"Some diseases take life but this just ruins it"

Stephen Rothman

1.1 Vitiligo

Vitiligo is a multifactorial polygenic skin disorder caused due to selective destruction of melanocytes associated with a complex pathogenesis, linked with both genetic and non-genetic factors. The precise *modus operandi* for vitiligo pathogenesis has remained elusive although being under investigation for several years. Castro *et al.,* (2005) have reported that vitiligo contributes around 35% among various dermatological disorders. Worldwide prevalence of vitiligo is ~0.5–1% (Ezzedine *et al.,* 2012); ~0.5-2.5 % in India (Handa and Kaur, 1999) and the states of Gujarat & Rajasthan have the highest prevalence i.e. around 8.8% (Valia and Dutta, 1996).

Usually, the incidence of vitiligo starts before the age of 20 years and affects both genders without any biasness (Taïeb and Picardo, 2009; Ezzedine *et al.,* 2012). As such vitiligo is hardly a disease of medical significance but there is more of a social stigma attached to it. It is just a cosmetic disfigurement without any health complications; still, it has a profound effect on quality of life, especially in younger patients (Silverberg and Silverberg, 2014). Most patients exhibit early age of onset (<20 years), and often face stigmatization during their personal, professional, and psychological development and, girls, in particular, are subjected to ostracization from the marital point of view (Mehta *et al.,* 1973; Parsad *et al.,* 2003; Silverberg and Silverberg, 2014; Al-Shobaili, 2014). A significant number of patients feel stressed by their condition and experience anxiety and depression leading to low self-esteem and fear of social isolation (Porter *et al.,* 1978; Nogueira *et al.,* 2009). Vitiligo can happen without predilection for gender or race and may occur anywhere on the body, but it's more likely to develop in some of these areas:

- Skin that's exposed to the sun, such as the face or hands,
- Skin that has folds, such as the elbows, knees, or groin,
- The skin around the eyes, nostrils, belly button, and genital areas.

In vitiligo patients, skin melanocytes are partially or completely lost, and several theories have been put forward to explain the etiology of vitiligo such as oxidative stress, autoimmune, neural and genetic hypotheses (Agrawal *et al.*, 2001; Shajil *et al.*, 2006; Kemp *et al.*, 2001; Ongenae *et al.*, 2003).

Vitiligo is majorly considered as an autoimmune disorder due to its frequent association with other autoimmune disorders as well as the presence of anti-melanocyte antibodies in the sera of vitiligo patients (Laddha *et al.*, 2014). Several factors inclusive of intrinsic and/or extrinsic factors are responsible for an enigmatic loss of melanocytes in vitiligo. A single dominant pathway appears unlikely to account for all cases of melanocyte loss in vitiligo and apparently, a complex interaction of genetic, environmental; biochemical and immunological events are likely to generate a permissive milieu. It is most likely that loss of melanocytes in vitiligo occurs through a combination of pathogenic mechanisms that act in concert. A generally accepted hypothesis is that the genetic factors render the melanocyte susceptible to developing apoptosis and immune presentation after oxidative stress that, in turn, predisposes individuals to develop vitiligo (Koshoffer and Boissy, 2014; Laddha *et al.*, 2013).

Histological investigations have demonstrated the presence of inflammatory infiltrate of mononuclear cells in the upper dermis and at the dermal-epidermal junction of the peri-lesional skin of vitiligo patients (Picardo *et al.*, 2010). The initiation mechanism of this micro-inflammatory reaction is still not clear, however, local triggers are reported to signal the innate immune system of skin that initiate adaptive immune responses targeting melanocytes (Kroll *et al.*, 2005; van den Boorn *et al.*, 2011). Alternatively, melanocytes exposed to oxidative stress in vitiligo patients could produce self-antigens and/or cytokines to activate an autoimmune response (Koshoffer and Boissy, 2014). Oxidative stress may play a role in vitiligo onset, while autoimmunity contributes towards the disease progression (Laddha *et al.*, 2013; Laddha *et al.*, 2014).

1.1.1 Historical aspects of Vitiligo

Vitiligo is a disease that was observed very early in the history of mankind and most ancient civilizations and religions have documented a lack of the pigmentation in the skin. Vitiligo was described as Swetakustha in Atharva Veda (1500-1000 BC) and was confused with leprosy from biblical times (Nair, 1978), hence the reason for the social and psychological stigma attached to white spots on the skin. The earliest mention of patchy skin disease that can be interpreted as vitiligo dates back to approximately 1500 B.C. (Panja, 1977).

In the Atharva Veda, particular reference was made to a disease called Kilas. The term “Kilas” comes from Sanskrit word kil, which means “white,” in the sense of “casting away.’’ In a 1905 translation of the Atharva Veda, Kilas was identified as vitiligo. In the same book, a plant with black seeds is mentioned as being used by Indians in an attempt to restore normal color to discolor skin: “O plant, thou produced even color! Render this (spot) its uniform color.” Ancient medical literature indicates that the plant generally used was Bavachee or Psoraleacorylifolia. Later it was discovered to contain psoralene, a photodynamically active furocoumariane. In the sacred Buddhist book, ‘Vinaypitah’ (624-544 B.C.) also the word ‘Kilas’ is mentioned in reference to those affected by leucoderma.

Around 4000 years of known history since man became aware of distressing white spots on the skin, its exact etiology is still under investigation (Panja, 1977). Many centuries went by and vitiligo continued to be one of the most important depigmentation ailments worldwide provoking discrimination or segregation in certain cultures, and its pathogenesis still remains an enigma.

1.2 Classification of Vitiligo

Vitiligo is most often classified clinically according to the extent and distribution of depigmentation (Figure 1). It has been proposed that the segmental and focal presentations of the disease constitute a separate subgroup to the non-segmental forms of vitiligo (Taieb and Picardo, 2010). Because, compared to focal and segmental vitiligo non-segmental forms show a later age of onset, a stronger association with autoimmunity and unstable results following autologous grafting (Table 1). Generalised vitiligo is often referred to as Non-segmental vitiligo (Faria *et al.*, 2014).

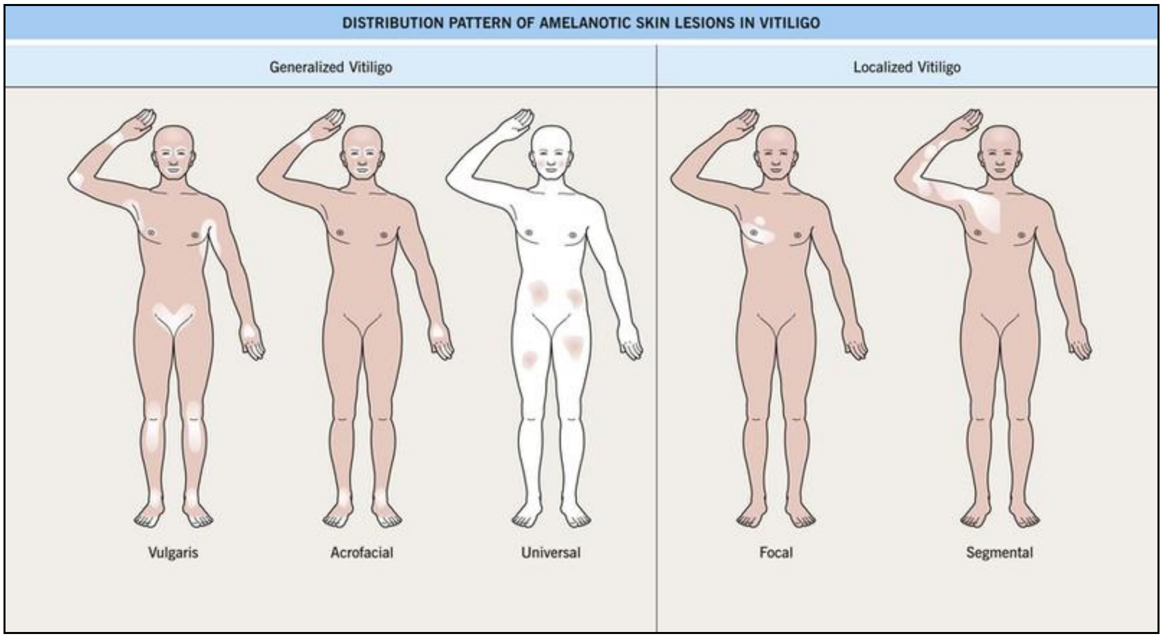


Figure 1: Clinical types of vitiligo

According to the review conducted by the Vitiligo Global Issues Consensus Conference (Ezzedine 2012; Faria *et al*., 2014) vitiligo can be classified into the following clinical forms:

I. Non-segmental vitiligo (NSV): It comprises of acrofacial, mucosal, generalized or common, universal, and mixed forms besides rare forms.

a. **Acrofacial:** It can affect the face, head, and hands and feet, and preferably involves the perioral region and the extremities of digits.

b. **Mucosal:** It affects the oral and genital mucosae. Furthermore, areas of mucosa may also be affected in patients with acrofacial, common, or universal forms; when it involves only one mucosal site, it is classified as indeterminate.

c. **Generalized or common:** It can affect any part of the tegument, mainly hands, fingers, face and trauma-exposed areas. Macules/patches are often symmetrical.

d. **Universal:** It affects the largest extent of tegument (80-90% of body surface), and it is the most common form in adulthood. The generalized form usually precedes universal.

e. **Mixed:** It is due to the concomitant involvement of segmental and non-segmental vitiligo. Most often, the segmental form precedes NSV.

f. **Rare forms:** These types were also considered unclassifiable: vitiligo punctate, minor and follicular.

II. Segmental Vitiligo: It can affect one, two or multiple segments. The unisegmental form is the most common one and consists of one or more white macules on one side of the body and there is also the involvement of body hair (leukotrichia) besides rapid onset of the condition.

Unclassifiable forms or undetermined vitiligo

a) Focal: Isolated white macule without segmental distribution. This form can evolve to segmental or NSV forms.

b) Mucosal: It is seen when only one mucosa is affected.

Table 1: Clinical distinction between the segmental and non-segmental forms of vitiligo and their various characteristics and prevalence (Taieb and Picardo, 2009)

	Non-segmental	Segmental
Prevalence	72-95%	5-28%
Distribution	Symmetrical	Unilateral
Onset	Any age	Early
Course	Variable rate of growth with new lesions throughout life	Rapid initial growth with non-progression within 2 years
Etiology (most plausible)	Autoimmune	Neurochemical

1.3 Skin

Skin is the largest organ of the human body and is the main component of an innate immune system. The skin layers are mainly represented by the epidermis and dermis (Figure 2). The epidermis is multilayered structure and composed of different cell populations; keratinocytes are the major populating cells and comprise ~95% of epidermal cell population while melanocytes are ~3-5% of epidermal cell pool.

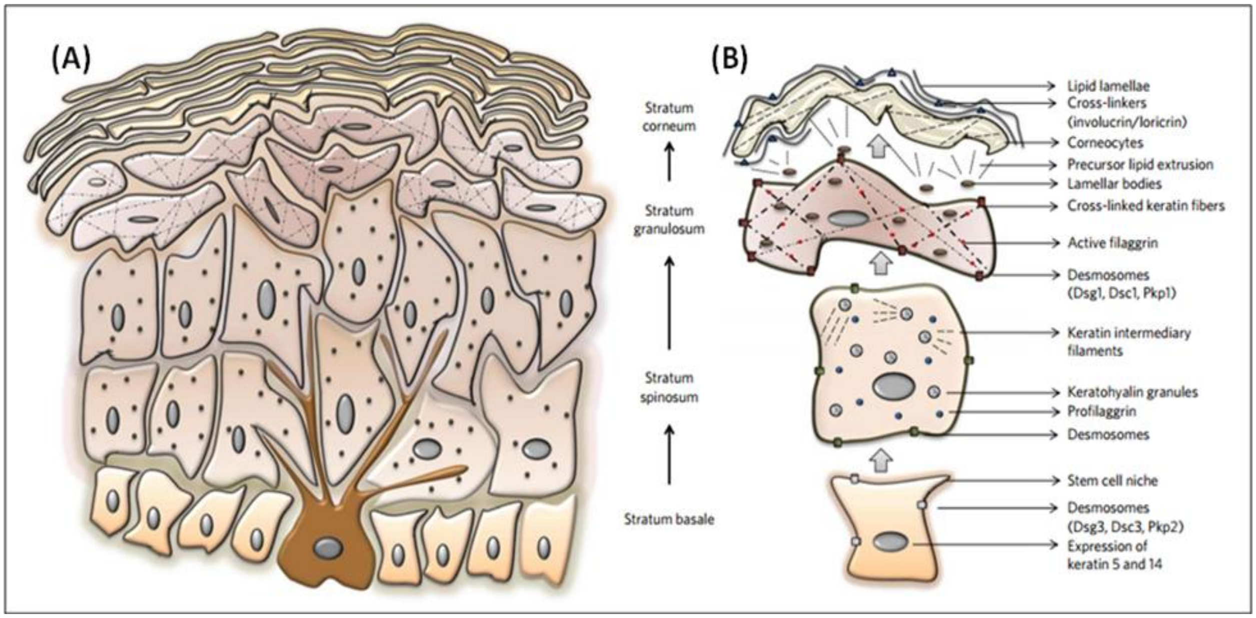


Figure 2: Structure of the skin: A) the different layers and components of human skin. B) Layers of the epidermis (Nararajan *et al*., 2014).

1.3.1 Epidermis

The epidermis is composed of the outermost layers of the skin. It forms a protective barrier over the body's surface responsible for homeostasis and prevents pathogens from entering (McGrath *et al*., 2004). It is composed of proliferating basal and differentiated suprabasal keratinocytes. It also helps the skin to regulate body temperature. Keratinocytes are the major cells, constituting 95% of the epidermis (McGrath *et al*., 2004) while Merkel cells, melanocytes, and Langerhans cells are also placed interstitially. The epidermis is devoid of blood vessels and can be further subdivided into the following strata or layers (beginning with the outermost layer)

- Stratum corneum
- Stratum lucidum
- Stratum granulosum
- Stratum spinosum
- Stratum germinativum

Basement membrane

The epidermis and dermis are separated by a thin sheet of fibres called the basement membrane, and is made through the action of both tissues. The basement membrane controls the traffic of the cells and molecules of the dermis and epidermis but also serves through the binding of a variety of cytokines and growth factors, as a reservoir for their controlled release during physiological remodeling or repair processes (Iozzo, 2005).

Dermis

It is the layer of skin beneath the epidermis that consists of connective tissue and cushions the body from stress and strain. It provides tensile strength and elasticity to the skin through an extracellular matrix composed of collagen fibrils, microfibrils, and elastic fibres, embedded in proteoglycans (Breitkreutz *et al*., 2009). It harbours many mechanoreceptors. It also contains the hair follicles, sweat glands, sebaceous glands, apocrine glands, lymphatic vessels and blood vessels.

