Vitiligo; Overview about Types, pathophysiology and Diagnosis

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Abstract
Vitiligo is now a consensus umbrella term for all forms of generalized vitiligo (formerly designated in the international nomenclature as non-segmental vitiligo) defined as an acquired chronic pigmentation disorder characterized by white patches, most often symmetrical, increasing in size progressively or during flares with time, corresponding histologically to a substantial loss of melanocytes from skin and hair. Two other subsets of vitiligo are segmental vitiligo and unclassified/undetermined vitiligo, which included focal disease and rare variants. A multitude of plausible theories have been put forward to explain the pathogenesis of vitiligo and mechanisms that finally lead to the loss of functional melanocytes from the epidermis. The important ones include a genetic predisposition, autoimmune destruction of melanocytes, altered redox status and free radical mediated melanocyte damage, heightened sympathetic response and catecholamines/neurotransmitter mediated melanocyte damage, and impaired melanocyte adhesion or melanocytorrhagy. The combination of all these effectively explains the vitiligo pathogenesis (the combination theory). The diagnosis of vitiligo is usually made on clinical features, through a wood light examination. Biopsy is sometimes helpful to differentiate vitiligo from other hypo pigmented or depigmented disorders.

Keywords: Vitiligo

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Introduction

Vitiligo has a pronounced impact on the physical and mental health of patients, including loss of skin photo protection, compromised cutaneous immunity, and an appreciable reduction in quality of life that is directly correlated with the early age of onset (typically in the first two decades of life) **(1).**

Classification of Vitiligo

According to the Vitiligo Global Issues Consensus Conference (2012) and expert panel discussion, vitiligo can be further classified as segmental, non-segmental, mixed, and unclassified **(2)**

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Clinical aspects

Non-segmental vitiligo (NSV) or vitiligo vulgaris

Non-segmental vitiligo usually occurs bilaterally and symmetrically. It can be further subdivided into generalized, acrofacial, mucosal, or localized variants. Two common phenotypes of NSV can be differentiated: phenotype I is characterized by prepubertal disease onset, a positive family history of vitiligo and premature hair graying, disseminated occurrence with frequent de- and repigmentation, and an association with halo nevi. Phenotype II, on the other hand, manifests itself after puberty, shows predominant involvement of the face and acral areas, and is associated with other autoimmune disorders. Twenty percent of patients have another autoimmune condition (thyroid disease, psoriasis, rheumatoid arthritis, type 1 diabetes, alopecia areata, and others) **(4)**

Generalized vitiligo

This most common form of vitiligo, characterized by milky-white macules involving multiple parts of the body, most often in a symmetrical pattern. Skin hypopigmentation is usually asymptomatic, may be preceded by mild pruritis. The disease can start at any site of the body, but the fingers, hands, and face are frequently the initial sites. Depigmentation of sites of trauma is a common manifestation of the Koebner's phenomenon. Koebner's phenomenon is usually contemporary of disease flares.Stable lesions are well demarcated **(3).**

Acrofacial vitiligo: Refers to depigmented macules limited to the distal extremities and/or the face. A distinctive feature is depigmentation of the distal fingers and facial orifices. It may later include other body sites, resulting in typical generalized vitiligo. Acrofacial vitiligo was shown to be more frequent in adult onset cases of vitiligo **(4)**

Mucosal vitiligo: Typically involves the oral and/or genital mucosae. It may occur as a part of generalized vitiligo or as an isolated condition. The Vitiligo Global Issues Consensus Conference (VGICC) participants decided, however, that it should be graded as undetermined vitiligo (UnV) when viewed in isolation **(5).**

Vitiligo universals: Refers to complete or nearly complete depigmentation of the skin (80–90% of body surface). It is usually preceded by generalized vitiligo that gradually progresses to complete or near complete depigmentation of the skin and hair **(6)**

Focal vitiligo: Refers to a small, isolated, depigmented lesion with no pattern of distribution and which not evolve after a period of 1–2 years **(6)**

Cases of long-lasting focal lesions or pure mucosal vitiligo can remain "unclassifiable" if not graded to SV **(7)**.

