SECTION 1

Pathogenesis and medical treatment

CHAPTER 1
Pathogenesis of vitiligo

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Introduction

Vitiligo is an acquired cutaneous hypomelanosis with a 0.5–2% incidence worldwide, without predilection for sex or ethnicity. The clinical presentation is characterized by well-circumscribed white macules. Several clinical phenotypes have been identified. Generalized vitiligo is characterized by acquired depigmentation due to melanocyte loss, in a pattern that is non-focal and generally bilateral across the midline, though not necessarily symmetric [1]. This definition differentiates generalized vitiligo from segmental vitiligo and other localized forms of vitiligo whose true pathogenic relationship to generalized vitiligo is as-yet unknown.

This chapter is a review of the recent developments of vitiligo pathogenesis. There are three major hypotheses for the pathogenesis of vitiligo that are not exclusive of each other – the autoimmune hypothesis, the neuronal dysfunction hypothesis, and the melanocyte self-destruction hypothesis. Several other hypotheses have been recently proposed.

Vitiligo: a melanocyte disorder or more?

Melanocytes present or absent in vitiligo macules?

Vitiligo is characterized by a disappearance of epidermal and/or follicular melanocytes. It is likely that melanocytes are destroyed by an as-yet unknown process. Indeed, melanocyte destruction has never been clearly demonstrated [2]. One recent study reports that melanocytes are never completely absent in the skin [3]. Melanocyte cultures were successfully established from depigmented epidermal suction blister roof of 12 randomly selected vitiligo patients. These "vitiligo" melanocytes produced melanin in vitro. Although interesting, these observations in a small group of patients cannot be generalized. The persistence of melanocytes within vitiligo macules was already reported in 1956 [4]. Besides the so-called "absolute" type of vitiligo in which there are no dopa-positive melanocytes in the vitiliginous epidermis, there are "relative" types of vitiligo in which melanocytes remain in the white macules with a decreased dopa-positivity. It is likely that the disappearance of epidermal melanocytes in vitiligo macules is not an immediate process, but is a progressive one. Indeed, it may be suggested that the "relative" types of vitiligo are considered possible forerunners of the "absolute" types. Thus, it would not be surprising to find melanocytes in the epidermis of the white macule of "relative" vitiligo. An immunohistological study of vitiliginous skin using a panel of melanocyte markers, related and unrelated to the melanogenic pathway, could not detect identifiable epidermal melanocytes [5]. From the presently available data, it is generally agreed that there are no longer functional melanocytes in vitiligo skin and that this loss of histochemically recognizable melanocytes is the result of their destruction.

The impact of vitiligo on melanocyte stem cells (MSC) is not known. MSC are present in the bulge region of hair follicles in the adult skin in mice. Undifferentiated MSCs in the bulge have been shown to express the three transcription factors, PAX 3, SOX 10, and MITF. These factors play a key role in controlling the balance between MSC maintenance and differentiation. Studies to evaluate MSCs in vitiligo-pigmented and depigmented hair follicles are strongly required to better understand the mechanism of poliosis in vitiligo patients and

the cellular event underlying perifollicular repigmentation of vitiligo [6].

Keratinocytes

Several observations suggest that epidermal cells other than melanocytes are also altered in vitiligo involved and uninvolved skin. Epidermal keratinocytes produce several factors that support the growth and differentiation of neighboring melanocytes, such as basic fibroblast growth factor (b-FGF) and stem cell factors (SCF). A recent study demonstrated that the expression of SCF ($P < 0.001$) and b-FGF was usually reduced in the depigmented compared with the normally pigmented vitiligo epidermis [7]. SCF has been demonstrated to prevent TRAIL-induced melanocyte apoptosis in vitro. These results suggest that melanocyte cell death in vitiligo can result from deprivation of keratinocyte-derived SCF.

