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Review

Physiopathology and genetics of vitiligo

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Abstract

Generalized vitiligo is an acquired disorder in which white patches of skin and overlying hair result from autoimmune loss of melanocytes from involved areas. The autoimmune pathogenesis of vitiligo has become a rapidly evolving field of research. A humoral immune reaction has been implicated through the detection of circulating antibodies. However, recent research focuses on a melanocyte-specific cytotoxic-T-cell immune reaction in the melanocyte destruction.

Several candidate genes have been proposed for vitiligo susceptibility. They include genes important for melanin biosynthesis, response to oxidative stress and/or regulation of autoimmunity. A recent genome-wide scan performed on families with numerous members presenting vitiligo has clearly revealed linkage of susceptibility loci.

Keywords: Autoimmunity; Pathogenesis; Genetics

1. Introduction

Vitiligo is an acquired cutaneous disorder of pigmentation, with a 0.5–2% incidence worldwide, without predilection for sex or race. The clinical presentation is characterized by well-circumscribed white cutaneous macules. Clinical presentation includes segmental vitiligo with a dermatomal pattern of the lesions, focal vitiligo characterized by a limited number of depigmented macules without segmental distribution, universal vitiligo which involves complete or almost complete body surface area and generalized vitiligo, the most common type, characterized by a bilateral and symmetrical distribution of the lesions (Fig. 1). Ultrastructural and immunohistological studies show the absence of melanocytes in vitiligo lesions. The mechanisms leading to the loss of pigment cells are not yet fully understood. Melanocytes could be destroyed by necrosis or more probably by apoptosis [1]. Recent data suggest a transepidermal elimination of melanocytes [2]. There are three major hypotheses for the pathogenesis of vitiligo that are not exclusive of each other: autoimmune, autocytotoxic/metabolic and neural dysfunctional. Recent data have brought strong evidence supporting an autoimmune pathogenesis of vitiligo. Familial clustering is not uncommon, indicative in a non-Mendelian pattern like a number of other autoimmune disorders, of polygenic, multifactorial inheritance of vitiligo. Several candidate genes have been proposed for vitiligo but none has been really convincing. For the first time, recent genome-wide scans performed on families with numerous members presenting vitiligo have clearly revealed linkage of susceptibility loci.

2. Vitiligo: an autoimmune disorder?

2.1. Association with autoimmune disorders

The association of vitiligo with other autoimmune disorders has been widely reported and has constituted one of the first clues for an autoimmune origin of vitiligo. A recent study performed on 2624 vitiligo probands from North America and the U.K. confirmed the significant increase of frequencies of six autoimmune disorders in vitiligo probands and their first-degree relatives: vitiligo itself, autoimmune thyroid disease (particularly hypothyroidism), pernicious anemia, Addison's disease, systemic lupus erythematosus, and probably

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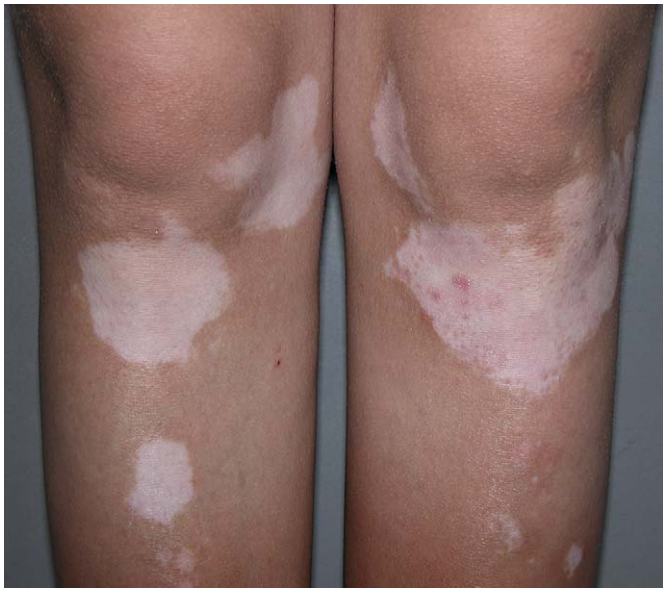

Fig. 1. Clinical presentation of generalized vitiligo. Note the symmetrical distribution of the lesions.

inflammatory bowel disease [3]. These associations indicate that vitiligo shares common genetic etiologic links with these other autoimmune disorders.