Segmental vitiligo: occurs in early onset, rapid progression, no specific precipitating factors, and linear spreading in the affected dermatomal area. The most commonly involved dermatome is the trigeminal. Only a few patients have an associated autoimmune disease **(8).**

Mixed vitiligo: Refers to the concomitant occurrence of SV and NSV. Leukotrichia and halo nevi at onset may be risk factors for developing MV in patients with SV **(6)**

Clinical variants of vitiligo (3).

1. **Marginal inflammatory vitiligo**: consists in depigmented patches with an erythematous micropapular edge. This condition is associated with inflammatory infiltrates in the margin of progressing lesions. It may occur in isolation but has unfrequently been associated with various disorders. Duration at diagnosis varied from 2 months to 2 years **(7).**

2. **Trichrome vitiligo**: an intermediate hypochromic zone is found between the achromic center and the non-affected peripheral skin. The natural evolution of the hypopigmented areas is transition to complete depigmentation resulting in three color shades in the same individual (brown, tan and white).

3. **Vitiligo quadrichrome**: reflects the appearance of a fourth (dark brown) color at perifollicular repigmentation sites.

4. **Blue vitiligo**: characterized by a blue-grey appearance of the skin, which corresponds histologically with absence of epidermal melanocytes and presence of numerous dermal melanophages.

5. **Koebner Phenomenon** (KP): vitiligo formation in particular trauma sites such as cutting, burning or abrasion.

6. **Unclassified and Rare Variants** (**7**):

• *Vitiligo Guttata/Punctata, Leukoderma Punctata, and Confetti Leukoderma;* refers to sharply demarcated depigmented punctiform 1- to 1.5-mm macules involving any area of the body. If these lesions do not coexist with classical vitiligo macules, they should be referred to as "leukoderma punctate".

•*Hypochromic vitiligo or vitiligo minor;* is described only in dark-skinned individuals, characterized by the presence of hypopigmented lesions alone or associated with suggestive achromic macules, which arise without any preceding clinical inflammation. Hypopigmented macules occur at onset of vitiligo/NSV or when vitiligo is unstable and spreading. The diagnosis of hypopigmented vitiligo remains thus very challenging and should be restricted to cases with long-term observation (more than 5 years) and serial negative biopsies for CTCL.

•*Follicular vitiligo*; Leukotrichia is considered as a marker of segmental vitiligo. In vitiligo/NSV body hairs are usually spared although hair depigmentation may occur with disease progression. Histologic examination of a punch biopsy specimen taken from an area with both depigmented skin and leukotrichia demonstrated the presence of a discrete perifollicular infiltrate in the infundibular region of the hair follicle and an absence of melanocytes in both the basal layer of the epidermis and the hair follicle with Melan-A staining.

Pathogenesis of vitiligo

A multitude of plausible theories have been put forward to explain the pathogenesis of vitiligo and mechanisms that finally lead to the loss of functional melanocytes from the epidermis. The important ones include a genetic predisposition, autoimmune destruction of melanocytes, altered redox status and free radical mediated melanocyte damage, heightened sympathetic response and catecholamines/neurotransmitter mediated melanocyte damage, and impaired melanocyte adhesion or melanocytorrhagy. The combination of all these effectively explains the vitiligo pathogenesis (the combination theory) **(9)**.

➢ Genetics

Numerous studies indicate the importance of genetic factors in the development of vitiligo, although it is clear that these influences are complex. Various studies have shown that vitiligo tends to aggregate in families and frequency of vitiligo among first-degree relatives varies from 0.14% to as high as 20%. However, the genetic risk is not absolute. It is interesting that the concordance for vitiligo in monozygotic twins was 23%, demonstrating a 60-fold increased risk in comparison with general population **(10)**.