Cytoplasmic vacuolization and/or the presence of an extracellular granular material that may be derived from the cytoplasm of altered keratinocytes have been reported mainly in the adjacent normal-appearing vitiligo skin, but also in the perilesional skin and rarely in the lesional skin [8]. Focal areas of vacuolar degeneration in the lowest layers of the epidermis, especially in the basal layer in association with mild mononuclear cell infiltrate, have also been observed [9].

The significance of these morphological observations is not known, but several hypotheses can be proposed. They may be related to architectural disturbances induced by a local immunological reaction. They may be due to toxic intermediate metabolites of melanogenesis, which destroy not only the pigment cell from which they originate [8], but also the adjoining keratinocytes. The recently proposed theory of a breakdown in the detoxification mechanisms in vitiligo skin fits very well with these observations.

Langerhans cells

The role of Langerhans cells in vitiligo has been open to controversy. The Langerhans cell density evaluated either by histochemical techniques (ATPase) or with the monoclonal antibodies OKT6 and anti-HLADR has been variably reported as decreased, normal, or increased [10]. In addition to these quantitative changes of Langerhans cells, a functional impairment of these cells has also been documented in vitiligo skin. How this functional impairment of Langerhans cells is related to the pathogenesis of vitiligo remains to be established.

All these observations suggest that vitiligo affects the entire keratinocyte–Langerhans cell-melanocyte unit (KLM) [11]. In the epidermis there is a complex exchange of messages between these three cell types that is just beginning to be understood. No doubt a better clarification of these epidermal cell interactions will help in understanding the basic mechanisms involved in vitiligo.

Genetics of vitiligo

Epidemiological data

Familial studies have shown the increased prevalence of vitiligo in close relatives of affected individuals. In a large series performed in India, this increase was about 4.5-fold in close biological relatives [12]. Another study performed on 160 white kindred living in US shows a relative risk (RR) for vitiligo of about 7 for parents, about 12 for siblings, and about 36 for children [13]. The pattern of relationship between RR and degree of kinship indicates involvement of genetic factors, although it is not consistent with single-locus Mendelian transmission. The major genetic component in vitiligo pathogenesis and also the role of environmental factors were recently emphasized [14]. In this epidemiological study the frequency of vitiligo in probands' siblings was 6.1%, about 18 times that of the population frequency. Nevertheless, the concordance of vitiligo in monozygotic twins was only 23%, indicating that a non-genetic component also plays an important role. Moreover, probands with earlier disease onset tended to have more relatives affected with vitiligo, suggesting a greater genetic component in early onset families.

One vitiligo or several vitiligos?

For most authors, vitiligo is a unique disorder with several clinical presentations but one physiopathology. Indeed, almost all the recent genetic studies have ignored the clinical presentation of patients. However, recent data strongly suggest that there is not one

vitiligo but several vitiligos. A complex segregation analysis was performed on 2247 Chinese patients and their families. For the first time the results were analyzed according to the clinical manifestations [15]. The results showed a different age of disease onset depending on the subtypes of vitiligo. More interestingly, a polygenetic additive model was found to be the best model for segmental, localized, acrofacial, and generalized vitiligo whereas the best model for universal vitiligo was an environmental model. All of these data suggest that heterogeneous pathogeneses underlie different phenotypes of vitiligo.

Genetic aspects of vitiligo

The earliest genetic studies of vitiligo were case-control association studies of the major histocompatibility complex (MHC). They were carried out by testing various different vitiligo phenotypes versus controls in many different populations. Genetic association of vitiligo with alleles of MHC loci appeared to be strongest in patients and families with various vitiligo-associated autoimmune/autoinflammatory disorders versus patients and families with only generalized vitiligo. Thus, it is not clear whether the MHC association is with vitiligo, vitiligo-associated autoimmune/autoinflammatory disorders, or both.

Allelic association between vitiligo and a number of other candidate genes has also been described (Table1.1).

Table 1.1 Susceptibility loci for vitiligo.

