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REVIEW

Highlights in pathogenesis of vitiligo

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Abstract

Vitiligo is a common pigmentary disorder. Many studies across decades and all over the world have attempted to illustrate the pathogenesis behind it; however, the pathogenesis of vitiligo remains elusive. This review article, we present the findings behind the most and updated theories behind this psychologically debilitating and disfiguring disease. The discussion begun with the role of genetic predisposition followed by neural theory first proposed in the 1950s. We highlight the autoimmune hypothesis, followed by the reactive oxygen species model, zinc-α2-glycoprotein deficiency hypothesis, viral theory, intrinsic theory and biochemical, molecular and cellular alterations accounting for loss of functioning melanocytes in vitiligo. Many theories were elaborated to clarify vitiligo pathogenesis. It is a multifactorial disease involving the interplay of several factors. Future research is needed to clarify the interaction of these factors for better understanding of vitiligo pathogenesis and subsequent successful treatment.

Key words: Etiopathogenesis; Pigmentary disorder; Non-segmental vitiligo; Segmental vitiligo; Vitiligo

Core tip: The pathogenesis of vitiligo elaborated by several theory. Future research needed to clarify the interaction of these factors for better understanding of vitiligo pathogenesis and subsequent successful treatment.

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INTRODUCTION

The pathogenesis is complex and involves the interplay of multiple factors; however, the exact pathogenesis is not well known. Lerner *et al*[1] in the 1950s firstly proposed the neural theory, and after that, model of reactive oxygen species (ROS), the autoimmune hypothesis and the melanocytorrhagy hypothesis have appeared.

DIFFERENT PATTERNS AND PHYSICAL DISTRIBUTION OF VITILIGO

Pruritus, elevated lesions, and erythematous margins present in inflammatory vitiligo. There are 2 main types: generalized vitiligo (GV) (widespread macules with a symmetrical distribution), whereas focal vitiligo (FV) (1 or few depigmented not elevated areas at a single site). After coalescing of vitiliginous areas in GV, or becomes extensive in the body with remaining of few normal areas, thus called vitiligo universalis. Non-segmental vitiligo enrolled FV and GV, but segmental vitiligo (SV) restricted to one unilateral region[2], (Figure 1). The lesions of vitiligo are asymptomatic except in inflammatory vitiligo, which is associated with pruritus and characterized by elevated lesions, and erythematous margins.

INHERITANCE OF VITILIGO

The inheritance is polygenic[3]. Family history exists in 6.25%-38% of patients with vitiligo[4]. Those who have recessive homozygosity at 3 epistatically interacting autosomal diallelic loci will be affected by vitiligo[5].

Molecular genetics-based studies

Spritz *et al*[6] (2004) revealed different loci or alleles for GV. Autoimmune susceptibility (AIS)-1, -2 (chromosome 7) and systemic lupus erythematosus vitiligo-related gene (SLEV1) (chromosome 17) both associated loci for GV and concomitant autoimmune diseases. Of 33 tested loci, only (XBP1, TSLP, and FOXP3) were primarily concomitant with GV. FOXP3 associated with X linked recessive multiple autoimmune disease syndrome. In addition, CTLA4 had association secondarily with GV, and the autoimmune diseases[7]. However, patients with GV also linked to AIS3 locus (chromosome 8)[6].

Methylation of deoxyribunucleic acid (DNA) conducted by DNA methyltransferases (DNMT1, -3a, -3b)[8]. Monocytes in vitiliginous patients and normal volunteers showed sensitivity to alterations in methylation and revealed association between IL-10 and reactivity of autoimmune system[9,10]. In comparison with controls, methylation was increased and hypermethylation of the methylation-sensitive region in IL-10 that could alter genes expression in autoimmunity[9]. In a similar way, the role of transforming growth factor beta-receptor Ⅱ (TGFBR2), which inhibits the inflammatory pathways and lymphocyte activation was revealed[11,12].

The ultraviolet radiation resistance-associated gene (UVRAG), resists photo-damage, and plays a role in autophagy[13]. In 439 controls and 225 NSV patients, UVRAG has 2 SNPs which were significantly different[14].