Vitiligo is a polygenic disease, numerous studies for identifying susceptibility genes for vitiligo, some of which are shared with other autoimmune diseases and some of which are specific to

vitiligo. Functional candidate gene association (FCGA) analyses studies revealed several candidate genes including major histocompatibility complex (MHC), angiotensin-converting enzyme (ACE), catalase (CAT), cytotoxic T lymphocyte antigen-4 (CTLA-4), catechol-O-methyltransferase (COMT), estrogen receptor (ESR), mannan-binding lectin (MBL2), protein tyrosine phosphatase, non-receptor type 22 (PTPN22), human leukocyte antigen (HLA), NACHT leucine-rich repeat protein 1 (NALP1), X-box binding protein 1 (XBP1), forkhead box P1 (FOXP1) and interleukin-2 receptor A (IL-2RA). These genes that are involved in immune regulation have been found genetic association with generalized vitiligo. Also In patients with autoimmune/auto-inflammatory syndromes associated with vitiligo, HLA haplotypes, especially HLA-A2, −DR4, −DR7 and −DQB1*0303, have been frequently found to play an important role. At the same time, in patients with vitiligo alone, PTPN22, NALP1 and XBP1 have been found to play a causal role. The GWA study indicated nearly 50 *loci* associated with genes controlling the innate (NLRP1, IFIH1, casp7, c1qtnf6, trif) and acquired (FOXP3, BACH2, CD80, CCR6, PTPN22, IL2R, αG2MB, HLA class I and II) immunity system (**11**).

Vitiligo is strongly connected with polymorphism in HLA-A, HLA-DRB1/DQA1, and CPVL. HLA genes are responsible for antigen presentation, while CPVL is postulated to play a role in antigen processing **(10)**.

Genomic-wide scans have provided a strong support for vitiligo susceptibility genes on chromosomes 4q13-q21, 1p31, 7q22, 8p12 and 17p13, while loci of interest at 6p, 6q, 14q, 9q, 13q, 19p and 22q required further follow-up. (**12**)

Thereupon, the data available so far suggest that vitiligo has a polygenic inheritance with no single gene dictating its pathogenesis

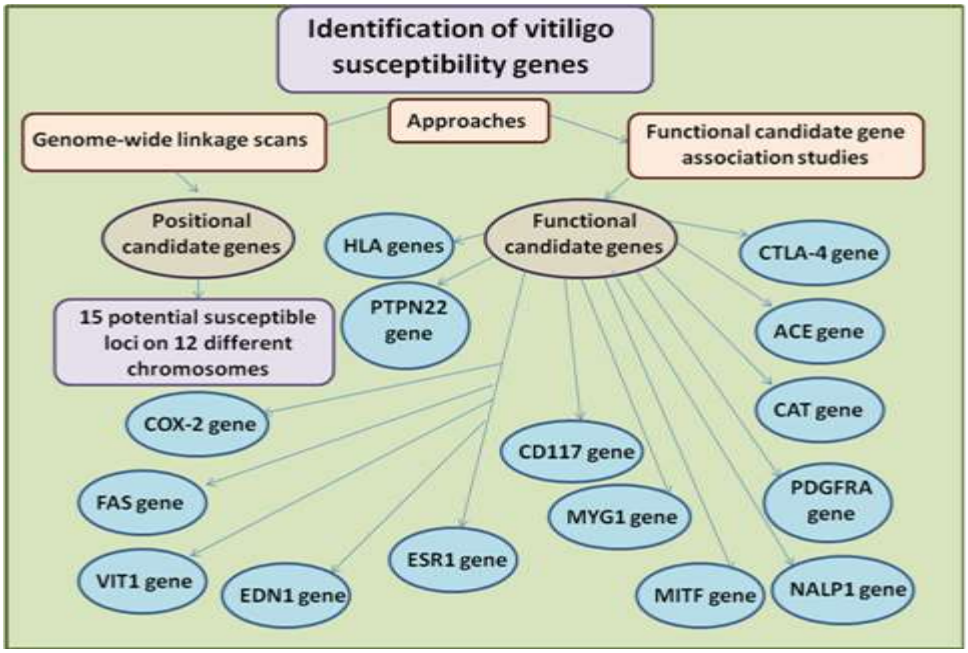

Figure1: Identification of vitiligo susceptibility genes (**12**).

➢ AUTOIMMUNE HYPOTHESIS

The autoimmune theory is one of the most plausible theories that have been proposed to understand the pathogenesis of vitiligo.in addition; many other theories finally converge on the autoimmune destruction of melanocytes. Vitiligo has been found to be associated with other prototype autoimmune diseases including alopecia areata, Hashimoto thyroiditis, pernicious anemia and type 1 diabetes mellitus **(9)**.