2.2. Effect of immunomodulating therapies

Routine non-surgical repigmenting treatments utilize immune-modulators including phototherapy, topical steroids and inhibitors of the calcineurin pathway [4,5]. Steroids are known for their anti-inflammatory and immunosuppressive properties. However, pharmacological actions of topical steroids are complex [6]. They can down regulate major histocompatibility (MHC) class II and promote Th2 response. The cytokine secretion is also regulated and tumor necrosis factor (TNF)-α is inhibited. Such phenomena are now described to be involved in the physiopathology of vitiligo (see below) [7]. Topical inhibitors of the calcineurin pathway including tacrolimus and pimecrolimus have demonstrated their efficacy in repigmenting vitiligo. They act by inhibiting the activation of T cells. Moreover, tacrolimus has been reported to decrease the expression of TNF-α on treated vitiligo lesions [8]. The mechanism of action of phototherapy is certainly the most complicated one. Ultraviolet (UV) radiation promotes the proliferation and differentiation of melanocytes. However, UV radiation also induces apoptosis of Langerhans and T cells, and leads to local and systemic immunosuppression and promotion of Th2 response [9,10].

On the other hand, some immunomodulating therapies have been reported to produce or stimulate vitiligo lesions. Self-antigens are used in the immunotherapy of melanoma. Many cases of vitiligo-like depigmentation have been described after such therapeutic approaches [11]. Most interestingly, interferon (IFN) therapy, used for melanoma treatment but also for other disorders such as hepatitis B or C infection, has been reported to induce vitiligo or make it worse [12,13]. Finally, transfer of vitiligo after allogeneic bone marrow transplantation also supports the autoimmune nature of vitiligo [14–16].

2.3. Animal models

An animal model to study spontaneously occurring autoimmune vitiligo is the mutant Smyth line of chickens. Recent data strongly suggest that the mechanism involved in the death of melanocytes in Smyth line vitiligo is an apoptosis induced by infiltrating cytotoxic T lymphocytes [17]. Interestingly, a strong causative link between herpes virus and Smyth line vitiligo has been reported, supporting the role of environmental factors in the expression of vitiligo in these chickens [18]. Although the pathogenesis of human vitiligo could be different from this animal model, the genetic background, the effect of immunity cells and the environmental role, all observed in Smyth line vitiligo, strongly recall data reported in human vitiligo.

2.4. Cellular immunity

The discovery of a T-cell infiltrate in the margin of inflammatory vitiligo was the first clue for a participation of cellular immunity in pathogenesis of vitiligo. CD4 and CD8 cells have been found but no B cells [19]. Local immune reactivity was then reported in generalized vitiligo but has still not been found in segmental vitiligo [20]. Such observations also suggest several pathogeneses depending on the clinical phenotype of vitiligo. Interestingly, both helper and cytotoxic T cells promote a Th1 response with secretion of TNF-α and IFN-γ. [21] These findings are corroborate those reported recently, showing a higher rate of TNF-α in vitiligo skin [22]. 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 a number of infiltrating T cells, all suggest an activation of circulating T cells and their recruitment to the vitiligo skin [19,23,24]. In vitiligo skin the CD4/

CD8 ratio is reversed with a predominant presence of CD8+ T cells. Interestingly, high frequencies of Melan-A specific CD8+ cells were found in vitiligo and seem to be correlated with the extent and severity of the disease [25,26]. Recently, a new understanding for the requirements for CD8+ T-cell mediated destruction of melanocytes was reached [27]. CD4+ T-cell help induced by systemic immunization and local inflammation are both required to break MHC class-I-restricted T-cell tolerance.

Myeloid cells are also implicated, in that monocytes from patients with active disease produce increased proinflammatory cytokines and CD68+ macrophages are abundant in the dermis [19]. The role of dendritic cells (DC) in vitiligo pathogenesis remains unclear, and several controversial studies have been published. However, recent data suggest that DC-mediated killing of stressed epidermal melanocytes may contribute to depigmentation in vitiligo [28].

2.5. Humoral immunity

Several circulating autoantibodies have been found in sera of vitiligo patients. A few of them are specific for pigment cells. Moreover, an antigen must be expressed on the cell surface to be destroyed by its antibody. Only TRP1 was found to be expressed on the surface of melanocytes [29]. Injection of TRP1 monoclonal antibodies to mice induces melanoma regression and vitiligo-like depigmentation [30]. However, these data cannot prove their direct implication in the loss of melanocytes in vitiligo patients. Thus, the variety of autoantibodies reacting with multiple antigens not only expressed on pigment cells, and their controversial pathogenic role, may suggest that humoral response could be secondary to the destruction of melanocytes by another process that could be a primary CD8+ T-cell cytotoxic effect.

