huntingtin gene among HD patients and normal populations of India. European Journal of Human Genetics 8 (9):678-682. doi:10.1038/sj.ejhg.5200515

33. Saleem Q, Roy S, Murgood U, Saxena R, Verma IC, Anand A, Muthane U, Jain S, Brahmachari SK (2003) Molecular analysis of Huntington's disease and linked polymorphisms in the Indian population. Acta neurologica Scandinavica 108 (4):281-286. doi:10.1034/j.1600-0404.2003.00133.x

34. Gusella JF, Wexler NS, Conneally PM, Naylor SL, Anderson MA, Tanzi RE, Watkins PC, Ottina K, Wallace MR, Sakaguchi AY, et al. (1983) A polymorphic DNA marker genetically linked to Huntington's disease. Nature 306 (5940):234-238. doi:10.1038/306234a0

35. Li SH, Schilling G, Young WS, 3rd, Li XJ, Margolis RL, Stine OC, Wagster MV, Abbott MH, Franz ML, Ranen NG, et al. (1993) Huntington's disease gene (IT15) is widely expressed in human and rat tissues. Neuron 11 (5):985-993. doi:10.1016/0896-6273(93)90127-d

36. Squitieri F, Jankovic J (2012) Huntington's disease: how intermediate are intermediate repeat lengths? Movement disorders : official journal of the Movement Disorder Society 27 (14):1714-1717. doi:10.1002/mds.25172

37. Ross CA, Tabrizi SJ (2011) Huntington's disease: from molecular pathogenesis to clinical treatment. The Lancet Neurology 10 (1):83-98. doi:10.1016/s1474-4422(10)70245-3

38. Squitieri F, Frati L, Ciarmiello A, Lastoria S, Quarrell O (2006) Juvenile Huntington's disease: does a dosage-effect pathogenic mechanism differ from the classical adult disease? Mechanisms of ageing and development 127 (2):208-212. doi:10.1016/j.mad.2005.09.012

39. Trottier Y, Lutz Y, Stevanin G, Imbert G, Devys D, Cancel G, Saudou F, Weber C, David G, Tora L, Agid Y, Brice A, Mandel J-L (1995) Polyglutamine expansion as a pathological epitope in Huntington's disease and four dominant cerebellar ataxias. Nature 378 (6555):403-406. doi:10.1038/378403a0

40. Wexler NS, Lorimer J, Porter J, Gomez F, Moskowitz C, Shackell E, Marder K, Penchaszadeh

G, Roberts SA, Gayán J, Brocklebank D, Cherny SS, Cardon LR, Gray J, Dlouhy SR, Wiktorski S, Hodes ME, Conneally PM, Penney JB, Gusella J, Cha JH, Irizarry M, Rosas D, Hersch S, Hollingsworth Z, MacDonald M, Young AB, Andresen JM, Housman DE, De Young MM, Bonilla E, Stillings T, Negrette A, Snodgrass SR, Martinez-Jaurrieta MD, Ramos-Arroyo MA, Bickham J, Ramos JS, Marshall F, Shoulson I, Rey GJ, Feigin A, Arnheim N, Acevedo-Cruz A, Acosta L, Alvir J, Fischbeck K, Thompson LM, Young A, Dure L, O'Brien CJ, Paulsen J, Brickman A, Krch D, Peery S, Hogarth P, Higgins DS, Jr., Landwehrmeyer B (2004) Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset. Proceedings of the National Academy of Sciences of the United States of America 101 (10):3498-3503. doi:10.1073/pnas.0308679101

41. Andrew SE, Goldberg YP, Kremer B, Telenius H, Theilmann J, Adam S, Starr E, Squitieri F, Lin B, Kalchman MA, et al. (1993) The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. Nature genetics 4 (4):398-403. doi:10.1038/ng0893-398

42. Lee JM, Ramos EM, Lee JH, Gillis T, Mysore JS, Hayden MR, Warby SC, Morrison P, Nance M, Ross CA, Margolis RL, Squitieri F, Orobello S, Di Donato S, Gomez-Tortosa E, Ayuso C, Suchowersky O, Trent RJ, McCusker E, Novelletto A, Frontali M, Jones R, Ashizawa T, Frank S, Saint-Hilaire MH, Hersch SM, Rosas HD, Lucente D, Harrison MB, Zanko A, Abramson RK, Marder K, Sequeiros J, Paulsen JS, Landwehrmeyer GB, Myers RH, MacDonald ME, Gusella JF (2012) CAG repeat expansion in Huntington disease determines age at onset in a fully dominant fashion. Neurology 78 (10):690-695. doi:10.1212/WNL.0b013e318249f683

43. Rosenblatt A, Brinkman RR, Liang KY, Almqvist EW, Margolis RL, Huang CY, Sherr M, Franz ML, Abbott MH, Hayden MR, Ross CA (2001) Familial influence on age of onset among siblings with Huntington disease*. American Journal of Medical Genetics 105 (5):399-403. doi:https://doi.org/10.1002/ajmg.1400

44. Rosenblatt A, Liang KY, Zhou H, Abbott MH, Gourley LM, Margolis RL, Brandt J, Ross CA (2006) The association of CAG repeat length with clinical progression in Huntington disease. Neurology 66 (7):1016-1020. doi:10.1212/01.wnl.0000204230.16619.d9

45. Ross CA, Aylward EH, Wild EJ, Langbehn DR, Long JD, Warner JH, Scahill RI, Leavitt BR, Stout JC, Paulsen JS, Reilmann R, Unschuld PG, Wexler A, Margolis RL, Tabrizi SJ (2014) Huntington disease: natural history, biomarkers and prospects for therapeutics. Nature reviews Neurology 10 (4):204-216. doi:10.1038/nrneurol.2014.24

46. Wild EJ, Tabrizi SJ (2007) Huntington's disease phenocopy syndromes. Current opinion in neurology 20 (6):681-687. doi:10.1097/WCO.0b013e3282f12074

47. Novak MJ, Tabrizi SJ (2010) Huntington's disease. BMJ (Clinical research ed) 340:c3109. doi:10.1136/bmj.c3109

48. Paulsen JS, Langbehn DR, Stout JC, Aylward E, Ross CA, Nance M, Guttman M, Johnson S, MacDonald M, Beglinger LJ, Duff K, Kayson E, Biglan K, Shoulson I, Oakes D, Hayden M (2008) Detection of Huntington's disease decades before diagnosis: the Predict-HD study. Journal of neurology, neurosurgery, and psychiatry 79 (8):874-880. doi:10.1136/jnnp.2007.128728

49. Stout JC, Paulsen JS, Queller S, Solomon AC, Whitlock KB, Campbell JC, Carlozzi N, Duff K, Beglinger LJ, Langbehn DR, Johnson SA, Biglan KM, Aylward EH (2011) Neurocognitive signs in prodromal Huntington disease. Neuropsychology 25 (1):1-14. doi:10.1037/a0020937

50. Paulsen JS, Nehl C, Hoth KF, Kanz JE, Benjamin M, Conybeare R, McDowell B, Turner B (2005) Depression and stages of Huntington's disease. The Journal of neuropsychiatry and clinical neurosciences 17 (4):496-502. doi:10.1176/jnp.17.4.496

51. Farrer LA (1986) Suicide and attempted suicide in Huntington disease: implications for preclinical testing of persons at risk. Am J Med Genet 24 (2):305-311. doi:10.1002/ajmg.1320240211

52. Tabrizi SJ, Scahill RI, Owen G, Durr A, Leavitt BR, Roos RA, Borowsky B, Landwehrmeyer B, Frost C, Johnson H, Craufurd D, Reilmann R, Stout JC, Langbehn DR (2013) Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. The Lancet Neurology 12 (7):637-649. doi:10.1016/s1474-4422(13)70088-7

53. Kirkwood SC, Su JL, Conneally P, Foroud T (2001) Progression of symptoms in the early and

middle stages of Huntington disease. Archives of neurology 58 (2):273-278. doi:10.1001/archneur.58.2.273

54. Duyao M, Ambrose C, Myers R, Novelletto A, Persichetti F, Frontali M, Folstein S, Ross C, Franz M, Abbott M, et al. (1993) Trinucleotide repeat length instability and age of onset in Huntington's disease. Nature genetics 4 (4):387-392. doi:10.1038/ng0893-387

55. Foroud T, Gray J, Ivashina J, Conneally PM (1999) Differences in duration of Huntington's disease based on age at onset. Journal of neurology, neurosurgery, and psychiatry 66 (1):52-56. doi:10.1136/jnnp.66.1.52

56. Unified Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group (1996). Movement disorders : official journal of the Movement Disorder Society 11 (2):136-142. doi:10.1002/mds.870110204

57. Shoulson I (1981) Huntington disease: functional capacities in patients treated with neuroleptic and antidepressant drugs. Neurology 31 (10):1333-1335. doi:10.1212/wnl.31.10.1333

58. Langbehn DR, Hayden MR, Paulsen JS (2010) CAG-repeat length and the age of onset in Huntington disease (HD): a review and validation study of statistical approaches. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics 153b (2):397-408. doi:10.1002/ajmg.b.30992

59. Videnovic A, Lazar AS, Barker RA, Overeem S (2014) 'The clocks that time us'--circadian rhythms in neurodegenerative disorders. Nature reviews Neurology 10 (12):683-693. doi:10.1038/nrneurol.2014.206

60. van der Burg JM, Björkqvist M, Brundin P (2009) Beyond the brain: widespread pathology in Huntington's disease. The Lancet Neurology 8 (8):765-774. doi:10.1016/s1474-4422(09)70178-4

61. Carroll JB, Bates GP, Steffan J, Saft C, Tabrizi SJ (2015) Treating the whole body in Huntington's disease. The Lancet Neurology 14 (11):1135-1142. doi:10.1016/s1474-4422(15)00177-5

62. Taylor GB, Liam C (2022) Neuropathology of Huntington’s Disease. In: Natalia S (ed) From

Pathophysiology to Treatment of Huntington's Disease. IntechOpen, Rijeka, p Ch. 2. doi:10.5772/intechopen.106664

63. Valor LM (2023) Molecular Research on Huntington's Disease. International journal of molecular sciences 24 (5). doi:10.3390/ijms24054310

64. Arbez N, Ratovitski T, Roby E, Chighladze E, Stewart JC, Ren M, Wang X, Lavery DJ, Ross CA (2017) Post-translational modifications clustering within proteolytic domains decrease mutant huntingtin toxicity. The Journal of biological chemistry 292 (47):19238-19249. doi:10.1074/jbc.M117.782300

65. Gu X, Greiner ER, Mishra R, Kodali R, Osmand A, Finkbeiner S, Steffan JS, Thompson LM, Wetzel R, Yang XW (2009) Serines 13 and 16 are critical determinants of full-length human mutant huntingtin induced disease pathogenesis in HD mice. Neuron 64 (6):828-840. doi:10.1016/j.neuron.2009.11.020

66. Bates G (2003) Huntingtin aggregation and toxicity in Huntington's disease. Lancet (London, England) 361 (9369):1642-1644. doi:10.1016/s0140-6736(03)13304-1

67. Jurcau A (2022) Molecular Pathophysiological Mechanisms in Huntington's Disease. Biomedicines 10 (6). doi:10.3390/biomedicines10061432

68. Puigdellívol M, Saavedra A, Pérez-Navarro E (2016) Cognitive dysfunction in Huntington's disease: mechanisms and therapeutic strategies beyond BDNF. Brain pathology (Zurich, Switzerland) 26 (6):752-771. doi:10.1111/bpa.12432

69. Ahveninen LM, Stout JC, Georgiou-Karistianis N, Lorenzetti V, Glikmann-Johnston Y (2018) Reduced amygdala volumes are related to motor and cognitive signs in Huntington's disease: The IMAGE-HD study. NeuroImage Clinical 18:881-887. doi:10.1016/j.nicl.2018.03.027

70. Seong IS, Woda JM, Song JJ, Lloret A, Abeyrathne PD, Woo CJ, Gregory G, Lee JM, Wheeler VC, Walz T, Kingston RE, Gusella JF, Conlon RA, MacDonald ME (2010) Huntingtin facilitates polycomb repressive complex 2. Human molecular genetics 19 (4):573-583. doi:10.1093/hmg/ddp524

71. From Pathophysiology to Treatment of Huntington's Disease (2022). IntechOpen, Rijeka. doi:10.5772/intechopen.94806

72. Sassone J, Colciago C, Cislaghi G, Silani V, Ciammola A (2009) Huntington's disease: the current state of research with peripheral tissues. Experimental neurology 219 (2):385-397. doi:10.1016/j.expneurol.2009.05.012

73. van der Burg JM, Winqvist A, Aziz NA, Maat-Schieman ML, Roos RA, Bates GP, Brundin P, Björkqvist M, Wierup N (2011) Gastrointestinal dysfunction contributes to weight loss in Huntington's disease mice. Neurobiology of disease 44 (1):1-8. doi:10.1016/j.nbd.2011.05.006

74. Sturrock A, Leavitt BR (2010) The clinical and genetic features of Huntington disease. Journal of geriatric psychiatry and neurology 23 (4):243-259. doi:10.1177/0891988710383573

75. Tabrizi SJ, Reilmann R, Roos RA, Durr A, Leavitt B, Owen G, Jones R, Johnson H, Craufurd D, Hicks SL, Kennard C, Landwehrmeyer B, Stout JC, Borowsky B, Scahill RI, Frost C, Langbehn DR (2012) Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. The Lancet Neurology 11 (1):42-53. doi:10.1016/s1474-4422(11)70263-0

76. Wild EJ, Mudanohwo EE, Sweeney MG, Schneider SA, Beck J, Bhatia KP, Rossor MN, Davis MB, Tabrizi SJ (2008) Huntington's disease phenocopies are clinically and genetically heterogeneous. Movement disorders : official journal of the Movement Disorder Society 23 (5):716-720. doi:10.1002/mds.21915