- ***Cellular immunity***

It has been proposed that vitiligo is a T cell-mediated autoimmune disease and the activated CD8+ cytotoxic T cells are involved in melanocyte dysfunction, depigmentation and apoptosis **(13).**

T cell infiltration in the margin of inflammatory vitiligo is detected as a participation of cellular immunity in pathogenesis of vitiligo. Immunohistochemical studies of the perilesional area in generalized vitiligo mainly detect CD4 and CD8 positive T cells in the infiltrate which express activation molecules such as IL-2 receptor, HLA-DR and MHC 3 complex. The dermal and epidermal infiltrates consist of cytotoxic and helper T cells that are closely associated with the areas of melanocyte depletion. Also decreased CD4/CD8 ratio was found. A study using melanocyte-specific T cell receptor (TCR) transgenic mouse models suggest that CD4 T cells are involved in depigmentation and that melanocyte loss in such models involve Fas-Fas ligand (FasL)-induced signaling **(14).**

Circulating melanocyte-specific cytotoxic T lymphocytes that target melanocyte-specific antigens, including Melan-A (MART-1), gp100 (Pmel17) and tyrosinase, have been detected in vitiligo patients. They express high levels of the skin-homing receptor cutaneous lymphocyte-associated antigen(CLA) and their frequency correlates with both the extent and activity of the disease. CD8 T cells from perilesional skin of vitiligo patients recognize melanocyte antigens; express granzyme B and the pro-inflammatory cytokines IFNγ, TNFα, and IL-17; and can induce autologous melanocyte apoptosis in normally pigmented skin in vitro, suggesting the involvement of a cytotoxic response to melanocytes **(15).**

It has been suggested that lymphocytes $CD4^+$, Th1 and Th17 are the major subset in vitiligo development. It has been proved that this subset of helper T cells is involved in expression of IL-17A, IL-17F, as well as IL-22. In turn, IL-22 affects keratinocytes by stimulating them to secretion of IL-1β, IL-1 and tumor necrosis factor. It was also showed that the transcription factor for aryl hydrocarbon receptor (AhR) and retinoid-related orphan receptor (RORC), which are involved in the production of IL-22 by cells Th17 and Th22, increased considerably. In addition, IL-17 adds a synergistic effect together with these local inflammatory mediators, which may further inhibit the proliferation of melanocytes. Regulatory T cells, a subset of CD4+ cells with phenotype CD4+ CD25+Foxp3+, exert their function by active suppression of other immune cells, either directly by cell-cell contact, or via secretion of inhibitory cytokines. Alterations in their number or function can lead to autoimmunity. Both T regulatory cells number and function have found to be impaired in vitiligo patients **(16).**

Such alterations in T regulatory cells number and function might lead to the reported higher levels and activation of cytotoxic T cells in individuals with the disease **(16).**

Perilesional melanocytes in vitiligo patients have shown abnormal expression of MHC class II antigen HLA-DR and increased expression of intercellular adhesion molecule-1 by compared with melanocytes from normal skin. These molecules have important roles in antigen presentation and in the activation of helper T cells; their expression by melanocytes could contribute to the anti-melanocyte cellular immune responses that are seen in vitiligo **(17).**

The expression of IFN-γ and the downstream genes has been found to be enhanced in the vitiligo skin. It has been observed that IFN-γ directly inhibits melanogenesis (functional or qualitative inhibition) and results in the apoptosis of the melanocytes (quantitative inhibition). It induces senescence of melanocytes and promotes the release of heat shock protein −70 which marks the melanocytes for damage by innate immune response. Also enhances the active influx of activated T-cells in the skin via chemokines released from the keratinocytes, causing a vicious cycle that culminates in depigmented patches on skin. The inhibition of this IFN-γ signaling can have an

important impact on the management of vitiligo **(9)**.