References	Susceptibility locus	Mapping
[73]	SLEV1	17p13
[18]		
[16]	AIS1	1p31.3–p32.2
[18]	AIS2	7p
[18]	AIS3	8q
[74]		6p21.3–21.4
[75]		4q13–q21

Modified from Passeron T, *J Autoimmun* 2005;**25**:63–8, and Spritz RA, *J Dermatol Sci* 2006;**41**:3–10.

Which gene(s) for vitiligo?

Two large genome-wide screens for generalized vitiligo showed significant linkage of an oligogenic autoimmune susceptibility locus, termed AIS1 (1p31.3–p32.2) [16,[17]. An additional seven signals on chromosome 1,7,8,11,19, and 22 met genome-wide criteria for "suggestive linkage." In an extended study with a cohort of 102 multiplex families the localization of AIS1 was confirmed and two new susceptibility loci have been found. AIS2 is located on chromosome 7 and AIS3 on chromosome 8. Additionally, the locus SLEV1 on chromosome 17 was confirmed and two new potential linkages on chromosome 9q and on 13q are also reported (Table 1.1) [18]. Interestingly, all loci except AIS3 derive principally from the autoimmunity-associated family subgroup. These loci may predispose to a vitiligo-associated autoimmunity diathesis. On the other hand, analyses suggest a linkage to SLEV1 in the autoimmune families and non-linkage in the non-autoimmune families. Thus, linkage to SLEV1 in these families indicates that SLEV1 confers susceptibility to a broader range of autoimmune diseases than just lupus and vitiligo. A genome-wide linkage analysis in Chinese families identified interesting linkage evidence in 1p36, 4q13–21, 6p21–p22, 6q24–q25, 14q12–q13, and 22q12. These findings in the Chinese population shared a minimal overlap with the linkage findings in the Caucasian population. Such little overlap between the linkage findings of this two populations may suggest that vitiligo is associated with a strong genetic heterogeneity [19].

Many candidate genes for vitiligo have been proposed so far (Table 1.2). However, most of the loci described do not correspond to positions of these proposed biological candidate genes.

Finally, one of the best candidate genes could be FOXD3 ("Forkhead box" D3). FOXD3 is located on chromosome 1 (1p32–p31) and is a transcription factor that suppresses melanoblast development from the neural crest [20]. Therefore, dysregulated (over-)expression might harm melanocytes. Moreover FOXD3 also regulates endodermal differentiation including thyroid, pancreas, adrenal, and gut [21] and other FOX factors are involved in autoimmune syndromes [22]. Mutations in FOXD3

Table 1.2 Vitiligo candidate genes.

Gene	Mapping	Product	Disease
PTPN 22	1p13	Lymphoid protein tyrosine phosphatase	Vitiligo vulgaris
FOXD3	1p32–p31	Transcriptor factor involved in melanoblast differentiation	Early and progressive vitiligo
VIT 1/FBX 011	2p21	?	Vitiligo vulgaris
CTLA 4	2q33	Antigen-4 of T-cytotoxic lymphocytes	Vitiligo vulgaris
MITF	3p14.1–p12.3	Transcription factor	Vitiligo vulgaris
KIT	4q12	Transmembrane tyrosine kinase	Vitiligo vulgaris
MHC (HLA-DRB1, HLA-DRB4, HLA-DQB1)	6p21.1	Major MHC	Vitiligo vulgaris
ESR 1	6p25.1	Oestrogen receptor 1	Vitiligo vulgaris
CAT	11p13	Catalase	Vitiligo vulgaris
GTPCH (GTP-cyclohydoxylase I gene)	14q22.1–q22.2	Rate-limiting enzyme of the tetrahydrobiopterin pathway	Vitiligo vulgaris
ACE	17q23	Angiotensin converting enzymes	Vitiligo vulgaris
AIRE	21q22.3	Transcriptor factor	APECED
COMT	22q11.2	Catecholamine O methyl transferase	Vitiligo vulgaris

Modified from Passeron T, *J Autoimmun* 2005;**25**:63–8, and Spritz RA, *J Dermatol Sci* 2006;**41**:3–10.

leading to elevated FOXD3 transcription have been recently reported in one AIS1-linked family [23]. Thus, FOXD3 is worth further investigation and represents a serious candidate gene in AIS1-linked autoimmune disease.

