Symposium - Vitiligo

On the pathophysiology of vitiligo: Possible treatment options

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ABSTRACT

Vitiligo is an acquired depigmenting disorder usually classified as non-segmental and segmental types with a higher incidence of the non-segmental ones. The cause of non-segmental vitiligo is still unknown. Currently, it is a dogma that there are several genes affecting the immune system and the pigment system that predisposes someone to develop vitiligo. A precipitating factor must then ellicit an interaction between the immune system and the melanocyte, resulting in destruction of the melanocyte population in discrete areas of the skin. Starting from the overlapping but distinct pathomechanisms, treatment should be finalized to the cellular targets and possibly related to the disease phase.

Key words: Pathogenesis, treatment options, vitiligo

INTRODUCTION

Vitiligo is an acquired depigmenting disorder usually classified as non-segmental and segmental types with a higher incidence of the non-segmental types. The definition of the two forms is still a matter of discussion, and is mainly based on clinical evidence. The cause of non-segmental vitiligo is still unknown. It seems to require the following three factors: (1) a complex of vitiligo susceptibility genes that influence the autoimmune response; (2) genetically abnormal melanocytes; and (3) an environmental or physiological factor(s) that activates the genetic program for melanocyte destruction.[1] The current dogma is that there are several genes affecting the immune system and the pigment system that predisposes someone to develop vitiligo. However, a precipitating factor must ellicit an interaction between the immune system and the melanocyte, resulting in the destruction of the melanocyte population in discrete areas of the skin. Regarding the segmental type, different pathogenic mechanisms have been proposed, mainly linked to mosaicism phenomenon. This review is mainly referred to the pathogenic mechanism involved in non-segmental vitiligo.

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INFLAMMATORY MEDIATORS

It is clear that the melanocyte population in the depigmented epidermis has been depleted. Accompanying this removal there can be a subtle appearance of immunocytes in these lesions, particularly at the border between the depigmented and normal appearing skin.[2] The presence of inflammatory cells at the border of a vitiligo lesion can become very marked, particularly in inflammatory vitiligo, which is manifested by red, edematous, and itchy skin. Many a time, these findings are subclinical. When present, these inflammatory cells are predominantly CD4+ and CD8+ T-cells[3,4] that can express the skin homing CLA marker.[5] In addition, CD11+ dendritic cells, capable of antigen presentation, have been identified in close proximity to the melanocytes in perilesional skin.[6] Functionally, T-cells isolated from vitiligo lesions

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can demonstrate melanocyte-specific cytotoxicity in non-lesional skin.[7] However, in a significant number of lesions, immunocytes may not be detectable, especially in lesions that are dormant.

There is additional evidence for a melanocyte-specific autoimmune response mediating melanocyte removal in vitiligo. Immunotherapy for metastatic melanoma utilizes melanocyte-specific T-cells to destroy the malignant melanocytes. Tumors regress at times and some patients develop depigmentation of normal-appearing skin.[8] The depigmentation resembles vitiligo, although it is not known if the mechanism of destruction is identical to/or similar to that which occurs in vitiligo. In one publication, a melanoma patient treated with CD8+ T-cell clone that was reactive for melanoma antigen recognized by T-cells (MelanA/MART-1) developed multiple depigmented lesions,[9] demonstrating that cytotoxic CD8+ cells against melanocyte differentiation antigens can cause melanocyte destruction that results in depigmentation.

The humoral immune system also has been implicated in the etiology of vitiligo. Serum autoantibodies against many melanocyte cytoplasmic antigens have been identified in vitiligo patients.[10] Serum from patients with vitiligo can cause antibody-dependent cellular cytotoxicity as well as complement-dependent cytotoxicity of cultured melanocytes.[11,12] In addition, injection of the IgG fraction of serum from patients with vitiligo into the human skin grafted on nude mice results in melanocyte destruction in the graft, suggesting a pathogenetic role for autoantibodies in vitiligo.[11,13] These antibodies are indeed able to destroy the melanocytes *in vitro* by complement-mediated damage and antibody-dependent cytotoxicity. Moreover, the antibodies against MCHR1 (melanin concentrating hormone receptor 1), found in vitiligo sera, can stimulate it and counteract the activity of alpha melanocyte stimulating hormone (αMSH). Histological evidence of B cells or immunoglobulin deposits in the epidermis of advancing lesions of vitiligo has not been demonstrated.[14,15] It is yet to be confirmed whether these melanocyte-specific antibodies play a direct or indirect role in the etiology of vitiligo.