As a pro-inflammatory cytokine, IFN-γ is mainly secreted by Th1 lymphocytes, $CD8^+$ cytotoxic T lymphocytes and NK cells. it has been reported that increased IFN-γ is essential for the pathogenesis of vitiligo by 1- induction of apoptosis of melanocytes 2- blocks maturation of melanosomes by regulating pigmentation genes. 3- IFN-γ regulate melanogenesis by upregulating STAT1 phosphorylation, and its inhibiting effect can be restrained by JAK1 inhibitors 4- IFN-γ inhibits IL-18-induced melanogenesis as IL-18 is produced by inflammatory stimuli in Langerhans cells (LC), dendritic cells (DC), Kupffer cells, activated monocytes/ macrophages, and keratinocytes in the epidermis. IL-18 has been revealed to increase the cascade expression of MITF and downstream enzymes by activating the p38/MAPK and PKA pathways, and thus promote melanogenesis and upregulate TYRP-1 and TYRP-2 expression. These results suggest that IL-18 may participate in the regulation of pigmentation by regulating melanocytes. Janus kinase-signal transducer and activator of transcription (JAK/STAT) is an intracellular pathway that drives downstream signaling of several proinflammatory pathways. Once a cytokine binds to its receptor, JAK is activated and in turn activates STAT. The latter then acts as transcription-activators of multiple mediators. In particular, JAK located inside keratinocytes is activated by IFN-gamma, and then STAT activates the transcription of genes such as CXCL9 and 10 that are potent chemokines. The result is a further recruitment of cytotoxic T-cells producing more IFN-gamma that directly inhibits melanogenesis, induces senescence of melanocytes and promotes the release of heat shock protein −70 which marks the melanocytes for damage by innate immune response **(18).**

The expression of CXCR3 and its ligands CXCL9 (also known as monokine induced by IFNγ, MIG) and CXCL10 (also known as IFNγ-inducible protein-10, IP-10) is increased in the skin of patients with vitiligo**.** Both CXCL9 and CXCL10 share a single receptor, CXCR3. Analysis of chemokine expression in mouse skin showed that CXCL9 and CXCL10 expression strongly correlates with disease activity, whereas CXCL10 alone correlates with severity, supporting them as potential biomarkers for following disease progression. Likewise, serum CXCL10 in patients with vitiligo also correlates with disease activity and severity and may be a novel biomarker in monitoring disease activity. Therapies that disrupt the pathway targeting IFN-γ, the IFN-γ receptor, the downstream signaling proteins JAK1, JAK2 and STAT1, and the chemokine CXCL10 and its receptor CXCR3 could represent attractive strategy in this disease **(19).**

Frisoli et al., (20) demonstrated that selective depletion of recirculating memory T cells or inhibition of their migration contributed to rapid repigmentation, in spite of that the number of T_{RM} cells did not change This led to the conclusion that T_{RM} cells are not fully responsible for relapsing skin lesions in vitiligo without additional recruiting of T cells. By secreting compounds like granzyme B, perforin, or IFN-γ, T_{RM} cells exert a cytotoxic effect on melanocytes, leading to their apoptosis. Importantly, $CD8^+$ T_{RM} cells which are present in healthy human skin do not demonstrate high expression of these effector molecules.

- ***Humoral Immunity***

Antibodies seen in patients with vitiligo, are categorized as those against cell surface pigment cell antigens, intracellular pigment cell antigens and non-pigment cell antigens. Melanocyte autoantibodies have been demonstrated that they belong to the subclasses IgG1, IgG2 and IgG3 although studies have also found that IgA levels of melanocyte autoantibodies are associated with disease activity. Several melanocyte- specific autoantibody targets have been identified including tyrosinase, tyrosinase- related protein (TRP)-1, dopachrome tautomerase (or TRP-2), PMEL and

GTP- binding protein Rab38. Also, autoantibodies have non melanocytes specific targets in patients with vitiligo including the melanin-concentrating hormone receptor 1, gamma-enolase, alpha-enolase, heat-shock protein 90, osteopontin, ubiquitin-conjugating enzyme, translation-initiation factor 2, tyrosine hydroxylase and laminA. In addition, organ-specific autoantibodies, particularly against the thyroid, adrenal glands, gastric parietal cells, and pancreatic islet cells are commonly found along with anti- nuclear autoantibodies and IgM-rheumatoid factor. Keratinocyte autoantibodies which correlate with vitiligo extent and activity have been reported. Furthermore, melanocyte autoantibodies from vitiligo patients can induce HLA-DR and ICAM-1 expression on and release of interleukin (IL)-8 from melanocytes **(16).**