77. Kwan W, Träger U, Davalos D, Chou A, Bouchard J, Andre R, Miller A, Weiss A, Giorgini F, Cheah C, Möller T, Stella N, Akassoglou K, Tabrizi SJ, Muchowski PJ (2012) Mutant huntingtin impairs immune cell migration in Huntington disease. The Journal of clinical investigation 122 (12):4737-4747. doi:10.1172/jci64484

78. Sapp E, Kegel KB, Aronin N, Hashikawa T, Uchiyama Y, Tohyama K, Bhide PG, Vonsattel JP, DiFiglia M (2001) Early and progressive accumulation of reactive microglia in the Huntington disease brain. Journal of neuropathology and experimental neurology 60 (2):161-172. doi:10.1093/jnen/60.2.161

79. Björkqvist M, Wild EJ, Thiele J, Silvestroni A, Andre R, Lahiri N, Raibon E, Lee RV, Benn CL, Soulet D, Magnusson A, Woodman B, Landles C, Pouladi MA, Hayden MR, Khalili-Shirazi A, Lowdell MW, Brundin P, Bates GP, Leavitt BR, Möller T, Tabrizi SJ (2008) A novel pathogenic pathway of immune activation detectable before clinical onset in Huntington's disease. The Journal of experimental medicine 205 (8):1869-1877. doi:10.1084/jem.20080178

80. Chang K-H, Wu Y-R, Chen Y-C, Chen C-M (2015) Plasma inflammatory biomarkers for Huntington's disease patients and mouse model. Brain, Behavior, and Immunity 44:121-127. doi:https://doi.org/10.1016/j.bbi.2014.09.011

81. Soltani Khaboushan A, Moeinafshar A, Ersi MH, Teixeira AL, Majidi Zolbin M, Kajbafzadeh A-M (2023) Circulating levels of inflammatory biomarkers in Huntington's disease: A systematic review and meta-analysis. Journal of neuroimmunology 385:578243. doi:https://doi.org/10.1016/j.jneuroim.2023.578243

82. Nambron R, Silajdžić E, Kalliolia E, Ottolenghi C, Hindmarsh P, Hill NR, Costelloe SJ, Martin NG, Positano V, Watt HC, Frost C, Björkqvist M, Warner TT (2016) A Metabolic Study of Huntington's Disease. PLoS One 11 (1):e0146480. doi:10.1371/journal.pone.0146480

83. Robbins AO, Ho AK, Barker RA (2006) Weight changes in Huntington's disease. European journal of neurology 13 (8):e7. doi:10.1111/j.1468-1331.2006.01319.x

84. Mochel F, Charles P, Seguin F, Barritault J, Coussieu C, Perin L, Le Bouc Y, Gervais C, Carcelain G, Vassault A, Feingold J, Rabier D, Durr A (2007) Early energy deficit in Huntington disease: identification of a plasma biomarker traceable during disease progression. PLoS One 2 (7):e647. doi:10.1371/journal.pone.0000647

85. Strand AD, Aragaki AK, Shaw D, Bird T, Holton J, Turner C, Tapscott SJ, Tabrizi SJ, Schapira AH, Kooperberg C, Olson JM (2005) Gene expression in Huntington's disease skeletal muscle: a potential biomarker. Human molecular genetics 14 (13):1863-1876. doi:10.1093/hmg/ddi192

86. Ciammola A, Sassone J, Alberti L, Meola G, Mancinelli E, Russo MA, Squitieri F, Silani V (2006) Increased apoptosis, huntingtin inclusions and altered differentiation in muscle cell cultures from Huntington's disease subjects. Cell Death & Differentiation 13 (12):2068-2078.

doi:10.1038/sj.cdd.4401967

87. Turner C, Cooper JM, Schapira AH (2007) Clinical correlates of mitochondrial function in Huntington's disease muscle. Movement disorders : official journal of the Movement Disorder Society 22 (12):1715-1721. doi:10.1002/mds.21540

88. Bär KJ, Boettger MK, Andrich J, Epplen JT, Fischer F, Cordes J, Koschke M, Agelink MW (2008) Cardiovagal modulation upon postural change is altered in Huntington's disease. European journal of neurology 15 (8):869-871. doi:https://doi.org/10.1111/j.1468-1331.2008.02173.x

89. Mihm MJ, Amann DM, Schanbacher BL, Altschuld RA, Bauer JA, Hoyt KR (2007) Cardiac dysfunction in the R6/2 mouse model of Huntington's disease. Neurobiology of disease 25 (2):297-308. doi:10.1016/j.nbd.2006.09.016

90. Stoker TB, Mason SL, Greenland JC, Holden ST, Santini H, Barker RA (2022) Huntington's disease: diagnosis and management. Practical Neurology 22 (1):32. doi:10.1136/practneurol-2021-003074

91. McCusker EA, Loy CT (2017) Huntington Disease: The Complexities of Making and Disclosing a Clinical Diagnosis After Premanifest Genetic Testing. Tremor and other hyperkinetic movements (New York, NY) 7:467. doi:10.7916/d8pk0tdd

92. Margolis RL, Ross CA (2003) Diagnosis of Huntington disease. Clinical chemistry 49 (10):1726-1732. doi:10.1373/49.10.1726

93. Möncke-Buchner E, Reich S, Mücke M, Reuter M, Messer W, Wanker EE, Krüger DH (2002) Counting CAG repeats in the Huntington's disease gene by restriction endonuclease EcoP15I cleavage. Nucleic acids research 30 (16):e83. doi:10.1093/nar/gnf082

94. DiFiglia M, Sapp E, Chase K, Schwarz C, Meloni A, Young C, Martin E, Vonsattel JP, Carraway R, Reeves SA, et al. (1995) Huntingtin is a cytoplasmic protein associated with vesicles in human and rat brain neurons. Neuron 14 (5):1075-1081. doi:10.1016/0896-6273(95)90346-1

95. Ferrante RJ, Gutekunst CA, Persichetti F, McNeil SM, Kowall NW, Gusella JF, MacDonald ME, Beal MF, Hersch SM (1997) Heterogeneous topographic and cellular distribution of

huntingtin expression in the normal human neostriatum. The Journal of neuroscience : the official journal of the Society for Neuroscience 17 (9):3052-3063. doi:10.1523/jneurosci.17-09-03052.1997

96. Fusco FR, Chen Q, Lamoreaux WJ, Figueredo-Cardenas G, Jiao Y, Coffman JA, Surmeier DJ, Honig MG, Carlock LR, Reiner A (1999) Cellular localization of huntingtin in striatal and cortical neurons in rats: lack of correlation with neuronal vulnerability in Huntington's disease. The Journal of neuroscience : the official journal of the Society for Neuroscience 19 (4):1189-1202. doi:10.1523/jneurosci.19-04-01189.1999

97. Kim MW, Chelliah Y, Kim SW, Otwinowski Z, Bezprozvanny I (2009) Secondary structure of Huntingtin amino-terminal region. Structure (London, England : 1993) 17 (9):1205-1212. doi:10.1016/j.str.2009.08.002

98. Perutz MF, Johnson T, Suzuki M, Finch JT (1994) Glutamine repeats as polar zippers: their possible role in inherited neurodegenerative diseases. Proceedings of the National Academy of Sciences of the United States of America 91 (12):5355-5358. doi:10.1073/pnas.91.12.5355

99. Andrade MA, Bork P (1995) HEAT repeats in the Huntington's disease protein. Nature genetics 11 (2):115-116. doi:10.1038/ng1095-115

100. Neuwald AF, Hirano T (2000) HEAT repeats associated with condensins, cohesins, and other complexes involved in chromosome-related functions. Genome research 10 (10):1445-1452. doi:10.1101/gr.147400

101. MacDonald ME (2003) Huntingtin: alive and well and working in middle management. Science's STKE : signal transduction knowledge environment 2003 (207):pe48. doi:10.1126/stke.2003.207.pe48

102. Cattaneo E, Zuccato C, Tartari M (2005) Normal huntingtin function: an alternative approach to Huntington's disease. Nature reviews Neuroscience 6 (12):919-930. doi:10.1038/nrn1806

103. Xia J, Lee DH, Taylor J, Vandelft M, Truant R (2003) Huntingtin contains a highly conserved nuclear export signal. Human molecular genetics 12 (12):1393-1403. doi:10.1093/hmg/ddg156

104. Cornett J, Cao F, Wang CE, Ross CA, Bates GP, Li SH, Li XJ (2005) Polyglutamine expansion of huntingtin impairs its nuclear export. Nature genetics 37 (2):198-204. doi:10.1038/ng1503

105. Graham RK, Deng Y, Slow EJ, Haigh B, Bissada N, Lu G, Pearson J, Shehadeh J, Bertram L, Murphy Z, Warby SC, Doty CN, Roy S, Wellington CL, Leavitt BR, Raymond LA, Nicholson DW, Hayden MR (2006) Cleavage at the caspase-6 site is required for neuronal dysfunction and degeneration due to mutant huntingtin. Cell 125 (6):1179-1191. doi:10.1016/j.cell.2006.04.026

106. Harjes P, Wanker EE (2003) The hunt for huntingtin function: interaction partners tell many different stories. Trends in biochemical sciences 28 (8):425-433. doi:10.1016/s0968-0004(03)00168-3

107. Nasir J, Floresco SB, O'Kusky JR, Diewert VM, Richman JM, Zeisler J, Borowski A, Marth JD, Phillips AG, Hayden MR (1995) Targeted disruption of the Huntington's disease gene results in embryonic lethality and behavioral and morphological changes in heterozygotes. Cell 81 (5):811-823. doi:10.1016/0092-8674(95)90542-1

108. White JK, Auerbach W, Duyao MP, Vonsattel JP, Gusella JF, Joyner AL, MacDonald ME (1997) Huntingtin is required for neurogenesis and is not impaired by the Huntington's disease CAG expansion. Nature genetics 17 (4):404-410. doi:10.1038/ng1297-404

109. Zeitlin S, Liu JP, Chapman DL, Papaioannou VE, Efstratiadis A (1995) Increased apoptosis and early embryonic lethality in mice nullizygous for the Huntington's disease gene homologue. Nature genetics 11 (2):155-163. doi:10.1038/ng1095-155

110. Dragatsis I, Levine MS, Zeitlin S (2000) Inactivation of Hdh in the brain and testis results in progressive neurodegeneration and sterility in mice. Nature genetics 26 (3):300-306. doi:10.1038/81593

111. Taran AS, Shuvalova LD, Lagarkova MA, Alieva IB (2020) Huntington's Disease-An Outlook on the Interplay of the HTT Protein, Microtubules and Actin Cytoskeletal Components. Cells 9 (6). doi:10.3390/cells9061514

112. Reiner A, Dragatsis I, Dietrich P (2011) Genetics and neuropathology of Huntington's disease.

International review of neurobiology 98:325-372. doi:10.1016/b978-0-12-381328-2.00014-6

113. Woda JM, Calzonetti T, Hilditch-Maguire P, Duyao MP, Conlon RA, MacDonald ME (2005) Inactivation of the Huntington's disease gene (Hdh) impairs anterior streak formation and early patterning of the mouse embryo. BMC developmental biology 5:17. doi:10.1186/1471-213x-5-17

114. Kohl Z, Regensburger M, Aigner R, Kandasamy M, Winner B, Aigner L, Winkler J (2010) Impaired adult olfactory bulb neurogenesis in the R6/2 mouse model of Huntington's disease. BMC neuroscience 11:114. doi:10.1186/1471-2202-11-114

115. Godin JD, Colombo K, Molina-Calavita M, Keryer G, Zala D, Charrin BC, Dietrich P, Volvert ML, Guillemot F, Dragatsis I, Bellaiche Y, Saudou F, Nguyen L, Humbert S (2010) Huntingtin is required for mitotic spindle orientation and mammalian neurogenesis. Neuron 67 (3):392-406. doi:10.1016/j.neuron.2010.06.027

116. Zuccato C, Tartari M, Crotti A, Goffredo D, Valenza M, Conti L, Cataudella T, Leavitt BR, Hayden MR, Timmusk T, Rigamonti D, Cattaneo E (2003) Huntingtin interacts with REST/NRSF to modulate the transcription of NRSE-controlled neuronal genes. Nature genetics 35 (1):76-83. doi:10.1038/ng1219

117. Walker FO (2007) Huntington's disease. Lancet (London, England) 369 (9557):218-228. doi:10.1016/s0140-6736(07)60111-1

118. Gauthier LR, Charrin BC, Borrell-Pagès M, Dompierre JP, Rangone H, Cordelières FP, De Mey J, MacDonald ME, Lessmann V, Humbert S, Saudou F (2004) Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. Cell 118 (1):127-138. doi:10.1016/j.cell.2004.06.018

119. Steffan JS, Kazantsev A, Spasic-Boskovic O, Greenwald M, Zhu YZ, Gohler H, Wanker EE, Bates GP, Housman DE, Thompson LM (2000) The Huntington's disease protein interacts with p53 and CREB-binding protein and represses transcription. Proceedings of the National Academy of Sciences of the United States of America 97 (12):6763-6768. doi:10.1073/pnas.100110097

120. Pal A, Severin F, Lommer B, Shevchenko A, Zerial M (2006) Huntingtin-HAP40 complex is a novel Rab5 effector that regulates early endosome motility and is up-regulated in Huntington's

disease. J Cell Biol 172 (4):605-618. doi:10.1083/jcb.200509091

121. Zuccato C, Ciammola A, Rigamonti D, Leavitt BR, Goffredo D, Conti L, MacDonald ME, Friedlander RM, Silani V, Hayden MR, Timmusk T, Sipione S, Cattaneo E (2001) Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. Science (New York, NY) 293 (5529):493-498. doi:10.1126/science.1059581