3. Genetic aspects of vitiligo

3.1. Epidemiological data

Depending on series, vitiligo has a 0.5–2% incidence worldwide, without predilection for sex or race. Many familial studies have shown the increase of prevalence in close relatives of affected individuals. In a large series performed in India this increase was about 4.5-fold in close biological relatives [31]. Another study performed on 160 white kindreds living in the United States shows a relative risk (RR) for vitiligo of about 7 for parents, about 12 for siblings, and about 36 for children [32]. 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 components in vitiligo pathogenesis as well as the role of environmental factors were recently emphasized [3]. In this epidemiological study the frequency of vitiligo in probands' siblings was 6.1%, about 18 times 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 by vitiligo, suggesting a greater genetic component in early-onset families.

3.2. 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 their clinical manifestations [33]. The results show 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 one. In an additional study, Human leukocyte antigen (HLA) class II associations with two subtypes of vitiligo, vitiligo vulgaris and halo nevi associated with vitiligo, were investigated [34]. A case-control association study showed a significant positive association of HLA-DR4 and DR53 and a negative association of HLA-DR3 with vitiligo vulgaris. The group with halo nevi associated with vitiligo did not show these associations but had a significant negative association with HLA-DR11. All of these data suggest that heterogeneous pathogeneses underlie different phenotypes of vitiligo.

3.3. Which gene(s) for vitiligo?

Two large genome-wide screenings for generalized vitiligo showed significant linkage of an oligogenic autoimmune susceptibility locus, termed AIS1 (1p31.3–p32.2) [35,36]. In an extended study with a cohort of 102 multiplex families the localization of AIS1 was confirmed and two new susceptibility loci were found. AIS2 is located at 89.4 cM on chromosome 7 and AIS3 at 54.2 cM on chromosome 8. Additionally, the locus SLEV1 at 4.3 cM on chromosome 17 was confirmed, and two new potential linkages at 88.1 cM on chromosome 9q and at 109.4 cM on 13q were also reported (Table 1) [37]. 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

Table 1
Susceptibility loci for vitiligo

Refs.	Susceptibility locus	Mapping
[37,54]	SLEV1	17p13
[35]	AIS1	1p31.3–p32.2
[37]	AIS2	7p
[37]	AIS3	8q
[38]		6p21.3–21.4
[55]		4q13–q21

Table 2
Vitiligo candidate genes

Gene	Mapping	Product	Disease
CAT	11p13	Catalase	Vitiligo vulgaris
VIT 1	2p21	?	Vitiligo vulgaris
AIRE	21q22.3	Transcription factor	APECED
COMT	22q11.2	Catecholamine-*O*-methyl transferase	Vitiligo vulgaris
MITF	3p14.1–p12.3	Transcription factor	Vitiligo vulgaris
GTPCH (GTP-cyclohydoxylase I gene)	14q22.1–q22.2	Rate-limiting enzyme of the tetrahydrobiopterin pathway	Vitiligo vulgaris
CTLA 4	2q33	Antigen-4 of T cytotoxic lymphocytes	Vitiligo vulgaris
KIT	4q12	Transmembrane tyrosine kinase	Vitiligo vulgaris
FOXD3	1p32–p31	Transcription factor involved in melanoblast differentiation	Early and progressive vitiligo

APECED, autoimmune polyendocrinopathy.

confers susceptibility to a broader range of autoimmune diseases than just lupus and vitiligo.

Many candidate genes for vitiligo have been proposed thus far (Table 2). However, most of the loci described do not correspond to positions of these proposed biological candidate genes (Fig. 2). A linkage study performed on 56 families strongly suggests that the region 6p21.3–21.4 contains a major genetic factor contributing strongly to the vitiligo phenotype [38]. In this region HLA and TNF genes both map. Due to the suspected autoimmune origin of vitiligo, many HLA linkage disequilibrium studies have been done and have consistently found a significant association between the HLA system and a predisposition to vitiligo [33,34,39–41]. Even less investigated, the potential role of TNF has to be considered. Indeed, it has been recently demonstrated that the expression of TNF-α is significantly increased in perilesional vitiligo as compared to healthy skin, suggesting that cytokine production may be involved in vitiligo [22]. Moreover, tacrolimus ointment, a topical immunosuppressive drug that has shown some efficacy for treating vitiligo, decreases TNF-α expression after application. This mechanism may explain its efficacy in vitiligo [8]. KIT also represents a very interesting gene for the potential pathogenesis of vitiligo. KIT encodes for a tyrosine kinase receptor named c-kit, expressed on the surface of melanocytes, mast cells, germ cells and hematopoietic stem cells [42]. The c-kit ligand, SCF (*stem cell factor*), is involved in proliferation and survival of