- **Oxidative stress**

The oxidative stress theory of vitiligo suggests that the main culprit in the pathogenesis of vitiligo is the intra-epidermal accumulation of reactive oxygen species (ROS), the most notorious of which is H2O2 whose concentration may reach upto one milimole. At this concentration, H2O2 leads to changes in the mitochondria and, consequently, apoptosis/ death of the melanocytes. Several in vitro and in vivo studies have revealed an altered redox status, with the presence of oxidative stress in cultured melanocytes coupled with an increased susceptibility to pro-oxidant agents (**21**).

Reactive oxygen species (ROS) are released from melanocytes in response to stress. In turn, this causes wide spread alteration of the antioxidant system: An imbalance of elevated oxidative stress markers (superoxide dismutase, malondialdehyde, ROS) and a significant depletion of antioxidative mechanisms (catalase, glutathione peroxidase, glutathione reductase, thioredoxin reductase and thioredoxin, superoxide dismutases, and the repair enzymes methionine sulfoxide reductases A and B) in the skin and in the blood. It has been suggested that this imbalance in vitiligo patients is responsible of the increased sensitivity of melanocytes to external pro-oxidant stimuli **(6)**

The increased ROS production by melanocytes could result from an external stress, such as ultraviolet (UV) radiation exposure or chemical damage (monobenzone or other phenols). ROS can be generated by many metabolic pathways and several evidence suggest that mitochondria could be the main source of ROS in vitiligo (**22**). `

In vitiligo, Stressed melanocytes result in production of pro-inflammatory cytokines as interleukin (IL)-6, matrix metalloproteinase 3 (MMP3), cyclooxygenase-2, insulin-like growth factor-binding protein 3 (IGFB3), and IGFBP7. In addition, melanocyte exposure to chemical agents (4-tertiary butyl phenol—and monobenzyl ether of hydroquinone) known to trigger vitiligo induces the disruption of the folding machinery of the endoplasmic reticulum (ER), leading to the accumulation of immature proteins and activation of the unfolded protein response (UPR) that may result in impaired protein synthesis and induction of cell apoptosis **(3).**

Westerhof et al., (23) suggested the haptenation theory, to detect the pathogenic role of oxidative stress in vitiligo. According to this hypothesis, high levels of H_2O_2 lead to increased levels of tyrosinase enzyme and its activity which, because of a genetic polymorphism specific to 'vitiligo' melanocytes, is capable of binding to a variety of substrates such as noradrenalin (during severe mental stress and bereavement), tri- iodothyronine and estrogen, thereby, generating orthoquinone metabolites. These metabolites act as putative haptogenic substrates for tyrosinase and convert the tyrosinase enzyme into a neoantigen, which eventually acts as an autoantigen for the immune system. Thus, an autoimmune reaction is triggered which brings about depigmentation by selective destruction of melanocytes.

- **Innate Immunity Bridges the Gap between Oxidative Stress and Adaptive Immunity**

After sensing stress signals the activation of innate immunity begins. Innate immunity rapidly triggered via pattern recognition receptors (PRRs) and their activators of ligands that are mainly referred to as DAMPs in vitiligo. In response to stress, intracellular inducible Hsp70i serves as a cytoprotector preventing apoptosis. Hsp70i acts as molecular chaperone. The uptake, processing, and presentation of Hsp70i-chaperoned proteins and peptides that are derived from cellular stress, promotes antigen-specific CTL-related immune responses **(24).**

- **Autocytotoxicity**

Accumulation of toxic metabolites in the melanocytes secondary to a defect in their metabolic clearance of the toxins leads to vitiligo. Toxic metabolites, both intracellular, such as those formed during melanin synthesis, and extracellular, such as phenols or quinones, may accumulate and damage the melanocytes of genetically susceptible individuals bringing about autocytotoxic injury to the melanocytes. It has been shown that tyrosine upon entering the melaninogenic pathways produces certain electrically unstable by-products, which have the potential to damage other cellular substrates resulting in death of the melanocytes **(8).**