Both diabetes mellitus type 1 and rheumatoid arthritis with SNPs found beside the insulin-dependent diabetes mellitus 8 locus (IDDM8)[15]. This region contains SMOC2, which enrolled in growth and development[16] and cell matrix interactions[17].

Also, melanocyte proliferating gene 1 (MYG1), is elevated in skin of both vitiliginous patients with activity, and without activity[18].

Human leukocyte antigen

Studies revealed that vitiligo associated with HLA-DRB1*07, HLA-A2, 11, 28, 31, 33, HLA-B17, 35, 40 and 44[19,20].

Susceptibility loci of vitiligo are on chromosome 6 and in the MHC[21]. A study genotyped 6623 patients with vitiligo and 10740 controls for 34 SNPs. *At 6q27, 2 SNPS* found with 3 unlinked genes. These gene include RNASET2, which responsible for ribonuclease (RNAse)[22]. The other two genes are the chemokine receptor 6 gene (*CCR6*)[21], and FGFR10P are imperative to progressing of the cycle of the cell that produce receptor of (FGF)[23]. Genes encode discoidin domain receptor 1 (DDR1)[24], and tyrosine kinase receptor play role in cell's progression and function[25], both were involved in vitiligo.

THEORIES FOR VITILIGO PATHOGENESIS

The neural theory

Early theories: The "neural theory" supposed by Lerner's (1959) was based on the fact that SV follows the course of the dermatome with exhibiting hyperhidrosis and emotional upset[1,26,27].

The sympathetic nervous system's role: Dysfunction of sympathetic nervous system's role (SNS) activity affect melanin production and lead to depigmentation. With iontophoresis and laser Doppler flowmetry level of microcirculation in lesions with vitiligo assessed to reveal SNS activity[28]. 10 subjects had facial SV, and 2 groups of controls were examined. 1 control group had 10 healthy, unaffected individuals, and the 2nd control group contained 10 non-segmental-type stable vitiligo patients. Patients were matched for gender and age. Approximately, the cutaneous blood flow was higher three times on the lesions *vs* normal skin in SV. The differences was not revealed in the non-SV.

Neuropeptide and neuronal markers: Neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP), vasoactive intestinal polypeptide (VIP), and polyclonal general neuronal marker (PGP) tested for their immuno-reactivity in 12 patients with vitiligo and 7 unaffected control subjects[29]. NPY increased in the marginal areas of lesions in half of the patients *vs* normal, and associated with noradrenaline with exerting a local autonomic effect[29]. Lazarova *et al*[30] (2000) confirmed this finding; however, they found that CGRP was also non-significantly increased in vitiligo. Precipitating factor, as, stress, produce significant level of neuropeptides such as NPY that induct the disease[30,31]. A cohort study revealed

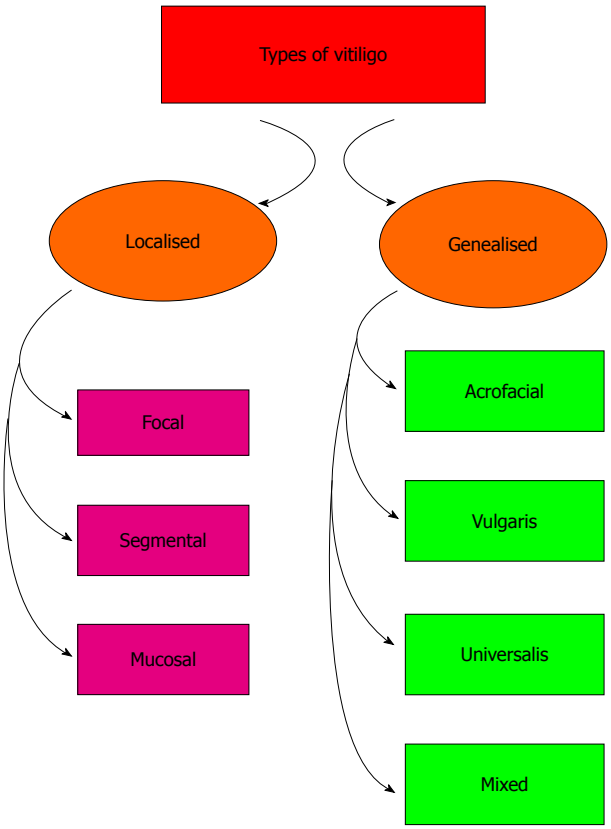

Figure 1 Types of vitiligo.