Hypodermis

The hypodermis lies below the dermis. Its purpose is to attach the skin to underlying bone and muscle as well as supplying it with blood vessels and nerves. It consists of loose connective tissue and elastin. The main cell types are fibroblasts, macrophages, and adipocytes.

1.3.2 Skin Pigmentation- Melanocytes, Melanin synthesis pathway

Melanocytes are neural crest derived specialized cells that majorly reside in the basal layer of the epidermis and produce melanin. Melanin is a protective, skin darkening, polymeric pigment, capable of ultra violet (UV) absorption and protects cells against different kinds of genotoxic stresses (Lin and Fisher, 2007; Hill *et al*., 1997). Melanocytes are of ectodermal origin and arise during gastrulation of the embryo at the dorsal edge of the neural plate (Thomas and Erickson, 2008). Once emerged, they migrate intensively to specific sites where they differentiate into a wide range of lineages including peripheral neurons, endocrine cells, bone, cartilage, connective tissue, melanocytes and many more (Anderson, 2000; Lin and Fisher, 2007; Adijanto *et al*., 2012). Apart from skin, melanocytes are also present in a range of other sites where their role as pigment-producing cells is less understood; such as the choroid layer of the eye, the Harderian gland, the anal canal, and in the stria vascularis of the inner ear where they play a vital role in the endolymph-controlled generation of action potential and suggesting their crucial role in hearing (Steel and Barkway 1989; Tachibana, 1999).

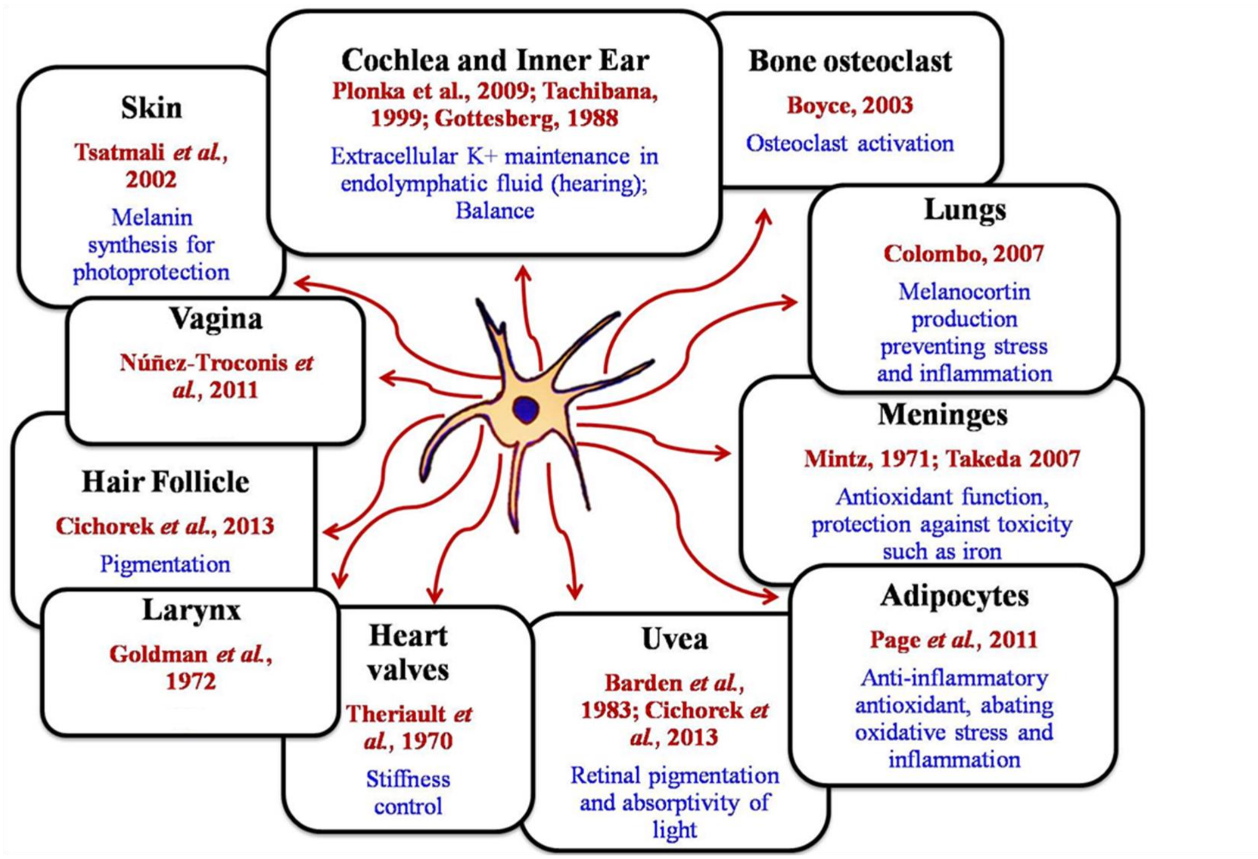


Figure 3: Different locations of melanocytes in the human body and their functions.

The exact functions of melanocytes are not well explored but their presence is important for the integrity and proper functioning of various tissues as illustrated in Figure 3. The term melanocyte was coined by Meyerson in the year 1889 whereas the true discovery of pigmentary cells 'melanocytes' began around 1940-1960 (Westerhof, 2006). The mechanisms by which multi-potent neural crest cells are assigned to evolve into different lineages remain unclear. But precursors for melanocytes, referred to as melanoblasts, originating from bi-potent glial melanoblast progenitors have been seen to occur through the action of Microphthalmia Associated Transcription Factor (MITF)-M and SRY-related HMG-box (Sox)-10 signaling (Dupin *et al.*, 2000; Mollaaghababa and Pavan, 2003). Reservoirs for melanocyte precursor stem cells 'melanoblasts' are primarily located at hair follicles and are also present in the dermal stem cells which are capable of melanocyte differentiation (Prasad *et al.*, 2012). These melanoblasts are therefore responsible for persistent pigmentation of the skin, hair, and eye.

1.4 Melanin synthesis pathway

Pheomelanin and eumelanin are the two pigments formed during melanogenesis. Pheomelanin and eumelanin differ not only in color but also in the size, shape, and packaging of their granules (Slominski *et al.*, 2004). Both melanins are derived from a common tyrosinase-dependent pathway with the same precursor, tyrosine. The obligatory step is hydroxylation of tyrosine to dopaquinone, from which L-DOPA can also be derived (Figure 4, Land *et al.*, 2000). From dopaquinone, the eumelanin and pheomelanin pathways diverge. Two enzymes crucial to eumelanogenesis are the tyrosinase-related proteins TRP1 (also known as GP75 or b-locus) and TRP2 (also known as dopachrome tautomerase, DCT) (Figure 4). Pheomelanin is derived from conjugation by thiol-containing cysteine or glutathione. As a result, pheomelanin is more photo labile and can produce, among its by-products, hydrogen peroxide, superoxide and hydroxyl radicals, and all known as triggers of oxidative stress, which can cause further DNA damage. Individual melanocytes typically synthesize both eumelanin and pheomelanin, with the ratio of the two being determined by a balance of variables, including pigment enzyme expression and the availability of tyrosine and sulphydryl containing reducing agents in the cell.

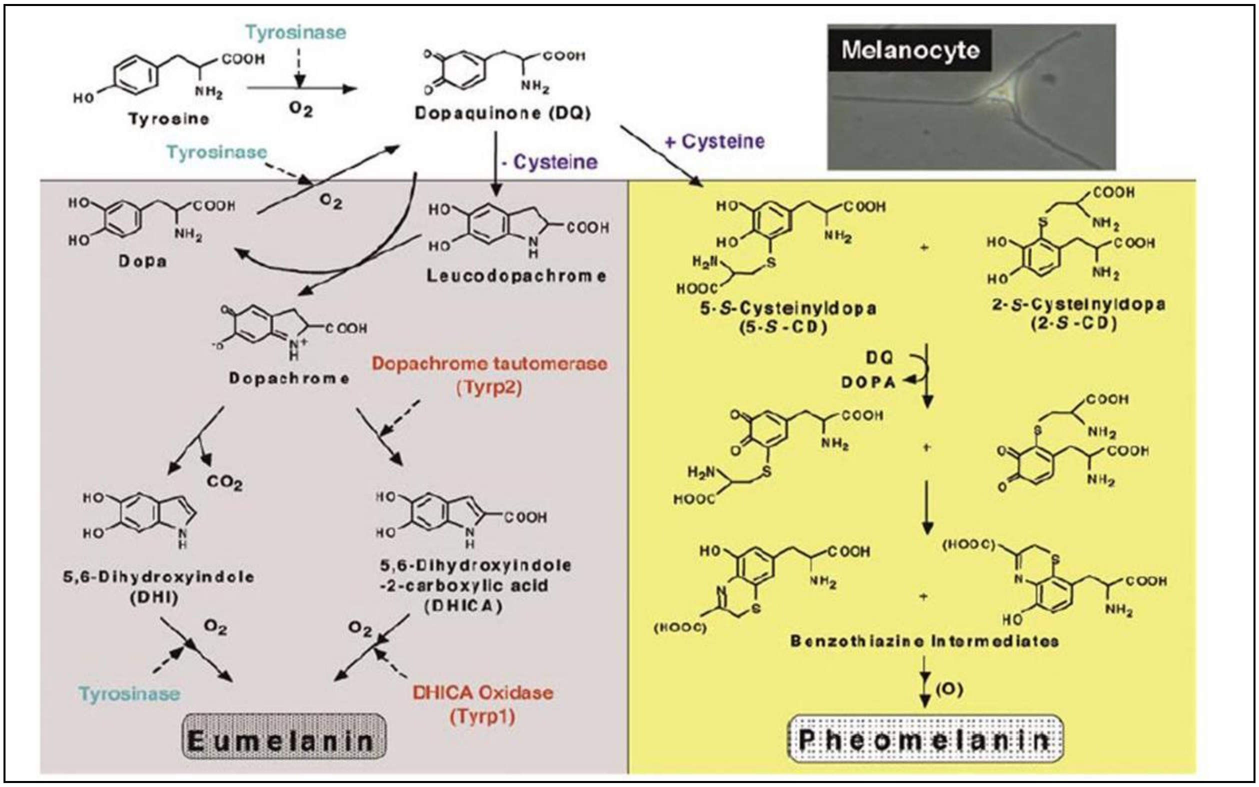


Figure 4: Production of Eumelanin and Pheomelanin in Melanocytes (Slominski *et al.*, 2004).

As shown in Figure 4, once melanin is produced, the melanosomes are transferred to the neighboring keratinocytes. The size of these organelles and their numbers are important in determining pigmentation. The melanosomes in the black skin are larger than their counterparts in white skin and are packaged as single units rather than in groups. This has the effect of retarding their degradation in the keratinocytes and contributes to a higher level of skin pigmentation. It appears that association of melanosomes with microtubules and actin filaments via motor proteins, such as kinesin, dynein, and myosin V, is important for melanosome movement along the dendrites and for subsequent transfer to keratinocytes. Melanocyte dendricity and contact with keratinocytes is likely to be essential for the transfer of melanin containing melanosomes. A recent study showed that Activation of the protease activated receptor 2 (PAR-2), which is expressed only on keratinocytes, increases melanin transfer to keratinocytes (Seiberg *et al.*, 2000). The synthesis of melanin takes place in the melanosome. The proteins that are required for melanin biogenesis are found in the melanosome and therefore termed melanosomal proteins. In addition to this MITF-M exists which is a master transcriptional regulator of melanogenesis and melanocyte survival. It regulates various melanosomal proteins such as TYR, TYRP1, DCT, MART etc. which plays an important role in melanin synthesis pathway (Levy *et al*., 2006). They are classified into two major groups (Rad *et al*., 2004; Hoashi *et al*., 2005).

1. Tyrosinase (TYR), tyrosinase-related protein 1 and 2 (TRP- 1 and TRP- 2), are the enzymes that catalyze the biochemical steps of melanin biosynthesis.

2. MART-1, Pmel17, Rab7, Rab27 etc. are the proteins that have a role in retaining melanosomal structures and/or transporting melanogenic proteins or melanin pigments. Once the melanocyte is stimulated, there is an upregulation, synthesis, and activation of these enzymes as the melanosome is going through its maturation process to enable melanin synthesis (Berson *et al*., 2001).

1.4.1 Functions of the Melanosomal Proteins

Tyrosinase

Tyrosinase is a glycoprotein located in the melanosomal membrane. It has an inner melanosomal domain that contains the catalytic region (~ 90% of the protein), followed by a short transmembrane domain and a cytoplasmic domain composed of approximately 30 amino acids (Sánchez-Ferrer *et al*., 1995). Histidine residues present in the inner (catalytic) portion of tyrosinase bind copper ions that are required for tyrosinase activity. The tyrosinase cytoplasmic domain, specifically the motif EXXQPLL (glutamic acid-X-X-glutamine-proline-leucine-leucine, where ‘X’ stands for any amino acid), directs tyrosinase trafficking into the melanosomes (Marmol and Beermann, 1996). In addition, PKC-β phosphorylates two serine residues on this domain, a modification required for tyrosinase activation (Hearing and Jimenez, 1987). Tyrosinase can also be indirectly activated by tyrosine hydroxylase isoenzyme I (THI) that was shown to be present in melanosomes and to catalyze L-dopa synthesis, thus activating tyrosinase (Hearing, 1993). In addition, the enzyme phenylalanine hydroxylase can contribute to tyrosinase activation because it catalyzes the conversion of L-phenylalanine to L-tyrosine, providing a substrate for tyrosinase (Schallreuter, 1994).

Tyrosinase mutations including missense, nonsense, frame shift and deletion mutations that lead to inactivation of the enzyme are the cause of oculocutaneous albinism, a group of hereditary disorders characterized by melanin deficiency or absence. Tyrosinase mutations may affect glycosylation of the protein, interfering with enzyme maturation; the copper (Cu) binding sites disrupting enzymatic activity; or the cytoplasmic domain, preventing enzyme activation (Gillbro and Olsson, 2011).

Tyrosinase-Related Protein 1 (TRP-1*)*

Tyrosinase-related protein 1 is expressed specifically in melanocytes and functions in melanin synthesis within melanosomes (Kobayashi *et al*., 1998). In the lumen of the endoplasmic reticulum (ER), TRP-1 helps to fold tyrosinase properly via chaperon-type interactions and functions to stabilize tyrosinase Kobayashi *et al*., 1994 by forming an enzymatic complex (these enzymes contain a cysteine-rich epidermal growth factor motif thought to be involved in protein–protein interactions). A mutation in TRP-1 can prevent tyrosinase export from the ER and/or affect the catalytic functions of TYR and its stability (Kobayashi *et al*., 1998,).

