Chapter 7:

Results and Discussion 4

Identification of differentially expressed proteins associated with mHTT expression using quantitative proteomics approach

This chapter focuses on the identification of proteins whose expression levels are altered in response to mutant huntingtin expression, utilizing a label-free quantitative proteomics approach. Understanding the molecular mechanisms of Huntington's Disease is crucial for developing effective therapeutic strategies, particularly given the complex and multifaceted nature of the disease. One of the key aspects of HD pathology is the toxicity associated with mutant huntingtin, which leads to widespread cellular dysfunction and neurodegeneration. Identifying differentially expressed proteins linked to mHTT expression can help in delineating the disease mechanisms and offer potential targets for intervention. Recent advancements in quantitative proteomics have provided significant insights into how mHTT influences cellular proteomes. Label-free quantitative proteomics provides a powerful approach for this investigation by enabling the comprehensive profiling of protein expression levels without the need for isotopic labels, thereby offering a more flexible and cost-effective approach. This method allows for the identification and quantification of proteins that are dysregulated in response to mHTT expression, offering a detailed view of the molecular alterations associated with HD. By elucidating these changes, researchers can uncover novel biomarkers and therapeutic targets that may help in slowing or reversing disease progression, ultimately advancing our understanding and treatment of HD.

7.1 Label-Free Quantitation and Comparative Analysis

The analysis of Information-Dependent Acquisition/Data-Dependent Acquisition (IDA/DDA) runs using MaxQuant resulted in the identification of 1,607 proteins. After excluding contaminants and reverse proteins, a total of 1,598 proteins were confirmed across five different conditions. Of these, 1,319 proteins were identified with at least two unique peptides. The comparative analysis revealed that approximately 779 proteins were consistently identified across all samples. The results of the fold change analysis highlighting proteins that are significantly upregulated (more than 1.5-fold) and downregulated (less than 0.66-fold). Additionally, further analysis identified 127 proteins exhibiting "switch" behavior; these proteins were downregulated upon Pon A treatment but became upregulated with subsequent treatments using Kinetin, BMS 345541, and Bay 11-7082, and vice versa (**Fig. 7.1.1**).

The Venn diagram (**Fig. 7.1.2**) illustrates the overlap in protein expression between different experimental groups. A significant number of proteins were uniquely identified in each condition, indicating distinct proteomic profiles. Notably, the largest unique protein set was found in the

HD150Q control group, followed by the Pon A alone group. Despite these unique profiles, a substantial overlap of 779 proteins was observed across all groups, suggesting a core set of proteins consistently expressed. These findings highlight the complexity of the proteomic response to different treatments and underscore the need for further investigation to elucidate the specific roles of these differentially expressed proteins.

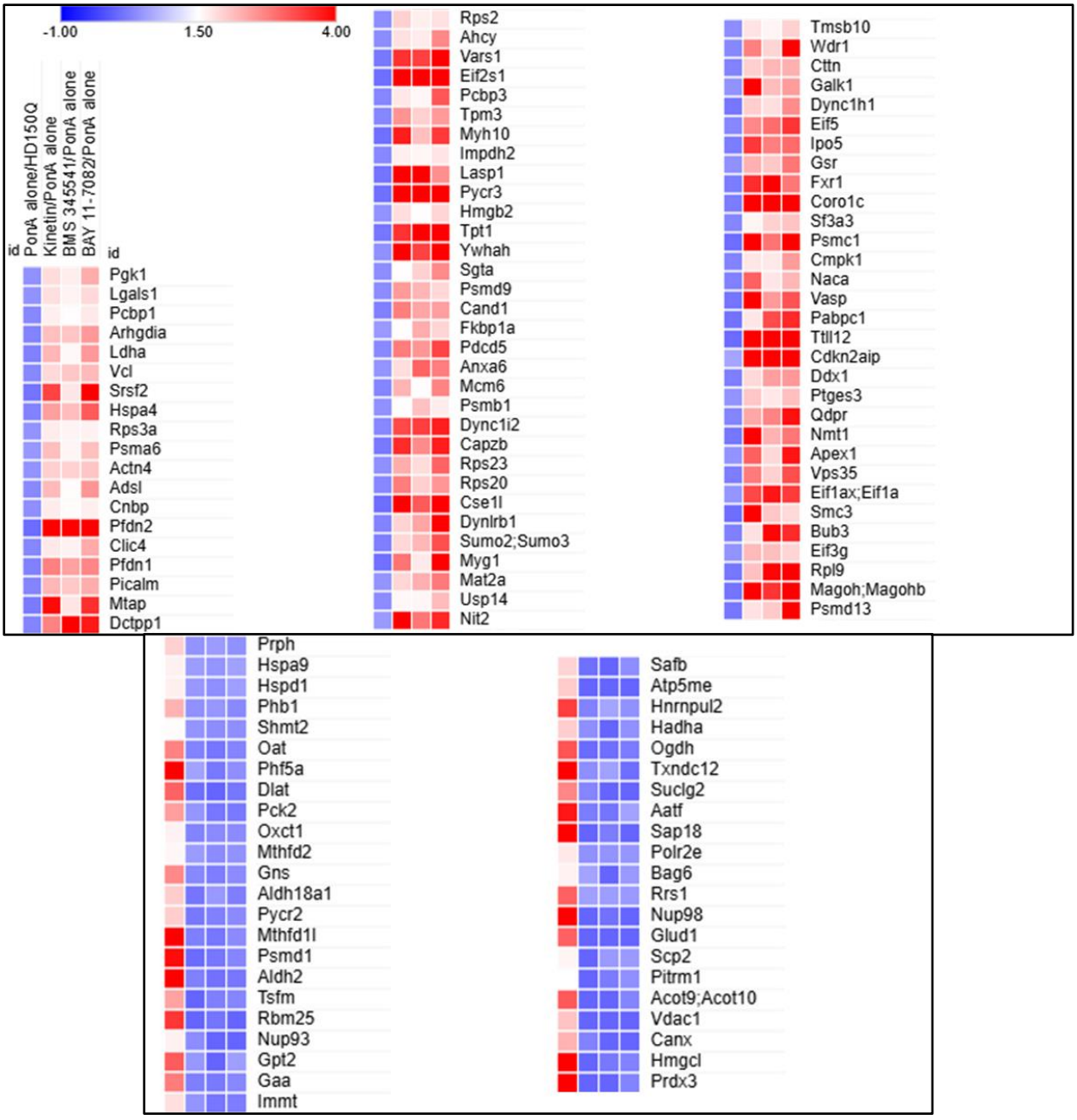

Figure 7.1.1: Heatmap showing the "switch" behavior of 127 proteins, downregulated upon Pon A treatment and upregulated with Kinetin, BMS 345541, and Bay 11-7082, and vice versa.