increased levels of nerve growth factor (NGF) significantly in vitiligo[32]. Stress up regulates NGF expression in hair follicles, decreases the high affinity TrkA receptor, increases production of p75NTR NGF-receptor, and increases in dorsal root ganglia the substance P neurons[33].

Catecholamine metabolite levels [homovanillic acid (HVA), vanilmandelic acid (VMA), 3-methoxytyramine (MT), normetanephrine (NMN), metanephrine (MN), 3,4-dihydroxy mandelic acid (DOMAC), and 3,4-dihydroxy phenylacetic acid (DOPAC)] were measured in 1-d urinary samples of 150 vitiliginous subjects and 50 normal subjects. HVA and VMA levels corresponded to the activity of the disease[34]. Stressors result in catecholamines discharge, which bind α-R in the mucosa and skin arteriolar wall leading to vasoconstriction, hypoxia, and overproduction of oxygen radicals that destroy melanocytes[34]. Mental stress could stimulate the hypothalamic-pituitary-adrenal axis and then secretion of catecholamines[34,35].

The autoimmune hypothesis

The etio-pathogenesis of "generalized" or non-segmental vitiligo is better explained by autoimmune mechanisms as vitiligo often has autoimmune comorbidities and it often responds to immunosuppressive treatments[36]. The reaction of immunity are cell-mediated, humoral (antibody-mediated), or through the cytokines.

The role of humoral immunity: In 2010, tyrosine hydroxylase antibodies checked with radioimmunoassay (RIA) in sera were obtained from 79 non-SV patients, 8 patients with SV, 91 subjects with other autoimmune diseases and 28 healthy subjects. TH antibodies revealed significantly in non-SV. Also, in non-SV, antibodies against MCHR1 (melanin-concentrating hormone receptor 1), tyrosinase[37] and pigment cell-surface antigens[38] were noted.

In 80% of active vitiligo patients, immunoglobulin G (IgG) and immunoglobulin M (IgM) against melanocytes were found. Low levels IgA also found in the inactive and control groups[38].

Furthermore, anti-thyroglobulin antibodies, antithyroid antibodies, anti-thyroperoxidase, and antismooth muscle antibody are present. Those are typically related to thyroid disease and other autoimmune diseases[39,40].

Melanin concentrating hormone (MCH) binds MCHR1 thus increase calcium influx and acting as an antagonist of α-melanocyte-stimulating hormone (α-MSH)[41-43].

The role of cell-mediated immunity: Immunohisto-chemical examination of the inflammatory infiltrates in perilesional vitiligo skin using single and double immunostaining for melanocytes, Langerhans cells, T-cells, and macrophages revealed higher densities of melanocytes in normal skin, *vs* non-affected skin in subjects with vitiligo. These T cell had dramatic production of (IL-2R), and increased CD8:CD4 ratio. Thus, melanocytes destruction may be cytotoxic CD8 T-cell mediated. Perilesional HLA-DR production (MHC class Ⅱ receptor) exhibited in all of the patients with vitiligo, especially along suprabasal and basal keratinocytes, due to local T cell reactivity. In addition, macrophages were numerous in vitiligo *vs* controls, whereas the CD36 subset of macrophages were higher in the later[44].

The role of cytokines in vitiligo: Beyond lymphocytes and antibodies, the immune system has a complex interplay of many cytokines. There are significantly increased expression of tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and IL-10[45]. As IFN-γ and TNF-α are T helper cell-1 (Th1) cytokines, so vitiligo is mediated by the Th1 response[46].