Tyrosinase-Related Protein 2 (TRP-2)

Tyrosinase-related protein 2 is an important regulatory enzyme that plays a pivotal role in the biosynthesis of melanin and in the rapid metabolism of its toxic intermediates. The enzymatic activity of TRP-2 determines whether the eumelanin or pheomelanin pathway is preferred for pigment biosynthesis (Sturm *et al*., 1995). Active and accelerated levels of TRP-2 increase the efficiency of eumelanin production through the isomerization of dopachrome to DHICA rather than the spontaneous conversion of dopachrome to DHI, which is a toxic intermediate thought to be the most effective in suppressing the growth of the cell. Pheomelanin pigments are visually dominant when TRP-2 levels are lower because of diminished flow of dopaquinone through dopachrome to eumelanin (Gillbro and Olsson, 2011).

Pmel17/gp100

The major scaffold protein Pmel17 is delivered to the premature melanosome, going on to proteolytic cleavage into several fragments; this then forms the fibrillar matrix of the organelle that enables the synthesis and deposition of melanin (Du *et al*., 2003).

MART1/MelanA, Pmel17

MART1 forms a complex with Pmel17 and affects its expression, stability, trafficking, and the processing that is required for melanosome structure and maturation. MART1 is indispensable for Pmel17 function and thus plays an important role in regulating mammalian pigmentation (Busam and Jungbluth, 1999).

Rab7 and Rab27

Rab27a is a member of the small GTPase Rab27 subfamily, which controls transport and exocytosis of lysosome-related organelles (LRO) in specific cell types (Izumi *et al*., 2003). Mutations in the RAB27A gene are associated with the ashen phenotype and Griscelli syndrome type II in mice and humans respectively (Anikster *et al*., 2002; Bahadoran *et al*., 2003).

Another member of the family of Rab GTPases associated with LRO is Rab7, which is involved in microtubule-based transport of late endosomes/lysosomes (Bucci *et al*., 2000; *et al*., 2001), major histocompatibility complex class II compartments (Jordens *et al*., 2001), Jordens cytolytic granules and phagosomes (Guignot *et al*., 2004).The minus-end microtubule-based motor complex dynein– dynactin is recruited to the Rab7-containing compartments through its effector Rab7-interacting lysosomal protein (RILP) (Jordens *et al*., 2001). Consequently, minus-end transport increases and compartments accumulate around the microtubule-organizing center (MTOC). Proteomics and immunofluorescence analyses showed that Rab7 is also associated with the melanosomal membrane. Moreover, Hirosaki *et al*. (2002) demonstrated that Rab7 is involved in the transport of the melanosome-specific proteins tyrosinase and tyrosinase-related protein 1 (Tyrp1), both involved in melanin synthesis, from the trans-Golgi network to melanosome.

Microphthalmia Associated Transcription Factor-M (MITF-M)

The Microphthalmia Associated Transcription Factor (MITF) is a member of the basic helix-loop-helix-leucine zipper (bHLH-LZ) transcription factor family having nine isoforms, fundamentally governing and regulating a broad range of genes important for melanin synthesis, cell cycle regulation, migration, and survival. The MITF-M is melanocyte specific while nine other isoforms are found in varying amounts in different cell types (Levy *et al.,* 2006; Wang *et al.,* 2011; Widlund and Fisher, 2003; Goding, 2000, Tassabehji *et al.,* 1994). The MITF gene was first discovered while working with spotted mutant mice (Hertwig, 1942) and was then histologically characterized to be occurring due to selective ablation of functional melanocytes, instead of defective pigmentation within viable melanocytes (Hodgkinson *et al.,* 1993; Hallsson *et al.,* 2004).

A dysfunctional MITF, exhibit defects in pigment cells of the skin, eye, hair follicles and inner ear, abnormalities in MITF also affects several other cell types such as bone resorbing osteoclasts, retinal pigment epithelial cells, and mast cells (Steingrímsson *et al.*, 2004).

1.4.2 Melanogenesis

Melanosomes are specialized subcellular organelles in which melanin is synthesized and deposited (Orlow, 1995). There are four stages in the maturation of melanosome (Figure 5):

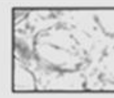
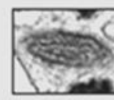
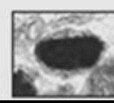
Stages	Description	Electron micrograph
I	Spherical; no melanin deposition	
II	Oval; obvious matrix in the form of parallel longitudinal filaments; minimal deposition of melanin; high tyrosinase activity	
III	Oval; moderate deposition of melanin; high tyrosinase activity	
IV	Oval; heavy deposition of melanin; electron-opeque, minimal tyrosinase activity	

Figure 5: Description and electron micrographs of the four major stages of eumelanin melanosome maturation within melanocytes and keratinocytes.

As shown in Figure 5 the following changes occur in the eumelanin melanosomes.

Stage I, the “premelanosome” a spherical organelle with ill defined matrix filaments is seen;

Stage II, the typical elliptical shape of the melanosome is filled with a well defined filamentous or laminar matrix;

Stage III, deposition of electron opaque melanin occurs in this matrix;

Stage IV, complete opacification of melanosomal contents takes place by the melanin deposited therein (Orlow, 1995). The transition to stage II melanosomes involves elongation of the vesicle and the appearance of distinct fibrillar structures. The production of internal matrix fibers and the maturation from stages I to II melanosomes depend on the presence of a structural protein termed Pmel 17 or gp100. A melanosomal protein called MART 1 forms a complex with Pmel 17 and thus plays an important role in melanogenesis by regulating the expression, stability, trafficking, and processing of Pmel 17, which in turn regulates the maturation of melanosomes (Hoashi *et al.*, 2005).

1.5 Etiopathogenesis Of Vitiligo

The etiopathogenesis of vitiligo has not been fully understood and several theories have been proposed (Passerson and Ortonne, 2005; Dell'Anna and Picardo, 2006; Westerhof and d'Ischia, 2007; Schallreuter *et al.,* 2008; Boissy and Spritz, 2009). So far there is no universally accepted hypothesis. Vitiligo corresponds to a 'syndrome' rather than a disease, with different but not mutually exclusive pathways resulting in melanocyte failure or its death. Genetic factors may determine which particular pathway is predominant in a patient. Le Poole *et al*., (1993) proposed the 'convergence' theory which was later refined by Schallreuter *et al*., (2008) that increased concentration of endogenous or exogenous phenol/catechol around the melanocytes competes with tyrosine for tyrosinase binding sites producing abnormal substrates, curtailing melanin production. These aberrant substrates generated during melanogenesis create reactive quinones and disturb redox balance, which impairs cell functions and bind covalently to the catalytic center of tyrosinase, impairing or inactivating the enzyme and further reducing melanogenesis (Passerson and Ortonne, 2005). Analogous detrimental effects occur with other reactive itermediates and enzymes due to excessive ROS. Another proposal emphasizes the immunogenicity of melanosomal proteins and melanocytes, with aberrant T-cell attack resulting in melanocyte destruction by apoptosis (Kobayashi *et al.*, 1998). Within these polar views of vitiligo pathogenesis, there is speculation that ROS and the immune system may interact synergistically so that both mechanisms might be relevant. Further hypotheses focus on cytokines, calcium imbalance, hormones, neural dysregulation, infections and melanocytorrhagy in the causation of vitiligo (Gauthier *et al*., 2003; Alikhan *et al*., 2011; Le Poole *et al*., 1993; Namazi, 2007).

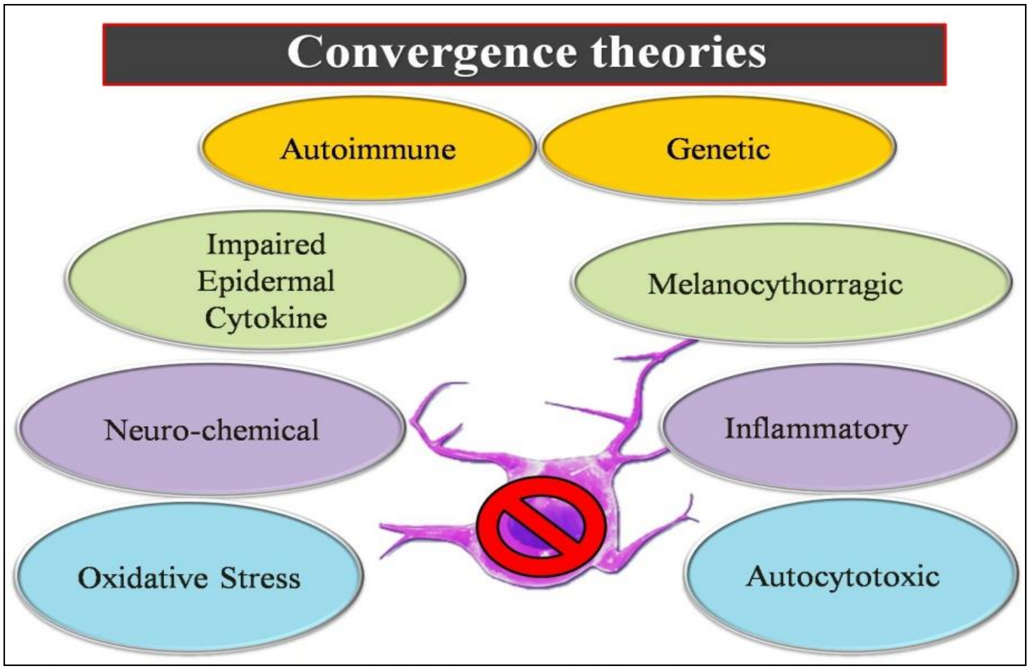


Figure 6: Different hypothesis proposed for vitiligo etiopathogenesis (Gauthier *et al*., 2003; Alikhan *et al*., 2011; Le Poole *et al*., 1993; Namazi, 2007).

1.5.1 Auto-cytotoxic Theory

Melanocytes due to their high metabolic load of melanin synthesis are under oxidative stress (Denat *et al.,* 2014). Toxic metabolites such as vitiligo inducing phenols or quinones or from intrinsic melanin synthesis pathways may accumulate and lead to the damage of melanocytes in genetically susceptible individuals (Hann and Chun, 2000). As tyrosine, itself a phenol, enters into the melanin synthesis pathways, electrically unstable by-products are generated with the potential to damage other cellular substrates (Schallreuter *et al.*, 1994). A defect in the melatonin receptor is also capable of resulting in toxic by-products leading to cellular damage (Hann and Chun, 2000).

1.5.2 Oxidative Stress Theory

Lesional and non-lesional skin from vitiligo patient's exhibit abnormally low levels of catalase, (Schallreuter *et al.,* 1991) correlating with high H_2O_2 levels throughout the epidermis (Schallreuter *et al.,* 1999). H_2O_2 accumulation also leads to inactivation of catalase, reducing its functionality. The resulting deranged melanin synthesis pathways involve reduced glutathione peroxidase activity (Schallreuter *et al.,* 1996), reduction in the functioning of glucose-6-phosphate dehydrogenase along with a concomitant decrease in tyrosinase activity. Increased levels of accumulating epidermal H_2O_2 also lead to a concomitant increase in the superoxide dismutase levels (SOD), especially of SOD2 and SOD3 along with higher lipid peroxidation levels (Schallreuter *et al.,* 2004; Agrawal *et al.,* 2004; Shajil and Begum, 2006; Glassman, 2011). However, a recent report by Zailaie (2017) has shown a non-significant difference in the H_2O_2 levels between vitiligo patients and controls. Moreover, oxidative stress and antioxidant imbalance are well documented in vitiligo patients as shown in Tables 2 and 3.

Table 2: Reports on H_2O_2 in vitiligo (Glassman, 2011)

Source	**Level**	**Reference(s)**
Catalase	Decreased	Mansuri *et al*., 2017; Schallreuter *et al.,* 1991; Maresca *et al.,* 1997; Dell'Anna *et al.,* 2001; Agrawal *et al*., 2004; Shajil and Begum, 2006; Dammak, *et al.,* 2009; Shajil *et al*., 2007
GPX/ GSH	Decreased	Mansuri *et al*., 2016; Beazley *et al.,* 1999; Dell'Anna *et al.,* 2001; Agrawal *et al.,* 2004; Shajil and Begum, 2006; Shajil *et al*., 2007
H_2O_2	Increased	Schallreuter *et al.,* 1999
Peroxynitrite	Increased	Salem *et al.,* 2009
TNF-α	Increased	Moretti *et al.,* 2002; Laddha *et al*., 2012
Oxidized pterins	Increased	Rokos *et al.,* 2002
$6BH_4$ recycling	Decreased	Schallreuter *et al.,* 1994b; Schallreuter *et al*., 2001; Rokos *et al.,* 2002
iNOS	Increased	Salem *et al.,* 2009

Source	Level	Reference(s)
Hcy	Increased	Shaker *et al.*, 2008
Monoamine oxidase A	Increased	Schallreuter *et al.*, 1996
SOD	Increased	Koca *et al.*, 2004; Picardo *et al.*, 1994; Agrawal *et al.*, 2004; Yildirim *et al.*, 2004; Hazneci *et al.*, 2005; Shajil and Begum, 2006; Khan *et al.*, 2009; Dammak, *et al.* ,2009; Laddha *et al.*, 2013
Thioredoxin reductase	Decreased	Gibbons *et al.*, 2006
Xanthine oxidase	Increased	Shalbaf *et al.*, 2008
Catecholamines	Increased	Westerhof *et al.*, 2007
GTP-cyclohydrolase I	Increased	Schallreuter *et al.*, 1994; Chavan *et al.*, 2009
Vitamin E	Decreased	Agrawal *et al.*, 2004; Jain *et al.*, 2008; Khan *et al.*, 2009
Monoamine oxidase A	Increased	Schallreuter *et al.*, 1996
NADPH oxidase	Increased	Schallreuter *et al.*, 1999
Photooxidation of pterins	Increased	Rokos *et al.*, 2002
TYRP1	Decreased	Jimbow *et al.*, 2001

Table 3: **Oxidative stress and Antioxidant status in vitiligo patients** (Agrawal *et al.*, 2004)

LPO	Increase
SOD	**Increase**
CAT	Decrease
GPx	Decrease
G6PDH	Decrease
GST	NS
GR	NS
GSH	Decrease

1.5.3 Melanocytorrhagy Theory

This theory proposes that imbalance in cytokines levels leads to increased ICAM-1 levels (intercellular adhesion molecule-1), which act on melanocytes causing their circularisation resulting in the weak anchorage of these cells in their niche. Any minor friction and/or other stress can, therefore, induce upward migration and loss through the induction of immune cells promoting the selective destruction of melanocytes (Gauthier *et al.*, 2003).