GENES

Genetic analysis of vitiligo, specifically with the use of genome-wide linkage and associated studies, is beginning to provide information about the genes that are associated with vitiligo.[16] Several recent genes identified as candidates in the etiology of vitiligo have effects on the immune response and are involved in the cause of other autoimmune disorders. One locus at chromosome 1p31.3-32.2 (labeled as an autoimmunity susceptibility locus – *AIS1*) contains multiple genes. Single nucleotide polymorphisms (SNPs) in one of these candidate genes (Forkhead box D3-*FOXD3*) co-segregated with vitiligo in the study of a single family.[17] *FOXD3* encodes a forkhead transcription factor that is a primary regulator of melanoblast differentiation in the embryonic neural crest.[18] However, other vitiligo patients do not appear to have mutations of *FOXD3*, and other families do not show linkage to the *AIS1* region of chromosome 1p,[19] suggesting that this mutation may be a unique isolate.

A second candidate gene is NACHT-LRR-PYD-containing protein 1 (*NALP1)* on chromosome 17p13.[20,21] This gene was first identified by Nath *et al*,[22] who noted that it is associated both with vitiligo and lupus erythematosus. This gene was later found to interact with a loci on chromosomes 7 and 9.[23] This is a very interesting gene because the NALP1 protein is a component of the inflammasome, a cytoplasmic multiprotein complex that regulates the innate immune system, mediates the maturation of proinflammatory cytokines like interleukin-1β and -18, and stimulates cellular apoptosis.[24] This gene and its activities could be involved in causing melanocyte destruction and thereby vitiligo.

Recently, significant associations between generalized vitiligo and SNPs at several other loci previously associated with other autoimmune disease have been detected.[25] The strongly associated SNPs were distributed across the major-histocompatibility-complex (MHC) loci on chromosome 6p21.3 between several MHC class I and class II encoding area. In addition, it has recently been reported that variants in protein tyrosine phosphatase, non receptor type 22 (*PTPN22)*,[26,27] that putatively functions as a general autoimmunity susceptibility loci, and SPARC-related modular calcium binding protein 2 (*SMOC2)*,[28] of unknown function, may also be associated with the risk of vitiligo.

MELANOCYTE AS THE FIRST PLAYER

In addition to a genetic aberration in the immune system, the etiology of vitiligo appears to also have a

genetic defect in the melanocyte itself. Prior studies have demonstrated that the melanocytes in the skin of vitiligo patients can exhibit morphologic abnormalities including enlargement, fragmentation, extracellular granular material, and dilated rough endoplasmic reticulum.[29] Several other studies have demonstrated that the melanocyte from vitiligo skin appears fragile. The inability to culture melanocytes from pigmented skin of vitiligo patients using routine procedures and the fragility of established cultures of melanocytes have been demonstrated.[30] The most suggestive evidence that vitiligo melanocytes possess a genetic aberration was demonstrated by a study where an isoform of tyrosinase was also identified to correlate with vitiligo by a genome-wide association study.[25] A more recent study assessed SNPs for genes encoding enzymes involved in melanin synthesis in patients with vitiligo and found evidence for association of tyrosinase and dopa chrome tautomerase with vitiligo susceptibility.[31] These studies confirm the long-held theory that an innate defect in vitiligo melanocytes exists.

CRASHING EVENTS

Despite the fact that genetic alterations in the immune system and the melanocyte may exist in vitiligo, a precipitating factor must be the basis for instigating melanocyte destruction in this post-natally acquired disease. Sometimes, occurrence of congenital vitiligo has been suggested, but until now, there is no population study confirming that. The concordance of vitiligo in monozygotic twins is only 23%, indicating that a non-genetic component also plays an important role in vitiligo.[32] Anecdotal correlations of personal events with the onset of vitiligo also imply the existence of a precipitating factor. These events include severe sunburn, pregnancy, physical and emotional stress/trauma, wounds or areas of microtrauma, etc.[30] Contact/occupational vitiligo is the most obvious form of the disease that correlates a precipitating factor (primarily phenolic and catecholic derivatives) with the onset of melanocyte destruction.[33,34] What most of these putative precipitating factors have in common is that they facilitate facultative pigmentation of the skin. Melanocyte-stimulating hormone induced by ultraviolet (UV) overexposure,[35] estrogens upregulated during pregnancy,[36,37] cytokines produced during emotional stress and/or physical trauma (i.e., nerve growth factor, neurotrophins, adrenocorticotrophichormone (ACTH), endorphins, etc.),[38-42] and cytokines released during wound healing, particularly at sites of microtrauma,[43] can all trigger facultative melanin synthesis by melanocytes. Therefore, enhanced facultative melanization could put undue intolerable stress on the vitiligo melanocyte resulting from an elevation in the cytotoxic oxidative melanin intermediates. Consistent with this is the correlation of a tyrosinase isoform with vitiligo as described above.[25] This isoform of tyrosinase could allow the melanocyte to present a melanocyte-specific autoantigen to the primed hyper-reactive immune system inducing autoimmunity. Alternatively, transcription and/or maintenance of this isoform of tyrosinase may render the melanocyte to be hyper-reactive to facultative stimulators of melanization and consequently increase pigment production beyond the threshold tolerated by the vitiligo melanocytes.