Pathogenesis

The classic hypotheses

Vitiligo is an autoimmune disease

This theory is the most long-standing and popular hypothesis for the pathogenesis of vitiligo. It proposes that melanocytes are killed by autoimmune effector mechanisms.

Association with autoimmune disease

Sporadic generalized vitiligo is associated with autoimmune thyroid disease, pernicious anemia, Addison's disease, systemic lupus erythematosus [14]. Familial generalized vitiligo is also characterized by a broad repertoire of associated autoimmune diseases, such as thyroiditis, rheumatoid arthritis, psoriasis, adult-onset-dependent diabetes mellitus, pernicious anemia, and Addison's disease [24]. Furthermore generalized vitiligo is a component of the APECED (APS1) and Schmidt (APS2) multiple autoimmune disease syndromes. These same vitiligo-associated autoimmune/autoinflammatory disorders also occur, at increased frequencies, in patients' first-degree relatives, regardless of whether or not those relatives have vitiligo themselves. These observations suggest that specific genes predispose to a specific group of autoimmune diseases that includes generalized vitiligo, autoimmune thyroid disease, rheumatoid arthritis, psoriasis, adult-onset insulin-dependent diabetes mellitus, and pernicious anemia.

Cellular immunity

Recent evidence has emerged for a role for cell-mediated immunity in vitiligo pathogenesis. The

discovery of a T-cell infiltrate in the margin of inflammatory vitiligo was the first clue for participation of cellular immunity in vitiligo pathogenesis. Infiltrating activated CD4 and CD8 T-cells, but not the B-cells, have been observed at the periphery of vitiligo lesions [25]. A more recent study of vitiligo lesional skin noted a high frequency of cutaneous lymphocyte antigen-positive-activated cytotoxic T-cells clustered in perilesional skin in the vicinity of disappearing melanocytes [26]. Furthermore, melanocytes in close proximity to activated lymphocytes focally expressed HLA-DR and intercellular adhesion molecule-1, suggesting a major role for skin-homing T-cells in melanocyte death [26]. The reports of an increase of CD45RO memory T-cells, increased levels of soluble interleukin-2 receptors and expression of the cutaneous lymphocyte antigen in number infiltrating T-cells, all suggest an activation of circulating T-cells and their recruitment to the vitiligo skin [27–29]. In vitiligo skin the CD4/CD8 ratio is reversed with a predominant presence of CD8 T-cells.

Further evidence for a role played by cytotoxic T-cells in vitiligo stems from studies of melanoma patients. Vitiligo-like depigmentation has been observed following successful immunotherapy of melanoma, including high-dose IL-2 therapy, infusion of peptide pulsed dendritic cells, and Melan A/MART-1 specific CTL clones [30]. A specific cellular immune response predominantly directed against the melanosomal protein Melan-A/MART-1 was observed in HLA-A2-positive vitiligo patients where CD8+ T-cells displaying Melan-A/Mart-1-specific reactivity ex vivo were demonstrated in the peripheral blood of these patients. Another study reported evidence of an association between CD8 + T-lymphocyte reactivity to the melanocyte antigen gp100 and to a lesser extent Melan-A/MART-1 and vitiligo [30]. These findings support the concept of an immunopathological mechanism in vitiligo in which cell-mediated play a crucial part. Recently, new understanding for the requirements for CD8+ T-cell mediated destruction of melanocytes was brought [31]. CD4+ T-cell help induced by systemic immunization and a local inflammation are both required to break MHC class-I-restricted T-cell tolerance.

Table 1.3 Identified target autoantibodies for vitiligo antibodies.