1.5.4 Autoimmune Hypothesis Of Vitiligo

Melanocytes also contribute to the skin immune system, secreting a wide range of signal molecules and responding to cytokines and growth factors. Melanocytes can phagocytize and eliminate exogenous antigens, which have penetrated the skin barrier (Le Poole *et al.*, 1993), and they can process and present antigens in the form of peptides with HLA (human leucocyte antigen) class II molecules to T-cells, triggering an adaptive immune response. Melanosomal proteins are involved in this antigen processing (Le Poole and Luiten, 2008). Activation of T-cells by melanocytes has shown by the secretion of co-stimulatory molecules like ICAM (intercellular adhesion molecule)-1 and LFA (leucocyte fusion-associated molecule)-3 (Le Poole *et al.*, 1993). Case reports on inflammatory vitiligo furnished the involvement of T cells in the pathogenesis of vitiligo

(Buckley, 1953; Michaelsson, 1968). Immune-mediated responses are consistently observed in progressive vitiligo at the periphery of depigmenting patches. Histopathological investigations of the peri-lesional skin suggest lymphocyte involvement in the depigmentation process. Immunohistochemical studies have also confirmed the presence of infiltrating T cells and their frequent opposition to peri-lesional melanocytes in skin biopsies from vitiligo patients (Le Poole *et al*, 1996; Yagi *et al*, 1997). Notably, similar *in situ* T cell infiltrates, primarily $CD8^+$ T cells, have also been detected in generalized vitiligo (Gross *et al*, 1987; Badri*et al*, 1993; Abdel-Naser*et al*, 1994; van den Wijngaard *et al*, 2000; Sanchez-Sosa *et al.*, 2013; Bertolotti *et al.*, 2014). T cells are more prevalent in vitiligo peri-lesional skin than in surrounding non-lesional skin. The lymphocyte infiltrates consists essentially of $CD8^+$ T cells with occasional $CD4^+$ T cells (Le Poole *et al.*, 1996). The prevalence of cytotoxic T cells and their co–localization with surviving melanocytes suggest T cell mediated cytotoxicity towards the melanocytes (Wankowicz-Kalinska *et al.*, 2003). Various other studies including ours show decrease in systemic $CD4^+$ T-cells and an increase in $CD8^+$ T-cells with consequent decrease in $CD4^+/CD8^+$ ratio in vitiligo patients, suggesting role of $CD8^+$ cells in melanocyte death (Grimes *et al.*, 1986; Halder *et al.*, 1986; Nigam *et al.*, 2011; Dwivedi *et al.*, 2013). Several studies have shown a defective functionality and decreased the frequency of regulatory T cells (Tregs) in vitiligo patients suggesting the unchecked activation of $CD8^+$cells (Dwivedi *et al.*, 2013a; Lili *et al.*, 2012). Furthermore, Bertolotti *et al*. (2014) have also reported the presence of IFNα secreting plasmacytoid dendritic cells (pDC) in the infiltrate of progressive vitiligo. IFN*α* induces the expression of *MxA*, which encodes a guanosine triphosphate (GTP)-metabolizing protein. Association of MxA with the expression of chemokine (C-X-C motif) ligand 9 (*CXCL9*) correlates well with the recruitment of chemokine (C-X-C motif) receptor 3^+($CXCR3^+$) immune cells. Further, they also showed increased expression of *MxA* in the peri-lesional skin in close opposition to surviving melanocytes within the T-cell infiltrate. In contrast, MxA was not evident in lesional skin, suggesting that IFN-*α* production is an early event in the progression of the disease. An autoimmune aspect of vitiligo pathogenesis is strongly supported by the presence of autoreactive T-cells (Ongenae *et al.*, 2003; Le Poole *et al.*, 1996). They target melanocyte-specific antigens, such as melan-A/MART1, Gp100/Pmel

17 (a melanosomal matrix glycoprotein), tyrosinase (Fishman *et al.,* 1993; Song *et al.,* 1994; Kemp *et al.,* 1997), TRP1 and TRP2 (Wankowicz-Kalinska *et al.,* 2003; Palermo *et al.,* 2001) that are localized primarily on melanosomes (Kemp *et al.,* 1998a; Kemp *et al.,* 1998b; Hearing *et al.,* 1999).

Auto-antibodies against melanocyte antigens have also been detected in the sera of vitiligo patients (Alkhateeb *et al.,* 2003, Pradhan *et al.,* 2013; Laddha *et al.,* 2014). The transcription factors SOX9 and SOX10 have also been identified as melanocyte auto antigens (Hedstrand *et al.,* 2001). Even auto antibodies against HLA Class I molecules have been detected in vitiligo (Ongenae *et al.,* 2003). A positive correlation has also been seen between the level of melanocyte antibodies and disease progression in vitiligo (Harning *et al.,* 1991; Naughton *et al.,* 1986). Overall, these studies point to a new innate immune pathway for vitiligo progression.

Genes within MHC class II region are associated with several autoimmune diseases (Pamer and Cresswell, 1998). This highly polymorphic region includes several genes involved in the processing and presentation of antigens to the immune system including low molecular weight polypeptide 2 and 7 (LMP2 and LMP7) and transporter associated with antigen processing 1and 2 (TAP1 and TAP2). Though *LMP/TAP* gene cluster is located on MHC class II region of chromosome 6, it is involved in antigen presenting function of MHC class I molecule. Different researchers have reported an association of *LMP7* and *TAP1* with susceptibility to vitiligo (Casp *et al.,* 2003). LMP2 and LMP7 are also involved in the degradation of ubiquitin tagged cytoplasmic proteins to peptides while, TAP1 and TAP2 are involved in transportation of peptides into the endoplasmic reticulum for exposure to nascent MHC class I molecules (Pamer and Cresswell, 1998). MHC-I molecules are critical in the regulation of cytotoxic effector functions of natural killer (NK) cells and T cells. MHC-I molecules present antigens to cytotoxic T cells and are part of the recognition signals that regulate activation of NK cells (Ulianich *et al.,* 2011). Usually, antigenic peptides are generated by proteasomal degradation of cytosolic proteins and consequently translocated to ER by TAP. In the ER, assembly of MHC class I α chain, β2-microglobulin and peptides are guided by chaperones (Pamer *et al.,* 1998). On the other hand, antigenic peptides are associated with the chaperones GRP94, GP96, PDI and calreticulin (Nieland *et al.,* 1996; Lammert *et al.,* 1997; Spee and Neefjes, 1997;

Nicchitta, 1998). Functional class I-peptide complexes are then transported to the cell surface. A necessary condition for the successful completion of this complex process is glycosylation and correct folding of MHC class 1 heavy chain in the ER. A failure in the above results in their slow or inefficient transport to the cell surface (Carreno *et al.*, 1995; Degen *et al.*, 1992; Noessner *et al.*, 1995; Rajagopalan and Brenner, 1994; Parham, 1996). ER stress may result in reduced expression of MHC class I on the cell surface, thereby preventing the recognition of cells by the adaptive and innate immune system (Gleimer *et al.*, 2003; Hickman-Miller *et al.*, 2004). It has been reported that defects in the expression of different varients of the MHC class I antigen processing machinery, such as the proteasomal subunits LMP2 and LMP7 and the peptide transporters TAP1 and TAP2, account for impaired MHC class I surface expression (Casp *et al.*, 2003). In addition, an inappropriate functioning or expression of LMP7 might inhibit antigen processing and presentation, leading to a loss of peripheral tolerance to self-antigens and occurrence of several autoimmune diseases (Casp *et al.*, 2003). In this context, Ulianich *et al*., (2011) have shown ER stress induced decrease/reduction in surface expression of MHC class I in thyroid cells. This effect was accompanied by activation of NK cells and their cytotoxicity to thyroid cells by increased IFN-γ production. Together, these data indicate ER stress induced a reduction in MHC class I expression and reduced NK-cells self-tolerance. It has been shown that IFN-γ induces LMP and TAP subunits (Casp *et al.*, 2003). Taken together these results suggest IFN-γ induces expression of MHC-I, MHC-II, and TAP on melanocytes. Recently it has been shown that IFN-γ induces senescence in melanocytes (Wang *et al.*, 2014). IFN-γ signaling impedes maturation of melanosomes by intensive down regulation of a few pigmentation genes that lead to IFN-γ–mediated hypo- pigmentation of melanocytes (Natrajan *et al.*, 2014). IFN-γ and TNF-α induce the expression of *ICAM1* on melanocytes (Yohn *et al.*, 1990). Our previous lab studies also showed increased levels of IFN-γ, TNF-α, TNF-β and *ICAM1* in vitiligo patients (Dwivedi *et al.*, 2013b; Laddha *et al.*, 2012; Laddha *et al.*, 2013). Further, levels of ICAM-1 were found to be upregulated in melanocytes of the peri-lesional skin of vitiligo patients and melanocyte- T cell binding was enhanced by elevated expression of ICAM-1 on melanocytes (Al Badri *et al.*, 1993). A melanocyte is in close association with ~32 keratinocytes in the epidermal melanin unit. Keratinocytes synthesize cytokines, such as

TNF-α, IL-1α, IL-6, and transforming growth factor-β (TGF-β), which are paracrine inhibitors of melanocyte proliferation and melanogenesis. In numerous cell types, TNF-α induces apoptosis by the activation of the receptor-mediated apoptotic pathway and also inhibits melanocyte stem cell differentiation (Alghamdi *et al.,* 2012). NACHT leucine-rich repeat protein 1 (NLRP1), known to be involved in inflammation and apoptosis (Martinon *et al.*, 2007), modulates the response of cells towards cytokines such as IL-1β, IFN- and TNF-α. Previously, the increased expression of *NLRP1* in vitiligo patients has been reported from Gujarat (Dwivedi *et al.,* 2013). Bassiouny *et al*., (2011) reported higher levels of IL17 in both the lesional skin and sera of vitiligo patients and its positive correlation with disease progression. Zhao *et al.,* (2006) found decreased levels of cytokine IL10 in vitiligo patients. All the above studies indicate the significant role of immune mechanisms in the progression of vitiligo which is further corroborated by the use of immunosuppressive treatments for vitiligo (Lepe *et al.,* 2003).

1.5.4.1 Impaired Cytokine Theory

Amidst various hypotheses proposed for vitiligo pathogenesis, an autoimmune theory is widely explored where cytokines are the key mediators for cellular communication and networking. Cytokines have crucial functions in the development, differentiation, and regulation of immune cells. As a result, dysregulation of cytokine production or their action is thought to have a central role in the development of autoimmunity (O'Shea *et al*., 2002). Melanocytes express and react to a panoply of cytokines and growth factors and hence they can be considered immuno-competent and immunomodulatory in nature. Moreover, keratinocytes themselves can produce and release pro-inflammatory cytokines such as Interleukin IL-6, IL-1α, and TNF-α which in turn promote the expression of adhesion molecules on the melanocyte membrane such as ICAM-1, promoting further lymphocyte recruitment (Dell'Anna and Picardo, 2006). Epidermal as well as systemic cytokine imbalance between Th1 and Th2 types & pro and anti inflammatory cytokines is well evident in vitiligo. Various cytokines and their possible role in melanocyte biology and vitiligo pathogenesis are described below:

1.5.4.1.1 Interferon gamma (IFN-γ)

IFN-γ is a type II interferon. It is an important activator of macrophages and inducer of MHC Class II molecules. Aberrant IFN-γ expression has been associated with a myriad of inflammatory and autoimmune diseases. Studies by Natarajan *et al.*, (2014) and Son *et al.*, (2014) have reported that IFN-γ inhibits melanogenesis *via* down regulating tyrosinase (*TYR*) and *MITF-M* expression as well as maturation of the melanosome in melanocytes (Yang *et al.*, 2015). A complex interplay of cytokines exists in the skin microenvironment and reports suggest that IFN-γ synergizes with TNF-α and TNF-β in inhibiting the proliferation of various cell types including melanocytes. IFN-γ may participate in the homing of $CD8^+$ T cells to the skin through local induction of chemokines and expression of adhesion molecules on endothelial cells (Bromley *et al.*, 2008). IFN-γ is Th1 cytokine capable of C-X-C Motif Chemokine (CXCL)-10 induction, which further promotes the migration of auto-reactive T cells into the epidermis implicating its importance in disease progression (Rashighi *et al.*, 2014). IFN-γ is able to induce apoptosis in melanocytes, and thus IFN-γ-mediated apoptosis may represent an alternative mechanism through which $CD8^+$ T cells kill their targets in vitiligo (Yang *et al.*, 2015). It has been established that IFN-γ is required for depigmentation in mouse models of vitiligo (Gregg *et al.*, 2010; Harris *et al.*, 2012; Harris, 2015) IFN-γ and IFN-γ-induced chemokines, most specifically CXCL10 and its cognate receptor C-X-C Motif Chemokine Receptor (CXCR)-3 are found to be increased in lesional skin and serum samples of patients with vitiligo, and also seen to be upregulated on autoreactive T cells in the blood and skin of vitiligo patients (Rashighi *et al*., 2014; Ezzedine *et al*., 2015; Harris, 2015)**.** Corroborated by mechanistic experiments in mouse models demonstrating the functional requirement of IFN-γ/CXCL10 axis in both, disease progression and maintenance; it is plausible that IFN-γ can be therapeutically targeted to reverse depigmentation (Ezzedine *et al*., 2015; Harris, 2015).

1.5.4.1.2 Tumor Necrosis Factor (TNF)-α and TNF-β

TNF-α is a pro-inflammatory cytokine involved in Th1 mediated response and plays an important role in immune homeostasis. *TNFA* gene resides in close proximity of Human Leucocyte Antigen (HLA) which is one of the most polymorphic sites in human genome. Melanocytes, keratinocytes, and fibroblasts which are predominant in epidermal microenvironment are capable of TNF-α synthesis which acts both in autocrine as well as paracrine manner and suppress growth and proliferation of melanocytes (Moretti *et al.*, 2002 a). Laddha *et al.,* 2012b, Namian *et al*., 2009; Salinas-Santander *et al*., 2012; Aydingoz *et al*., 2014).

Increased levels of TNF-α have been reported in the lesional skin samples of vitiligo patients (Moretti *et al.*, 2002 a; Grimes *et al.*, 2004; Birol *et al.*, 2006). Laddha *et al.*, (2012 b) have shown increased transcript levels of *TNFA* in PBMCs. However, Yu *et al.*, (1997), Singh *et al.*, (2012) and Birol *et al.*, (2006) found no significant difference in TNF-α levels in serum/plasma samples of vitiligo patients. Over all studies suggest that levels of TNF-α definitely play an important role in vitiligo pathogenesis. We have also reported the association of genetic polymorphisms and increased transcript levels of *TNFB* in vitiligo patients and found the same to be correlated with disease activity (Laddha *et al*., 2013 c). TNF-α and TNF-β have found to reduce the expression of the pigment cell-associated antigens Homatropine Methylbromide (HMB)-45 and K.1.2, and enhance the expression of Vascular cell adhesion molecule-1 (VCAM-1) binding integrin (VLA)-2, ICAM-1 and HLA class I antigens and strongly induce HLA-DR (Krasagakis *et al*., 1995). Moreover, reports have shown that TNF-α inhibits melanocyte proliferation and tyrosinase activity in primary cultured melanocytes (Lee *et al*., 2013a; Swope *et al.*, 1991). Up regulation of ICAM-1, which is inducible by TNF-α recruit melanocyte directed $CD8^+$ T cells provide an explanation for the selective destruction of melanocytes in vitiligo (Yohn *et al*., 1990).