122. Luo S, Rubinsztein DC (2010) Apoptosis blocks Beclin 1-dependent autophagosome synthesis: an effect rescued by Bcl-xL. Cell death and differentiation 17 (2):268-277. doi:10.1038/cdd.2009.121

123. Wang G, Liu X, Gaertig MA, Li S, Li XJ (2016) Ablation of huntingtin in adult neurons is nondeleterious but its depletion in young mice causes acute pancreatitis. Proceedings of the National Academy of Sciences of the United States of America 113 (12):3359-3364. doi:10.1073/pnas.1524575113

124. Damiano M, Galvan L, Déglon N, Brouillet E (2010) Mitochondria in Huntington's disease. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 1802 (1):52-61. doi:https://doi.org/10.1016/j.bbadis.2009.07.012

125. Träger U, Andre R, Lahiri N, Magnusson-Lind A, Weiss A, Grueninger S, McKinnon C, Sirinathsinghji E, Kahlon S, Pfister EL, Moser R, Hummerich H, Antoniou M, Bates GP, Luthi-Carter R, Lowdell MW, Björkqvist M, Ostroff GR, Aronin N, Tabrizi SJ (2014) HTT-lowering reverses Huntington's disease immune dysfunction caused by NFκB pathway dysregulation. Brain : a journal of neurology 137 (Pt 3):819-833. doi:10.1093/brain/awt355

126. Vijayvargia R, Epand R, Leitner A, Jung TY, Shin B, Jung R, Lloret A, Singh Atwal R, Lee H, Lee JM, Aebersold R, Hebert H, Song JJ, Seong IS (2016) Huntingtin's spherical solenoid structure enables polyglutamine tract-dependent modulation of its structure and function. eLife 5:e11184. doi:10.7554/eLife.11184

127. Poirier MA, Li H, Macosko J, Cai S, Amzel M, Ross CA (2002) Huntingtin Spheroids and Protofibrils as Precursors in Polyglutamine Fibrilization*. Journal of Biological Chemistry 277 (43):41032-41037. doi:https://doi.org/10.1074/jbc.M205809200

128. Ossato G, Digman MA, Aiken C, Lukacsovich T, Marsh JL, Gratton E (2010) A two-step path to inclusion formation of huntingtin peptides revealed by number and brightness analysis. Biophysical journal 98 (12):3078-3085. doi:10.1016/j.bpj.2010.02.058

129. Davies SW, Turmaine M, Cozens BA, DiFiglia M, Sharp AH, Ross CA, Scherzinger E, Wanker EE, Mangiarini L, Bates GP (1997) Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. Cell 90 (3):537-548. doi:10.1016/s0092-8674(00)80513-9

130. Yang W, Dunlap JR, Andrews RB, Wetzel R (2002) Aggregated polyglutamine peptides delivered to nuclei are toxic to mammalian cells. Human molecular genetics 11 (23):2905-2917. doi:10.1093/hmg/11.23.2905

131. Weiss A, Klein C, Woodman B, Sathasivam K, Bibel M, Régulier E, Bates GP, Paganetti P (2008) Sensitive biochemical aggregate detection reveals aggregation onset before symptom development in cellular and murine models of Huntington's disease. Journal of neurochemistry 104 (3):846-858. doi:10.1111/j.1471-4159.2007.05032.x

132. Sontag EM, Lotz GP, Yang G, Sontag CJ, Cummings BJ, Glabe CG, Muchowski PJ, Thompson LM (2012) Detection of Mutant Huntingtin Aggregation Conformers and Modulation of SDS-Soluble Fibrillar Oligomers by Small Molecules. Journal of Huntington's disease 1 (1):119-132. doi:10.3233/jhd-2012-129004

133. Chen S, Berthelier V, Hamilton JB, O'Nuallain B, Wetzel R (2002) Amyloid-like features of polyglutamine aggregates and their assembly kinetics. Biochemistry 41 (23):7391-7399. doi:10.1021/bi011772q

134. Lunkes A, Lindenberg KS, Ben-Haïem L, Weber C, Devys D, Landwehrmeyer GB, Mandel JL, Trottier Y (2002) Proteases acting on mutant huntingtin generate cleaved products that differentially build up cytoplasmic and nuclear inclusions. Molecular cell 10 (2):259-269. doi:10.1016/s1097-2765(02)00602-0

135. Hoffner G, Island M-L, Djian P (2005) Purification of neuronal inclusions of patients with Huntington's disease reveals a broad range of N-terminal fragments of expanded huntingtin and

insoluble polymers. Journal of neurochemistry 95 (1):125-136. doi:https://doi.org/10.1111/j.1471-4159.2005.03348.x

136. Hodgson JG, Agopyan N, Gutekunst CA, Leavitt BR, LePiane F, Singaraja R, Smith DJ, Bissada N, McCutcheon K, Nasir J, Jamot L, Li XJ, Stevens ME, Rosemond E, Roder JC, Phillips AG, Rubin EM, Hersch SM, Hayden MR (1999) A YAC mouse model for Huntington's disease with full-length mutant huntingtin, cytoplasmic toxicity, and selective striatal neurodegeneration. Neuron 23 (1):181-192. doi:10.1016/s0896-6273(00)80764-3

137. Arrasate M, Mitra S, Schweitzer ES, Segal MR, Finkbeiner S (2004) Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. Nature 431 (7010):805-810. doi:10.1038/nature02998

138. Leitman J, Ulrich Hartl F, Lederkremer GZ (2013) Soluble forms of polyQ-expanded huntingtin rather than large aggregates cause endoplasmic reticulum stress. Nature Communications 4 (1):2753. doi:10.1038/ncomms3753

139. Lin CH, Tallaksen-Greene S, Chien WM, Cearley JA, Jackson WS, Crouse AB, Ren S, Li XJ, Albin RL, Detloff PJ (2001) Neurological abnormalities in a knock-in mouse model of Huntington's disease. Human molecular genetics 10 (2):137-144. doi:10.1093/hmg/10.2.137

140. Wexler NS, Young AB, Tanzi RE, Travers H, Starosta-Rubinstein S, Penney JB, Snodgrass SR, Shoulson I, Gomez F, Ramos Arroyo MA, et al. (1987) Homozygotes for Huntington's disease. Nature 326 (6109):194-197. doi:10.1038/326194a0

141. Mangiarini L, Sathasivam K, Seller M, Cozens B, Harper A, Hetherington C, Lawton M, Trottier Y, Lehrach H, Davies SW, Bates GP (1996) Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. Cell 87 (3):493-506. doi:10.1016/s0092-8674(00)81369-0

142. Hackam AS, Singaraja R, Wellington CL, Metzler M, McCutcheon K, Zhang T, Kalchman M, Hayden MR (1998) The influence of huntingtin protein size on nuclear localization and cellular toxicity. J Cell Biol 141 (5):1097-1105. doi:10.1083/jcb.141.5.1097

143. Cooper JK, Schilling G, Peters MF, Herring WJ, Sharp AH, Kaminsky Z, Masone J, Khan

FA, Delanoy M, Borchelt DR, Dawson VL, Dawson TM, Ross CA (1998) Truncated N-terminal fragments of huntingtin with expanded glutamine repeats form nuclear and cytoplasmic aggregates in cell culture. Human molecular genetics 7 (5):783-790. doi:10.1093/hmg/7.5.783

144. Jackson GR, Salecker I, Dong X, Yao X, Arnheim N, Faber PW, MacDonald ME, Zipursky SL (1998) Polyglutamine-expanded human huntingtin transgenes induce degeneration of Drosophila photoreceptor neurons. Neuron 21 (3):633-642. doi:10.1016/s0896-6273(00)80573-5

145. Schilling G, Becher MW, Sharp AH, Jinnah HA, Duan K, Kotzuk JA, Slunt HH, Ratovitski T, Cooper JK, Jenkins NA, Copeland NG, Price DL, Ross CA, Borchelt DR (1999) Intranuclear inclusions and neuritic aggregates in transgenic mice expressing a mutant N-terminal fragment of huntingtin. Human molecular genetics 8 (3):397-407. doi:10.1093/hmg/8.3.397

146. Rockabrand E, Slepko N, Pantalone A, Nukala VN, Kazantsev A, Marsh JL, Sullivan PG, Steffan JS, Sensi SL, Thompson LM (2007) The first 17 amino acids of Huntingtin modulate its sub-cellular localization, aggregation and effects on calcium homeostasis. Human molecular genetics 16 (1):61-77. doi:10.1093/hmg/ddl440

147. Steffan JS, Agrawal N, Pallos J, Rockabrand E, Trotman LC, Slepko N, Illes K, Lukacsovich T, Zhu YZ, Cattaneo E, Pandolfi PP, Thompson LM, Marsh JL (2004) SUMO modification of Huntingtin and Huntington's disease pathology. Science (New York, NY) 304 (5667):100-104. doi:10.1126/science.1092194

148. Atwal RS, Xia J, Pinchev D, Taylor J, Epand RM, Truant R (2007) Huntingtin has a membrane association signal that can modulate huntingtin aggregation, nuclear entry and toxicity. Human molecular genetics 16 (21):2600-2615. doi:10.1093/hmg/ddm217

149. Tam S, Spiess C, Auyeung W, Joachimiak L, Chen B, Poirier MA, Frydman J (2009) The chaperonin TRiC blocks a huntingtin sequence element that promotes the conformational switch to aggregation. Nature structural & molecular biology 16 (12):1279-1285. doi:10.1038/nsmb.1700

150. Li SH, Cheng AL, Li H, Li XJ (1999) Cellular defects and altered gene expression in PC12 cells stably expressing mutant huntingtin. The Journal of neuroscience : the official journal of the Society for Neuroscience 19 (13):5159-5172. doi:10.1523/jneurosci.19-13-05159.1999

151. Shacham T, Sharma N, Lederkremer GZ (2019) Protein Misfolding and ER Stress in Huntington's Disease. Frontiers in Molecular Biosciences 6

152. Hay DG, Sathasivam K, Tobaben S, Stahl B, Marber M, Mestril R, Mahal A, Smith DL, Woodman B, Bates GP (2004) Progressive decrease in chaperone protein levels in a mouse model of Huntington's disease and induction of stress proteins as a therapeutic approach. Human molecular genetics 13 (13):1389-1405. doi:10.1093/hmg/ddh144

153. Jana NR, Tanaka M, Wang G, Nukina N (2000) Polyglutamine length-dependent interaction of Hsp40 and Hsp70 family chaperones with truncated N-terminal huntingtin: their role in suppression of aggregation and cellular toxicity. Human molecular genetics 9 (13):2009-2018. doi:10.1093/hmg/9.13.2009

154. Kobayashi Y, Kume A, Li M, Doyu M, Hata M, Ohtsuka K, Sobue G (2000) Chaperones Hsp70 and Hsp40 suppress aggregate formation and apoptosis in cultured neuronal cells expressing truncated androgen receptor protein with expanded polyglutamine tract. J Biol Chem 275 (12):8772-8778. doi:10.1074/jbc.275.12.8772

155. Kazemi-Esfarjani P, Benzer S (2000) Genetic suppression of polyglutamine toxicity in Drosophila. Science (New York, NY) 287 (5459):1837-1840. doi:10.1126/science.287.5459.1837

156. Warrick JM, Chan HY, Gray-Board GL, Chai Y, Paulson HL, Bonini NM (1999) Suppression of polyglutamine-mediated neurodegeneration in Drosophila by the molecular chaperone HSP70. Nature genetics 23 (4):425-428. doi:10.1038/70532

157. Adachi H, Katsuno M, Minamiyama M, Sang C, Pagoulatos G, Angelidis C, Kusakabe M, Yoshiki A, Kobayashi Y, Doyu M, Sobue G (2003) Heat shock protein 70 chaperone overexpression ameliorates phenotypes of the spinal and bulbar muscular atrophy transgenic mouse model by reducing nuclear-localized mutant androgen receptor protein. The Journal of neuroscience : the official journal of the Society for Neuroscience 23 (6):2203-2211. doi:10.1523/jneurosci.23-06-02203.2003

158. Wacker JL, Huang SY, Steele AD, Aron R, Lotz GP, Nguyen Q, Giorgini F, Roberson ED, Lindquist S, Masliah E, Muchowski PJ (2009) Loss of Hsp70 exacerbates pathogenesis but not

levels of fibrillar aggregates in a mouse model of Huntington's disease. The Journal of neuroscience : the official journal of the Society for Neuroscience 29 (28):9104-9114. doi:10.1523/jneurosci.2250-09.2009

159. Zhou H, Li S-H, Li X-J (2001) Chaperone Suppression of Cellular Toxicity of Huntingtin Is Independent of Polyglutamine Aggregation*. Journal of Biological Chemistry 276 (51):48417-48424. doi:https://doi.org/10.1074/jbc.M104140200

160. Determination of neuroprotective effects of medium chain fatty acids and their derivatives on mutant huntingtin aggregates, oxidative stress and ATP levels in HD150Q cell line model of Huntington's disease (2023). Indian Journal of Biochemistry and Biophysics. doi:10.56042/ijbb.v60i9.4047

161. Gutekunst CA, Li SH, Yi H, Mulroy JS, Kuemmerle S, Jones R, Rye D, Ferrante RJ, Hersch SM, Li XJ (1999) Nuclear and neuropil aggregates in Huntington's disease: relationship to neuropathology. The Journal of neuroscience : the official journal of the Society for Neuroscience 19 (7):2522-2534. doi:10.1523/jneurosci.19-07-02522.1999

162. Saudou F, Finkbeiner S, Devys D, Greenberg ME (1998) Huntingtin acts in the nucleus to induce apoptosis but death does not correlate with the formation of intranuclear inclusions. Cell 95 (1):55-66. doi:10.1016/s0092-8674(00)81782-1