Autoantigen	Function
Tyrosinase	Melanogenic enzyme
TRP-2	Melanogenic enzyme
TRP-1	Melanogenic enzyme
Pmel-17	Melanocyte-specific protein
MCHR1	Melanin concentrating hormone receptor 1
SOX 9	Transcription factor
SOX 10	Transcription factor

Humoral immunity

Several circulating autoantibodies (Table 1.3) have been found in sera of vitiligo patients. These include antibodies to non-pigment cell antigens (common tissue antigens), cytoplasmic pigment cell antigens, and pigment cell surface antigens [32]. The heterogeneity of this antibody response is surprising and does not fit with a selective destruction of melanocytes. One reasonable explanation is that this humoral response could be secondary to a primary melanocyte destruction mediated by other mechanisms.

The incidence and serum level of antibodies was found to correlate with the disease activity and the extent of the cutaneous depigmentation. Functional in vitro assays have shown the ability of antibodies to damage melanocytes, both by complement activation and by ADCC [33]. Furthermore injections of IgG fractions of serum from patients with vitiligo have a destructive effect on melanocytes of the human skin grafted onto nude mice [34].

Antibody-dependent immunity against the mélanosome membrane protein-1 (TYRP-1) of melanocytes leads to autoimmune hypopigmentation. Hypopigmentation occurred in mice deficient in activating FcR containing the common γ subunit and in mice deficient in the C3 complement but not in mice doubly deficient in both FcγRγ and C3 [35].

The neural hypothesis

There are several observations, clinical findings, and laboratory evidence that suggest the involvement of the nervous system in the pathogenesis of

vitiligo. Embryologically, melanocytes are derived from the neural crest. There are isolated reports of vitiligo associated with viral encephalitis and transverse myelitis. Communication between the nervous system and epidermal melanocytes has been proved [36]. Ultrastructural studies demonstrate frequent direct contacts between dermal nerve endings and melanocytes in vitiligo skin [37] or structural alterations (swelling of axons, duplication of the basement membrane, etc.) [38,39], but the significance of these morphological findings is unknown. The neural hypothesis is based in the first place on the presence of segmental vitiligo. The distribution of segmental vitiligo is often said to be dermatomal, suggesting the role of regional nerves in this condition. In actuality it is unilateral, but not dermatomal (i.e. it does not follow a specific pattern of cutaneous sensory nerves) [40].

Thus, the role of the nervous system in the pathogenesis of vitiligo is still undefined.

A few physiological studies have demonstrated altered bleeding times, epinephrine vasoconstrictor effect, and abnormal sympathetic skin responses in lesions of vitiligo [41,42]. Other studies have shown altered neuropeptides in vitiligo. Aberrations in β-endorphin and met-enkephalin secretion have been reported [43]. The plasma met-enkephalin levels were generally higher in vitiligo patients, especially in those with active vitiligo, than in controls. Immunohistological observations suggest that the immunoreactivity to neuropeptide Y and vasoactive intestinal polypeptide is increased at the marginal areas or within vitiligo macules. These observations support the hypothesis of neural involvement and neuro-immunomodulation in vitiligo [39]. Still other studies have demonstrated a reduction in the immunoreactive nerve growth factors (NGFr-IR) [44] and an absence of Merkel cells [45].

Several studies demonstrating abnormalities of acetylcholine, catecholamines, or related enzymes (catechol-*o*-methyltransferase (COMT) and monoamino oxidase [46,47]) have also been reported with conflicting results [48–50]. A reduced acetylcholinesterase activity in vitiliginous skin as compared to adjacent normal skin has been reported [51]. Increased urinary levels of catecholamines have been found during the active phase of vitiligo [52,53].

The autocytotoxic theory

In 1971, Lerner [54] postulated that melanocytes have a genetically based protective mechanism that eliminates toxic products like DOPA, DOPAchrome, and 5,6-dihydroxyindole, manufactured during melanogenesis. Individuals who are deficient in this mechanism have accumulation of these melanotoxic products, which results in depigmentation. Another possible mechanism could be damage by genetic mechanisms or by perioxidation [55] to the membranes of melanosomes, which prevent leakage of these compounds into the cellular milieu [56,57].