TNF-β association with vitiligo is limited to a few studies including ours, where significant association of intron 1 (+252A/G) and exon 3 (C/A) polymorphisms of *TNFB* and vitiligo along with increased levels of *TNFB* and *ICAM1* in vitiligo patients is reported (Laddha *et al*., 2013c; Al-Harthi *et al*., 2013). The intron 1 (+252A/G) polymorphism affects a phorbol ester-response element and distinguishes the two alleles suggesting an influence of this SNP on TNFB plasma levels (Messer *et al*., 1991). *In vitro* SNP validation data have shown that *TNFB* exon 3 C/A (Thr26Asn) polymorphism is associated with an increase in the induction of several cell adhesion molecules including ICAM1 (Ozaki *et al*., 2002). Additionally, *in vitro* studies on Normal Human

Melanocyte (NHM) showed that TNF-β stimulation increased ICAM1 expression on melanocytes cell surface (Kirnbauer *et al*., 1992).

1.5.4.1.3 Interleukin (IL)-17

IL-17 is a cystine-linked homodimeric proinflammatory cytokine produced by Th17 cells, which forms a distinct subset of the $CD4^+$ T-cell lineage. IL-17 stimulates the production of IL-1β, TNF-α, and IL-6 (Kolls and Linden, 2004; Liang *et al*., 2006). Th17 cells have been identified in autoimmune skin inflammatory disorders such as psoriasis and atopic dermatitis (Asarch *et al*., 2008; Fitch *et al*., 2009). Bassiouny and Shaker demonstrated elevated IL-17 levels in lesional skin and serum of patients with vitiligo (Bassiouny and Shaker, 2011). A few studies have also reported high serum levels of IL-17 in patients with vitiligo (Khan *et al*., 2012; Zhou *et al*., 2015; Esmaeili *et al*., 2011; Habeb *et al*., 2013). Another study showed a positive correlation between serum IL-17 levels and the extent of the depigmentation patch area in vitiligo, thus suggesting that Th17 cells are involved in vitiligo (Basak *et al*., 2009). Kotobuki *et al*., (2012) have reported infiltration of Th17 cells in addition to $CD8^+$ cells in lesional skin of vitiligo patients. They have also demonstrated that IL-17 affected adversely on the function of melanocytes and dramatically induced IL-1β, IL-6 and TNF-α production in skin-resident cells such as keratinocytes and fibroblasts (Kotobuki *et al*., 2012).

1.5.4.1.4 Interleukin (IL)-1 gene cluster

The IL-1 family consists of the cytokines IL-1α, IL-1β and the IL-1 receptor antagonist (IL-1RN), mapped on chromosome 2q14 (Smith *et al*., 2000a; Patterson *et al*., 1993). The importance of IL-1 regulation is evident by the presence of natural antagonist, decoy receptor and other IL-1 family members for its fine regulation. Increased levels of IL-1α and IL-1β are reported in vitiligo (Birol *et al*., 2006; Tu *et al*., 2003; Dani *et al*., 2017). Moreover, our earlier studies have shown increased levels of *IL1B* in non-lesional skin of vitiligo patients indicating its important role in disease progression. However, there was no difference in *IL1A, IL1R1* and *IL1RN* transcript levels in skin samples of vitiligo patients compared to controls (Singh *et al*., 2015; Mansuri *et al*., 2016). Moreover, an association of promoter polymorphisms and transcript levels of *IL1B* with vitiligo was observed in our previous studies (Laddha *et al*., 2014 a). Additionally, our *in vitro* studies on primary melanocytes have shown that IL1-α decreases melanocyte viability along with its receptor activation (IL1R1). Further, *IL1RN, IL1A, IL1B, IL6, TNFA, ICAM1* showed significantly increased expression while *MITF-M* showed significantly decreased expression upon IL-1α stimulation on NHM; whereas *TYR*, Tyrosinase related protein *(TYRP)1*, *IL8* and *IL1R1* showed no difference (Singh *et al*., 2016). Similarly, Kotobuki *et al.*, (2012) have shown MITF suppression upon exogenous stimulation of IL-1β on NHM. Currently, there is a paucity of data correlating *IL1RN* polymorphism and vitiligo, where available reports Lee *et al*., (1995b) and Pehlivan *et al*., (2009) showed lack of association which may be attributed to their low sample size warranting further investigation.

1.5.4.1.5 Interleukin (IL)-2

IL-2 exerts a wide spectrum of effects on the immune system, playing a crucial role in the regulation of both immune activation and homeostasis (Gaffen *et al*., 2004). IL-2 signals through the IL-2 receptor, a complex consisting of three chains – α, β and γ. It is a pleiotropic cytokine that drives T-cell growth, augments Natural killer (NK) cells' cytolytic activity, induces the differentiation of regulatory T (T reg) cells and mediates activation-induced cell death (Liao *et al*., 2011). An increased level of soluble interleukin 2 receptors (sIL-2R) is reported in skin as well as sera of vitiligo patients and in few cases was associated with onset of disease (Kasumagic-Halilovic *et al*., 2016; Shi *et al*., 2013 a; Yeo *et al*., 1999; Caixia *et al*., 1999; Honda *et al*., 1997). Moreover, increased serum IL-2 levels have been reported by Khan *et al*., (2012) and Kasumagic-Halilovic *et al*., (2016) in vitiligo patients as compared to controls.

1.5.4.1.6 Interleukin (IL)-6

IL-6 plays an important role during the transition from innate to acquired immunity. Increased levels of IL-6 in the skin (Moretti *et al.*, 2009) and serum (Farhan *et al.*, 2014; Singh *et al.*, 2012; Yu *et al*., 1997; Tu *et al*., 2003) have been reported in vitiligo patients. IL-6 secreted by neighboring keratinocytes in epidermal melanin unit is reported to be a paracrine inhibitor of growth and proliferation of melanocytes (Swope *et al.*, 1991).

Moreover, IL-6 also induces and enhances ICAM-1 expression on melanocytes, which promotes melanocyte-leukocyte attachment (Yohn *et al.,* 1990). Additionally, Toosi *et al*., (2012) have reported that exposure of vitiligo inducing phenols (4-tertiary butyl phenol and monobenzyl ether of hydroquinone) to NHM increased expression of X-box binding protein (XBP) 1, XBP1 activation increases IL-6 and IL-8 production. There is a paucity of data on the study of *IL6* genetic variants and vitiligo susceptibility. A single report by Aydingoz *et al*., (2014) have observed the lack of association of *IL6* polymorphism (-174G/C) and vitiligo. Various pro-inflammatory cytokines which are reported to be increased in vitiligo have been found to induce *IL6* expression upon exogenous treatment for e.g. TNF-α induced IL-6 synthesis in glioma cells and human cardiac fibroblasts (Turner *et al*., 2007); IL6 and IL6 receptor modulation by IFN-γ and TNF-α in human monocytic cell line (Sanceau *et al*., 1991).

Kamaraju *et al*., (2002) have demonstrated the inhibition of melanogenesis in melanoma cells by IL-6 through the suppression of MITF-M and tyrosinase expression. MITF is a master transcriptional regulator of melanogenesis and melanocyte survival (Vachtenheim and Borovansky, 2010). Over expression of IL-6 by monocytes and macrophages has systemically profound effects, seen to induce MITF-M suppression (Choi *et al*., 2005).

1.5.4.1.7 Interleukin (IL)-10

IL-10 acts as an anti-inflammatory cytokine wherein Zhao *et al*., (2010) and Ala *et al*., (2015) showed significant decrease in the expression of IL-10 in vitiligo. In addition, Taher *et al*., (2009) have found increased levels of IL-10 after application of topical tacrolimus treatment to patients with vitiligo. On the contrary Grimes *et al*., (2004) and Aydingoz *et al*., (2015) have reported increased levels of *IL10* in skin and serum samples of patients with vitiligo respectively; and after topical application of tacrolimus, Grimes *et al*., (2004) did not find any significant difference in the *IL10* gene expression levels. Genetic variants study of *IL10* -1082, -592 and -819 promoter polymorphisms revealed association of *IL10* single nucleotide polymorphism (SNP) with vitiligo susceptibility (Aydingoz *et al*., 2015, Abanmi *et al*., 2008).

1.5.4.1.8 Interleukin (IL)-4

IL-4 is a hallmark cytokine for Th1 and Th2 polarization inducing differentiation of naive helper T cells (Th0 cells) to Th2 cells. Stimulation of IL-4 leads to further IL-4 production by Th2 cells exhibiting positive feedback loop (Sakol *et al*., 2008). IL-4 levels were decreased in peri-lesional skin, when compared to non-lesional and lesional skin (Wang *et al*., 2011) and significantly lower *IL4* transcript levels were reported by Nouri-Koupaee *et al*., (2015) in vitiligo patients. Suppressing the expression of early cytokines e.g. IL-4, IFN-γ, IL-2 and IL-10, has been found to be effective in vitiligo treatment (Grassberger *et al*., 1999; Nihei *et al*., 1998). On the contrary, Imran *et al*., (2012) have reported increased transcript as well as protein levels of IL-4 in vitiligo patients along with possible genotype phenotype correlation of intron 3 variable number of tandem repeats (VNTR) and -590 C ⁄T (rs2243250) promoter polymorphism. However, Pehlivan *et al*., (2009) did not report any significant association of *IL4* -590 promoter polymorphism with vitiligo.

1.5.4.1.9 Interleukin (IL)-8

Interleukin-8 [C-X-C Motif Ligand (CXCL8)] is a chemo attractant cytokine recruiting neutrophils in inflammatory regions further which might play an important role in the onset of vitiligo. IL-8 is produced by monocytes, mast cells, fibroblasts, endothelial cells, dendritic cells as well as keratinocytes (Luger *et al*., 1990). TNF-α has been shown to induce *IL8* mRNA expression in melanoma cells (Mohler *et al*., 1996) and up regulates IL-8 receptor expression in NHM (Norgauer *et al*., 2002). IL-1β and TNF-α stimulation on NHM showed increased expression of IL-8 both at transcript as well as protein levels. Dani *et al*., (2017) and Miniati *et al*., (2014) have shown increased *IL8* transcript levels in lesional skin of vitiligo patients. Furthermore, anti melanocyte antibodies induce HLA-DR and ICAM-1 expression on melanocytes along with release of IL-8 (Li *et al*., 2000). Moreover, Toosi *et al*., (2012) have shown that vitiligo inducing phenols lead to increased expression of IL-8 in NHM. An immunomodulator 'Imiquimod' promotes secretion of IL-6, IL-8 and IL-10, which are pro-inflammatory and pro-apoptotic cytokines that may cause vitiligo (Dahl *et al*., 2002). Significant increase in spontaneous production of IL-6 and IL-8 in mononuclear cells (MNC) isolated from vitiligo patients was observed (Yu *et al*., 1997). These changes may enhance the antigen-presenting activity of the cells and potentiate the antigen-specific immune effector cell attack resulting in melanocytotoxicity.

1.5.4.1.10 Interleukin (IL)-21

IL-21 is produced by Th17 cells and other activated $CD4^+$ T cells with pleiotropic functions (Caruso *et al*., 2009). Shi and Erf (2012) have shown increased production of IL-21 in addition to IL-10, IFN-γ with progressive melanocyte loss in the Smyth line (SL) of chicken vitiligo model. Moreover, increased levels of IL-21, IL-17A and Th-17 cells are reported in the sera of non-segmental vitiligo patients (Zhou *et al.*, 2015). Dysregulated cytokine milieu in the skin microenvironment provides a suppressive environment for Treg cell differentiation, migration and function (Ben Ahmed *et al*., 2012; Elela *et al*., 2013). Serum levels of IL-22 were found to be non-significant in vitiligo patients when compared to controls (Zhou *et al.*, 2015).

1.5.4.1.11 Interleukin (IL)-23

IL-23 is a cytokine secreted by activated dendritic and phagocytic cells, dermal Langerhans cells in addition to keratinocytes and play an important role in autoimmune disorders (Piskin *et al*., 2006). IL-23 induces the differentiation of Th17 cells in a pro-inflammatory context, especially in the presence of transforming growth factor (TGF)-β and IL-6 (Maddur *et al*., 2012). IL-23R is expressed by inflammatory macrophages, which are activated to produce IL-1, TNF-α, and IL-23 itself (Duvallet *et al*., 2011). However, there are inconsistent reports associating IL-23 and vitiligo. Vaccaro *et al*., (2015) and Wang *et al*., (2010) have shown increased serum levels of IL-23 whereas Osman *et al*., (2015) and Zhou *et al.*, (2015) have shown non-significant difference of IL-23 levels. There was a significant positive correlation of IL-23 serum levels with disease duration and extent of vitiligo and disease activity (Vaccaro *et al*., 2015).

1.5.4.1.12 Interleukin (IL)-33

Vaccaro *et al*., (2016) and Li *et al*., (2015) have shown increased levels of IL-33 in serum and skin respectively in vitiligo patients. IL-33 levels are found to be co-related with disease activity (Vaccaro *et al*., 2016). IL-33 is newly discovered IL-1 family member which binds to interleukin 1 receptor-like 1 protein (ST2) present on keratinocytes in addition to other epithelial cells. Apoptotic keratinocytes secrete IL-33 in response to combined TNF-α and IFN-γ stimulation. IL-33 has been reported to inhibit stem cell factor (SCF) and basic Fibroblast Growth Factor (bFGF) and augment TNF-α and IL-6 expression in keratinocytes (Li *et al*., 2015).

1.5.4.1.13 Granulocyte-macrophage colony stimulating factor (GM-CSF)

GM-CSF is a part of the family of hematopoietic cytokines associated with modulation of the immune system. Moretti *et al.*, (2002) have shown decreased expression of GM-CSF in skin of vitiligo patients which are consistent with various other studies (Yu *et al*., 1997; Abdellatif *et al*., 2015). On the contrary, Tu *et al*., (2003) have found increased serum levels of GM-CSF. GM-CSF secreted by keratinocytes plays an essential role in the maintenance of melanocyte proliferation and UVA-induced pigmentation in the epidermis (Moretti *et al.*, 2002; Imokawa *et al*., 1996). Other melanogenic cytokines, including stem cell factor and endothelin-1 (EDN-1), are also lowered in depigmented lesions (Moretti *et al*., 2002).