163. Bennett EJ, Shaler TA, Woodman B, Ryu KY, Zaitseva TS, Becker CH, Bates GP, Schulman H, Kopito RR (2007) Global changes to the ubiquitin system in Huntington's disease. Nature 448 (7154):704-708. doi:10.1038/nature06022

164. Venkatraman P, Wetzel R, Tanaka M, Nukina N, Goldberg AL (2004) Eukaryotic proteasomes cannot digest polyglutamine sequences and release them during degradation of polyglutamine-containing proteins. Molecular cell 14 (1):95-104. doi:10.1016/s1097-2765(04)00151-0

165. Bett JS, Goellner GM, Woodman B, Pratt G, Rechsteiner M, Bates GP (2006) Proteasome impairment does not contribute to pathogenesis in R6/2 Huntington's disease mice: exclusion of proteasome activator REGgamma as a therapeutic target. Human molecular genetics 15 (1):33-44.

doi:10.1093/hmg/ddi423

166. Bowman AB, Yoo SY, Dantuma NP, Zoghbi HY (2005) Neuronal dysfunction in a polyglutamine disease model occurs in the absence of ubiquitin-proteasome system impairment and inversely correlates with the degree of nuclear inclusion formation. Human molecular genetics 14 (5):679-691. doi:10.1093/hmg/ddi064

167. Bett JS, Cook C, Petrucelli L, Bates GP (2009) The ubiquitin-proteasome reporter GFPu does not accumulate in neurons of the R6/2 transgenic mouse model of Huntington's disease. PLoS One 4 (4):e5128. doi:10.1371/journal.pone.0005128

168. Wang CE, Tydlacka S, Orr AL, Yang SH, Graham RK, Hayden MR, Li S, Chan AW, Li XJ (2008) Accumulation of N-terminal mutant huntingtin in mouse and monkey models implicated as a pathogenic mechanism in Huntington's disease. Human molecular genetics 17 (17):2738-2751. doi:10.1093/hmg/ddn175

169. Tonoki A, Kuranaga E, Tomioka T, Hamazaki J, Murata S, Tanaka K, Miura M (2009) Genetic evidence linking age-dependent attenuation of the 26S proteasome with the aging process. Molecular and cellular biology 29 (4):1095-1106. doi:10.1128/mcb.01227-08

170. Tydlacka S, Wang CE, Wang X, Li S, Li XJ (2008) Differential activities of the ubiquitin-proteasome system in neurons versus glia may account for the preferential accumulation of misfolded proteins in neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience 28 (49):13285-13295. doi:10.1523/jneurosci.4393-08.2008

171. Zhou H, Cao F, Wang Z, Yu ZX, Nguyen HP, Evans J, Li SH, Li XJ (2003) Huntingtin forms toxic NH2-terminal fragment complexes that are promoted by the age-dependent decrease in proteasome activity. J Cell Biol 163 (1):109-118. doi:10.1083/jcb.200306038

172. Ravikumar B, Vacher C, Berger Z, Davies JE, Luo S, Oroz LG, Scaravilli F, Easton DF, Duden R, O'Kane CJ, Rubinsztein DC (2004) Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. Nature genetics 36 (6):585-595. doi:10.1038/ng1362

173. Ravikumar B, Imarisio S, Sarkar S, O'Kane CJ, Rubinsztein DC (2008) Rab5 modulates

aggregation and toxicity of mutant huntingtin through macroautophagy in cell and fly models of Huntington disease. Journal of cell science 121 (Pt 10):1649-1660. doi:10.1242/jcs.025726

174. Iwata A, Riley BE, Johnston JA, Kopito RR (2005) HDAC6 and microtubules are required for autophagic degradation of aggregated huntingtin. J Biol Chem 280 (48):40282-40292. doi:10.1074/jbc.M508786200

175. King MA, Hands S, Hafiz F, Mizushima N, Tolkovsky AM, Wyttenbach A (2008) Rapamycin inhibits polyglutamine aggregation independently of autophagy by reducing protein synthesis. Molecular pharmacology 73 (4):1052-1063. doi:10.1124/mol.107.043398

176. Li X, Wang CE, Huang S, Xu X, Li XJ, Li H, Li S (2010) Inhibiting the ubiquitin-proteasome system leads to preferential accumulation of toxic N-terminal mutant huntingtin fragments. Human molecular genetics 19 (12):2445-2455. doi:10.1093/hmg/ddq127

177. Shibata M, Lu T, Furuya T, Degterev A, Mizushima N, Yoshimori T, MacDonald M, Yankner B, Yuan J (2006) Regulation of intracellular accumulation of mutant Huntingtin by Beclin 1. J Biol Chem 281 (20):14474-14485. doi:10.1074/jbc.M600364200

178. Liu P-P, Xu Y-J, Teng Z-Q, Liu C-M (2017) Polycomb Repressive Complex 2: Emerging Roles in the Central Nervous System. The Neuroscientist 24 (3):208-220. doi:10.1177/1073858417747839

179. Liu X, Yang J, Wu N, Song R, Zhu H (2015) Evolution and Coevolution of PRC2 Genes in Vertebrates and Mammals. Advances in protein chemistry and structural biology 101:125-148. doi:10.1016/bs.apcsb.2015.06.010

180. Margueron R, Reinberg D (2011) The Polycomb complex PRC2 and its mark in life. Nature 469 (7330):343-349. doi:10.1038/nature09784

181. Cao R, Wang L, Wang H, Xia L, Erdjument-Bromage H, Tempst P, Jones RS, Zhang Y (2002) Role of histone H3 lysine 27 methylation in Polycomb-group silencing. Science (New York, NY) 298 (5595):1039-1043. doi:10.1126/science.1076997

182. Jiao L, Liu X (2015) Structural basis of histone H3K27 trimethylation by an active polycomb

repressive complex 2. Science (New York, NY) 350 (6258):aac4383. doi:10.1126/science.aac4383

183. Margueron R, Justin N, Ohno K, Sharpe ML, Son J, Drury WJ, 3rd, Voigt P, Martin SR, Taylor WR, De Marco V, Pirrotta V, Reinberg D, Gamblin SJ (2009) Role of the polycomb protein EED in the propagation of repressive histone marks. Nature 461 (7265):762-767. doi:10.1038/nature08398

184. Rajasekhar VK, Begemann M (2007) Concise review: roles of polycomb group proteins in development and disease: a stem cell perspective. Stem cells (Dayton, Ohio) 25 (10):2498-2510. doi:10.1634/stemcells.2006-0608

185. Thornton SR, Butty VL, Levine SS, Boyer LA (2014) Polycomb Repressive Complex 2 regulates lineage fidelity during embryonic stem cell differentiation. PLoS One 9 (10):e110498. doi:10.1371/journal.pone.0110498

186. Riising EM, Comet I, Leblanc B, Wu X, Johansen JV, Helin K (2014) Gene silencing triggers polycomb repressive complex 2 recruitment to CpG islands genome wide. Molecular cell 55 (3):347-360. doi:10.1016/j.molcel.2014.06.005

187. von Schimmelmann M, Feinberg PA, Sullivan JM, Ku SM, Badimon A, Duff MK, Wang Z, Lachmann A, Dewell S, Ma'ayan A, Han MH, Tarakhovsky A, Schaefer A (2016) Polycomb repressive complex 2 (PRC2) silences genes responsible for neurodegeneration. Nature neuroscience 19 (10):1321-1330. doi:10.1038/nn.4360

188. Moritz LE, Trievel RC (2018) Structure, mechanism, and regulation of polycomb-repressive complex 2. J Biol Chem 293 (36):13805-13814. doi:10.1074/jbc.R117.800367

189. Kahn TG, Dorafshan E, Schultheis D, Zare A, Stenberg P, Reim I, Pirrotta V, Schwartz YB (2016) Interdependence of PRC1 and PRC2 for recruitment to Polycomb Response Elements. Nucleic acids research 44 (21):10132-10149. doi:10.1093/nar/gkw701

190. Kouznetsova VL, Tchekanov A, Li X, Yan X, Tsigelny IF (2019) Polycomb repressive 2 complex-Molecular mechanisms of function. Protein science : a publication of the Protein Society 28 (8):1387-1399. doi:10.1002/pro.3647

191. Hyun K, Jeon J, Park K, Kim J (2017) Writing, erasing and reading histone lysine methylations. Experimental & molecular medicine 49 (4):e324. doi:10.1038/emm.2017.11

192. Laugesen A, Højfeldt JW, Helin K (2016) Role of the Polycomb Repressive Complex 2 (PRC2) in Transcriptional Regulation and Cancer. Cold Spring Harbor perspectives in medicine 6 (9). doi:10.1101/cshperspect.a026575

193. Laugesen A, Højfeldt JW, Helin K (2019) Molecular Mechanisms Directing PRC2 Recruitment and H3K27 Methylation. Molecular cell 74 (1):8-18. doi:10.1016/j.molcel.2019.03.011

194. Kim MO, Chawla P, Overland RP, Xia E, Sadri-Vakili G, Cha JH (2008) Altered histone monoubiquitylation mediated by mutant huntingtin induces transcriptional dysregulation. The Journal of neuroscience : the official journal of the Society for Neuroscience 28 (15):3947-3957. doi:10.1523/jneurosci.5667-07.2008

195. Jimenez-Sanchez M, Licitra F, Underwood BR, Rubinsztein DC (2017) Huntington's Disease: Mechanisms of Pathogenesis and Therapeutic Strategies. Cold Spring Harbor perspectives in medicine 7 (7). doi:10.1101/cshperspect.a024240

196. Landles C, Bates GP (2004) Huntingtin and the molecular pathogenesis of Huntington's disease. Fourth in molecular medicine review series. EMBO reports 5 (10):958-963. doi:10.1038/sj.embor.7400250

197. Cha JH (2000) Transcriptional dysregulation in Huntington's disease. Trends in neurosciences 23 (9):387-392. doi:10.1016/s0166-2236(00)01609-x

198. Browne SE, Ferrante RJ, Beal MF (1999) Oxidative stress in Huntington's disease. Brain pathology (Zurich, Switzerland) 9 (1):147-163. doi:10.1111/j.1750-3639.1999.tb00216.x

199. Reddy PH, Shirendeb UP (2012) Mutant huntingtin, abnormal mitochondrial dynamics, defective axonal transport of mitochondria, and selective synaptic degeneration in Huntington's disease. Biochimica et biophysica acta 1822 (2):101-110. doi:10.1016/j.bbadis.2011.10.016

200. Jana NR, Nukina N (2003) Recent advances in understanding the pathogenesis of

polyglutamine diseases: involvement of molecular chaperones and ubiquitin-proteasome pathway. J Chem Neuroanat 26 (2):95-101. doi:10.1016/s0891-0618(03)00029-2

201. Li X, Li H, Li XJ (2008) Intracellular degradation of misfolded proteins in polyglutamine neurodegenerative diseases. Brain research reviews 59 (1):245-252. doi:10.1016/j.brainresrev.2008.08.003

202. Rubinsztein DC (2006) The roles of intracellular protein-degradation pathways in neurodegeneration. Nature 443 (7113):780-786. doi:10.1038/nature05291

203. Smith GA, Rocha EM, McLean JR, Hayes MA, Izen SC, Isacson O, Hallett PJ (2014) Progressive axonal transport and synaptic protein changes correlate with behavioral and neuropathological abnormalities in the heterozygous Q175 KI mouse model of Huntington's disease. Human molecular genetics 23 (17):4510-4527. doi:10.1093/hmg/ddu166

204. Sheldon AL, Robinson MB (2007) The role of glutamate transporters in neurodegenerative diseases and potential opportunities for intervention. Neurochemistry international 51 (6-7):333-355. doi:10.1016/j.neuint.2007.03.012

205. Cowan CM, Raymond LA (2006) Selective neuronal degeneration in Huntington's disease. Current topics in developmental biology 75:25-71. doi:10.1016/s0070-2153(06)75002-5

206. Coyle JT, Schwarcz R (1976) Lesion of striatal neurones with kainic acid provides a model for Huntington's chorea. Nature 263 (5574):244-246. doi:10.1038/263244a0

207. McGeer EG, McGeer PL (1976) Duplication of biochemical changes of Huntington's chorea by intrastriatal injections of glutamic and kainic acids. Nature 263 (5577):517-519. doi:10.1038/263517a0

208. Beal MF, Kowall NW, Ellison DW, Mazurek MF, Swartz KJ, Martin JB (1986) Replication of the neurochemical characteristics of Huntington's disease by quinolinic acid. Nature 321 (6066):168-171. doi:10.1038/321168a0

209. Hansson O, Guatteo E, Mercuri NB, Bernardi G, Li X-J, Castilho RF, Brundin P (2001) Resistance to NMDA toxicity correlates with appearance of nuclear inclusions, behavioural

deficits and changes in calcium homeostasis in mice transgenic for exon 1 of the huntington gene. European Journal of Neuroscience 14 (9):1492-1504. doi:https://doi.org/10.1046/j.0953-816x.2001.01767.x

210. Zeron MM, Hansson O, Chen N, Wellington CL, Leavitt BR, Brundin P, Hayden MR, Raymond LA (2002) Increased Sensitivity to N-Methyl-D-Aspartate Receptor-Mediated Excitotoxicity in a Mouse Model of Huntington's Disease. Neuron 33 (6):849-860. doi:https://doi.org/10.1016/S0896-6273(02)00615-3

211. Sattler R, Xiong Z, Lu WY, Hafner M, MacDonald JF, Tymianski M (1999) Specific coupling of NMDA receptor activation to nitric oxide neurotoxicity by PSD-95 protein. Science (New York, NY) 284 (5421):1845-1848. doi:10.1126/science.284.5421.1845