The oxidative stress theory proposes that melanocyte death results from an intrinsic increased sensitivity to oxidative stress either from toxic intermediates of melanin precursors or from other sources. In vivo and in vitro evidence for hydrogen peroxide (H_2O_2) accumulation in the epidermis of vitiligo patients has been reported, resulting from low epidermal catalase levels [58]. Several studies suggest that (a) cultured vitiligo melanocytes exhibit increased sensitivity to oxidative stress and (b) catalase helps to establish vitiligo melanocyte cultures and to restore melanocyte functions after exposure to H_2O_2 [2]. According to Schallreuter and her group, the origin of the epidermal H_2O_2 accumulation and low epidermal catalase levels within the entire skin of vitiligo patients may arise from several potential sources: (1) perturbed (6*R*)-L-erythro-5,6,7,8-tetrahydrobiopterin (6BH4) de novo synthesis/recycling/regulation; the absence of catalase leads to accumulation of toxic superoxide radicals. One such mechanism involves a group of compounds called pteridines. L-tyrosine is the central substrate for catechol synthesis in keratinocytes and melanin synthesis in melanocytes L-tyrosine itself is produced from L-phenylalanine and the reaction is regulated by the enzyme phenylalanine hydroxylase. This enzyme is under the control of pteridines including 5,6,7,8-tetrahydrobioopterin ($6BH_4$). Defects in the production of pteridines lead to the accumulation of epidermal phenylalnine and shortage of L-tyrosine. A clinical study using a loading oral dose of L-phenylalanine showed slower turnover of L-phenylalanine to L-tyrosine in patients compared with controls [59]. The defective deranged synthesis of pteridins leads to the concomitant accumulation of H_2O_2;

(2) impaired catecholamines synthesis with increased monooxidase A activities; (3) low glutathione peroxidase activities; (4) "oxygen burst" via NADPH oxidase from a cellular infiltrate [58]. Under in vitro conditions, vacuole of vitiligo melanocytes has been demonstrated which was reversible upon exogenous addition of bovine catalase to the culture medium [3]. Until now, this interesting concept has not yet been validated in vivo in patients with vitiligo. Whether H_2O_2 is the cause or the consequence of vitiligo remains to be identified. Another mechanism involves the ion calcium. In the epidermis there is an efficient antioxidant mechanism of thioredoxin/thioredoxin reductase (T/TR) which reduces H_2O_2 to water. The activity of this system is allosterically regulated by ionic calcium and defective uptake of calcium could result in altered redox status and accumulation of H_2O_2 [60]. Estrogens can also contribute to hydrogen peroxide [61]. Successful removal by a UVB-activated pseudocatalase has also been reported. However, this conclusion arises from an open trial including only 33 patients and the results have not been confirmed by further studies. The efficacy of pseudocatalase to promote vitiligo repigmentation is still a matter of debate. However, there is no abnormality in blood antioxidant status in patients with vitiligo. Blood levels of superoxidase dismutase, glutathione peroxidase, glutathione reductase, non-enzymatic oxidants such as α-tocopherol (Vit E), retinol (Vit A), ascorbic acid (Vit C) have been found to be normal.

In the context of the oxidative stress theory, selenium is widely prescribed to stabilize and to repigment vitiligo. However, two distinct studies demonstrated that there is an increase in total blood antioxidant status (high serum selenium levels) in vitiligo patients [62,63]. As a consequence, oral supplementation should not be practiced in patients who exhibit a spontaneous increase in selenium levels, as it could be potentially harmful (selenium toxicity).