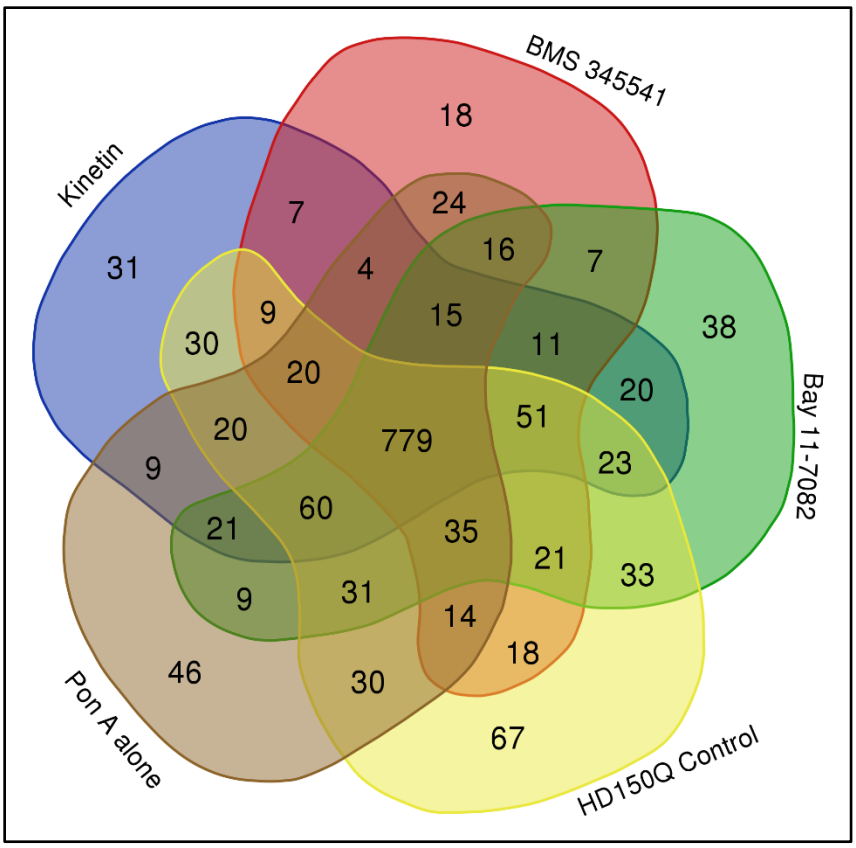

Figure 7.1.2: The Venn diagram illustrates the overlap in protein expression between different experimental groups.

In **Fig. 7.1.3**, the Venn diagram depicts the overlap in upregulated proteins among Kinetin, BMS 345541, and Bay 11-7082 treatment groups compared to the Pon A alone (disease condition). Bay 11-7082 has the largest set of uniquely upregulated proteins (99), followed by Kinetin (56), suggesting distinct therapeutic mechanisms. However, a substantial overlap of 87 proteins is shared among all treatments, indicating potential common regulatory pathways. The Venn diagram (**Fig. 7.1.4**) shows the overlap in downregulated proteins among Kinetin, BMS 345541, and Bay 11-7082 treatment groups compared to the Pon A alone (disease condition). BMS 345541 has the largest set of uniquely downregulated proteins (137), followed by Bay 11-7082 (27), suggesting distinct therapeutic mechanisms. However, a substantial overlap of 80 proteins is shared among all treatments, indicating potential common regulatory pathways. These findings highlight the complex interplay of these compounds and suggest the potential for combinatorial therapies to achieve broader therapeutic effects.

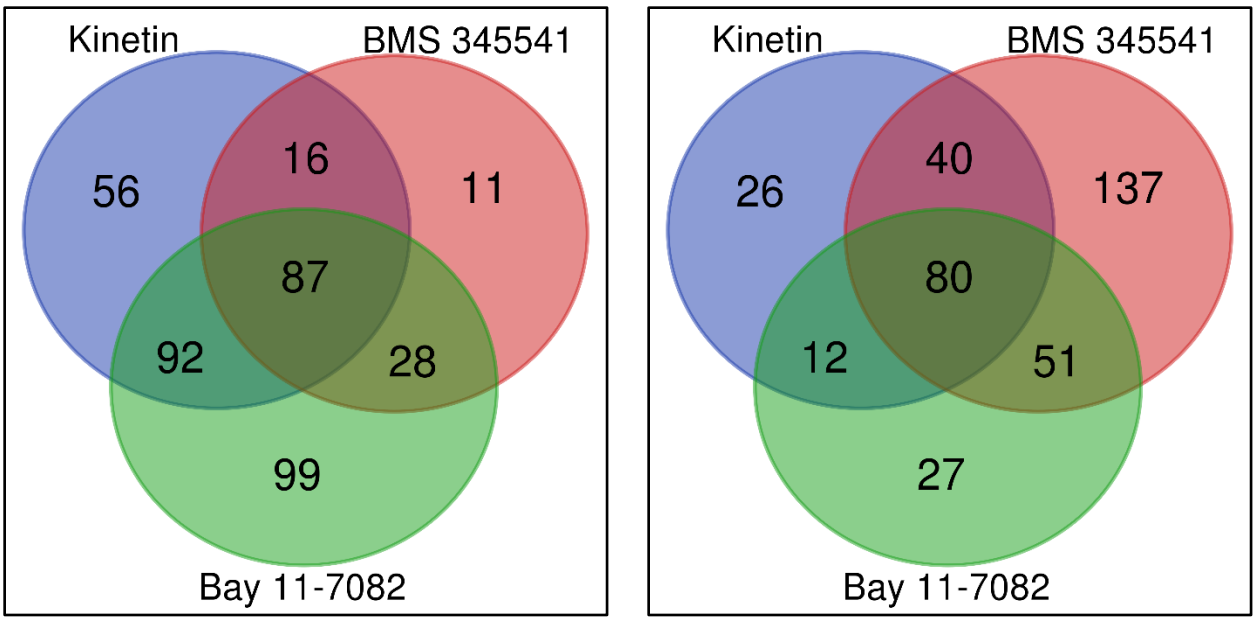

Figure 7.1.3: Venn diagram illustrating the overlap of upregulated proteins among Kinetin, BMS 345541, and Bay 11-7082 treatment groups compared to Pon A alone (disease condition).

Figure 7.1.4: The Venn diagram shows the overlap in downregulated proteins among Kinetin, BMS 345541, and Bay 11-7082 treatment groups compared to Pon A alone (disease condition).

7.2 Comparative Analysis of Proteomic Alterations in HD150Q Cells treated with Pon A alone and Post-Treatment with Kinetin, BMS 345541, and Bay 11-7082

To understand the proteomic alterations in HD150Q cells under different treatment conditions, we performed an in-depth comparative analysis using ShinyGO 0.80 for overrepresentation analysis of differentially regulated proteins. This analysis provides insights into the molecular pathways modulated by Kinetin, BMS 345541, and Bay 11-7082 treatments. By comparing the downregulated pathways in the HD condition with the upregulated pathways post-treatment and vice versa, we aim to elucidate the therapeutic potential of these compounds in reversing or mitigating the proteomic disruptions caused by Huntington's disease. Some of the very important pathways playing a role in HD are discussed below.