212. Sun Y, Savanenin A, Reddy PH, Liu YF (2001) Polyglutamine-expanded huntingtin promotes sensitization of N-methyl-D-aspartate receptors via post-synaptic density 95. J Biol Chem 276 (27):24713-24718. doi:10.1074/jbc.M103501200

213. Orrenius S, Zhivotovsky B, Nicotera P (2003) Regulation of cell death: the calcium-apoptosis link. Nature reviews Molecular cell biology 4 (7):552-565. doi:10.1038/nrm1150

214. Okamoto S, Pouladi MA, Talantova M, Yao D, Xia P, Ehrnhoefer DE, Zaidi R, Clemente A, Kaul M, Graham RK, Zhang D, Vincent Chen HS, Tong G, Hayden MR, Lipton SA (2009) Balance between synaptic versus extrasynaptic NMDA receptor activity influences inclusions and neurotoxicity of mutant huntingtin. Nature medicine 15 (12):1407-1413. doi:10.1038/nm.2056

215. Li Z, Okamoto K, Hayashi Y, Sheng M (2004) The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses. Cell 119 (6):873-887. doi:10.1016/j.cell.2004.11.003

216. Giacomello M, Drago I, Pizzo P, Pozzan T (2007) Mitochondrial Ca2+ as a key regulator of cell life and death. Cell Death & Differentiation 14 (7):1267-1274. doi:10.1038/sj.cdd.4402147

217. Giacomello M, Pyakurel A, Glytsou C, Scorrano L (2020) The cell biology of mitochondrial membrane dynamics. Nature reviews Molecular cell biology 21 (4):204-224. doi:10.1038/s41580-020-0210-7

218. Costa V, Giacomello M, Hudec R, Lopreiato R, Ermak G, Lim D, Malorni W, Davies KJ, Carafoli E, Scorrano L (2010) Mitochondrial fission and cristae disruption increase the response of cell models of Huntington's disease to apoptotic stimuli. EMBO molecular medicine 2 (12):490-503. doi:10.1002/emmm.201000102

219. Song W, Chen J, Petrilli A, Liot G, Klinglmayr E, Zhou Y, Poquiz P, Tjong J, Pouladi MA, Hayden MR, Masliah E, Ellisman M, Rouiller I, Schwarzenbacher R, Bossy B, Perkins G, Bossy-Wetzel E (2011) Mutant huntingtin binds the mitochondrial fission GTPase dynamin-related protein-1 and increases its enzymatic activity. Nature medicine 17 (3):377-382. doi:10.1038/nm.2313

220. Kim J, Moody JP, Edgerly CK, Bordiuk OL, Cormier K, Smith K, Beal MF, Ferrante RJ (2010) Mitochondrial loss, dysfunction and altered dynamics in Huntington's disease. Human molecular genetics 19 (20):3919-3935. doi:10.1093/hmg/ddq306

221. Kuwert T, Lange HW, Boecker H, Titz H, Herzog H, Aulich A, Wang BC, Nayak U, Feinendegen LE (1993) Striatal glucose consumption in chorea-free subjects at risk of Huntington's disease. Journal of neurology 241 (1):31-36. doi:10.1007/bf00870669

222. Jenkins BG, Koroshetz WJ, Beal MF, Rosen BR (1993) Evidence for irnnairment of energy metabofism in vivo in Huntington's disease using localized 1H NMR spectroscopy. Neurology 43 (12):2689-2689. doi:10.1212/WNL.43.12.2689

223. Tabrizi SJ, Cleeter MWJ, Xuereb J, Taanman JW, Cooper JM, Schapira AHV (1999) Biochemical abnormalities and excitotoxicity in Huntington's disease brain. Annals of Neurology 45 (1):25-32. doi:https://doi.org/10.1002/1531-8249(199901)45:1<25::AID-ART6>3.0.CO;2-E

224. Lim D, Fedrizzi L, Tartari M, Zuccato C, Cattaneo E, Brini M, Carafoli E (2008) Calcium homeostasis and mitochondrial dysfunction in striatal neurons of Huntington disease. J Biol Chem 283 (9):5780-5789. doi:10.1074/jbc.M704704200

225. Li X-J, Orr AL, Li S (2010) Impaired mitochondrial trafficking in Huntington's disease. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 1802 (1):62-65. doi:https://doi.org/10.1016/j.bbadis.2009.06.008

226. Powers WJ, Videen TO, Markham J, McGee-Minnich L, Antenor-Dorsey JV, Hershey T, Perlmutter JS (2007) Selective defect of in vivo glycolysis in early Huntington's disease striatum. Proceedings of the National Academy of Sciences 104 (8):2945-2949. doi:10.1073/pnas.0609833104

227. Seong IS, Ivanova E, Lee JM, Choo YS, Fossale E, Anderson M, Gusella JF, Laramie JM, Myers RH, Lesort M, MacDonald ME (2005) HD CAG repeat implicates a dominant property of huntingtin in mitochondrial energy metabolism. Human molecular genetics 14 (19):2871-2880. doi:10.1093/hmg/ddi319

228. Bossy-Wetzel E, Petrilli A, Knott AB (2008) Mutant huntingtin and mitochondrial dysfunction. Trends in neurosciences 31 (12):609-616. doi:10.1016/j.tins.2008.09.004

229. Quintanilla RA, Johnson GVW (2009) Role of mitochondrial dysfunction in the pathogenesis of Huntington's disease. Brain Res Bull 80 (4-5):242-247. doi:10.1016/j.brainresbull.2009.07.010

230. Damiano M, Galvan L, Déglon N, Brouillet E (2010) Mitochondria in Huntington's disease. Biochimica et biophysica acta 1802 (1):52-61. doi:10.1016/j.bbadis.2009.07.012

231. Gohil VM, Offner N, Walker JA, Sheth SA, Fossale E, Gusella JF, MacDonald ME, Neri C, Mootha VK (2011) Meclizine is neuroprotective in models of Huntington's disease. Human molecular genetics 20 (2):294-300. doi:10.1093/hmg/ddq464

232. Shirendeb UP, Calkins MJ, Manczak M, Anekonda V, Dufour B, McBride JL, Mao P, Reddy PH (2012) Mutant huntingtin's interaction with mitochondrial protein Drp1 impairs mitochondrial biogenesis and causes defective axonal transport and synaptic degeneration in Huntington's disease. Human molecular genetics 21 (2):406-420. doi:10.1093/hmg/ddr475

233. Yablonska S, Ganesan V, Ferrando LM, Kim J, Pyzel A, Baranova OV, Khattar NK, Larkin TM, Baranov SV, Chen N, Strohlein CE, Stevens DA, Wang X, Chang YF, Schurdak ME, Carlisle DL, Minden JS, Friedlander RM (2019) Mutant huntingtin disrupts mitochondrial proteostasis by interacting with TIM23. Proceedings of the National Academy of Sciences of the United States of America 116 (33):16593-16602. doi:10.1073/pnas.1904101116

234. Intihar TA, Martinez EA, Gomez-Pastor R (2019) Mitochondrial Dysfunction in Huntington's

Disease; Interplay Between HSF1, p53 and PGC-1α Transcription Factors. Front Cell Neurosci 13:103-103. doi:10.3389/fncel.2019.00103

235. Milnerwood AJ, Gladding CM, Pouladi MA, Kaufman AM, Hines RM, Boyd JD, Ko RW, Vasuta OC, Graham RK, Hayden MR, Murphy TH, Raymond LA (2010) Early increase in extrasynaptic NMDA receptor signaling and expression contributes to phenotype onset in Huntington's disease mice. Neuron 65 (2):178-190. doi:10.1016/j.neuron.2010.01.008

236. Browne SE, Bowling AC, MacGarvey U, Baik MJ, Berger SC, Muqit MM, Bird ED, Beal MF (1997) Oxidative damage and metabolic dysfunction in Huntington's disease: selective vulnerability of the basal ganglia. Ann Neurol 41 (5):646-653. doi:10.1002/ana.410410514

237. Arning L, Haghikia A, Taherzadeh-Fard E, Saft C, Andrich J, Pula B, Höxtermann S, Wieczorek S, Akkad DA, Perrech M, Gold R, Epplen JT, Chan A (2010) Mitochondrial haplogroup H correlates with ATP levels and age at onset in Huntington disease. Journal of molecular medicine (Berlin, Germany) 88 (4):431-436. doi:10.1007/s00109-010-0589-2

238. Taherzadeh-Fard E, Saft C, Andrich J, Wieczorek S, Arning L (2009) PGC-1alpha as modifier of onset age in Huntington disease. Mol Neurodegener 4:10-10. doi:10.1186/1750-1326-4-10

239. Tsunemi T, Ashe TD, Morrison BE, Soriano KR, Au J, Roque RA, Lazarowski ER, Damian VA, Masliah E, La Spada AR (2012) PGC-1α rescues Huntington's disease proteotoxicity by preventing oxidative stress and promoting TFEB function. Science translational medicine 4 (142):142ra197. doi:10.1126/scitranslmed.3003799

240. Tsunemi T, La Spada AR (2012) PGC-1α at the intersection of bioenergetics regulation and neuron function: from Huntington's disease to Parkinson's disease and beyond. Progress in neurobiology 97 (2):142-151. doi:10.1016/j.pneurobio.2011.10.004

241. Munoz-Sanjuan I, Bates GP (2011) The importance of integrating basic and clinical research toward the development of new therapies for Huntington disease. The Journal of clinical investigation 121 (2):476-483. doi:10.1172/jci45364

242. Amor S, Puentes F, Baker D, Van Der Valk P (2010) Inflammation in neurodegenerative diseases. Immunology 129 (2):154-169. doi:https://doi.org/10.1111/j.1365-2567.2009.03225.x

243. Pavese N, Gerhard A, Tai YF, Ho AK, Turkheimer F, Barker RA, Brooks DJ, Piccini P (2006) Microglial activation correlates with severity in Huntington disease: a clinical and PET study. Neurology 66 (11):1638-1643. doi:10.1212/01.wnl.0000222734.56412.17

244. Tai YF, Pavese N, Gerhard A, Tabrizi SJ, Barker RA, Brooks DJ, Piccini P (2007) Microglial activation in presymptomatic Huntington's disease gene carriers. Brain : a journal of neurology 130 (Pt 7):1759-1766. doi:10.1093/brain/awm044

245. Giorgini F, Guidetti P, Nguyen Q, Bennett SC, Muchowski PJ (2005) A genomic screen in yeast implicates kynurenine 3-monooxygenase as a therapeutic target for Huntington disease. Nature genetics 37 (5):526-531. doi:10.1038/ng1542

246. Schwarcz R, Guidetti P, Sathyasaikumar KV, Muchowski PJ (2010) Of mice, rats and men: Revisiting the quinolinic acid hypothesis of Huntington's disease. Progress in neurobiology 90 (2):230-245. doi:10.1016/j.pneurobio.2009.04.005

247. Hsiao H-Y, Chen Y-C, Chen H-M, Tu P-H, Chern Y (2013) A critical role of astrocyte-mediated nuclear factor-κB-dependent inflammation in Huntington's disease. Human molecular genetics 22 (9):1826-1842. doi:10.1093/hmg/ddt036

248. Webb JL, Ravikumar B, Atkins J, Skepper JN, Rubinsztein DC (2003) Alpha-Synuclein is degraded by both autophagy and the proteasome. J Biol Chem 278 (27):25009-25013. doi:10.1074/jbc.M300227200

249. Wang Y, Martinez-Vicente M, Krüger U, Kaushik S, Wong E, Mandelkow EM, Cuervo AM, Mandelkow E (2009) Tau fragmentation, aggregation and clearance: the dual role of lysosomal processing. Human molecular genetics 18 (21):4153-4170. doi:10.1093/hmg/ddp367

250. Ravikumar B, Acevedo-Arozena A, Imarisio S, Berger Z, Vacher C, O'Kane CJ, Brown SD, Rubinsztein DC (2005) Dynein mutations impair autophagic clearance of aggregate-prone proteins. Nature genetics 37 (7):771-776. doi:10.1038/ng1591

251. Sarkar S, Rubinsztein DC (2008) Huntington's disease: degradation of mutant huntingtin by autophagy. The FEBS journal 275 (17):4263-4270. doi:10.1111/j.1742-4658.2008.06562.x

252. Mizushima N, Levine B, Cuervo AM, Klionsky DJ (2008) Autophagy fights disease through cellular self-digestion. Nature 451 (7182):1069-1075. doi:10.1038/nature06639

253. Ravikumar B, Duden R, Rubinsztein DC (2002) Aggregate-prone proteins with polyglutamine and polyalanine expansions are degraded by autophagy. Human molecular genetics 11 (9):1107-1117. doi:10.1093/hmg/11.9.1107

254. Kegel KB, Kim M, Sapp E, McIntyre C, Castaño JG, Aronin N, DiFiglia M (2000) Huntingtin expression stimulates endosomal-lysosomal activity, endosome tubulation, and autophagy. The Journal of neuroscience : the official journal of the Society for Neuroscience 20 (19):7268-7278. doi:10.1523/jneurosci.20-19-07268.2000

255. Kaushik S, Massey AC, Mizushima N, Cuervo AM (2008) Constitutive activation of chaperone-mediated autophagy in cells with impaired macroautophagy. Molecular biology of the cell 19 (5):2179-2192. doi:10.1091/mbc.e07-11-1155

256. Dice JF (2007) Chaperone-mediated autophagy. Autophagy 3 (4):295-299. doi:10.4161/auto.4144

257. Koga H, Cuervo AM (2011) Chaperone-mediated autophagy dysfunction in the pathogenesis of neurodegeneration. Neurobiology of disease 43 (1):29-37. doi:10.1016/j.nbd.2010.07.006