The new hypotheses

A disorder of melanocyte survival

The active mechanism by which melanocytes are destroyed in vitiligo skin has not yet been determined. Several morphological observations suggest the involvement of melanocyte apoptosis and of the SCF/c-kit/MITF/Bcl-2 pathway in the pathogenesis of vitiligo. This pathway plays a key role in the maintenance of melanocyte survival. SCF of keratinocyte origin strongly protects melanocytes from TNF-related apoptosis inducing ligand (TRAIL) [64]. Bcl-2, a MITF-dependent kit transcriptional target in melanocytes, is essential for the maintenance of an appropriate lifetime for melanocytes. The decrease of Bcl-2 expression of melanocytes increases their susceptibility to apoptosis. Bcl-$2^{-/-}$ mice develop graying and whitening of hair early in life during the second hair cycle, due to disappearance of follicular melanocytes. Levels of SCF expression ($P < 0.001$) are reduced in the depigmented epidermis of vitiligo patients compared to normally pigmented paired epidermis [7].

A reduction in the number of kit-positive melanocytes in the perilesional skin of vitiligo patients has also been reported. Immunohistochemistry with antibodies to melanocyte markers revealed that at the edges of the lesional vitiligo epidermis, melanocytes do not express the kit-protein and the melanocyte-specific microphthalmia transcription factor (MITF-M) [65]. Western blotting confirmed down-regulated expression of c-kit and MITF-M proteins at the edge of the lesional epidermis in vitiligo. These findings strongly suggest a deficiency of the melanocyte survival pathway SCF/c-kit/MITF/Bcl-2 which might be responsible for dysfunction and/or loss of melanocytes in vitiligo epidermis.

Interestingly, we have observed a marked progression of a vitiligo which was stable since many years after treatment with tyrosine kinase inhibitors that inhibit c-kit [66]. Moreover, several cases of vitiligo-like depigmentation occurring after treatment with new tyrosine kinase inhibitors that inhibit c-kit (STI-571 and SU 11428) have been reported [67,68].

The melanocyte growth factor deficient theory

Defective growth and passage capacities of vitiligo melanocytes derived from uninvolved and perilesional skin in vitro have been described [69]. Interestingly, these growth defects of vitiligo melanocytes could be partially corrected in vitro by

the adjunction of fetal lung fibroblast-derived growth factors. In addition, melanocytes taken from actively repigmenting vitiligo macules grow correctly, suggesting a correction of the growth defect. Based on these results, it has been suggested that a decreased concentration of melanocyte growth factor(s) could play a role in the pathogenesis of vitiligo [70].

Viral infections

Viral infections have been implicated in the pathogenesis of autoimmune diseases. In one study, CMV DNA was detected in the involved and uninvolved skin of 38% of vitiligo patients and 0% of control subjects. EBV, CMV, Herpes simplex, varicella-zoster, and human T-lymphotropic virus were negative. There are no definitive data to confirm or refute the viral hypothesis. Additional studies are needed to confirm these results [71].

Melanocyte defective adhesion

Interaction between melanocytes and the dermoepidermal basement membrane are mediated by integrins ($\alpha 6\beta 1$). Interactions between melanocytes and keratinocytes are mediated by cadherins in association with β-catenin.

Repeated friction in non-lesional skin of vitiligo patients induces detachment and transepidermal elimination of melanocytes [72]. This suggests that minor mechanical trauma in non-lesional vitiligo skin is probably the cause of depigmentation occurring in the Köbner's phenomenon. Transepidermal elimination of melanocytes in vitiligo may be a possible mechanism of chronic loss of melanocytes, perhaps previously damaged by another process [2].

Conclusion

From the available data, it is likely that the loss of epidermal and follicular melanocytes in vitiligo results in melanocyte death. The identification of at least two different clinical phenotypes of vitiligo suggests that melanocyte destruction may be the result of several different pathogenetic mechanisms. Many different hypotheses have been proposed. Recent developments of the genetics of generalized vitiligo strongly suggest a role of immunological factors in generalized vitiligo susceptibility. Besides genetic and immunologic factors, the environment is likely to be involved in the pathogenesis of vitiligo in ways that are not yet known. There are now probably too many hypotheses of vitiligo. All hypotheses are not mutually exclusive. A "consequence" theory suggests that genetic factors, stress, accumulation of toxic compounds, infection, autoimmunity, altered cellular environment, and impaired melanocyte migration and proliferation can all contribute to the phenomenon of vitiligo.

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