THE OXIDATIVE PATHWAY FORWARDS THE DESTRUCTION

How can the various precipitating factors initiate the interplay between the sensitive vitiligo melanocytes and the autoimmune response leading to melanocyte removal? The induction and/or combating of oxidative stress have been implicated in numerous studies.[44] Disruption of the biopterin metabolic pathway and network can induce H_2O_2 generation or impede its neutralization.[45,46] Generation of reactive oxygen species is hazardous to the cells initially causing lipid peroxidation, etc.[47] and ultimately inducing apoptosis.[48] It has recently been demonstrated that vitiligo melanocytes exhibit (1) more reactive oxygen species, (2) membrane peroxidation, (3) impaired mitochondrial electron transport chain complex 1, and (4) more readily induced apoptosis, all characteristics of cells susceptible to death by oxidative stress.[49] It has been demonstrated by several independent studies that the antioxidant catalase, and putatively the ability to combat oxidative stress, appears to be genetically impaired in some patients with vitiligo. Specifically, (1) levels of catalase in the epidermis of some patients with vitiligo are reduced,[50] (2) a variant genotype of catalase (C>T SNP in codon 419 of exon 10) has been associated with susceptibility to vitiligo,[51] and (3) a promoter variant of the *Catalase* gene (-89A>T) correlates with susceptibility to vitiligo in the Chinese population.[52] Many alternative cellular abnormalities have also been suggested to occur in vitiligo melanocytes such as lipid alterations in the mitochondria,[53] impairment in the survival/

apoptosis regulation of cell survival,[54] and inability to be stably attached to the basement membrane.[55] However, a common cellular/molecular denominator among these possible inherent defects have yet to be identified. It is possible that multiple and distinct genetically determined inherent defects can perturb the melanocytes and promote apoptosis that may occur throughout the vitiligo syndrome. Regardless, cells that dysfunction and head towards apoptosis have been demonstrated to induce a consequential autoimmune response that perpetuates the disease.[56]

THE CELLULAR-ORIENTED TREATMENT

Starting from the overlapping but distinct pathomechanisms, treatment should be finalized to the cellular targets and possibly related to the disease phase.

Regardless of the pathogenetic role, aberrant immune response can be counteracted, at least, at onset or during the relapse phases. High potent topical or systemic corticosteroids have been used with variable effectiveness.[57] Dexamethasone 10 mg divided in 2 days as pulse therapy in adults has been reported to stop rapidly progressive vitiligo, causing less severe side effects compared to the continuous regimen. Topical immunomodulators (TIMS), act both on inflammatory and differentiation processes. Tacrolimus has provided excellent repigmentation mainly when administered under occlusion (hydrocolloid dressing).[58] Both tacrolimus and pimecrolimus are able to modulate the maturation/activation of T cells and the migration of melanocytes and melanoblasts. This last property of the TIM may thus affect the differentiation process, probably compromised during vitiligo. Currently, tacrolimus ointment is provided as a 0.1% cream applied for at least 10 weeks.

Controversial opinion exists about the effectiveness of antioxidant molecules. The debate arises from the poor understanding of the pathogenetic role of the redox equilibrium loss, as well as from the frequent uncontrolled and miraculous suggestions. Starting from the above described and experimentally tested relevance of the cellular oxidative stress, the restoration of the redox balance has therapeutical value. A balanced pool of antioxidants should be preferred to a single molecule one. It should be orally administered during the reactivation phases and as adjuvant to the phototherapies. Arrest of the progression and repigmentation have been observed and published.[59]

To the best of our the knowledge, the gold standard therapy is phototherapy. The biological basis for its use, origins from the *in vitro* ability of UV to induce migration and differentiation of the melanocytes. Several different sources are available: UVA, BB-UVB, NB-UVB, excimer. Most of the trials conducted with NB-UVB, were able to provide up to 70% repigmentation. However, the protocols are still different among the various European and World dermatologic centers. The initial dose may be 70% of the minimum erythema dose (MED) or a defined absolute value (100-280 mJ/cm^2), the progressive increments range from 20 to 50%, the overall treatment ranges from 6 to 12 months. Consequently, the effectiveness is too hard to compare.[60]

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