1.5.4.1.14 Regulatory T cell (Treg) and transforming growth factor (TGF)-β

TGF-β is an important immunoregulatory cytokine mainly produced by immune cells inclusive of T-regulatory $CD4^+$ cell subset (Treg). TGF-β plays an important role in conversion of inducible Treg cells by Forkhead Box P3 (FOXP3) induction on $CD4^+CD25^-$ cells (Fu *et al*., 2004). Various reports including ours suggest decreased levels of skin and blood Treg cells in vitiligo with concomitant decrease in FOXP3 expression which is a marker for Treg cells identification (Dwivedi *et al*., 2015). However, various reports suggest both increased (Zhou *et al*., 2015; Tembhre *et al*., 2013) as well as decreased levels of TGF-β in vitiligo patients (Basak *et al*., 2009; Khan *et al*., 2012; Tu *et al*., 2011; Osman *et al*., 2015). Moreover, Gambichler *et al*., (2007) have reported decreased levels of TGF-β upon topical therapies and phototherapy which are frequently used for vitiligo treatment. Fully restored depigmentation in h3TA2-IFN-γ deficient mice with the Treg cell depletion correlates with increased IL-17 expression in autoreactive T cells (Chatterjee *et al*., 2014).

1.5.4.1.15 PRO2268

This gene of unidentified function lies adjacent to a region containing the *IFNG-IL26-IL22* gene cluster (12q14 chromosomal region) and its gene product plays crucial role in vitiligo pathogenesis. Douroudis *et al*., (2011a and 2011b) reported increased levels of PRO2268 in vitiligo patients and psoriasis vulgaris skin respectively. Moreover, *PRO2268* (rs10784680) has shown to confer genetic susceptibility towards vitiligo (Douroudis *et al*., 2011a).

The reports of various polymorphisms in vitiligo patients and controls, along with genotype-phenotype correlation, sample size have been discussed in Table 4.

Table 4: Reports of various polymorphisms in vitiligo patients and controls

Cytokine	**Sample Type/ Sample Size: Patients (Controls) & Ethnicity**	**Genotype-Phenotype correlation**	**Salient features of polymorphism**
Interleukin 1 *(IL1)*			
**IL1B* promoter -511 C/T (rs16944) (Laddha *et al.*, 2014)	PBC/ 448 (785) Indian (Gujarat)	Increased *IL1B* in vitiligo patients, AV and females.	TT genotype showed significantly increased *IL1B*
ILRN	PBC/	-	These tandem VNTR might act

intron 2 VNTR (rs2234663) (Pehlivan *et al.*, 2009)	48 (50) Turkish		as putative binding sites for transcription factors. (Tarlow *et al.*, 1993)
ILRN (rs2234663) (Lee *et al.*, 1995)	PBC/ 31 (79) Korean	-	
Interleukin 4 *(IL4)*			
**IL4* intron 3 VNTR (rs2243250) promoter -590 (rs2243250) (Imran *et al.*, 2012)	PBC/Serum 1101 (1141) Indian (Gujarat & North India)	Increased what in Gujarat (low prevalence in North India)	The three tandem repeat alleles enhance *IL*4 transcription (Nakashima *et al.*, 2002). -590 (rs2243250) C to T transition is associated with enhanced promoter strength
IL4 promoter -590 (rs2243250) **IL4R* exon (rs1801275) (Q155R) (Al-Shobaili *et al.*, 2012)	Whole blood/ 96 (87) Arab	N/A	Q551R : The R576 allele was associated with higher levels of expression of CD23 by interleukin-4 than the wild-type allele (Hershey *et al.*, 1997)
IL4 promoter -590 C/T (rs2243250) (Pehlivan *et al.*, 2009)	PBC/ 48 (50) Turkish	Increased susceptibility to vitiligo	
Interleukin 6 (*IL6*)			
promoter -174 C/G (rs1800795) (Aydıngoz *et al.*, 2014)	PBC/ 105 (211) Turkish	N/A	Regulatory effect on its transcript as well as protein levels with respect to G allele (Fishman *et al.*, 1998)
Interleukin 10 (*IL10*)			
*promoter -1082 (rs1800896) (Aydıngoz *et al.*, 2014)	Serum/ 105 (211) Turkish	N/A	-1082 GG, -819 CC & -592 CC promoter alleles are associated with higher *IL10*

*promoter -1082 C/G (rs1800896) * -819 C/T (rs1800871) * -592C/A (rs1800872) (Abanmi *et al.*, 2008)	Whole blood/ 83 (101) Arab	N/A	production. (Asadullah *et al.*, 2003)
Transforming growth factor, beta receptor II (*TGFBR2*)			
*intron variant C/T (rs2005061) C/G (rs3773645) G/A (rs3773649) (Yun *et al.*, 2010)	Whole blood /233 (415) Korean	N/A	-
Interferon-γ (*IFNG*)			
intron 1 +874 A/T (rs2430561) * CA microsatellite (rs3138557) (Dwivedi *et al.*, 2013)	PBC/ 517 (881) Indian (Gujarat)	N/A increased IFN-γ & ICAM-1, higher in females	Allele 2, with 12 CA repeats is associated with *in vitro* constitutive high IFN-γ production (Dwivedi *et al.*, 2013). Presence of *IFNG* (+874A/T) polymorphism creates a putative NF-kB binding site showing preferential binding to the T allele corresponding to increased IFN-γ production (Pravica *et al.*, 2000).
intron 1 +874 A/T (rs2430561) (Namian *et al.*, 2009)	PBC/ 176 (545) Iranian	N/A	
NACHT, LRR and PYD domains-containing protein 1 (*NLRP*1)			
*promoter A/G (rs2670660) T/C (rs6502867) A/T (rs12150220) (Dwivedi *et al.*, 2013)	PBC/ 537 (645) Indian (Gujarat)	N/A	*NLRP1* (rs2670660) and (rs6502867) SNPs are associated with increased *NLRP1* mRNA expression.(Dwivedi *et al.*, 2013)
*promoter A/G (rs1008588) A/G (rs2670660)	PBC/ 26 (61)	N/A	

T/A (rs11078587) T/C (rs8182352) A/T (rs12150220) A/G (rs16954840) T/C (rs8074853) T/C (rs6502867) (Alkhateeb *et al.*, 2010)	Jordanian Arab		
intron variant *G/A (rs6502867) T/C (rs2670660) *A/G (rs8182352) A/G (rs8074853) T/C (rs16954840) T/A (rs11078587) C/T (rs1008588) (Jin *et al.*, 2007)	PBC/ 66 (93) Caucasian/ Romanian		
Melanocyte proliferating gene 1 (*MYG1*)			
*promoter -119 (rs1465073) (Dwivedi *et al.*, 2013)	PBC/ 846 (726) Indian (Gujarat)	N/A	-119C/G promoter poly-morphisms in the mitochondrial signal of *MYG1* have a functional impact on the regulation of the *MYG1* gene. (Philips *et al.*, 2010)
*promoter -119 (rs1465073) (Philips *et al.*, 2010)	Skin biopsies/ 124 (325) & Europeans	Expressed more in AV	
Tumor Necrosis Factor-β *(TNFB)*			
* intron 1 +252 G/A (rs909253) (Al-Harthi *et al.*, 2013)	Whole blood/ 123(200) Saudi	Marginally increased expression	rs909253 and rs1041981 are found to influence *TNFB* expression *in vitro* (Messer *et al.*, 1991; Whichelow *et al.*, 1996)
* intron 1 +252	Whole blood	Increased	

A/G(rs909253); IVS1 +90 A/G exon 3 C/A (rs1041981) (Laddha *et al.*, 2013)	524 (592) Indian (Gujarat)	*TNF*-β and *ICAM*-1	
Tumor Necrosis Factor-α *(TNFA)*			
* promoter -308 G/A (rs1800629) (Al-Harthi *et al.*, 2013)	Whole blood/ 123 (200) Saudi	N/A	The promoter polymorphisms at positions: -238, -308, -857, and -1031 may lead to a higher rate of *TNFA* gene transcription whereas -863 leads to decrease in the *TNFA*.
*promoter -308 G/A (rs1800629) (Salinas-Santander *et al.*, 2012)	Whole blood/ 198 (395) North eastern Mexican population	N/A	
*promoter -308 G/A (rs1800629) (Laddha *et al.*, 2012)	Whole blood/ 977 (990) Indian (Gujarat)	Increased *TNF*-α transcript protein	
* -238 G/A (rs361525), -857 C/T (rs1799724), *-1031 (rs1799964) (Laddha *et al.*, 2012)	Whole blood 524 (592) Indian (Gujarat)	-238: Increased susceptibility -857: Increased susceptibility -1031: Decreased susceptibility to vitiligo	

*promoter -308 G/A (rs1800629) (Namian *et al.*, 2009)	PBC/ 176 (545) Iranian	N/A	
promoter -308 G/A (rs1800629) (Yazici *et al.*, 2006)	Whole blood/ 61 (123) Turkish	N/A	
Cytotoxic T-lymphocyte-associated protein 4 (*CTLA4*)			
exon 1 +49 (rs231775) * 3'UTR CT60 (rs3087243) (Dwivedi *et al.*, 2011)	PBC/ 437(746) Indian (Gujarat)	N/A GG genotype shows higher phenotypic occurrence	Increased *sCTLA-4 / flCTLA-4* mRNA ratio with +49AG and CT60GG genotypes in vitiligo patients suggest that G allele confers lower *sCTLA-4* transcript levels. (Dwivedi *et al.*, 2011 ; Atabani *et al*. 2005)
*exon 1 +49 (rs231775) Pehlivan *et al.*, 2009	PBC/ 48 (50) Turkish	Susceptibility increased in patients with GG genotype, while reduced in AA phenotype	
3'UTR CT60 (rs3087243) exon 1 +49 (rs231775) (rs1863800) (rs11571302) (rs11571297) (rs10932037) LaBerge *et al.*, 2008	PBC/ saliva/ 712(none) Caucasian	N/A	
3'UTR (rs3087243) (rs11571302) (rs11571297)	Whole blood/ 100 (140)	N/A	

exon 1 +49 (rs231775) (Blomhoff *et al.*, 2005)	UK		
exon3, 106 bp allele (Kemp *et al.*, 1999)	Whole blood/ 74 (173) British	Susceptibility observed only for patients who have other autoimmune disease condition	
C-C Chemokine Receptor 5 (*CCR5*)			
32 bp deletion (Pehlivan *et al.*, 2009)	PBC/ 48 (50) Turkish	N/A	32 base pair deletion (CCR5-delta32) that introduces a premature stop-codon into the CCR5 locus (Bream *et al.*, 1999)
Protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*)			
*1858T C/T (rs2476601) (La Berge *et al.*, 2008)	PBC/ saliva/ 126 (none) Caucasian	N/A	The C1858T substitution causes a change R to W at codon 620 preventing the binding of P1 proline-rich motif to the SH3 domain of Csk. *In vitro* experiments have shown that the T-allele binds less efficiently to Csk than the C-allele, suggesting that T-cells expressing the T-allele may be hyper-responsive, and consequently, individuals carrying this allele may be prone to autoimmunity (Bottini
1858T C/T (rs2476601) (Laddha *et al.*, 2008)	Whole blood/ 126 (140) Indian (Gujarat)	N/A	
*missense R620W, codon620 1858T C/T (rs2476601) (Canton *et al.*, 2005)	Whole blood/ 165(304) Caucasian	Expression observed typically in GV	

			et al., 2004; Begovich *et al.*, 2004)
Autoimmune Regulator (*AIRE*)			
*C–103T,*C4144G, *T5238C, *G6528A, *T7215C, T11787C, (Tazi-Ahnini *et al.*, 2008)	Whole blood 86 (63) Caucasian	T11787C, susceptibility increased only for those who have other autoimmune disease along with vitiligo	*AIRE* C–103T, G6528A, T7215C and T11787C haplotype CGCC gives the most stable mRNA secondary structure, suggesting that *AIRE* CGCC mRNA could have a longer half-life and produce more AIRE protein, leading to dysregulation of downstream genes. (Tazi-Ahnini *et al.*, 2008)
Glutathione Peroxidase (*GPX*)			
* exon 1 R5P G/C (rs8179169) *exon 1 L6P T/C (rs4991448) exon2 A194T C/T (rs6446261) (Mansuri *et al.*, 2016)	PBC/ 521 (614) Indian (Gujarat)	decreased GPx1 activity decreased GPx1 activity N/A	R/P genotype forR5P SNP; L6P SNP, P/P and L/P genotypes, showed significantly decreased GPX1 activity and decreased stability of L6P and A194T variants. (Mansuri *et al.*, 2016)
codon 200 P to L (rs1050450) (Casp *et al.*, 2002)	PBC/ 126 (143) Indian (Gujarat)	N/A	
Superoxide Dismutase (*SOD*)			
**SOD1* (Laddha *et al.*, 2013) C/T I40T, C/T V82V (rs11556619) A/G N87S(rs11556620), C/T N140N (rs1804449)	PBC/ 950 (1650) Indian (Gujarat)	Increased susceptibility to vitiligo observed	The SOD2 T/C (V16A) polymorphism in the mitochondrial targeting sequence may influence the efficiency of SOD2 transport followed by the alteration of

**SOD2* (Laddha *et al.*, 2013) C/T T58I (rs35289490),C/T L84F(rs11575993), C/T V16A (rs4880)		Altered oxidative metabolism along with increased susceptibility to AV	SOD2 activity in Val allele carriers. (Sutton *et al.*, 2003)
**SOD3* (Laddha *et al.*, 2013) G/A R213G(rs8192291)		increased susceptibility to vitiligo	
Melanocortin-1 Receptor (*MC1R*)			
* G274A (V92M), A488G (R163Q) (Na *et al.*, 2003)	PBC/ 114 (111) Korean	Presence of both SNPs together causes higher vitiligo susceptibility	V92M is commonly associated with poor tanning. (Valverde *et al.*, 1995)
Transporter associated with Antigen Processing 1 (*TAP1*)			
TAP1 exon10 A/G (Casp *et al.*, 2003)	Whole blood/ 230 (188) Caucasian	-	*TAP1* exon 10 A>G leads to variation in TAP1 protein from Aspartic acid to Glycine at position 637 (Quadri and Singal,1998)
Proteasome subunit beta type-8 (PSMB8)/ Low Molecular Mass Polypeptide 7 (*LMP7*)			
LMP7 intron 6 G/T (Casp *et al.*, 2003).	Whole blood/ 230 (188) Caucasian	Heterozygous , MHC class 1 Ag	-
**LM7/PSMB8* exon 2 A/C (Dani *et al.*, 2017).	1320 (752) North Indian		*PSMB8* exon 2, in codon 49, substitution of C to A leads to amino acid change from

			glutamine to Lysine
Estrogen Receptor 1 (*ESR1*)			
*intron 1 C/T (rs2234693), *exon 4 C/G (rs1801132), *exon 8 A/G (rs2228480) (Jin *et al.*, 2004)	Serum/ 120 (254) Korean	Expressivity higher in Female GV patients.	-
Uncharacterized protein PRO2268 (*PRO2268*)			
*(rs10784680) (Douroudis *et al.*, 2011)	PBC/ 100 (194) Caucasian	Increased susceptibility to vitiligo	-
Endothelin 1 (*EDN1*)			
G5665T, T-1370G C +70G, G-231A Bingül *et al.*, 2016.	PBC/ 100 (185) Turkish	Decreased susceptibility to vitiligo	GG genotype of T-1370G polymorphism is associated with the low production of *EDN1*. (Barden *et al.*, 2001)
*intron 4 G/A (rs2071942) * exon 5 G/T (rs5370) (Kim *et al.*, 2007)	Cultured keratinocytes from skin 312 (313) Korean	-	GG genotype of T-1370G polymorphism is associated with the low production of *EDN1*. (Barden *et al.*, 2001)
Toll Like Receptor (*TLR*)			
**TLR2* R753Q	Whole blood/ 100 (100) Turkish	N/A	TLR2 R753G could lead to diminished activation of intracellular signaling pathways (Xiong *et al.*, 2012)
**TLR4* D299G (Karaca *et al.*, 2012)	Whole blood/ 100 (100) Turkish	N/A	D299G is in the leucine-rich repeat (LRR) domain of Exon 3 which is associated with the recognition of pathogen-associated molecular patterns (PAMPs) (Smirnova *et al.*, 2000).