258. Koga H, Martinez-Vicente M, Arias E, Kaushik S, Sulzer D, Cuervo AM (2011) Constitutive upregulation of chaperone-mediated autophagy in Huntington's disease. The Journal of neuroscience : the official journal of the Society for Neuroscience 31 (50):18492-18505. doi:10.1523/jneurosci.3219-11.2011

259. Sarkar S, Ravikumar B, Floto RA, Rubinsztein DC (2009) Rapamycin and mTOR-independent autophagy inducers ameliorate toxicity of polyglutamine-expanded huntingtin and related proteinopathies. Cell Death & Differentiation 16 (1):46-56. doi:10.1038/cdd.2008.110

260. Martinez-Vicente M, Talloczy Z, Wong E, Tang G, Koga H, Kaushik S, de Vries R, Arias E, Harris S, Sulzer D, Cuervo AM (2010) Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease. Nature neuroscience 13 (5):567-576. doi:10.1038/nn.2528

261. Vidal R, Caballero B, Couve A, Hetz C (2011) Converging pathways in the occurrence of endoplasmic reticulum (ER) stress in Huntington's disease. Current molecular medicine 11 (1):1-12. doi:10.2174/156652411794474419

262. Haze K, Yoshida H, Yanagi H, Yura T, Mori K (1999) Mammalian transcription factor ATF6 is synthesized as a transmembrane protein and activated by proteolysis in response to endoplasmic reticulum stress. Molecular biology of the cell 10 (11):3787-3799. doi:10.1091/mbc.10.11.3787

263. Rojas-Rivera D, Caballero B, Zamorano S, Lisbona F, Hetz C (2010) Alternative functions of the BCL-2 protein family at the endoplasmic reticulum. Advances in experimental medicine and biology 687:33-47. doi:10.1007/978-1-4419-6706-0_2

264. Kanda H, Miura M (2004) Regulatory roles of JNK in programmed cell death. Journal of biochemistry 136 (1):1-6. doi:10.1093/jb/mvh098

265. Cho KJ, Lee BI, Cheon SY, Kim HW, Kim HJ, Kim GW (2009) Inhibition of apoptosis signal-regulating kinase 1 reduces endoplasmic reticulum stress and nuclear huntingtin fragments in a mouse model of Huntington disease. Neuroscience 163 (4):1128-1134. doi:https://doi.org/10.1016/j.neuroscience.2009.07.048

266. Noh JY, Lee H, Song S, Kim NS, Im W, Kim M, Seo H, Chung CW, Chang JW, Ferrante RJ, Yoo YJ, Ryu H, Jung YK (2009) SCAMP5 links endoplasmic reticulum stress to the accumulation of expanded polyglutamine protein aggregates via endocytosis inhibition. J Biol Chem 284 (17):11318-11325. doi:10.1074/jbc.M807620200

267. Duennwald ML, Lindquist S (2008) Impaired ERAD and ER stress are early and specific events in polyglutamine toxicity. Genes & development 22 (23):3308-3319. doi:10.1101/gad.1673408

268. Li H, Li SH, Yu ZX, Shelbourne P, Li XJ (2001) Huntingtin aggregate-associated axonal degeneration is an early pathological event in Huntington's disease mice. The Journal of neuroscience : the official journal of the Society for Neuroscience 21 (21):8473-8481. doi:10.1523/jneurosci.21-21-08473.2001

269. Trushina E, Dyer RB, Badger JD, 2nd, Ure D, Eide L, Tran DD, Vrieze BT, Legendre-

Guillemin V, McPherson PS, Mandavilli BS, Van Houten B, Zeitlin S, McNiven M, Aebersold R, Hayden M, Parisi JE, Seeberg E, Dragatsis I, Doyle K, Bender A, Chacko C, McMurray CT (2004) Mutant huntingtin impairs axonal trafficking in mammalian neurons in vivo and in vitro. Molecular and cellular biology 24 (18):8195-8209. doi:10.1128/mcb.24.18.8195-8209.2004

270. Caviston JP, Ross JL, Antony SM, Tokito M, Holzbaur EL (2007) Huntingtin facilitates dynein/dynactin-mediated vesicle transport. Proceedings of the National Academy of Sciences of the United States of America 104 (24):10045-10050. doi:10.1073/pnas.0610628104

271. Dompierre JP, Godin JD, Charrin BC, Cordelières FP, King SJ, Humbert S, Saudou F (2007) Histone deacetylase 6 inhibition compensates for the transport deficit in Huntington's disease by increasing tubulin acetylation. The Journal of neuroscience : the official journal of the Society for Neuroscience 27 (13):3571-3583. doi:10.1523/jneurosci.0037-07.2007

272. Morfini GA, You YM, Pollema SL, Kaminska A, Liu K, Yoshioka K, Björkblom B, Coffey ET, Bagnato C, Han D, Huang CF, Banker G, Pigino G, Brady ST (2009) Pathogenic huntingtin inhibits fast axonal transport by activating JNK3 and phosphorylating kinesin. Nature neuroscience 12 (7):864-871. doi:10.1038/nn.2346

273. Sapp E, Penney J, Young A, Aronin N, Vonsattel JP, DiFiglia M (1999) Axonal transport of N-terminal huntingtin suggests early pathology of corticostriatal projections in Huntington disease. Journal of neuropathology and experimental neurology 58 (2):165-173. doi:10.1097/00005072-199902000-00006

274. Twelvetrees AE, Yuen EY, Arancibia-Carcamo IL, MacAskill AF, Rostaing P, Lumb MJ, Humbert S, Triller A, Saudou F, Yan Z, Kittler JT (2010) Delivery of GABAARs to synapses is mediated by HAP1-KIF5 and disrupted by mutant huntingtin. Neuron 65 (1):53-65. doi:10.1016/j.neuron.2009.12.007

275. Her LS, Goldstein LS (2008) Enhanced sensitivity of striatal neurons to axonal transport defects induced by mutant huntingtin. The Journal of neuroscience : the official journal of the Society for Neuroscience 28 (50):13662-13672. doi:10.1523/jneurosci.4144-08.2008

276. Amm I, Sommer T, Wolf DH (2014) Protein quality control and elimination of protein waste:

The role of the ubiquitin–proteasome system. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research 1843 (1):182-196. doi:https://doi.org/10.1016/j.bbamcr.2013.06.031

277. Tanaka K (2009) The proteasome: overview of structure and functions. Proceedings of the Japan Academy Series B, Physical and biological sciences 85 (1):12-36. doi:10.2183/pjab.85.12

278. Schipper-Krom S, Juenemann K, Reits EA (2012) The Ubiquitin-Proteasome System in Huntington's Disease: Are Proteasomes Impaired, Initiators of Disease, or Coming to the Rescue? Biochemistry research international 2012:837015. doi:10.1155/2012/837015

279. Martín-Aparicio E, Yamamoto A, Hernández F, Hen R, Avila J, Lucas JJ (2001) Proteasomal-dependent aggregate reversal and absence of cell death in a conditional mouse model of Huntington's disease. The Journal of neuroscience : the official journal of the Society for Neuroscience 21 (22):8772-8781. doi:10.1523/jneurosci.21-22-08772.2001

280. Bradford J, Shin JY, Roberts M, Wang CE, Li XJ, Li S (2009) Expression of mutant huntingtin in mouse brain astrocytes causes age-dependent neurological symptoms. Proceedings of the National Academy of Sciences of the United States of America 106 (52):22480-22485. doi:10.1073/pnas.0911503106

281. Shin JY, Fang ZH, Yu ZX, Wang CE, Li SH, Li XJ (2005) Expression of mutant huntingtin in glial cells contributes to neuronal excitotoxicity. J Cell Biol 171 (6):1001-1012. doi:10.1083/jcb.200508072

282. Brundin P, Melki R, Kopito R (2010) Prion-like transmission of protein aggregates in neurodegenerative diseases. Nature reviews Molecular cell biology 11 (4):301-307. doi:10.1038/nrm2873

283. Cicchetti F, Lacroix S, Cisbani G, Vallières N, Saint-Pierre M, St-Amour I, Tolouei R, Skepper JN, Hauser RA, Mantovani D, Barker RA, Freeman TB (2014) Mutant huntingtin is present in neuronal grafts in Huntington disease patients. Ann Neurol 76 (1):31-42. doi:10.1002/ana.24174

284. Nicholls DG (2004) Mitochondrial dysfunction and glutamate excitotoxicity studied in primary neuronal cultures. Current molecular medicine 4 (2):149-177.

doi:10.2174/1566524043479239

285. Beal MF, Ferrante RJ, Swartz KJ, Kowall NW (1991) Chronic quinolinic acid lesions in rats closely resemble Huntington's disease. The Journal of neuroscience : the official journal of the Society for Neuroscience 11 (6):1649-1659. doi:10.1523/jneurosci.11-06-01649.1991

286. Guidetti P, Bates GP, Graham RK, Hayden MR, Leavitt BR, MacDonald ME, Slow EJ, Wheeler VC, Woodman B, Schwarcz R (2006) Elevated brain 3-hydroxykynurenine and quinolinate levels in Huntington disease mice. Neurobiology of disease 23 (1):190-197. doi:10.1016/j.nbd.2006.02.011

287. Liévens JC, Woodman B, Mahal A, Spasic-Boscovic O, Samuel D, Kerkerian-Le Goff L, Bates GP (2001) Impaired glutamate uptake in the R6 Huntington's disease transgenic mice. Neurobiology of disease 8 (5):807-821. doi:10.1006/nbdi.2001.0430

288. Dalrymple A, Wild EJ, Joubert R, Sathasivam K, Björkqvist M, Petersén A, Jackson GS, Isaacs JD, Kristiansen M, Bates GP, Leavitt BR, Keir G, Ward M, Tabrizi SJ (2007) Proteomic profiling of plasma in Huntington's disease reveals neuroinflammatory activation and biomarker candidates. Journal of proteome research 6 (7):2833-2840. doi:10.1021/pr0700753

289. Wild E, Magnusson A, Lahiri N, Krus U, Orth M, Tabrizi SJ, Björkqvist M (2011) Abnormal peripheral chemokine profile in Huntington's disease. PLoS currents 3:Rrn1231. doi:10.1371/currents.RRN1231

290. Politis M, Lahiri N, Niccolini F, Su P, Wu K, Giannetti P, Scahill RI, Turkheimer FE, Tabrizi SJ, Piccini P (2015) Increased central microglial activation associated with peripheral cytokine levels in premanifest Huntington's disease gene carriers. Neurobiology of disease 83:115-121. doi:10.1016/j.nbd.2015.08.011

291. Weiss A, Träger U, Wild EJ, Grueninger S, Farmer R, Landles C, Scahill RI, Lahiri N, Haider S, Macdonald D, Frost C, Bates GP, Bilbe G, Kuhn R, Andre R, Tabrizi SJ (2012) Mutant huntingtin fragmentation in immune cells tracks Huntington's disease progression. The Journal of clinical investigation 122 (10):3731-3736. doi:10.1172/jci64565

292. Träger U, Andre R, Magnusson-Lind A, Miller JR, Connolly C, Weiss A, Grueninger S,

Silajdžić E, Smith DL, Leavitt BR, Bates GP, Björkqvist M, Tabrizi SJ (2015) Characterisation of immune cell function in fragment and full-length Huntington's disease mouse models. Neurobiology of disease 73:388-398. doi:10.1016/j.nbd.2014.10.012

293. Silvestroni A, Faull RL, Strand AD, Möller T (2009) Distinct neuroinflammatory profile in post-mortem human Huntington's disease. Neuroreport 20 (12):1098-1103. doi:10.1097/WNR.0b013e32832e34ee

294. Palazuelos J, Aguado T, Pazos MR, Julien B, Carrasco C, Resel E, Sagredo O, Benito C, Romero J, Azcoitia I, Fernández-Ruiz J, Guzmán M, Galve-Roperh I (2009) Microglial CB2 cannabinoid receptors are neuroprotective in Huntington's disease excitotoxicity. Brain : a journal of neurology 132 (Pt 11):3152-3164. doi:10.1093/brain/awp239

295. Bouchard J, Truong J, Bouchard K, Dunkelberger D, Desrayaud S, Moussaoui S, Tabrizi SJ, Stella N, Muchowski PJ (2012) Cannabinoid receptor 2 signaling in peripheral immune cells modulates disease onset and severity in mouse models of Huntington's disease. The Journal of neuroscience : the official journal of the Society for Neuroscience 32 (50):18259-18268. doi:10.1523/jneurosci.4008-12.2012

296. Zwilling D, Huang SY, Sathyasaikumar KV, Notarangelo FM, Guidetti P, Wu HQ, Lee J, Truong J, Andrews-Zwilling Y, Hsieh EW, Louie JY, Wu T, Scearce-Levie K, Patrick C, Adame A, Giorgini F, Moussaoui S, Laue G, Rassoulpour A, Flik G, Huang Y, Muchowski JM, Masliah E, Schwarcz R, Muchowski PJ (2011) Kynurenine 3-monooxygenase inhibition in blood ameliorates neurodegeneration. Cell 145 (6):863-874. doi:10.1016/j.cell.2011.05.020

297. Hsiao HY, Chiu FL, Chen CM, Wu YR, Chen HM, Chen YC, Kuo HC, Chern Y (2014) Inhibition of soluble tumor necrosis factor is therapeutic in Huntington's disease. Human molecular genetics 23 (16):4328-4344. doi:10.1093/hmg/ddu151

298. Kwan W, Magnusson A, Chou A, Adame A, Carson MJ, Kohsaka S, Masliah E, Möller T, Ransohoff R, Tabrizi SJ, Björkqvist M, Muchowski PJ (2012) Bone marrow transplantation confers modest benefits in mouse models of Huntington's disease. The Journal of neuroscience : the official journal of the Society for Neuroscience 32 (1):133-142. doi:10.1523/jneurosci.4846-11.2012