IL-17 plays role with macrophages, keratinocytes, and fibroblasts. In addition, it activates the expression of others, as IL-1 and IL-6, and TNF-α[47,48]. Examination of sera and tissue of 30 vitiliginous subjects and 20 normal subjects showed significant higher levels of IL-17 toward vitiliginous subjects and disease duration[47].

The biochemical Theory- reactive oxygen species model

Oxidative stress hypothesis suggests that imbalanced redox (reduction-oxidation) state of the vitiliginous skin. This results in the dramatic production of reactive oxygen species (ROS), as H_2O_2. ROS oxidize components of the cell leading to melanocytes destruction and creating the depigmented macules[49].

The redox status of vitiligo patients: Sera of

thirty-six patients with vitiligo (18 with inactive and 18 with unstable disease), and 40 normal subjects were examined for main factors of redox status involving selenium, malondialdehyde (MDA), vitamins A and E, and glutathione peroxidase (GPx) in the erythrocyte activities, catalase (CAT) and superoxide dismutase (SOD). Superoxide radicals are scavenged and their toxicity is reduced with SOD which transforms O_2- to H_2O_2 and O_2, and catalase transforms (H_2O_2) to (H_2O) and (O_2)[50]. As MDA results from lipid peroxidation, it is a marker of oxidative stress[51,52]. Selenium is required for GPx activity and vitamins A and E are important in antioxidant activity. Serum selenium, SOD and MDA are prominent in both unstable and inactive types. By enhancing SOD activity, the H_2O_2 accumulates. In addition, GPx detoxifies H_2O_2 (downstream enzyme). Therefore, GPx levels decreased in patients with vitiligo[50,53].

Increased SOD activity in patients with vitiligo is a response to oxidative stress; thus, H_2O_2 elevate as could not be eradicated by low level of CAT[53,54].

The role of tetrahydrobiopterin recycling in vitiligo: Another cellular pathway affected by accumulating H_2O_2 involves tetrahydrobiopterin. Tyrosinase is an imperative enzyme in formation of melanin[55]. L-tyrosine synthased from L-phenylalanine by the phenylalanine hydroxylase (PAH). The 5, 6, 7, 8-tetrahydrobiopterin or 6BH4 is essential cofactor for this process is. Defective recycling of 6BH4 lead to excess 7BH4 that is an inhibitor of PAH. Uncoupled PAH and 7BH4 found in suction blister material from the skin of vitiligo patients[56]. Kowlessur *et al*[57] (1996) also found that 7BH4 production yields H_2O_2. Haase *et al*[58] (2004) studied the enzyme dihydropteridine reductase (DHPR) (imperative to end the normal 6BH4 recycling). They assessed whole blood samples from 27 untreated vitiligo subjects and 8 normal subjects. The results showed that DHPR activity decrease with high concentrations of H_2O_2 and *vice versa*.

Effect of H_2O_2 on acetylcholinesterase (AchE) decrease in patients with vitiligo *vs* healthy controls[59,60]. Thus, AchE dependent on H_2O_2 concentration levels, *i.e.*, low H_2O_2 concentrations (approximately 10-6M or mol/L) activate AchE whereas high concentrations (10-3M or mol/L) deactivate AchE[60]. Butyrylcholinesterase (BchE) mediates the hydrolysis of acetylcholine. The hydrolysis reaction is one of the rate-limiting steps in cholinergic signal transduction[61,62].

In 2008, showed that xanthine oxidase (XO) is a source of H_2O_2. High concentrations of H_2O_2 inhibit the activity of XO, and *vice versa*[63].

Briefly, there are at least 5 important pathways enrolled in H_2O_2 overproduction in vitiligo: (1) Defective recycling of 6BH4[56,64,65]; (2) Catecholamine formation increased as levels of monoamine oxidase A (MAO) increased[34,66,67]; (3) Inhibition of thioredoxin/thioredoxin reductase by calcium[68-70]; (4) NADPH oxidase activities increased by the cellular infiltrate[71]; and (5) Nitric oxide synthase (NOS) activities increased[71].