X-box binding protein 1 (*XBP1*)			
*-116 G/C (rs2269577) Ren *et al.*, 2009 *-116 G/C (rs2269577) (Birlea *et al.*, 2011)	PBC/ 319(294) Chinese 2629 (1392) Caucasian	Increased expression of *XBP1* in the lesional skin of patients carrying the risk associated C allele.	*XBP1*-116 C/G SNP changing the consensus motif ACGT into AGGT at nucleotide−116 of the *XBP1*, identified by Kakiuchi *et al.*, and it associated with significantly decreased XBP1 transcriptional activity (Kakiuchi *et al.*, 2003)

1.6 Cytokine interplay affecting melanin synthesis via Microphthalmia Associated Transcription Factor (MITF)-M

The MITF is a master transcriptional regulator of melanogenesis and melanocyte survival (Levy *et al*., 2006). It has been shown that exogenous stimulation of vitiligo inducing phenols to melanocytes causes increased expression of IL-17 and TNF-α with a concomitant increase in the expression of cytokines CXCL1 and 3, IL-6, IL-8, and C-C Motif Chemokine (CCL)-20 (Toosi *et al*., 2012). Kotobuki *et al*., (2012) have reported that a combination of cytokines i.e. TNF-α, IL-1β, IL-6 and IL-17 could inhibit melanin production. Cytokines and oxidative stress are also reported to regulate the melanin synthesis pathway and one of the target molecules for this could be MITF. It is a positive regulator of TYR, TYRP1, TYRP2 and Dopachrome Tautomerase (DCT) and is crucial for lineage commitment of melanocytes during differentiation from neuronal crest derived cells (Widlund and Fisher; 2003). MITF-M is a melanocyte specific isoform and plays an important role in melanocyte biology. However, there is paucity of studies correlating vitiligo and MITF.

Vitiligo patients show reduced expression of MITF-M in perilesional (Kitamura *et al*., 2004) and lesional as well as non lesional skin compared to controls (Kingo *et al*., 2008). Various pro inflammatory cytokines and H_2O_2 have been reported to suppress melanin synthesis. TNF-α, which is increased in vitiligo down regulates MITF expression in NHM (Wang *et al.*, 2013; Skov *et al.,* 1998). IL-17 can dramatically amplify the inhibitory effect of TNF-α on melanogenesis (Wang *et al.*, 2013). Significantly high levels of both IL-1α and IL-1β have been detected in patients with vitiligo (Kholmansik *et al*., 2010). Moreover, IL-1α is shown to significantly down-regulate MITF-M levels in NHM (Singh *et al.*, 2016). IL-1β seems to have a characteristic role in the down-regulation of MITF-M at the gene and protein levels (Arts *et al*., 2015).

Cytokines exhibit a complex network of auto and paracrine regulation of other cytokines and numerous studies have shown their inducible nature, for example IL-17A has been shown to extensively upregulate IL-6, IL-1β and TNF-α production in fibroblast and keratinocytes of the skin (Kotobuki *et al*., 2012). Kamaraju *et al*., (2002) have demonstrated the inhibition of melanogenesis in melanoma cells by IL-6 through the suppression of MITF and tyrosinase expression. Lack of a direct inhibition of melanin pigment synthesis, IFN-γ and IL-17A increased the synthesis of an anti-melanogenic cytokine IL-6 in NHM (Choi *et al*., 2005). NHM secreted IL-6 proteins in culture supernatants in response to IFN-γ or IL-17A treatment (Choi *et al.*, 2005). Melanogenesis of NHM is inhibited by IL-6 produced by keratinocytes through paracrine regulation (Imokawa, 2004; Choi *et al*., 2005). IFN-γ and IL-17A increased IL-6 production in epidermal keratinocytes (Fujisawa *et al*., 1997; Peric *et al*., 2008). Studies by Gutknecht *et al.,* (2015), have shown that IL-10 congruently inhibits the PI3K/Akt signaling and other pigmentary pathways through activation of MITF in dendritic cells, resulting in a tolerogenic phenotype. IL-4 directly inhibited melanogenesis in NHM and down-regulates both transcription and translation of melanin synthesis associated genes, such as *MITF* and *DCT* (Choi *et al.,* 2005). IL-4 treatment significantly down regulates the mRNA levels of *MITF*, *TYR*, *DCT*, melanoma antigen recognized by T cells *(MART)-1*, and Glycoprotein 100/ Premelanosome Protein *(gp100/PMEL17)* (Choi *et al.,* 2005).

Oxidative stress seems to have a crucial role in triggering onset of vitiligo (Shi *et al*., 2015; Laddha *et al*., 2014 b). Shi *et al*., (2015) suggest that the activation of miR-25 under oxidative stress could suppress the antioxidant response through inhibiting MITF-APE1 pathway, which makes melanocytes more susceptible to oxidative stress-induced destruction. Studies by Liu *et al.,* (2008) and Jiménez-Cervantes *et al.,* (2001) also suggest MITF-M down-regulation *via*. apurinic/apyrimidinic endonuclease (APE-1) under oxidative stress.

1.7 Role of cytokines in Endoplasmic Reticulum stress

ER stress-induced UPR signaling is also associated with the production of cytokines such as TNF-α, IL-6, IL-8, IL-1β, IL-23, Monocyte Chemoattractant Protein (MCP)-1, etc. (Li *et al*., 2005; Garg *et al*., 2012). All three main branches of the UPR i.e., PERK, IRE1α, and ATF6 have been shown to mediate pro-inflammatory transcriptional programs, which are mainly governed by transcription factors such as NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) and AP-1 (Activator protein 1) (Verfaillie *et al*., 2010; Hotamisligil *et al*., 2008; Zhang *et al*., 2008). NF-kB is one of the central mediators of pro-inflammatory pathways. Genes transcribed by NF-kB include those encoding crucial pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-6, IL-8, IL-1β, IL-23, IL-17 (Li *et al*., 2005; Zhang *et al*., 2008; Rius *et al*., 2008; Pahl *et al*., 1999). Toosi *et al*., (2012) have reported that vitiligo inducing phenols activate UPR in melanocytes and upregulate the expression of IL-6 and IL-8. In addition *XBP1* inhibitors have been shown to reduce IL-6 and IL-8 production induced by phenols (Toosi *et al*., 2012). We recently reported significantly increased transcript levels of CCAAT-Enhancer-Binding Protein (CHOP) and IL-23 in the skin of vitiligo patients providing an evidence of ER stress induced inflammation in vitiligo (Mansuri *et al*., 2016). Expression of IFN-γ (Watanabe *et al*., 2003), IL-1β (Akerfeldt *et al*., 2008, Gurzov *et al*., 2009), TNF-α, IL-6 (Zhang, *et al*., 2006), IL-17 by immune cells can generate further ER stress. Xin *et al*., (2005) have observed that TNF-α induces the UPR in a ROS-dependent fashion and leads to cell death. It has been reported that IL-17 mediates the production of other cytokines, including IL-1 and IL-6 and can potentiate other local inflammatory mediators like TNF-α (Kolls *et al*., 2004).

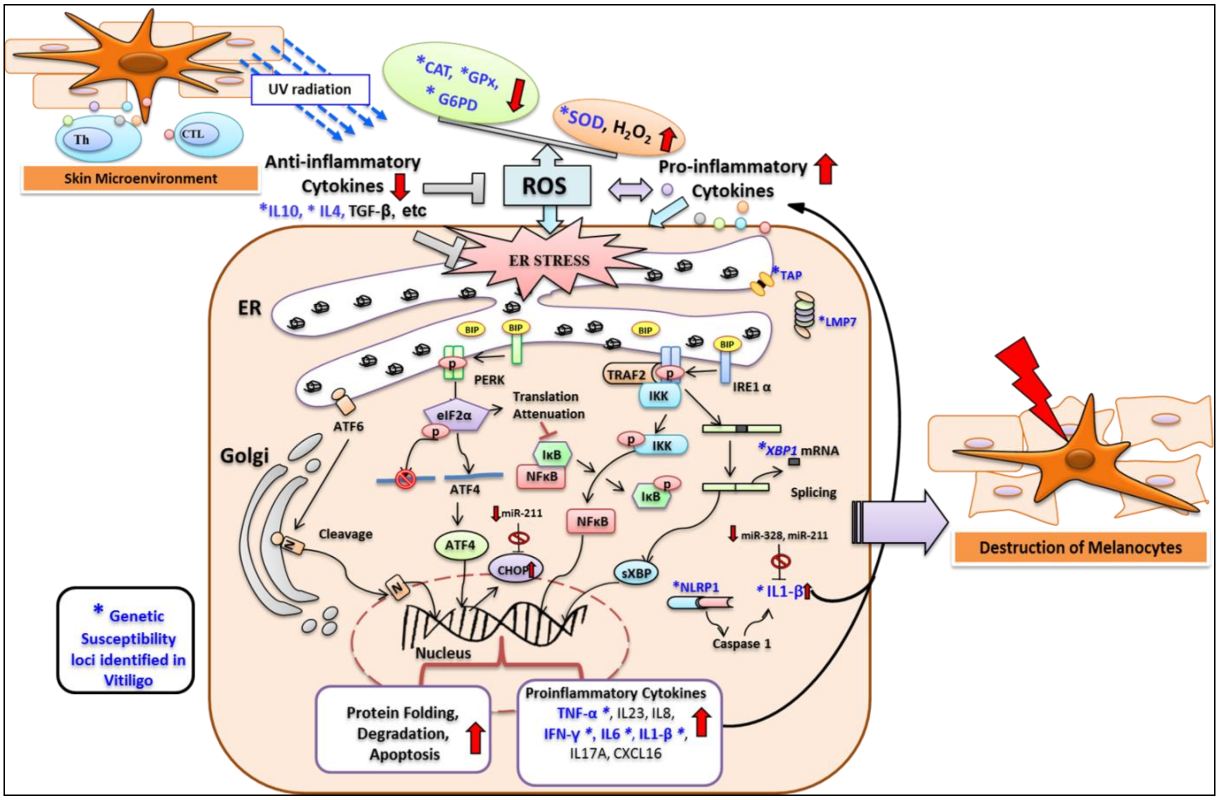


Figure 7: Interplay of oxidative stress, ER stress and inflammatory cytokines leading to melanocyte destruction in vitiligo

Various stressors in the skin microenvironment such as UV radiation, H_2O_2, pro-inflammatory cytokines secreted by immune cells and decreased levels of antioxidant and anti-inflammatory cytokines leads to generate oxidative stress and ER stress in the vitiliginous skin. ER stress activates unfolded protein response to resolve the stress however; prolonged ER stress leads to IRE1-α, PERK, and ATF6-mediated inflammatory transcriptional program through NFκB activation. NFκB induces expression of proinflammatory cytokines such as TNF-α, IL6, IL8, IL23, IL-1β, IL17A, etc which further generates ER stress and oxidative stress. Thus, altogether cross talk of oxidative stress, ER stress and immunity in addition to genetic predisposition and altered miRNA regulation leads to destruction of melanocytes in vitiligo.

1.8 Immunoregulatory role of miRNAs in Vitiligo

Micro-RNAs (miRNAs) are involved in the cellular regulatory pathways by affecting the expression of approximately 60% human genes at both post-transcriptional and translational levels (Sayed and Abdellatif, 2011). Atypical expression of several miRNAs in the skin and blood of patients with vitiligo has been demonstrated by several reports (Mansuri *et al*., 2014, 2016; Shi *et al*., 2013; Wang *et al*., 2015). Recently, Shahmatova *et al*., (2016) have reported up regulation of miR-155 in the lesional skin of vitiligo patients. Interestingly, miR-155 was also induced in response to TNF-α, IFN-α, IFN-γ, and IL-1β in melanocytes and keratinocytes. Upon over expression, miR-155 inhibited the expression of genes known to affect melanocyte differentiation and melanogenesis, such as *TYRP1*, *YWHAE*, *SDCBP* and *SOX10* in melanocytes (Shahmatova *et al*., 2016). Our recent study revealed that miR-1, miR-184, miR-328, miR-383, and miR-577 hold the similar pattern of expression in blood as that of skin (Mansuri *et al*., 2016). Our *in silico* results suggest that both miR-328 and miR-211 might target *IL1B* whereas; miR-1 and miR-211 might target IL1R1. Interestingly, our study suggests the down regulation of *PTPN22* might be influenced by miR-577 in skin as well as in circulation of vitiligo patients (Mansuri *et al*., 2016). The up-regulation of *IL1B*, *IL1R1*, and *IL23A* and, down-regulation of *PTPN22* in patients advocates its crucial role in the autoimmune pathogenesis of vitiligo. miR-211 also regulates *CHOP via* directly targeting the *CHOP* promoter (Chitnis *et al*., 2012). Further, CHOP regulates *IL23* expression and secretion from dendritic cells (Goodall *et al*., 2010). miR-211 also targets *IL23A* and is mainly produced by dendritic cells and macrophages, and in conjunction with IL6 and TGF-β1 plays a pivotal role in the induction of Th17 cells and secretion of IL17A (Bettelli *et al*., 2008). Our study showed significantly increased expression of *CHOP* and *IL23A* in lesional skin of vitiligo patients (Mansuri *et al*., 2016). Thus, the reports indicate that miRNAs have a collective role in oxidative stress, ER stress and autoimmunity in melanocyte destruction and further progression of the disease.