299. Sugars KL, Rubinsztein DC (2003) Transcriptional abnormalities in Huntington disease. Trends in genetics : TIG 19 (5):233-238. doi:10.1016/s0168-9525(03)00074-x

300. Cha JH (2007) Transcriptional signatures in Huntington's disease. Progress in neurobiology 83 (4):228-248. doi:10.1016/j.pneurobio.2007.03.004

301. Chan EY, Luthi-Carter R, Strand A, Solano SM, Hanson SA, DeJohn MM, Kooperberg C, Chase KO, DiFiglia M, Young AB, Leavitt BR, Cha JH, Aronin N, Hayden MR, Olson JM (2002) Increased huntingtin protein length reduces the number of polyglutamine-induced gene expression changes in mouse models of Huntington's disease. Human molecular genetics 11 (17):1939-1951. doi:10.1093/hmg/11.17.1939

302. Kita H, Carmichael J, Swartz J, Muro S, Wyttenbach A, Matsubara K, Rubinsztein DC, Kato K (2002) Modulation of polyglutamine-induced cell death by genes identified by expression profiling. Human molecular genetics 11 (19):2279-2287. doi:10.1093/hmg/11.19.2279

303. Luthi-Carter R, Strand AD, Hanson SA, Kooperberg C, Schilling G, La Spada AR, Merry DE, Young AB, Ross CA, Borchelt DR, Olson JM (2002) Polyglutamine and transcription: gene expression changes shared by DRPLA and Huntington's disease mouse models reveal context-independent effects. Human molecular genetics 11 (17):1927-1937. doi:10.1093/hmg/11.17.1927

304. Luthi-Carter R, Hanson SA, Strand AD, Bergstrom DA, Chun W, Peters NL, Woods AM, Chan EY, Kooperberg C, Krainc D, Young AB, Tapscott SJ, Olson JM (2002) Dysregulation of gene expression in the R6/2 model of polyglutamine disease: parallel changes in muscle and brain. Human molecular genetics 11 (17):1911-1926. doi:10.1093/hmg/11.17.1911

305. Sipione S, Rigamonti D, Valenza M, Zuccato C, Conti L, Pritchard J, Kooperberg C, Olson JM, Cattaneo E (2002) Early transcriptional profiles in huntingtin-inducible striatal cells by microarray analyses. Human molecular genetics 11 (17):1953-1965. doi:10.1093/hmg/11.17.1953

306. Wyttenbach A, Swartz J, Kita H, Thykjaer T, Carmichael J, Bradley J, Brown R, Maxwell M, Schapira A, Orntoft TF, Kato K, Rubinsztein DC (2001) Polyglutamine expansions cause decreased CRE-mediated transcription and early gene expression changes prior to cell death in an inducible cell model of Huntington's disease. Human molecular genetics 10 (17):1829-1845.

doi:10.1093/hmg/10.17.1829

307. Mantamadiotis T, Lemberger T, Bleckmann SC, Kern H, Kretz O, Martin Villalba A, Tronche F, Kellendonk C, Gau D, Kapfhammer J, Otto C, Schmid W, Schütz G (2002) Disruption of CREB function in brain leads to neurodegeneration. Nature genetics 31 (1):47-54. doi:10.1038/ng882

308. McCampbell A, Taylor JP, Taye AA, Robitschek J, Li M, Walcott J, Merry D, Chai Y, Paulson H, Sobue G, Fischbeck KH (2000) CREB-binding protein sequestration by expanded polyglutamine. Human molecular genetics 9 (14):2197-2202. doi:10.1093/hmg/9.14.2197

309. Holbert S, Denghien I, Kiechle T, Rosenblatt A, Wellington C, Hayden MR, Margolis RL, Ross CA, Dausset J, Ferrante RJ, Néri C (2001) The Gln-Ala repeat transcriptional activator CA150 interacts with huntingtin: neuropathologic and genetic evidence for a role in Huntington's disease pathogenesis. Proceedings of the National Academy of Sciences of the United States of America 98 (4):1811-1816. doi:10.1073/pnas.98.4.1811

310. Dunah AW, Jeong H, Griffin A, Kim YM, Standaert DG, Hersch SM, Mouradian MM, Young AB, Tanese N, Krainc D (2002) Sp1 and TAFII130 transcriptional activity disrupted in early Huntington's disease. Science (New York, NY) 296 (5576):2238-2243. doi:10.1126/science.1072613

311. Li SH, Cheng AL, Zhou H, Lam S, Rao M, Li H, Li XJ (2002) Interaction of Huntington disease protein with transcriptional activator Sp1. Molecular and cellular biology 22 (5):1277-1287. doi:10.1128/mcb.22.5.1277-1287.2002

312. Boutell JM, Thomas P, Neal JW, Weston VJ, Duce J, Harper PS, Jones AL (1999) Aberrant interactions of transcriptional repressor proteins with the Huntington's disease gene product, huntingtin. Human molecular genetics 8 (9):1647-1655. doi:10.1093/hmg/8.9.1647

313. Cui L, Jeong H, Borovecki F, Parkhurst CN, Tanese N, Krainc D (2006) Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. Cell 127 (1):59-69. doi:10.1016/j.cell.2006.09.015

314. Hu J, Matsui M, Corey DR (2009) Allele-selective inhibition of mutant huntingtin by peptide nucleic acid-peptide conjugates, locked nucleic acid, and small interfering RNA. Annals of the

New York Academy of Sciences 1175:24-31. doi:10.1111/j.1749-6632.2009.04975.x

315. Garriga-Canut M, Agustín-Pavón C, Herrmann F, Sánchez A, Dierssen M, Fillat C, Isalan M (2012) Synthetic zinc finger repressors reduce mutant huntingtin expression in the brain of R6/2 mice. Proceedings of the National Academy of Sciences of the United States of America 109 (45):E3136-3145. doi:10.1073/pnas.1206506109

316. Shin B, Jung R, Oh H, Owens GE, Lee H, Kwak S, Lee R, Cotman SL, Lee JM, MacDonald ME, Song JJ, Vijayvargia R, Seong IS (2018) Novel DNA Aptamers that Bind to Mutant Huntingtin and Modify Its Activity. Molecular therapy Nucleic acids 11:416-428. doi:10.1016/j.omtn.2018.03.008

317. Gu X, Greiner ER, Mishra R, Kodali R, Osmand A, Finkbeiner S, Steffan JS, Thompson LM, Wetzel R, Yang XW (2009) Serines 13 and 16 are critical determinants of full-length human mutant huntingtin induced disease pathogenesis in HD mice. Neuron 64 (6):828-840. doi:10.1016/j.neuron.2009.11.020

318. Tabrizi S, Leavitt B, Kordasiewicz H, Czech C, Swayze E, Norris DA, Baumann T, Gerlach I, Schobel S, Smith A, Lane R, Bennett CF (2018) Effects of IONIS-HTTRx in Patients with Early Huntington's Disease, Results of the First HTT-Lowering Drug Trial (CT.002). Neurology 90 (15 Supplement):CT.002

319. Vacher C, Garcia-Oroz L, Rubinsztein DC (2005) Overexpression of yeast hsp104 reduces polyglutamine aggregation and prolongs survival of a transgenic mouse model of Huntington's disease. Human molecular genetics 14 (22):3425-3433. doi:10.1093/hmg/ddi372

320. Chopra V, Fox JH, Lieberman G, Dorsey K, Matson W, Waldmeier P, Housman DE, Kazantsev A, Young AB, Hersch S (2007) A small-molecule therapeutic lead for Huntington's disease: preclinical pharmacology and efficacy of C2-8 in the R6/2 transgenic mouse. Proceedings of the National Academy of Sciences of the United States of America 104 (42):16685-16689. doi:10.1073/pnas.0707842104

321. Gharami K, Xie Y, An JJ, Tonegawa S, Xu B (2008) Brain-derived neurotrophic factor over-expression in the forebrain ameliorates Huntington's disease phenotypes in mice. Journal of

neurochemistry 105 (2):369-379. doi:https://doi.org/10.1111/j.1471-4159.2007.05137.x

322. Simmons DA, Rex CS, Palmer L, Pandyarajan V, Fedulov V, Gall CM, Lynch G (2009) Up-regulating BDNF with an ampakine rescues synaptic plasticity and memory in Huntington's disease knockin mice. Proceedings of the National Academy of Sciences 106 (12):4906-4911. doi:10.1073/pnas.0811228106

323. Landwehrmeyer GB, Dubois B, de Yébenes JG, Kremer B, Gaus W, Kraus PH, Przuntek H, Dib M, Doble A, Fischer W, Ludolph AC (2007) Riluzole in Huntington's disease: a 3-year, randomized controlled study. Ann Neurol 62 (3):262-272. doi:10.1002/ana.21181

324. Hurelbrink CB, Tyers P, Armstrong RJ, Dunnett SB, Barker RA, Rosser AE (2003) Long-term hibernation of human fetal striatal tissue does not adversely affect its differentiation in vitro or graft survival: implications for clinical trials in Huntington's disease. Cell transplantation 12 (7):687-695. doi:10.3727/000000003108747307

325. Palfi S, Condé F, Riche D, Brouillet E, Dautry C, Mittoux V, Chibois A, Peschanski M, Hantraye P (1998) Fetal striatal allografts reverse cognitive deficits in a primate model of Huntington disease. Nature medicine 4 (8):963-966. doi:10.1038/nm0898-963

326. Benraiss A, Goldman SA (2011) Cellular therapy and induced neuronal replacement for Huntington's disease. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics 8 (4):577-590. doi:10.1007/s13311-011-0075-8

327. Labbadia J, Cunliffe H, Weiss A, Katsyuba E, Sathasivam K, Seredenina T, Woodman B, Moussaoui S, Frentzel S, Luthi-Carter R, Paganetti P, Bates GP (2011) Altered chromatin architecture underlies progressive impairment of the heat shock response in mouse models of Huntington disease. The Journal of clinical investigation 121 (8):3306-3319. doi:10.1172/jci57413

328. Mielcarek M, Benn CL, Franklin SA, Smith DL, Woodman B, Marks PA, Bates GP (2011) SAHA Decreases HDAC 2 and 4 Levels In Vivo and Improves Molecular Phenotypes in the R6/2 Mouse Model of Huntington's Disease. PLOS ONE 6 (11):e27746. doi:10.1371/journal.pone.0027746

329. Goemans NM, Tulinius M, van den Akker JT, Burm BE, Ekhart PF, Heuvelmans N, Holling

T, Janson AA, Platenburg GJ, Sipkens JA, Sitsen JM, Aartsma-Rus A, van Ommen GJ, Buyse G, Darin N, Verschuuren JJ, Campion GV, de Kimpe SJ, van Deutekom JC (2011) Systemic administration of PRO051 in Duchenne's muscular dystrophy. The New England journal of medicine 364 (16):1513-1522. doi:10.1056/NEJMoa1011367

330. Rand TA, Petersen S, Du F, Wang X (2005) Argonaute2 cleaves the anti-guide strand of siRNA during RISC activation. Cell 123 (4):621-629. doi:10.1016/j.cell.2005.10.020

331. Bennett CF, Swayze EE (2010) RNA targeting therapeutics: molecular mechanisms of antisense oligonucleotides as a therapeutic platform. Annual review of pharmacology and toxicology 50:259-293. doi:10.1146/annurev.pharmtox.010909.105654

332. Kay C, Skotte NH, Southwell AL, Hayden MR (2014) Personalized gene silencing therapeutics for Huntington disease. Clinical genetics 86 (1):29-36. doi:10.1111/cge.12385

333. Watts JK, Corey DR (2012) Silencing disease genes in the laboratory and the clinic. The Journal of Pathology 226 (2):365-379. doi:https://doi.org/10.1002/path.2993

334. Yamamoto A, Lucas JJ, Hen R (2000) Reversal of neuropathology and motor dysfunction in a conditional model of Huntington's disease. Cell 101 (1):57-66. doi:10.1016/s0092-8674(00)80623-6

335. Drouet V, Perrin V, Hassig R, Dufour N, Auregan G, Alves S, Bonvento G, Brouillet E, Luthi-Carter R, Hantraye P, Déglon N (2009) Sustained effects of nonallele-specific Huntingtin silencing. Ann Neurol 65 (3):276-285. doi:10.1002/ana.21569

336. Kordasiewicz HB, Stanek LM, Wancewicz EV, Mazur C, McAlonis MM, Pytel KA, Artates JW, Weiss A, Cheng SH, Shihabuddin LS, Hung G, Bennett CF, Cleveland DW (2012) Sustained therapeutic reversal of Huntington's disease by transient repression of huntingtin synthesis. Neuron 74 (6):1031-1044. doi:10.1016/j.neuron.2012.05.009

337. Tabrizi SJ, Leavitt BR, Landwehrmeyer GB, Wild EJ, Saft C, Barker RA, Blair NF, Craufurd D, Priller J, Rickards H, Rosser A, Kordasiewicz HB, Czech C, Swayze EE, Norris DA, Baumann T, Gerlach I, Schobel SA, Paz E, Smith AV, Bennett CF, Lane RM (2019) Targeting Huntingtin Expression in Patients with Huntington's Disease. The New England journal of medicine 380

(24):2307-2316. doi:10.1056/NEJMoa1900907

338. Sah DW, Aronin N (2011) Oligonucleotide therapeutic approaches for Huntington disease. The Journal of clinical investigation 121 (2):500-507. doi:10.1172/jci45130

339. Stanek LM, Sardi SP, Mastis B, Richards AR, Treleaven CM, Taksir T, Misra K, Cheng SH, Shihabuddin LS (2014) Silencing mutant huntingtin by adeno-associated virus-mediated RNA interference ameliorates disease manifestations in the YAC128 mouse model of Huntington's disease. Human gene therapy 25 (5):461-474. doi:10.1089/hum.2013.200