- **Neural theory**

The neural hypothesis is supported by clinical, ultrastructural, and biochemical studies. Segmental vitiligo follows dermatomal distribution and it has been suggested that it arises from the dysfunction of sympathetic nerves that innervate the affected dermatome. As melanocytes were first believed to be under neural control because melanocytes originate from neural crest cells; thus, the degeneration of nerves and nerve endings was proposed as a possible mechanism for vitiligo **(25).**

The abnormal release of catecholamines from autonomic nerve endings may play an etiologic role of vitiligo through the production of toxic radicals in the microenvironment of melanocytes or through a direct cytotoxic action of catecholamines or their metabolites. Plasma and urinary catecholamines and 5-hydroxyindoleacetic acid (5-HIAA) (the main metabolite of serotonin) in non-segmental vitiligo patients were significantly increased compared to the control group and marked elevation was seen in the active phase of the disease. The increase in the level of monoamines may be the initiating event in the pathogenesis of NSV. The pathogenesis of vitiligo is related to the metabolites of catecholamines and 5-hydroxytryptamine (5-HT). Catecholamines and 5-hydroxytryptamine 5-HT play an essential role in mental factors such as depression and anxiety, the pathogenesis of vitiligo is related to mental factors too. Different types of emotional stress can stimulate tyrosine to synthesize catecholamines, more catecholamines can promote melatonin biosynthesis, and activate melatonin receptors to reduce melanin synthesis. Increased catecholamines levels also lead to excessive production of H_2O_2 and oxidative stress in melanocytes **(26).**

- **Melanocytorrhagy**

This theory proposes that NSV is a primary melanocytorrhagic disorder with altered melanocyte responses to friction, which induces their detachment, apoptosis and subsequent transepidermal loss. This theory adequately explains the Koebner's phenomenon because it proposes that weakly anchored melanocytes upon facing minor friction and/or other stress undergo separation from the basement membrane, migrate upward across the epidermis and are eventually lost to the environment resulting in vitiligo at the sites of trauma.Tenascin, an extracellular matrix molecule that inhibits adhesion of melanocytes to fibronectin, has been detected in the basal membrane in the papillary dermis and can contribute toward chronic detachment and epidermal loss of melanocytes. The origin of the tenascin deposits is currently unclear. In addition, perilesional skin melanocytes from patients with unstable vitiligo have shown significantly low adhesion to collagen

type IV compared with control and stable vitiligo. These same melanocytes are also more susceptible to apoptosis as they expressed increased caspase 3 and annexin V **(27).**

Dendrites are critically important for melanosome transfer, because one melanocyte contacts several keratinocytes in the epidermis through dendritic cell processes**.** In NSV, melanocytes lose their dendrites either by oxyradicals (impaired redox status hypothesis) or by increased release of catecholamines (neural biochemical hypothesis) which could not only affect melanosome transfer but also adhesion to surrounding structures **(25).**