7.2.1 Downregulated Pathways in HD Condition vs. Upregulated Pathways Post-Treatment (Fig. 7.2.1 and 7.2.2)

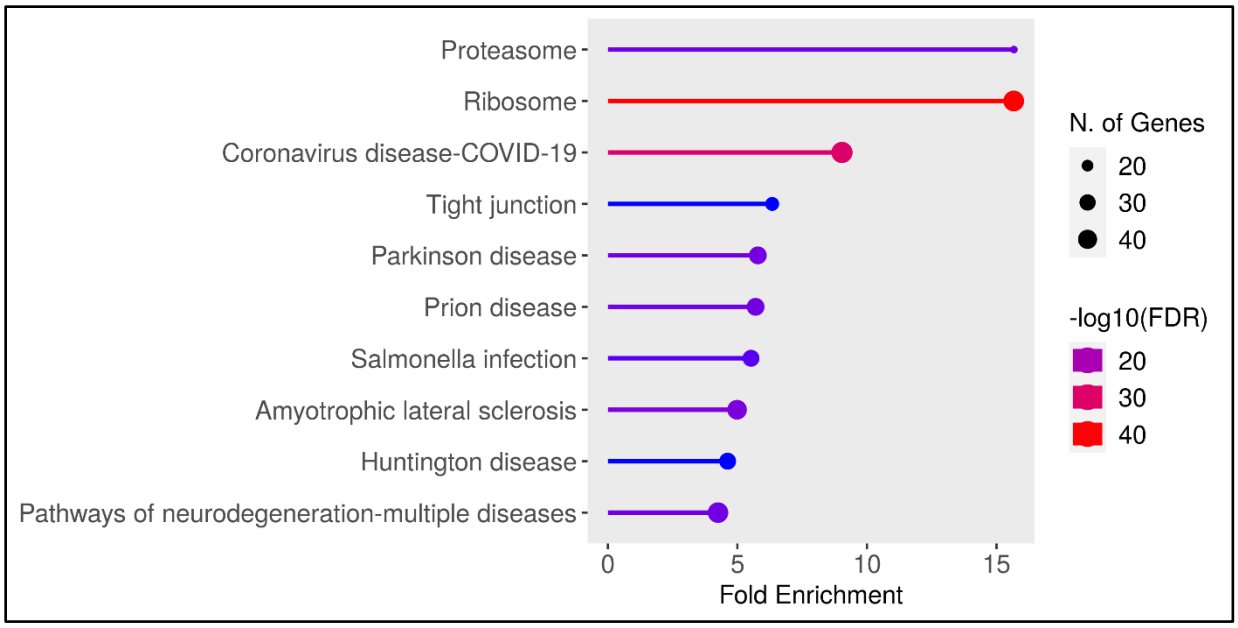

Figure 7.2.1: Downregulated Pathways in Ponasterone A alone (HD Condition). Different KEGG pathways are indicated on the Y-axis; color indicates -log (FDR) values; and the size of the circle indicates the number of genes featured in the enriched KEGG pathway.

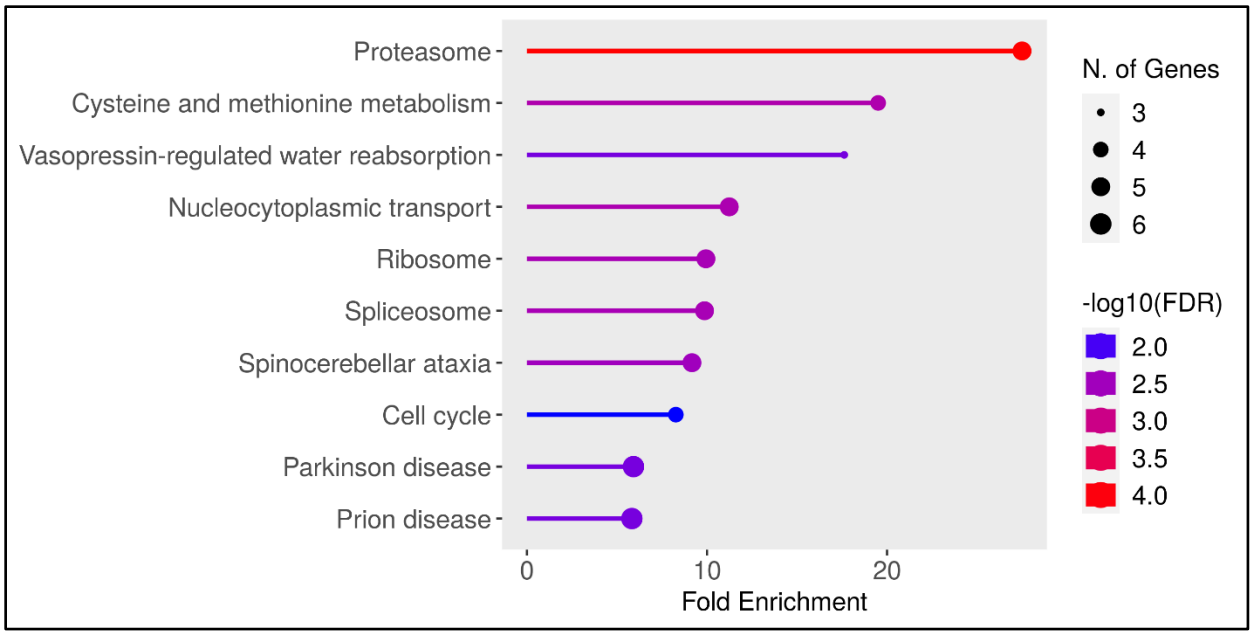

Figure 7.2.2: Upregulated Pathways Post-Treatments with Ponasterone A and different concentrations of Kinetin, BMS 345541 and Bay 11-7082. Different KEGG pathways are indicated on the Y-axis; color indicates -log (FDR) values; and the size of the circle indicates the number of genes featured in the enriched KEGG pathway.

Proteasome Pathway

In HD condition, the proteasome pathway exhibited significant downregulation, which aligns with the well-documented impairment of protein degradation mechanisms in HD [1-3]. The accumulation of misfolded proteins due to dysfunctional proteasome activity contributes to cellular toxicity and the formation of intracellular aggregates [4,5]. Treatment with Kinetin, BMS 345541, and Bay 11-7082 led to notable upregulation of proteins involved in this pathway. This enhancement suggests that these compounds may restore proteasome function, thereby facilitating the clearance of misfolded proteins and improving overall proteostasis. The upregulation indicates a potential therapeutic benefit by mitigating one of the central pathogenic features of HD.

Ribosome Pathway

The ribosome pathway, crucial for protein synthesis, was downregulated in HD cells, indicative of compromised translational capacity. This downregulation can lead to insufficient production of essential proteins, exacerbating cellular dysfunction [6-8]. Upon treatment, the ribosome pathway showed significant upregulation, implying a recovery in protein synthesis capacity. Restoring ribosomal function is vital for maintaining cellular homeostasis and can counteract the defects in protein production observed in HD. This upregulation may help to improve cell viability and functionality by ensuring adequate protein synthesis.

7.2.2 Upregulated Pathways in HD Condition vs. Downregulated Pathways Post-Treatment (Fig. 7.2.3 and 7.2.4)

One Carbon Pool by Folate and Carbon Metabolism

These pathways were upregulated in HD condition, likely as compensatory responses to increased demand for DNA repair and synthesis due to ongoing cellular stress and damage. The upregulation signifies an attempt by the cells to cope with the heightened repair needs. Post-treatment, these pathways were downregulated, indicating a reduction in cellular stress and damage. The normalization of these pathways suggests that the treatments effectively mitigate the underlying stressors, reducing the need for compensatory mechanisms and restoring cellular equilibrium.

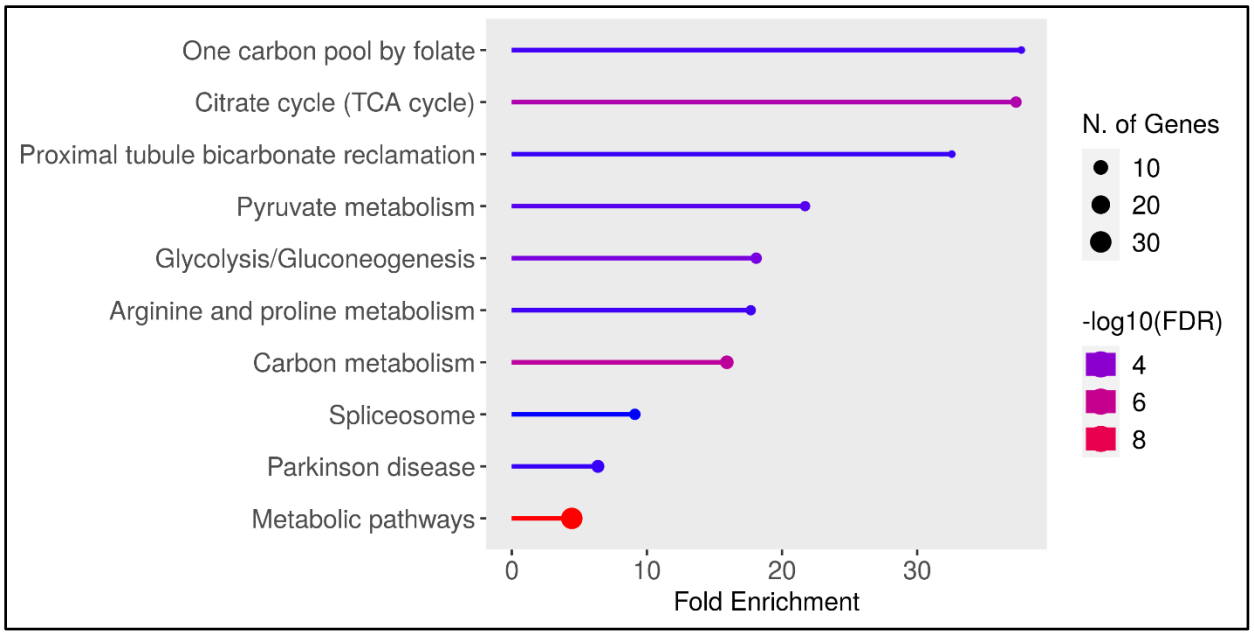

Figure 7.2.3: Upregulated Pathways in Ponasterone A alone (HD Condition). Different KEGG pathways are indicated on the Y-axis; color indicates -log (FDR) values; and the size of the circle indicates the number of genes featured in the enriched KEGG pathway.