340. Grondin R, Kaytor MD, Ai Y, Nelson PT, Thakker DR, Heisel J, Weatherspoon MR, Blum JL, Burright EN, Zhang Z, Kaemmerer WF (2012) Six-month partial suppression of Huntingtin is well tolerated in the adult rhesus striatum. Brain : a journal of neurology 135 (Pt 4):1197-1209. doi:10.1093/brain/awr333

341. Gagnon KT, Pendergraff HM, Deleavey GF, Swayze EE, Potier P, Randolph J, Roesch EB, Chattopadhyaya J, Damha MJ, Bennett CF, Montaillier C, Lemaitre M, Corey DR (2010) Allele-selective inhibition of mutant huntingtin expression with antisense oligonucleotides targeting the expanded CAG repeat. Biochemistry 49 (47):10166-10178. doi:10.1021/bi101208k

342. Yu D, Pendergraff H, Liu J, Kordasiewicz HB, Cleveland DW, Swayze EE, Lima WF, Crooke ST, Prakash TP, Corey DR (2012) Single-stranded RNAs use RNAi to potently and allele-selectively inhibit mutant huntingtin expression. Cell 150 (5):895-908. doi:10.1016/j.cell.2012.08.002

343. Fiszer A, Olejniczak M, Switonski PM, Wroblewska JP, Wisniewska-Kruk J, Mykowska A, Krzyzosiak WJ (2012) An evaluation of oligonucleotide-based therapeutic strategies for polyQ diseases. BMC molecular biology 13:6. doi:10.1186/1471-2199-13-6

344. Pfister EL, Kennington L, Straubhaar J, Wagh S, Liu W, DiFiglia M, Landwehrmeyer B, Vonsattel JP, Zamore PD, Aronin N (2009) Five siRNAs targeting three SNPs may provide therapy for three-quarters of Huntington's disease patients. Current biology : CB 19 (9):774-778. doi:10.1016/j.cub.2009.03.030

345. Lombardi MS, Jaspers L, Spronkmans C, Gellera C, Taroni F, Di Maria E, Donato SD,

Kaemmerer WF (2009) A majority of Huntington's disease patients may be treatable by individualized allele-specific RNA interference. Experimental neurology 217 (2):312-319. doi:10.1016/j.expneurol.2009.03.004

346. van Bilsen PH, Jaspers L, Lombardi MS, Odekerken JC, Burright EN, Kaemmerer WF (2008) Identification and allele-specific silencing of the mutant huntingtin allele in Huntington's disease patient-derived fibroblasts. Human gene therapy 19 (7):710-719. doi:10.1089/hum.2007.116

347. Carroll JB, Warby SC, Southwell AL, Doty CN, Greenlee S, Skotte N, Hung G, Bennett CF, Freier SM, Hayden MR (2011) Potent and selective antisense oligonucleotides targeting single-nucleotide polymorphisms in the Huntington disease gene / allele-specific silencing of mutant huntingtin. Molecular therapy : the journal of the American Society of Gene Therapy 19 (12):2178-2185. doi:10.1038/mt.2011.201

348. Østergaard ME, Southwell AL, Kordasiewicz H, Watt AT, Skotte NH, Doty CN, Vaid K, Villanueva EB, Swayze EE, Bennett CF, Hayden MR, Seth PP (2013) Rational design of antisense oligonucleotides targeting single nucleotide polymorphisms for potent and allele selective suppression of mutant Huntingtin in the CNS. Nucleic acids research 41 (21):9634-9650. doi:10.1093/nar/gkt725

349. Southwell AL, Skotte NH, Kordasiewicz HB, Østergaard ME, Watt AT, Carroll JB, Doty CN, Villanueva EB, Petoukhov E, Vaid K, Xie Y, Freier SM, Swayze EE, Seth PP, Bennett CF, Hayden MR (2014) In vivo evaluation of candidate allele-specific mutant huntingtin gene silencing antisense oligonucleotides. Molecular therapy : the journal of the American Society of Gene Therapy 22 (12):2093-2106. doi:10.1038/mt.2014.153

350. Drouet V, Ruiz M, Zala D, Feyeux M, Auregan G, Cambon K, Troquier L, Carpentier J, Aubert S, Merienne N, Bourgois-Rocha F, Hassig R, Rey M, Dufour N, Saudou F, Perrier AL, Hantraye P, Déglon N (2014) Allele-specific silencing of mutant huntingtin in rodent brain and human stem cells. PLoS One 9 (6):e99341. doi:10.1371/journal.pone.0099341

351. Zhao T, Hong Y, Li XJ, Li SH (2016) Subcellular Clearance and Accumulation of Huntington Disease Protein: A Mini-Review. Frontiers in molecular neuroscience 9:27. doi:10.3389/fnmol.2016.00027

352. Harding RJ, Tong Y-f (2018) Proteostasis in Huntington's disease: disease mechanisms and therapeutic opportunities. Acta Pharmacologica Sinica 39 (5):754-769. doi:10.1038/aps.2018.11

353. Tomoshige S, Nomura S, Ohgane K, Hashimoto Y, Ishikawa M (2017) Discovery of Small Molecules that Induce the Degradation of Huntingtin. Angewandte Chemie (International ed in English) 56 (38):11530-11533. doi:10.1002/anie.201706529

354. Tomoshige S, Nomura S, Ohgane K, Hashimoto Y, Ishikawa M (2018) Degradation of huntingtin mediated by a hybrid molecule composed of IAP antagonist linked to phenyldiazenyl benzothiazole derivative. Bioorganic & medicinal chemistry letters 28 (4):707-710. doi:10.1016/j.bmcl.2018.01.012

355. Díaz-Villanueva JF, Díaz-Molina R, García-González V (2015) Protein Folding and Mechanisms of Proteostasis. International journal of molecular sciences 16 (8):17193-17230. doi:10.3390/ijms160817193

356. Kalchman MA, Graham RK, Xia G, Koide HB, Hodgson JG, Graham KC, Goldberg YP, Gietz RD, Pickart CM, Hayden MR (1996) Huntingtin is ubiquitinated and interacts with a specific ubiquitin-conjugating enzyme. J Biol Chem 271 (32):19385-19394. doi:10.1074/jbc.271.32.19385

357. Subramaniam S, Sixt KM, Barrow R, Snyder SH (2009) Rhes, a striatal specific protein, mediates mutant-huntingtin cytotoxicity. Science (New York, NY) 324 (5932):1327-1330. doi:10.1126/science.1172871

358. Humbert S, Saudou F (2003) Huntingtin phosphorylation and signaling pathways that regulate toxicity in Huntington's disease. Clinical Neuroscience Research 3 (3):149-155. doi:https://doi.org/10.1016/S1566-2772(03)00057-4

359. Tözsér J, Bagossi P, Zahuczky G, Specht SI, Majerova E, Copeland TD (2003) Effect of caspase cleavage-site phosphorylation on proteolysis. The Biochemical journal 372 (Pt 1):137-143. doi:10.1042/bj20021901

360. Poon IK, Jans DA (2005) Regulation of nuclear transport: central role in development and transformation? Traffic (Copenhagen, Denmark) 6 (3):173-186. doi:10.1111/j.1600-0854.2005.00268.x

361. Warby SC, Montpetit A, Hayden AR, Carroll JB, Butland SL, Visscher H, Collins JA, Semaka A, Hudson TJ, Hayden MR (2009) CAG expansion in the Huntington disease gene is associated with a specific and targetable predisposing haplogroup. American journal of human genetics 84 (3):351-366. doi:10.1016/j.ajhg.2009.02.003

362. Zala D, Colin E, Rangone H, Liot G, Humbert S, Saudou F (2008) Phosphorylation of mutant huntingtin at S421 restores anterograde and retrograde transport in neurons. Human molecular genetics 17 (24):3837-3846. doi:10.1093/hmg/ddn281

363. Warby SC, Chan EY, Metzler M, Gan L, Singaraja RR, Crocker SF, Robertson HA, Hayden MR (2005) Huntingtin phosphorylation on serine 421 is significantly reduced in the striatum and by polyglutamine expansion in vivo. Human molecular genetics 14 (11):1569-1577. doi:10.1093/hmg/ddi165

364. Luo S, Vacher C, Davies JE, Rubinsztein DC (2005) Cdk5 phosphorylation of huntingtin reduces its cleavage by caspases: implications for mutant huntingtin toxicity. J Cell Biol 169 (4):647-656. doi:10.1083/jcb.200412071

365. Schilling B, Gafni J, Torcassi C, Cong X, Row RH, LaFevre-Bernt MA, Cusack MP, Ratovitski T, Hirschhorn R, Ross CA, Gibson BW, Ellerby LM (2006) Huntingtin phosphorylation sites mapped by mass spectrometry. Modulation of cleavage and toxicity. J Biol Chem 281 (33):23686-23697. doi:10.1074/jbc.M513507200

366. Gafni J, Hermel E, Young JE, Wellington CL, Hayden MR, Ellerby LM (2004) Inhibition of calpain cleavage of huntingtin reduces toxicity: accumulation of calpain/caspase fragments in the nucleus. J Biol Chem 279 (19):20211-20220. doi:10.1074/jbc.M401267200

367. Anne SL, Saudou F, Humbert S (2007) Phosphorylation of huntingtin by cyclin-dependent kinase 5 is induced by DNA damage and regulates wild-type and mutant huntingtin toxicity in neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience 27 (27):7318-7328. doi:10.1523/jneurosci.1831-07.2007

368. Aiken CT, Steffan JS, Guerrero CM, Khashwji H, Lukacsovich T, Simmons D, Purcell JM, Menhaji K, Zhu Y-Z, Green K, Laferla F, Huang L, Thompson LM, Marsh JL (2009)

Phosphorylation of threonine 3: implications for Huntingtin aggregation and neurotoxicity. J Biol Chem 284 (43):29427-29436. doi:10.1074/jbc.m109.013193

369. Thompson LM, Aiken CT, Kaltenbach LS, Agrawal N, Illes K, Khoshnan A, Martinez-Vincente M, Arrasate M, O'Rourke JG, Khashwji H, Lukacsovich T, Zhu Y-Z, Lau AL, Massey A, Hayden MR, Zeitlin SO, Finkbeiner S, Green KN, LaFerla FM, Bates G, Huang L, Patterson PH, Lo DC, Cuervo AM, Marsh JL, Steffan JS (2009) IKK phosphorylates Huntingtin and targets it for degradation by the proteasome and lysosome. J Cell Biol 187 (7):1083-1099. doi:10.1083/jcb.200909067

370. Humbert S, Bryson EA, Cordelières FP, Connors NC, Datta SR, Finkbeiner S, Greenberg ME, Saudou F (2002) The IGF-1/Akt pathway is neuroprotective in Huntington's disease and involves Huntingtin phosphorylation by Akt. Developmental cell 2 (6):831-837. doi:10.1016/s1534-5807(02)00188-0

371. Colin E, Zala D, Liot G, Rangone H, Borrell-Pagès M, Li XJ, Saudou F, Humbert S (2008) Huntingtin phosphorylation acts as a molecular switch for anterograde/retrograde transport in neurons. Embo j 27 (15):2124-2134. doi:10.1038/emboj.2008.133

372. Lee Y, Kim H, Barker D, Vijayvargia R, Atwal RS, Specht H, Keshishian H, Carr SA, Lee R, Kwak S, Hyun KG, Loupe J, MacDonald ME, Song JJ, Seong IS (2023) Huntingtin turnover: modulation of huntingtin degradation by cAMP-dependent protein kinase A (PKA) phosphorylation of C-HEAT domain Ser2550. Human molecular genetics 32 (1):30-45. doi:10.1093/hmg/ddac165

373. Atwal RS, Desmond CR, Caron N, Maiuri T, Xia J, Sipione S, Truant R (2011) Kinase inhibitors modulate huntingtin cell localization and toxicity. Nature chemical biology 7 (7):453-460. doi:10.1038/nchembio.582

374. White A, McGlone A, Gomez-Pastor R (2022) Protein Kinase CK2 and Its Potential Role as a Therapeutic Target in Huntington's Disease. Biomedicines 10 (8). doi:10.3390/biomedicines10081979

375. Bowie LE, Maiuri T, Alpaugh M, Gabriel M, Arbez N, Galleguillos D, Hung CLK, Patel S,

Xia J, Hertz NT, Ross CA, Litchfield DW, Sipione S, Truant R (2018) N6-Furfuryladenine is protective in Huntington's disease models by signaling huntingtin phosphorylation. Proceedings of the National Academy of Sciences of the United States of America 115 (30):E7081-e7090. doi:10.1073/pnas.1801772115

376. Nisha, Thapliyal D, Gohil B, Modak AS, Ahuja S, Singh NT, Sahu BS, Singh MD (2024) Protective role of Pten downregulation in Huntington's Disease models. bioRxiv:2024.2003.2028.587147. doi:10.1101/2024.03.28.587147

377. Mousavi MA, Rezaee M, Pourhamzeh M, Salari M, Hossein-Khannazer N, Shpichka A, Nabavi SM, Timashev P, Vosough M (2024) Translational Approach Using Advanced Therapy Medicinal Products for Huntington's Disease. Current reviews in clinical and experimental pharmacology. doi:10.2174/0127724328300166240510071548

378. Lui A, Vanleuven J, Perekopskiy D, Liu D, Xu D, Alzayat O, Elgokhy T, Do T, Gann M, Martin R, Liu DZ (2022) FDA-Approved Kinase Inhibitors in Preclinical and Clinical Trials for Neurological Disorders. Pharmaceuticals (Basel, Switzerland) 15 (12). doi:10.3390/ph15121546