1.9 Poy(ADP-ribose) polymerase-1 (PARP-1) and vitiligo

Poly (ADP-ribose) polymerase-1 (PARP-1), a 116-kDa nuclear multitasking protein is involved in modulation of chromatin condensation leading to altered gene expression. It belongs to a family of ubiquitous nuclear enzymes that catalyzes NAD+ dependent addition of ADP- ribose polymers (PAR) to an array of acceptor proteins (D'Amours *et al*., 1999). In response to activation signals, it adds ADP-ribose units to various target proteins including itself, thus regulating various key cellular processes like DNA repair, cell death, transcription, mRNA splicing etc. (Jubin *et al*., 2016).

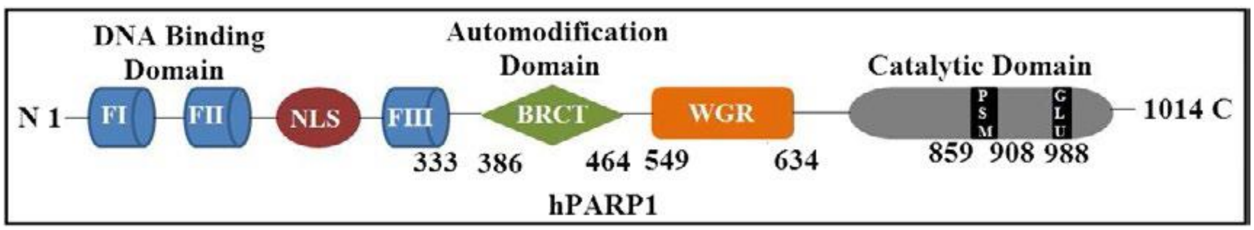


Figure 8: Structural organization of human PARP-1 (hPARP-1) It is characterized by FI, FII: Zinc finger motifs, FIII: Zinc ribbon domain (1-333 aa); NLS: Nuclear localization sequence; BRCT: BRCA1 C terminal motif (386-464 aa); WGR domain (549-634 aa) and the most conserved catalytic domain with PARP signature motif (PSM) between 859-908 aa and Glutamate (Glu) at 988 position (Jubin *et al*., 2016).

1.9.1 PARylation

Ubiquitous PARP activity has been found in organisms ranging from archae bacteria to mammals, apparently absent in yeast (Rolli *et al*., 2000). PARP-1's basal enzymatic activity is very low, but is stimulated dramatically in the presence of a variety of allosteric activators, including damaged DNA, some undamaged DNA structures, nucleosomes, and a variety of protein-binding partners (D'Amours *et al*., 1999; Oei and Shi 2001; Kun *et al*. 2002, 2004; Kim *et al*. 2004). PARP-1 binds to a variety of DNA structures, including single- and double-strand breaks, crossovers, cruciforms and supercoils as well as some specific double-stranded sequences (Lonskaya *et al*., 2005). PARP-1 mainly functions as a DNA damage sensor. In response to DNA damage, PARP-1 activity is rapidly increased upon binding to DNA strands containing nicks or breaks. On binding to the damaged DNA, PARP-1 forms homodimers and catalyzes the cleavage of NAD^+ and converting it into nicotinamide and ADP-ribose. ADP-ribose formed is utilized in formation of PAR polymer which is covalently attached to the acceptor protein. The attachment of PAR to the protein is at Glutamate and Lysine residues through an ester linkage.

1.9.2 Functions of PARP-1

PARP-1 is involved in various biological and cellular processes like DNA damage detection and repair, chromatin modification, transcription, cell death pathways, insulator function, and mitotic apparatus function.

PARP-1 identifies the genomic lesions such as SSBs, DSBs, non-BDNA structures etc., gets activated, and recruits itself at the deformed site, forming homodimers and triggering the transfer of an ADP-ribosyl moiety from NAD+ to aspartate or glutamate residues of its target substrates in the chromatin, mainly linker histone H1. This leads to structural changes involving unwinding of the highly condensed chromatin that renders the DNA easily accessible to transcription and repair enzymes (Rouleau *et al.,* 2011; Tulin and Spradling, 2003).

1.9.3 PARP-1 in Cellular-Stress Responses

PARP-1 has been shown to be involved in cellular stress responses and cell death. From different studies, it became clear that PARP-1 also modulates the molecular biology and biochemistry of stress responses at multiple levels. It alters cellular stress responses through a series of regulatory processes that occur at the genomic, transcriptional, posttranscriptional, translational, and post-translational levels (Kim *et al*., 2005).

Depending on the type and level of stress, PARP-1 elucidates different responses. Levels of PARP-1 activation decide the cell fate (i.e. cell survival or death). PARP-1 activation by mild or moderate stresses leads to transcription and DNA repair responses that help to maintain genome stability and re-establish homeostasis (Kim *et al*., 2005; Gagne *et al*., 2006). In contrast, severe, or sustained stresses cause hyper-activation of PARP- 1 resulting in distinct cell death programs (severe responses), such as apoptosis or necrosis (Koh *et al*., 2005; David *et al*., 2009). Various PARP inhibitors like PJ-34, DPQ, ABT-888 etc. are under clinical trials for various kinds of cancer (Jubin *et al*., 2016).

The mechanisms by which PARP-1 activation leads to cell death are still under active debate in the literature. Several mechanisms have been proposed, including energy-failure-induced necrosis and apoptosis-inducing factor (AIF)-dependent apoptosis.

1.10 Treatment of Vitiligo

The goal of vitiligo treatment is to control the autoimmune damage to melanocytes and stimulate their migration from surrounding skin and adnexal reservoirs. Treatment may be divided into non-surgical, surgical and herbal products, which can sometimes be combined.

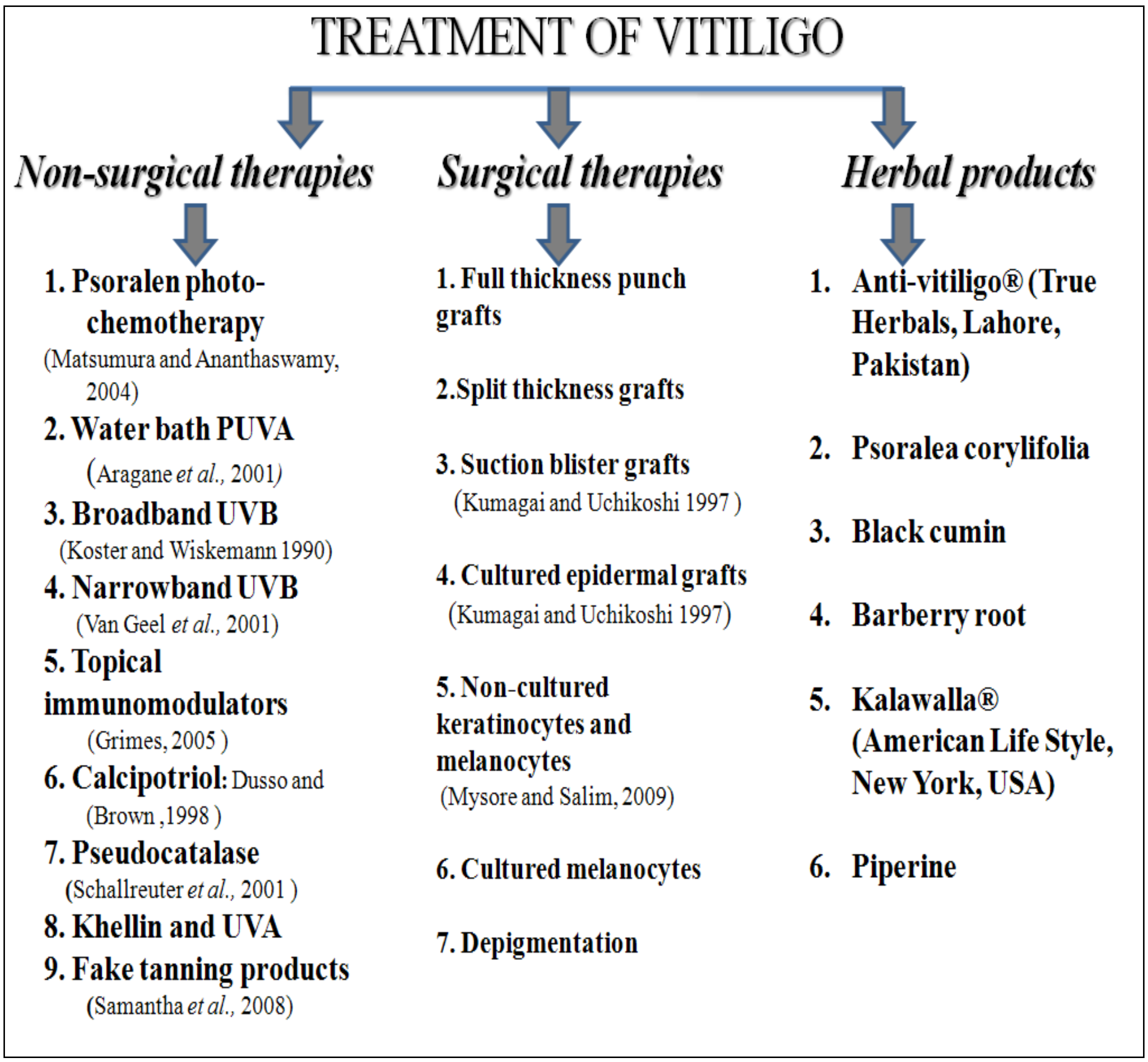


Figure 9: Developments in the direction of treatment are starting to become public, opening new approaches toward the full understanding of the genetic basis of complex diseases in general and especially of vitiligo.

1.10.1 Translational relevance of cytokines in Vitiligo

There is large body of evidence indicating imbalance of cytokines in Vitiligo suggesting Vitiligo could be an immune-mediated inflammatory disease. Not surprisingly, *biologics*, a new class of immune-modulators are being tested to assess their therapeutic potential in treating Vitiligo.

TNF-α inhibitors

Biologics of TNF-α antagonists are based on the observation that TNF-α protein expression and immunoreactivity is elevated in sera and lesional skin of Vitiligo patients. Till date five TNF-αantagonists (Table 5) have been studied in pilot clinical trials in treating pre-existing Vitiligo. Intriguingly, all of them have shown adverse reactions limiting their potential as therapeutic agents and warranting further research in the role of TNF-α in Vitiligo (Ramirez-Hernandez *et al*., 2005; Ismail *et al*., 2011; Posada *et al*., 2011; Smith and Heffernan, 2008).

Table 5: List of TNF-α antagonists used as biologics in clinical trials for Vitiligo therapy.

Biologics	**Type of biologic**
Infliximab, (Carvalho *et al*., 2014; Mattox *et al*., 2013)	Monoclonal antibody containing mouse variable region and a human IgG1 constant region.
Adalimumab, (Toissirot *et al*., 2013)	Monoclonal antibody containing human variable region and a human IgG1 constant region.
Golimumab	Monoclonal antibody containing human variable region and a human IgG1 constant region.
Etanercept (Rigopoulos *et al*., 2007)	Fusion protein of human TNFR2 and a truncated human IgG constant region
Certolizumab	Monoclonal antibody covalently attached to polyethylene glycol chains (PEGylated)

Infliximab, Adalimumab and Golimumab act as decoy receptors to bind TNF-α, hence it cannot bind and act through its true receptors. Notably, these TNF-α antagonists have proven successful in treating other autoimmune diseases namely psoriasis, psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, and Crohn disease (Simon and Burgos-Vargas, 2008; Campanati *et al*., 2010; Tolaymat and Sluzevich, 2010, Maruthappu *et al*., 2013).

It is plausible that inhibiting TNF-α by antagonists promote depigmentation by decreasing production and activation of Tregs which facilitate T cell autoreactivity against melanocytes. These antagonists also create cytokine imbalance mainly of IFN-γ that plays a central role in Vitiligo by suppressing Treg function. Majority of the other side effects due to treatment with TNF-α antagonists will result in other autoimmune diseases such as Uveitis, Psoriasis, Hidradnetis supparativa, Crohns' disease, Sarcoidosis etc. that are all attributed to cytokine imbalance related to IL-23/Th-17 axis, IFN-γ and IFN-α.

Antagonists to IFN-γ have not been tested extensively in clinical trials. Nevertheless, in a small preclinical study, Vitiligo patients treated with polyclonal IFN-γ antibodies by intradermal injection followed by intramuscular injection showed some promise in repigmentation. Another biologic, Efalizumab a T-cell targeted recombinant antibody binding to the CD11a subunit of LFA-1 has shown some therapeutic value in long standing stable Vitiligo patient. This biologic blocks the interaction between LFA-1 and ICAM-1 that is expressed by perilesional melanocytes surrounding the Vitiligo patch (Skurkovich *et al*., 2002, Webb *et al*., 2015).

An emerging class of inhibitors of JAK-STAT (Janus kinase signal transducer and activator of transcription) pathway has shown promise as biologics for Vitiligo (Damsky and King, 2017). JAK-STAT pathway which is required for transmitting signals from the nucleus to the cell membrane is indispensable for immune functions and is mediated by signalling molecules including cytokines, interferons and interleukins. Amongst the cytokines IFN-γ which plays a crucial role in Vitiligo pathogenesis utilises JAK-STAT pathway, thus it is plausible that JAK inhibitors can be effective in Vitiligo treatment. Pilot clinical trials of JAK inhibitors, tofacitinib (Craiglow and King, 2015) and ruxolitinib (Harris *et al*., 2016) on vitiligo patients showed significant repigmentation, however depigmentation recurred after discontinuing the treatment. Moreover, there is concern regarding continuous use of JAK inhibitors as they may increase risk of malignancy by reducing antitumor immune surveillance. Nevertheless, basic research and clinical trials to understand mechanism of JAK inhibitors and to test their potential in effective vitiligo treatment is warranted.

Plethora of scattred reports discussed above suggests the empirical need to address the expression levels and role of candidate cytokines in vitiligo pathogenesis. Therefore, for further experimentation we developed an ideal *in vitro* model system which is primary cultured normal human melanocytes in low serum, PMA and TPA free medium to investigate the role of cytokines in melanocyte biology. Furthermore, we aimed to monitor the expression levels of *TNFA, IL1A, IL1B, IL4, IL6, IL10, IL1R1, IL1RN* and *IFNG* in vitiliginous and control skin for screening of candidate cytokines. Important pro and anti-inflammtory cytokines TNF-α, IL-1, IL-6 and IL-10 screened from skin expression analysis were selected for further downstream effect of cytokines on melanocyte biology; particularly emphasizing their effect on receptor expression, genes involved in melanin synthesis and expression of other immune regulatory molecules. Moreover, we have also screened the genetic association of *IL10*, *IL1RN* and *IL6* polymorphisms, transcript levels as well as possible genotype-phenotype correlation analysis in vitiligo patients and controls from Gujarat population to access their effect on vitiligo suspectibility.Therefore, we have tried to monitor the effect of cytokine imbalance in vitiligo microenvironment, *in vitro* as well as population studies are also supplementing the above mentioned aspect to obtain a holistic figure of effect of cytokine imbalance in vitiligo pathogenesis.

1.11 References

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