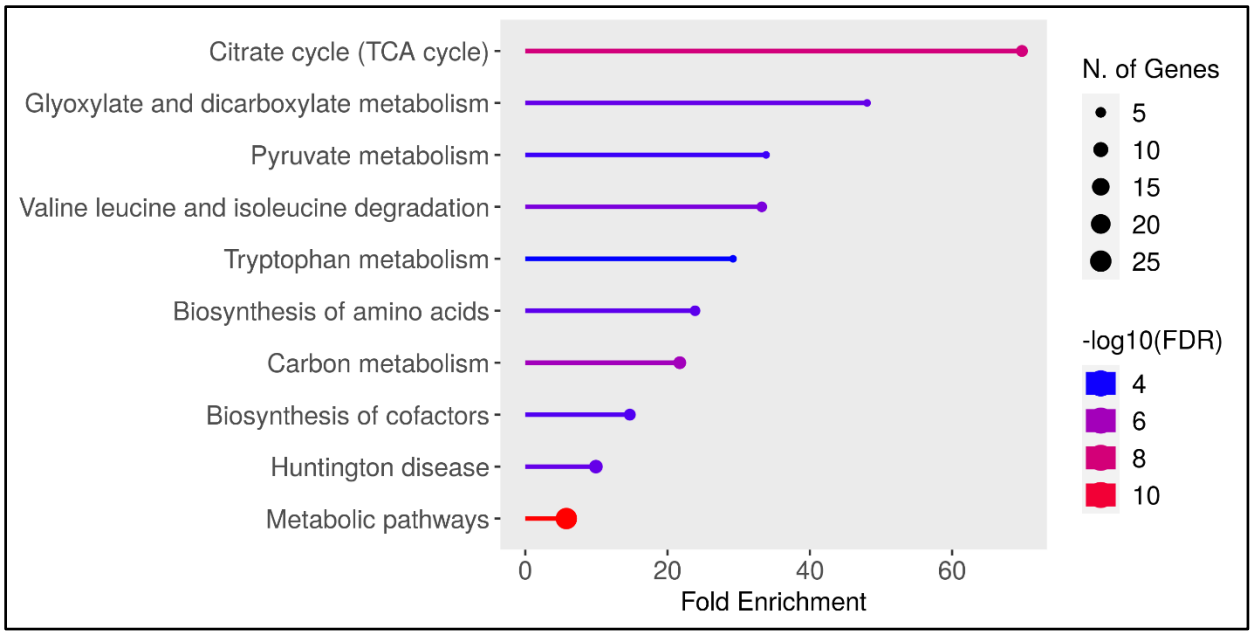

Figure 7.2.4: Downregulated Pathways Post-Treatments with Ponasterone A and different concentrations of Kinetin, BMS 345541 and Bay 11-7082. Different KEGG pathways are indicated on the Y-axis; color indicates -log (FDR) values; and the size of the circle indicates the number of genes featured in the enriched KEGG pathway.

Proximal Tubule Bicarbonate Reclamation and Pyruvate Metabolism

These metabolic pathways were upregulated in HD cells, reflecting altered metabolic states as the cells attempt to adapt to the disease condition. Treatment-induced downregulation of these pathways suggests a return to normal metabolic functioning [9,10]. This normalization indicates that the compounds may correct the metabolic imbalances seen in HD, improving overall cellular health and function. Proper metabolic regulation is essential for maintaining energy homeostasis and supporting the cellular activities necessary for neuron survival [11].

Spliceosome

The spliceosome pathway was upregulated in HD cells, highlighting issues with mRNA processing and splicing fidelity. Aberrant splicing can lead to the production of dysfunctional proteins and exacerbate disease pathology [12]. Post-treatment downregulation suggests an improvement in RNA processing efficiency and splicing accuracy. By normalizing the spliceosome activity, the treatments may reduce the production of aberrant proteins, thus alleviating some of the molecular defects associated with HD.

Our comparative proteomics analysis reveals significant alterations in critical pathways in HD condition, particularly those involved in protein degradation, synthesis, and mitochondrial function. Treatment with Kinetin, BMS 345541, and Bay 11-7082 leads to upregulation of pathways that were downregulated in HD, suggesting a restoration of cellular functions and mitigation of HD pathology. Conversely, pathways upregulated in HD condition, likely as compensatory responses, were downregulated post-treatment, indicating normalization of cellular processes and reduced stress. These findings highlight the therapeutic potential of Kinetin, BMS 345541, and Bay 11-7082 in addressing the molecular dysfunctions in Huntington's Disease and improving cellular homeostasis.

7.3 Comparative Analysis of Biological Processes in Pon A treated HD150Q Cells and Post-Treatment with Kinetin, BMS 345541, and Bay 11-7082

To further explore the therapeutic impacts of Kinetin, BMS 345541, and Bay 11-7082, we conducted a comparative analysis of biological processes affected in HD150Q cells treated with Pon A alone versus post-treatment with these compounds. Using ShinyGO 0.80 for overrepresentation analysis, we focused on identifying biological processes that were dysregulated

in the HD condition and subsequently restored following treatment. This approach helps to reveal the potential of these treatments to restore normal cellular functions and counteract the pathological alterations associated with Huntington's disease. Below, several key biological processes that play a critical role in HD are discussed.

7.3.1 Downregulated Biological Processes in HD Condition vs. Upregulated Biological Processes Post-Treatment (Fig. 7.3.1 and 7.3.2)

Cytoplasmic Translation and Translation

In HD condition, cytoplasmic translation and overall translation processes were significantly downregulated, indicating impaired protein synthesis machinery [6,13]. This impairment contributes to decreased cellular function and survival due to the lack of essential proteins [13]. Following treatment with Kinetin, BMS 345541, and Bay 11-7082, both cytoplasmic translation and translation processes were upregulated, signifying a restoration of protein synthesis capabilities. This suggests that these treatments can reinstate normal protein production, which is critical for maintaining cellular functions and combating the toxic effects of mHTT aggregation.