Oxidative stress affects calcium homeostasis at the cellular level[72] in melanocytes and keratinocytes in vitiliginous patients[69].

Zinc-α2-Glycoprotein deficiency hypothesis

For the first time, Bagherani *et al*[73] and Yaghoobi *et al*[74] pointed the probable association which might be present between ZAG and vitiligo[73,74]. It was suggested that the pathogenesis of vitiligo could be attributed to decrease in ZAG as follows: (1) Studies have demonstrated that ZAG is acting as a keratinocyte-derived factor influencing melanocyte proliferation and dendricity[75,76]. So, ZAG could be considered as a marker of cells differentiation and maturation[76]; (2) A chronic detachment of melanocytes is an imperative pillar in the pathogenesis of vitiligo[74,77,78]. Thus, melanocyte adhesions to the other cells in epidermis will be impaired in the lack of ZAG; (3) Topical steroids are the most safeand effective forms of treatment for vitiligo, especially for the localized one[74,79], because of their ability to increase ZAG expression[80,81]; (4) Some studies have shown that zinc can precipitate ZAG[74,82]. Thus, the effectivity of zinc in treating this disease is related to its ability to precipitate circulating ZAG at the site of vitiligo[73]; and (5) The linkage signals on chromosome 7 in patients with GV and associated autoimmune diseases have been reported[73,83]. Surprisingly, ZAG gene is located on the chromosome 7[76].

Viral theory

There is a strong association between vitiligo and chronic hepatitis C virus (HCV) infection and autoimmune hepatitis[84]. Akcan *et al*[85] in 2006 reported a low hepatitis B virus (HBV) sero-positivity in vitiliginous patients. Previous or concurrent cytomegalovirus (CMV) infections may induce the etio-pathogenesis or deterioration of vitiligo[85,86].

Furthermore, other viruses as Epstein-Barr virus, hepatitis E virus, herpes virus and the human immuno-deficiency virus (HIV) also have suspicious association with vitiligo[86,87].

Intrinsic theory

Melanocytes in vitiligo have an intrinsic defect leading to their death. They demonstrate different abnormalities, including abnormal rough endoplasmic reticulum or deficiency of unidentified melanocyte growth factors such as basic fibroblast growth factor (bFGF) and decrease in the number of melanocytes expressing the c-kit receptor in lesional skin[88,89].

Melanocytes require a constant keratinocyte-derived c-Kit stimulation for their maintenance[90], thus weak expression of keratinocyte-derived factors, as stem cell factor (SCF), may lead to passive melanocyte death and might explain the Koebner phenomenon[91].

Cellular, molecular and biochemical alterations and melanocytes loss of in vitiligo

Recently, malfunctioning melanocytes found in vitiliginous lesions[92]. Electron microscopy, reverse transcription PCR (polymerase chain reaction) and southern blotting experiments revealed sporadic survival of melanocyte in vitiliginous lesions[93,94]. Thus, this points to presence of immature melanocyte precursors/stem cells[95,96]. Now, 2 pathways have been supposed for melanocytes loss: highly programmed death by apoptosis[77,91,97,98] and accelerated cell senescence[99].

Apoptosis and accelerated cell senescence: Melanocytes from non-lesional skin of vitiligo patients have abnormalities as cytoplasm vacuolization, rough endoplasmic reticulum dilatation, DNA marginalization in the nucleus, loss of dendrites and detachment[88,99,100].

Regarding keratinocytes, apoptosis occurs at least in the traumatized vitiligo skin[101]. Thus, basal and suprabasal epidermal cells in the depigmented and normally pigmented skin show degeneration due to swelling of the membrane-bound organelles, formation of vacuoles and cytoplasm condensation[102].

As vitiligo could inducted by trauma (Koebner's phenomenon). Lee *et al*[97] revealed the lower expression levels of the antiapoptotic Bcl-2 and FLIP proteins in vitiliginous skin *vs* the normally pigmented skin. On the other hand, there was dramatic levels of the proapoptoticBax and p53 proteins and of the active forms of caspase-3, 8 and 9[97].