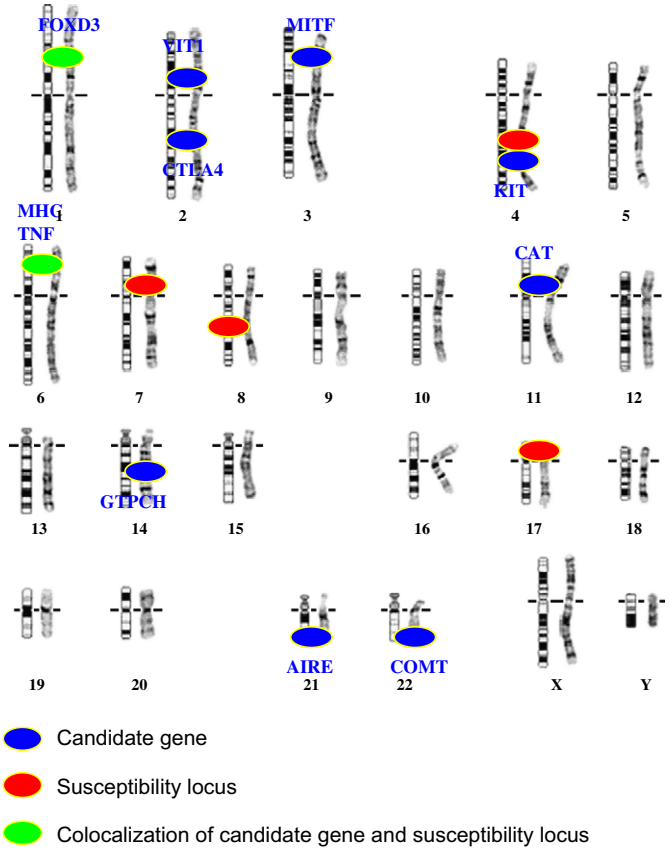

Fig. 2. Representation of reported susceptibility loci and candidate genes for vitiligo. Blue ovals, candidate gene; red ovals, susceptibility locus; green ovals, colocalization of candidate gene and susceptibility locus.

melanoblasts [43]. In vitiligo the expression of c-kit and its downstream effectors MITF is reduced and may be associated with the dysfunction and/or loss of melanocytes in vitiligo epidermis [44,45]. Interestingly, we have observed a marked progression of a vitiligo that had remained stable for many years after treatment with tyrosine kinase inhibitors (Legros L, et al., submitted). Moreover, several cases of vitiliginous depigmentation occurring after treatment with new tyrosine kinase inhibitors (STI-571 and SU 11428) have been reported [46,47]. BCL2 is a MITF-dependent KIT transcriptional target in melanocytes [48]. The decrease of BCL2 expression in melanocytes increases their susceptibility to apoptosis. Interestingly, SCF strongly protects melanocytes from TNF-related apoptosis inducing ligand (TRAIL) [49]. SCF/c-KIT thus brings new interesting potential clues regarding the physiopathology of vitiligo. 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 [50]. Therefore dysregulated (over-)expression might harm melanocytes. Moreover, FOXD3 also regulates endodermal differentiation including thyroid, pancreas, adrenal and gut [51], and other FOX factors are involved in autoimmune syndromes [52]. Mutations in FOXD3 leading to elevated FOXD3 transcription has been recently reported in one AIS1-linked family [53]. Thus, FOXD3 is worthy of further investigation and represents a serious candidate gene in AIS1-linked autoimmune disease.

4. Conclusion

The pathogenesis of vitiligo remains complex and partially understood. However, work done in recent years has brought forth very interesting clues. The immune system now clearly appears to play a key role in vitiligo but we still do not know whether it is directly responsible for the loss of melanocytes or is involved in a second step. More than 120 genes regulate the mammalian pigmentation. Each of them as well as those regulating the immune system represent potential candidate genes for vitiligo and underline the importance of the research work that remains to be done. It is highly probable that the several clinical phenotypes of vitiligo are underlined by different physiopathological mechanisms. Indeed, further studies (including genetic ones) should analyze results that take into account the clinical phenotypes of the vitiligo patients.

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