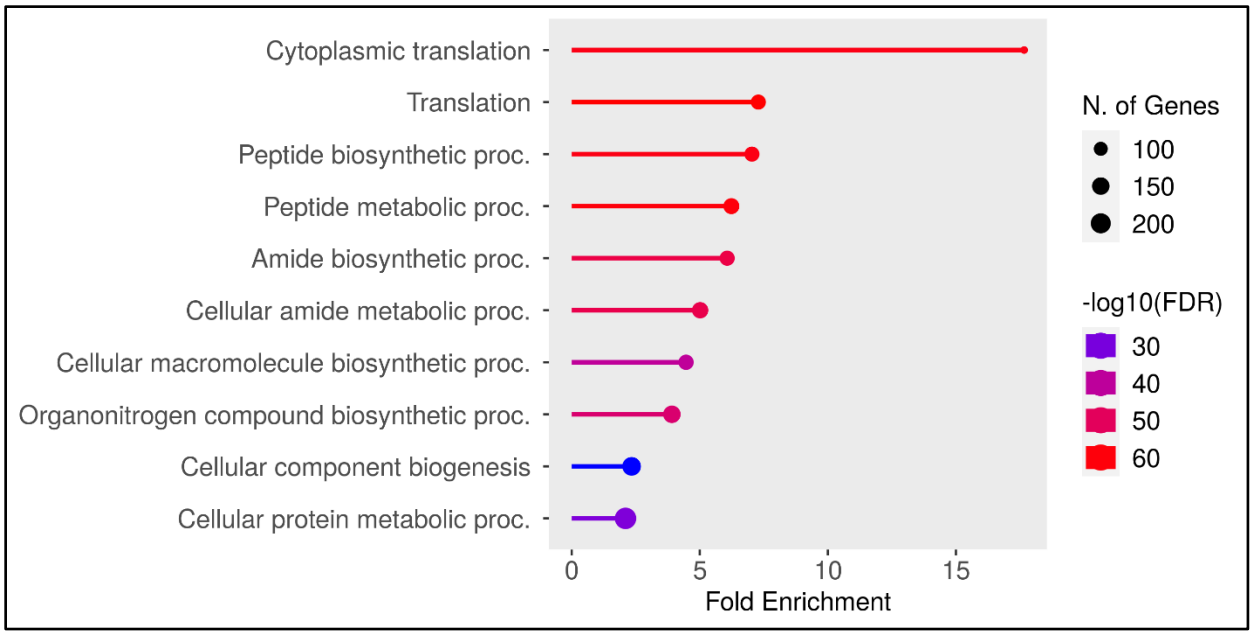

Figure 7.3.1: Downregulated Biological Processes in Ponasterone A alone (HD Condition). Different Biological Processes are indicated on the Y-axis; color indicates -log (FDR) values; and the size of the circle indicates the number of genes featured in the enriched GO term.

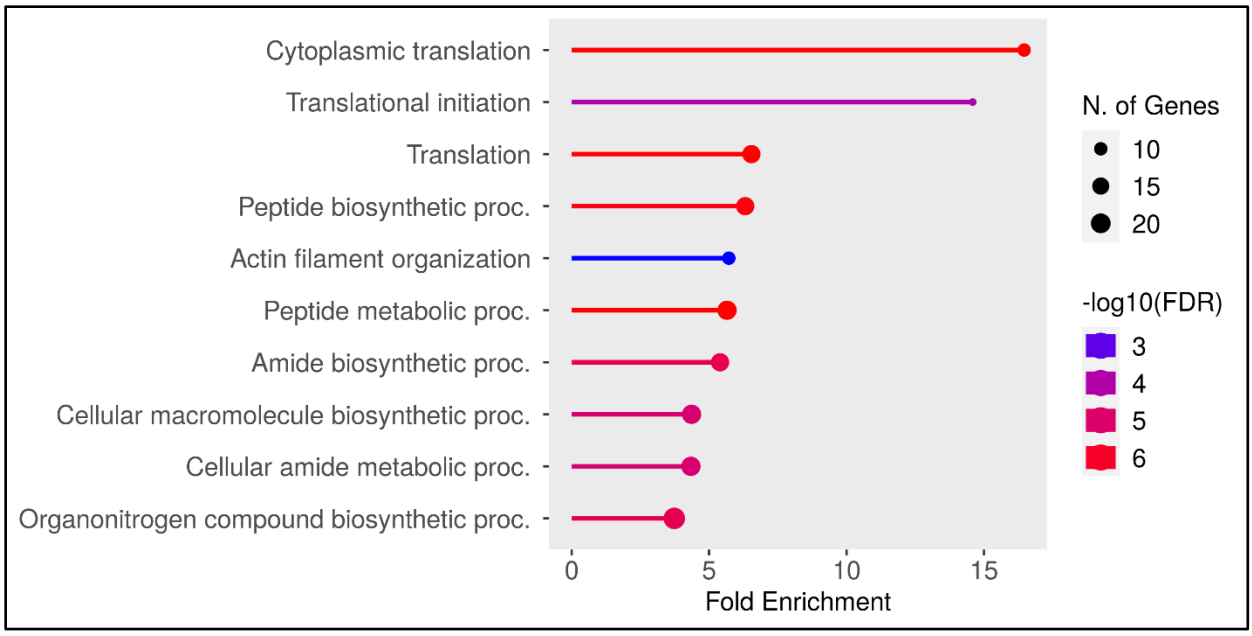

Figure 7.3.2: Upregulated Biological Processes Post-Treatments with Ponasterone A and different concentrations of Kinetin, BMS 345541 and Bay 11-7082. Different Biological Processes are indicated on the Y-axis; color indicates -log (FDR) values; and the size of the circle indicates the number of genes featured in the enriched GO term.

Peptide Biosynthetic and Metabolic Processes

The downregulation of peptide biosynthetic and metabolic processes in HD cells indicates a reduction in the synthesis and processing of peptides, which are essential for protein function and regulation [14,15]. Post-treatment, these processes showed upregulation, implying that the compounds effectively enhance peptide biosynthesis and metabolism. This restoration is vital for the correct assembly and functioning of proteins, which can alleviate some of the cellular dysfunctions observed in HD.

7.3.2 Upregulated Biological Processes in HD Condition vs. Downregulated Biological Processes Post-Treatment (Fig. 7.3.3 and 7.3.4)

Dicarboxylic Acid, Carboxylic Acid, and Oxoacid Metabolic Processes

These metabolic processes were upregulated in HD cells, likely as a response to altered cellular metabolism and energy deficits. The upregulation suggests an attempt by the cells to manage increased metabolic demands and oxidative stress [16,17]. Post-treatment downregulation indicates a normalization of these metabolic processes, suggesting that the treatments help restore

metabolic balance and reduce cellular stress. This normalization can improve energy homeostasis and reduce the metabolic strain on the cells, contributing to better cellular health.

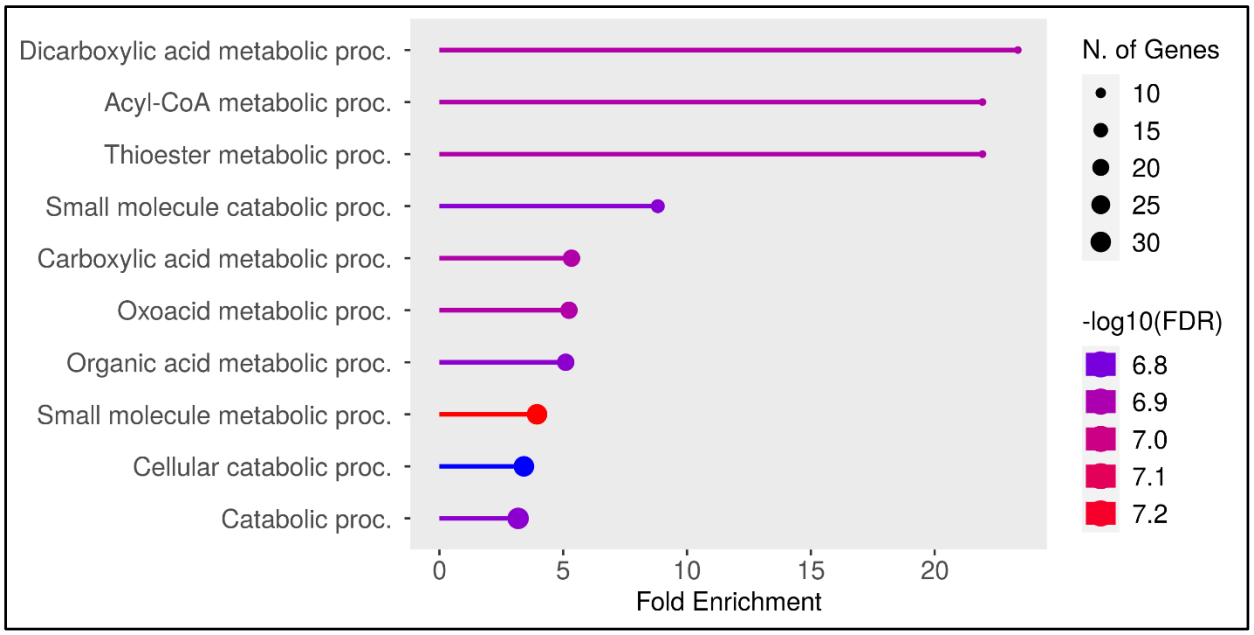

Figure 7.3.3: Upregulated Biological Processes in Ponasterone A alone (HD Condition). Different Biological Processes are indicated on the Y-axis; color indicates -log (FDR) values; and the size of the circle indicates the number of genes featured in the enriched GO term.