Apoptosis triggered by normal developmental program, UV light, H_2O_2, staurosporine and other stimuli[91,103]. *NALP1* gene that stimulates cellular apoptosis[102,104], is associated with vitiligo susceptibility[105,106].

Epidermal melanocytes from epidermal melanin unit produce growth factors (GF) for melanocytes[107]. Therefore, its damage have imperative effects on melanocyte survival[91]. Thus, low levels of GF as SCF, endothelin-1 (ET-1) or high levels of melanocyte inhibiting cytokines, as TNF-α and IL-6 may lead to keratinocyte apoptosis, and then apoptosis of melanocytes[108].

Life span of lesional keratinocytes is greatly shortened when compared to the life span of normal and non-lesional vitiligo keratinocytes. It also shows modification of proliferation and senescence marker expression (p16, p53, p21), when compared to keratinocytes from clinically noninvolved skin[98].

Although apoptosis and senescence of epidermal keratinocytes is a response to various stimuli, they also share some cellular mechanisms and controlled by similar molecular regulators[109]. Both apoptosis and aging induced by stress signals as ROS accumulation and DNA damage[110]. The paradigmatic proapoptotic factor p53[111], is also a guard keeper of DNA integrity which triggers cell cycle arrest in DNA damaged cells[109].

Melanocytorrhagy theory: Gauthier *et al*[78] in 2003 mentioned that NSV occurs due to "melanocytorrhagy", or a chronic melanocytes detachment and loss caused by trauma and other stressors include catecholamines, ROS, or autoimmune elements. This theory combined the concepts from other theories mentioned before to elaborate a single integrated explanation of vitiligo pathogenesis[78].

A study done by Tobin *et al*[92] in 2000 proposed loss of melanocytes in vitiligo. They explained these findings because of oxidative stress caused by H_2O_2. Gauthier *et al*[78] (2003) also reported that impaired cell adhesion plays a role in vitiligo pathogenesis as the synthesis of extracellular matrix components by keratinocytes may be defective, the presence of focal gaps in the basement membrane and impaired formation of basement membrane. These abnormalities weaken the basal attachment of melanocytes. Trauma could aggravate this susceptibility with subsequent chronic melanocyte loss, known as melanocytorrhagy.

Le Poole *et al*[112] mentioned that the protein tenascin may play a role in decreasing melanocytes adhesion in vitiligo. This protein was highly expressed in patients with vitiligo than the controls[112]. This can explain the development of vitiligo by Koebner phenomenon, which represent "transepidermal migration"[78,113].

Integrated theory (Conversion theory)

Despite all the mentioned theories are attractive, it is likely that vitiligo is a result of the convergence of these pathological pathways. Most experts agree that vitiligo may be a syndrome with a multi-factorial etiology rather than a single entity[114] (Figure 2).

TREATMENT

The disfigurement associated with vitiligo could cause serious emotional stress for the patient and affect his quality of life[115]. Sun protection of vitiliginous areas with sun blocks is imperative[115,116] to prevent sunburn, photodamage and occurrence of Koebner phenomenon. In addition, sun blocks decrease tanning of the uninvolved skin and thus lessen the contrast with vitiliginous lesions[117].

There is no treatment ensures complete cure of vitiligo. Therefore, there is a plethora of modalities, such as topical corticosteroids, vitamin-D derivatives, calcineurin inhibitors, photochemotherapy [psoralen plus UV-A (PUVA), psoralen with sunlight (PUVAsol)], phototherapy (UV-A, narrowband UV-B), surgical techniques[117-122], excimer laser[115,117,118-123], topical prostaglandin E (PGE2)[118], and combinations of topical therapies and light treatment[79]. Complementary and integrative therapies are also used, as ginkgo biloba[79], and levamisole[124], because of their immune-modulating properties[117].