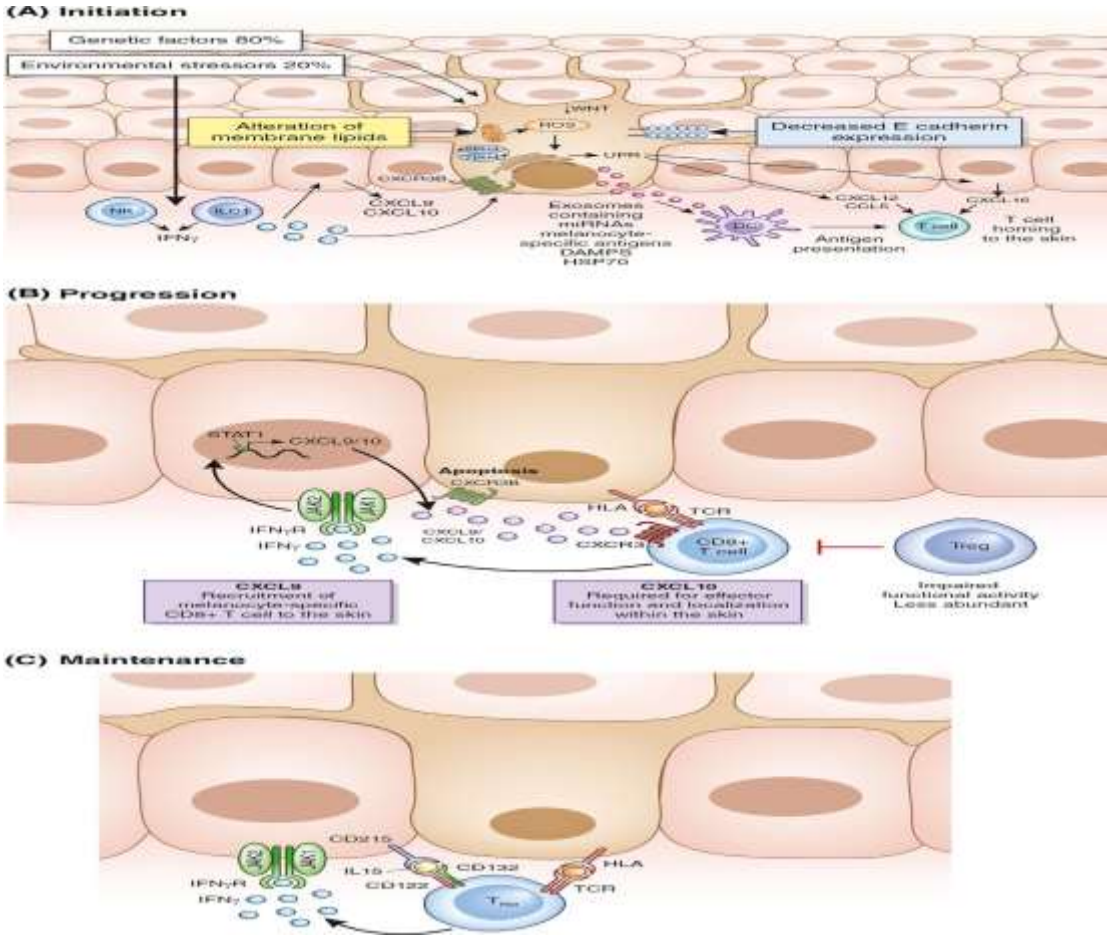

FIGURE 2: Vitiligo pathogenesis **(6)**

Diagnosis of Vitiligo:

The diagnosis of vitiligo is usually made on clinical features, through a wood light examination.biopsy is sometimes helpful to differentiate vitiligo from other hypo pigmented or depigmented disorders. The histopathological examinations of the skin reveal the absence of melanocytes and complete epidermal pigmentation loss. Superficial perifollicular and perivascular lymphocytic infiltrates may be present at the margin of the vitiligo lesions, due to the cell-mediated process that destroys the melanocytes. Dermoscopy can be used to differentiate vitiligo from other depigmenting disorders. Vitiligo typically shows residual perifollicular pigmentation and telangiectasia, which are absent in other hypopigmentation disorders. More importantly, it can be useful in assessing disease activity in vitiligo and the stage of evolution: progressive lesions display perifollicular pigmentation, whereas stable or remitting lesions display perifollicular depigmentation (**28**).

Differential diagnosis of vitiligo:

(6)

1-Chemically-induced leukoderma (occupational); Phenols and other derivatives

2-Topical or systemic drug-induced depigmentation

3-Genetic syndromes; Piebaldism, Hypomelanosis of Ito, Tuberous sclerosis**,**Vogt-Koyanagi-Harada syndrome, Waardenburg syndrome**,** Hermanski-Pudlak syndrome, Menke's syndrome,Ziprkowski-Margolis syndrome, Griscelli's syndrome

4-Postinflammatory hypopigmentation: Pityriasis alba - Lichen planus - Atopic dermatitis/allergic contact dermatitis Psoriasis - Toxic drug reactions - Pityriasis versicolor - Mycosis fungoides - Posttraumatic hypopigmentation (scar) - Leishmaniasis - Onchocerciasis - Leprosy – syphilis - Phototherapy and radiotherapy-induced - Melanoma-associated leukoderma

5-Idiopathic: Idiopathic guttate hypomelanosis, Progressive (or acquired) macular hypomelanosis

6-Congenital: Nevus anemicus, Nevus depigmentosus

7-Others: Lichen sclerosus et atrophicus,Melasma**.**

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