Small Molecule Catabolic and Metabolic Processes

The upregulation of these processes in HD reflects increased breakdown and turnover of small molecules, which might be a compensatory response to metabolic disturbances. Downregulation after treatment indicates a stabilization of small molecule metabolism, reducing the need for excessive catabolic activity. This stabilization suggests that the treatments help achieve metabolic equilibrium, which is essential for normal cellular operations and survival.

The comparative analysis of biological processes highlights significant alterations in HD condition and the potential therapeutic effects of Kinetin, BMS 345541, and Bay 11-7082. Downregulated processes in HD, such as translation and peptide biosynthesis, were upregulated post-treatment, suggesting restored protein synthesis and cellular function. Upregulated metabolic and catabolic processes in HD were normalized after treatment, indicating reduced cellular stress and improved metabolic balance. These findings underscore the potential of these compounds to correct the

underlying biological dysfunctions in Huntington's Disease, offering promising therapeutic avenues for improving cellular homeostasis and viability.

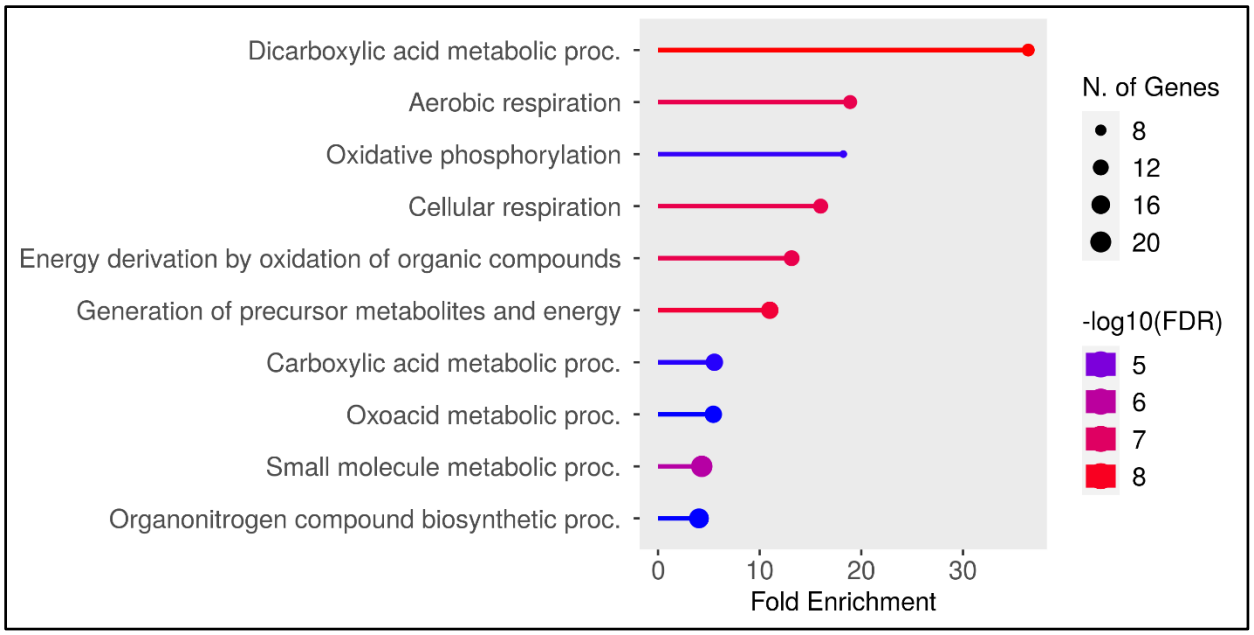

Figure 7.3.4: Downregulated Biological Processes Post-Treatments with Ponasterone A and different concentrations of Kinetin, BMS 345541 and Bay 11-7082. Different Biological Processes are indicated on the Y-axis; color indicates -log (FDR) values; and the size of the circle indicates the number of genes featured in the enriched GO term.

7.4 Comparative Analysis of Cellular Components in Pon A treated HD150Q Cells and Post-Treatment with Kinetin, BMS 345541, and Bay 11-7082

To gain deeper insights into the cellular component alterations associated with Huntington's disease and the potential restorative effects of Kinetin, BMS 345541, and Bay 11-7082, we performed a detailed analysis of cellular component changes. By examining HD150Q cells treated with Pon A alone and comparing them with post-treatment conditions, we aimed to identify shifts in cellular components that are downregulated in the disease state and subsequently upregulated with treatment, as well as those upregulated in the disease state and downregulated post-treatment. This comprehensive analysis, facilitated by ShinyGO 0.80, provides a clearer understanding of how these treatments might contribute to cellular homeostasis and mitigate the detrimental impacts of HD at the cellular level. The following section explores crucial cellular components implicated in HD.

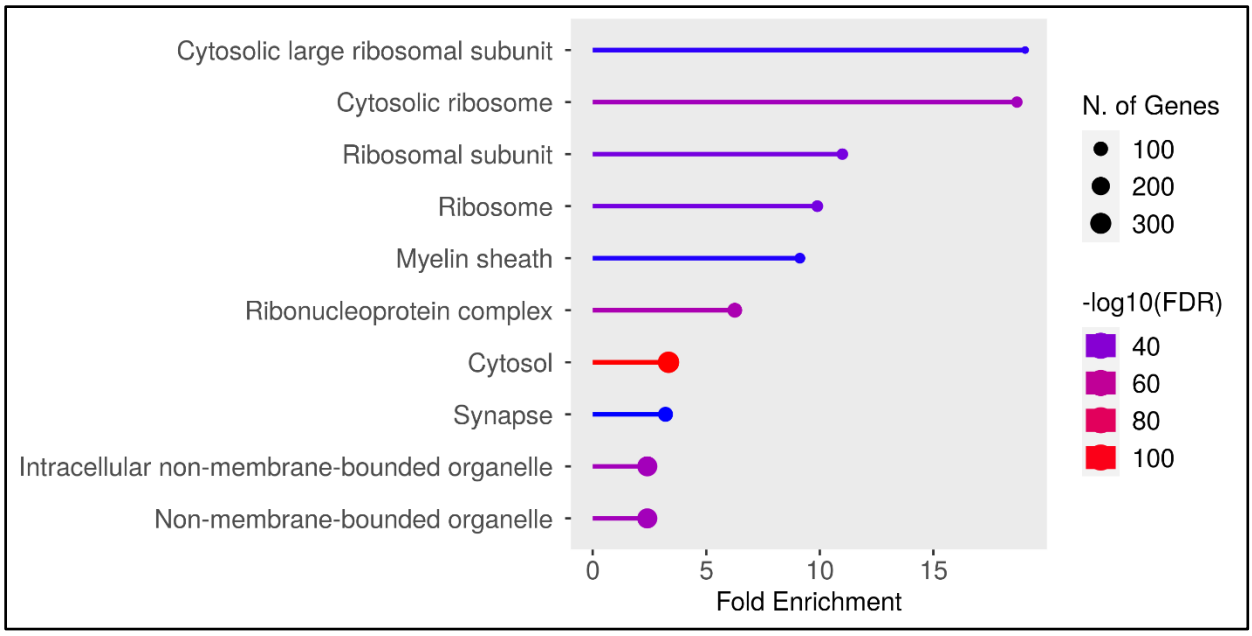

Figure 7.4.1: Downregulated Cellular Components in Ponasterone A alone (HD Condition). Different Cellular Components are indicated on the Y-axis; color indicates -log (FDR) values; and the size of the circle indicates the number of genes featured in the enriched GO term.

