

As the heritability of vitiligo is observed to be around 50% (1), environment should contribute largely to the development of vitiligo. As with many complex diseases, we believe that an interleaving net constructed by both genetic and environmental factors should be considered as a general model of vitiligo pathogenesis. Identifying those disease-modulatory environmental factors is both a formidable and important task for epidemiologists and dermatologists in the next decade.

We hope that this contribution will stimulate more research into the environmental determinants of vitiligo. As the genetic constitution of an individual cannot be changed, perhaps 1 day in-depth knowledge on environmental risk factors can prevent vitiligo in some individuals by changing the unfavourable environment.

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Commentary 7

Vitiligo is a common cutaneous disorder that affects between 1% and 2% of the population and can broadly be classified into generalized or localized varieties (1,2). Generalized vitiligo is characterized by lesions of depigmented skin which are often symmetrically placed and frequently affect the body orifices and acral areas (1,3). While the condition is not life threatening, it is associated with low self-esteem, depression and can be particularly distressing when mistaken for tuberculoid leprosy (4–6).

The aetiology of vitiligo is controversial and working hypotheses include a genetic predilection, abnormalities in biochemical/neural intermediates and autoimmunity [reviewed in Ref. (7)]. However, the majority of evidence supports the supposition that there is an underlying autoimmune disorder resulting in the targeted destruction of melanocytes and the subsequent characteristic formation of depigmented macules. Clinical data linking vitiligo with other autoimmune conditions (including diabetes, Addison's disease, lupus erythematosus and rheumatoid arthritis) supports the autoimmune hypothesis, and immuno-modulatory agents have been used to treat the condition (8). Vitiligo is accompanied by abnormalities in both the humoral and cellular immune compartments and high levels of circulating autoantibodies, predominantly of

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the IgG class, have been detected in the sera of patients (9,10). However, the role of anti-melanocyte antibodies in the pathogenesis of vitiligo remains unclear and it has been suggested that their presence may be secondary to cellular damage (10).

Vitiligo pathogenesis: CD4 T cells should move to centre stage

The identification of cytotoxic lymphocytes responsible for the initiation of the autoimmune process has been seen as a critical first step towards developing effective therapeutics. The use of MHC tetramer technology has allowed the isolation and characterization of CD8⁺ T cells, from patients with vitiligo, which can mediate targeted melanocyte cell death (11,12). These same cytotoxic lymphocytes may be important for the treatment of malignant melanoma, as the same melanocyte-specific antigens which are autoimmune targets in vitiligo are expressed on melanoma cells and immune responses directed toward these antigens can eliminate cancerous cells (13,14). Patients with melanoma who are successfully treated with interleukin-2 often present with vitiligo (15). As CD8⁺ cells are the principal cytotoxic T cell *in vivo*, there is a concerted effort to manipulate this cellular subset to improve prognosis in cutaneous disease. Immuniza-

tion regimes using a highly tumorigenic and poorly immunogenic melanoma cell line have demonstrated that tumor regression and subsequent depigmentation show an absolute requirement for CD8⁺ cells (16). Other studies support this hypothesis and as such many new therapeutics aim to augment the action of cytotoxic CD8⁺ T cells (17,18).

However, the current focus on CD8⁺ T cells may be deflecting attention from the equally or more important role of CD4⁺ T cells in initiating melanocyte-specific autoimmunity (13,19,20). Clonotype-specific CD4⁺ T cells have been more difficult to identify by tetramer staining, but recent findings suggest that these cells are of critical importance in mediating cutaneous autoimmunity. In addition to sustaining and regulating the humoral and cellular responses, CD4⁺ T can also act in the absence of B cells and CD8⁺ T cells to selectively target melanocytes for cell death, an action which is partially dependent on Fas–FasL signalling (20). The immunosuppressive role of antigen-specific CD4⁺ Treg cells in dampening autoimmune responses also needs to be considered in the design of effective treatments for both melanoma and vitiligo (21,22). Thus, CD4⁺ T cells play a multi-faceted role in cutaneous disease and moving CD4⁺ T cells to centre stage may help to increase the range of therapeutic options in these prevalent conditions.

Viewpoint 5

Most ongoing research on vitiligo is based on the long-standing hypothesis that in vitiligo lesions melanocytes are actually lost rather than inactivated. Before entering into the details of vitiligo pathogenesis, it is worth revisiting briefly the evidence that supports this hypothesis.

Loss of epidermal melanocytes in vitiligo: any reason to doubt?

Most studies based on standard histology, electron microscopy and immunohistochemistry suggest that melanocytes are absent from vitiligo lesions (1). However, if vitiliginous melanocytes were inactivated, one might not expect melanocyte-specific antigen expression at the protein level in these cells. Two studies have reported findings that are compatible with this view. First, melanocytes cultures were successfully established from depigmented epidermal suction blister tissue of 12 patients with vitiligo (2). Secondly, tyrosinase and DCT mRNA could be detected in vitiliginous skin of three patients by RT-PCR (3).

Although scarce, this type of findings should not be overlooked, and it may be worth searching for additional

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melanocyte-specific transcripts in vitiliginous skin. In addition, an analysis of repigmentation patterns in patients treated for vitiligo shows that while PUVA therapy induces perifollicular repigmentation, steroids induce diffuse repigmentation. This suggests that, at least in some vitiligo lesions, follicular melanocytes might not be the unique source of melanin production during repigmentation (4). It would be interesting to gain more insight into repigmenting vitiligo lesions by means of modern skin imaging techniques such as cutaneous spectrophotometry (Siascopy) or *in vivo* confocal microscopy.

Persistence of follicular melanocytes in vitiligo: why are they spared?

While the absence of epidermal melanocytes in vitiligo has been the focus of numerous studies, the sparing of follicular melanocytes has been less investigated. Developmental differences can account for the different fates of epidermal and follicular melanocytes, as lower portions of mouse hair follicles are known to contain stem cells of the melanocyte lineage (5). In the case of hair greying caused by defective