Pseudocatalase cream with Dead Sea climatotherapy can also promote repigmentation[117]. Topical flu-

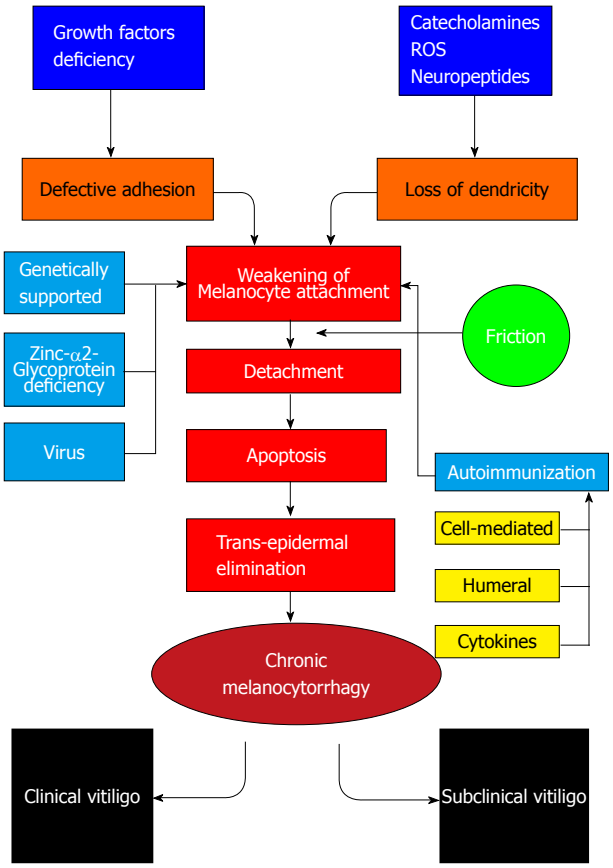

Figure 2 Pathogenesis of vitiligo.

orouracil[125], topical melagenina Ⅰ and Ⅱ, minoxidil[118], oral L-phenylalanine[117,126-129], homeopathy, ayurvedic medicine, climtologic and balneologic therapies are other therapeutic options for vitiligo[118]. Patients with widespread disease (affecting more than half of body) seeking stable matching of skin color but for whom repigmentation is not expected will be more satisfied if normal pigmented areas are depigmented with 20% monobenzyl ether of hydroquinone, twice per day for almost one year. Another helpful modality for vitiligo universalis, is combined both the topical application of 4-methoxyphenol and the Q-switched (QS) ruby laser[115]. Q-Switched ruby laser destroy the melanosomes present in melanocytes and keratinocytes by selective photothermolysis[130].

According to the impact of oxidative stress on vitiligo, α-tochopherol can be used alone or with topical corticosteroids in combinedation with psoralen plus ultraviolet A (PUVA)[131,132]. Antioxidant pool (tochopherol acetate, ubiquinone, selenomethionine, methionine) could be used in vitiligo aiming to enhance the enzymatic and the non-enzymatic antioxidant activity[131,132]. Food additives, contaminants, preservatives and cosmetic products could exacerbate vitiligo due to oxidative stress in melanocytes[133].

High consumption of omega-6 and decreased omega-3 intake produce free radicals and pro-inflammatory cytokines. On the other hand, omega-3 intake exert protection by enhancing TGF-β mRNA levels and antioxidant enzymes[134] and inhibiting pro-inflammatory cytokines as TNF-α[135].

Cell membranes enriched with omega-3 polyunsaturated fatty acids have elevated activity of glutathione peroxidase (GSH)[136]. In addition, omega-3 fatty acids contains indole-3-carbinol which activates CYP1A1 that is responsible for hydroxylation of estrogens to 2-hydroxyestrone[137]. Furthermore, omega-3 fatty acids have a vital role in the function of the central nervous system and affect the susceptibility and prognosis of depression[135]. Twenty percent of patients with vitiligo are found to have depression. This highlights the benefits of these lipids in vitiligo[137].

In conclusion, many theories were elaborated to clarify vitiligo pathogenesis. It is a multifactorial disease involving the interplay of several factors. Future research is needed to clarify the interaction of these factors for better understanding of vitiligo pathogenesis and subsequent successful treatment.

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