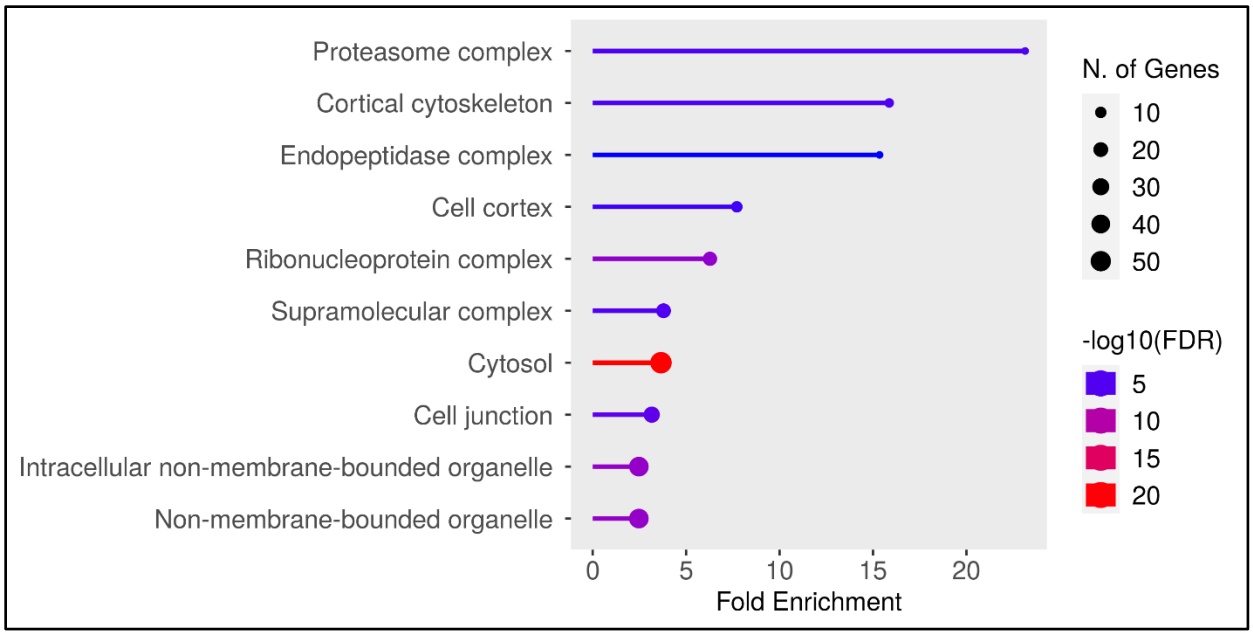

Figure 7.4.2: Upregulated Cellular Components Post-Treatments with Ponasterone A and different concentrations of Kinetin, BMS 345541 and Bay 11-7082. Different Cellular Components are indicated on the Y-axis; color indicates -log (FDR) values; and the size of the circle indicates the number of genes featured in the enriched GO term.

7.4.1 Downregulated Cellular Components in HD Condition vs. Upregulated Cellular Components Post-Treatment (Fig. 7.4.1 and 7.4.2)

Cytosolic Large Ribosomal Subunit, Cytosolic Ribosome, Ribosomal Subunit, and Ribosome

In HD condition, the significant downregulation of ribosomal components, including the cytosolic large ribosomal subunit, cytosolic ribosome, ribosomal subunit, and overall ribosome, indicates impaired protein synthesis capacity. This impairment could lead to decreased cellular functionality and viability due to the inability to produce essential proteins [6,7]. Following treatment with Kinetin, BMS 345541, and Bay 11-7082, there is an upregulation of components like the proteasome complex, which plays a critical role in degrading misfolded or damaged proteins. The enhancement of the proteasome complex suggests improved protein quality control mechanisms, compensating for the impaired ribosomal function in HD cells.

Ribonucleoprotein Complex

The downregulation of ribonucleoprotein complexes in HD reflects a disruption in RNA processing and ribonucleoprotein assembly, which are essential for various cellular functions. The treatment-induced upregulation of these complexes signifies a restoration of RNA processing and assembly mechanisms, critical for maintaining cellular homeostasis and function [18,19].

7.4.2 Upregulated Cellular Components in HD Condition vs. Downregulated Cellular Components Post-Treatment (Fig. 7.4.3 and 7.4.4)

Mitochondrial Components

HD cells show a significant upregulation of mitochondrial components, including the mitochondrial matrix, mitochondrial protein-containing complex, mitochondrial inner membrane, organelle inner membrane, mitochondrial membrane, mitochondrial envelope, and overall mitochondrion. This upregulation is likely a compensatory response to increased energy demands and oxidative stress. It is well documented that ATP levels are significantly reduced in HD. The treatment-induced downregulation of these mitochondrial components suggests a normalization of mitochondrial function and a reduction in cellular stress. This indicates that the treatments help in balancing mitochondrial activities, thereby reducing oxidative stress and improving cellular energy homeostasis [9,20-26].

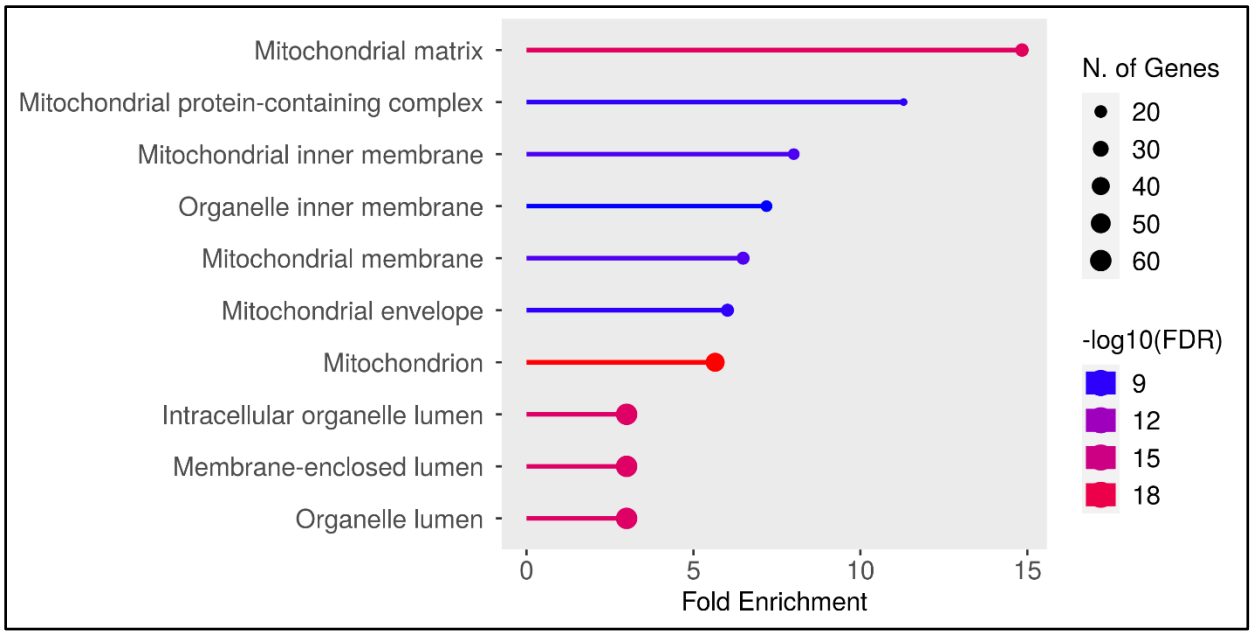

Figure 7.4.3: Upregulated Cellular Components in Ponasterone A alone (HD Condition). Different Cellular Components are indicated on the Y-axis; color indicates -log (FDR) values; and the size of the circle indicates the number of genes featured in the enriched GO term.

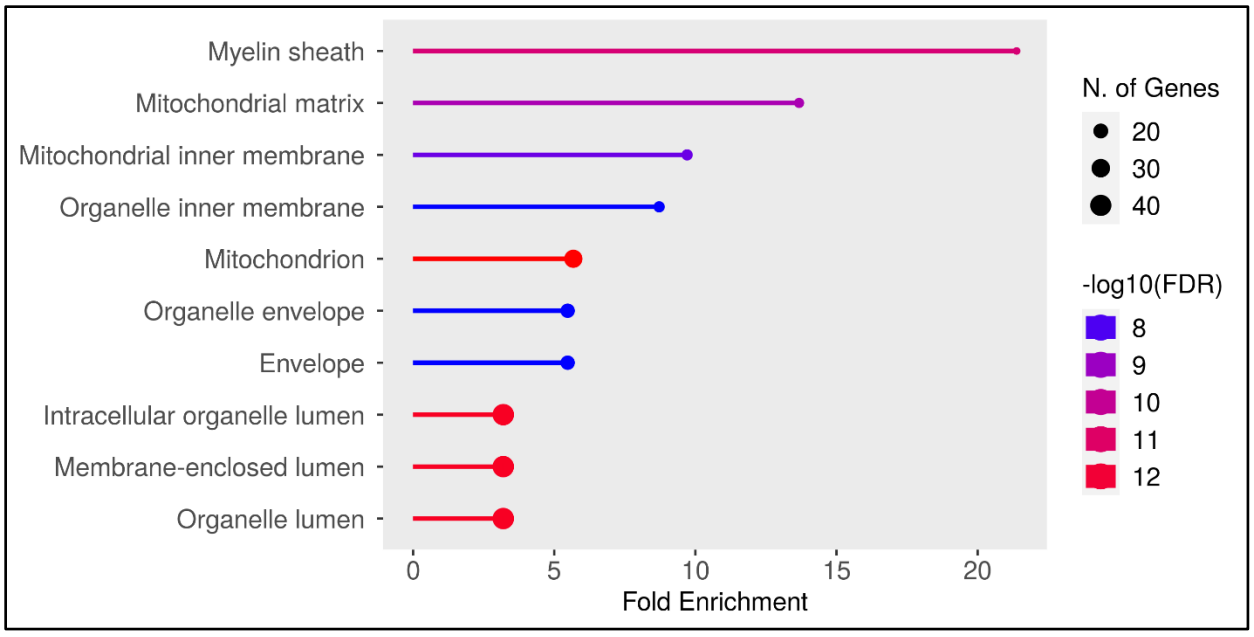

Figure 7.4.4: Downregulated Cellular Components Post-Treatments with Ponasterone A and different concentrations of Kinetin, BMS 345541 and Bay 11-7082. Different Cellular Components are indicated on the Y-axis; color indicates -log (FDR) values; and the size of the circle indicates the number of genes featured in the enriched GO term.

Intracellular Organelle Lumen and Membrane-Enclosed Lumen

The upregulation of intracellular organelle lumen and membrane-enclosed lumen in HD reflects an increase in the metabolic and catabolic activities within these compartments, possibly as a response to cellular damage and stress. The downregulation of these components post-treatment indicates a stabilization of intracellular metabolic processes, reducing the need for excessive catabolic activities. This stabilization can lead to a more balanced cellular environment, promoting better cell function and viability [27-29].

The comparative analysis of cellular components reveals significant alterations in HD condition and the potential restorative effects of Kinetin, BMS 345541, and Bay 11-7082 treatments. Downregulated components in HD, such as ribosomal and cytosolic structures, were upregulated post-treatment, indicating a restoration of protein synthesis and cellular integrity. Conversely, the upregulated mitochondrial components and intracellular lumens in HD were normalized after treatment, suggesting reduced cellular stress and improved metabolic balance. These findings underscore the potential of these compounds to correct cellular component dysfunctions in Huntington's Disease, offering promising therapeutic avenues for enhancing cellular homeostasis and viability.

7.5 Discussion

The comprehensive analysis of the proteome in response to mutant huntingtin expression using a label-free quantitative proteomics approach provides significant insights into the molecular mechanisms underlying Huntington's Disease. This investigation has revealed significant alterations in protein expression, which are pivotal for understanding disease pathology and identifying potential therapeutic targets.

The results highlight a crucial disruption in cellular proteostasis due to mHTT toxicity. Specifically, the downregulation of the proteasome pathway in HD cells, aligns with established findings on impaired protein degradation mechanisms in HD [1-3]. The upregulation of this pathway following treatment with Kinetin, BMS 345541, and Bay 11-7082 suggests that these compounds may restore proteasome function, enhancing the clearance of misfolded proteins. Indeed, we also observed significantly reduced mHTT aggregates upon treatment with Kinetin, BMS 345541, and Bay 11-7082. This mechanism is essential for alleviating cellular toxicity and preventing the accumulation of toxic mHTT aggregates [4,5]. In our study, PFDN2 emerged as a

key protein involved in the aggregation of mHTT. This protein is notably reduced in HD conditions; however, its levels are significantly restored following treatment with all three compounds. Tashiro *et al.* also reported that knockdown of PFDN2 in undifferentiated neuronal cells led to an increased formation of aggregates containing polyglutamine stretches and polyglutamine-expanded huntingtin, which are associated with the genetic defects observed in HD [30].

Similarly, the observed downregulation of the ribosome pathway in HD conditions and its subsequent upregulation post-treatment reflect a restoration of protein synthesis capabilities. This finding is consistent with previous reports indicating compromised translational capacity in HD [6,7]. Restoring ribosomal function is critical for maintaining cellular homeostasis and counteracting the defects in protein production that are characteristic of HD [8]. The significant overlap in proteins identified across different treatments further suggests that Kinetin, BMS 345541, and Bay 11-7082 may share common regulatory pathways, yet each compound also exerts unique effects, as evidenced by distinct sets of upregulated and downregulated proteins.

The comparative analysis also reveals alterations in key metabolic and cellular processes. The upregulation of one-carbon pool and carbon metabolism pathways in HD cells indicates compensatory responses to increased DNA repair and synthesis demands [31,32]. The downregulation of these pathways post-treatment suggests an effective reduction in cellular stress and restoration of normal metabolic balance. Similarly, the upregulation of mitochondrial components and intracellular organelle lumens in HD highlights increased oxidative stress and altered metabolic states. The normalization of these components post-treatment indicates an improvement in mitochondrial function and overall cellular energy homeostasis [26,33,34].

The analysis of biological processes and cellular components further corroborates the therapeutic potential of the studied compounds. The downregulation of cytoplasmic translation and peptide biosynthetic processes in HD, and their subsequent upregulation with treatment, underscores the restoration of essential protein synthesis and peptide metabolism [35-37]. Conversely, the upregulated metabolic and catabolic processes in HD and their normalization post-treatment reflect the potential for these compounds to correct metabolic imbalances and reduce cellular stress.

Overall, these findings provide valuable insights into the complex interplay of molecular pathways affected by mHTT expression and the potential therapeutic benefits of Kinetin, BMS 345541, and

Bay 11-7082. By targeting various aspects of cellular dysfunction, these compounds offer promising avenues for therapeutic intervention in HD. Further validation and *in vivo* studies will be essential to fully establish the efficacy of these treatments and their potential for clinical application.

7.6 References

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