

mechanism for the destruction of melanocytes. Cellular autoimmunity can therefore be proposed as the sole cause and origin of vitiligo.

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## Commentary 5

Studies on the pathogenesis focussing on melanocyte biology, melanin biochemistry or skin immunity have yielded a variety of hypotheses to explain the disappearance of melanocytes in vitiligo, including a genetic predisposition, increased oxidative stress and toxic metabolites, neurochemical factors and autoimmunity (1). Whereas these factors probably all contribute to the development of depigmentation (convergence theory) (2), their interaction is not clearly defined. This commentary presents a multi-disciplinary view of the pathogenesis of vitiligo (Fig. 1).

Melanin synthesis in melanocytes is a tightly regulated process. Defects in the protective mechanism in the skin that scavenge radicals and toxic intermediates of melanin production may lead to vitiligo. The increased levels of oxidative stress in the vitiligo skin leads to the deactivation of catalase (3).  $H_2O_2$  can also oxidize (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin to 6-biopterin, which is cytotoxic to melanocytes.

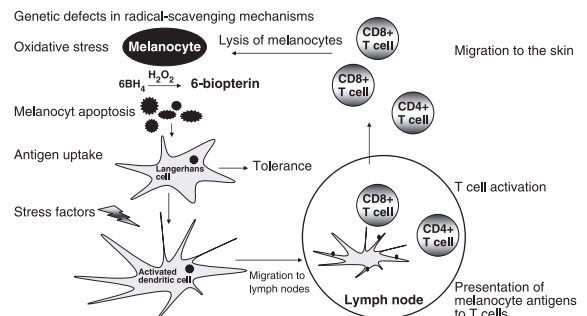
Although this melanocyte death may account for part of the depigmentation, dying melanocyte fragments will be taken up by epidermal Langerhans cells. The uptake of self-antigens from dying melanocytes in the absence of activation signals does not activate the Langerhans cells and will therefore not lead to immunity against melanocytes. Concurrent external stress factors, such as wounding, high dose of UV radiation or hormonal changes, however, activate Langerhans cells and dendritic cells in the skin, leading to breakage of tolerance (4).

Clinically, these stress factors induce progression of depigmentation. The Koebner phenomenon results from stress factors at remote skin sites that induce local activation of Langerhans cells and reactivation of anti-mela-

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nocyte immunity, leading to the formation of new lesions. The lower threshold for breakage of tolerance in patients with vitiligo is illustrated by the increased incidence of autoimmune diseases in patients with vitiligo (5–12). Normally, regulatory T cells maintain peripheral tolerance by suppressing autoreactive T-cell activity. In patients with vitiligo, however, decreased levels of regulatory T cells in the skin lower the threshold for autoimmunity.

Activated Langerhans cells containing melanocyte antigens migrate to the lymph nodes and present melanocyte antigenic peptides bound to HLA molecules to T cells. The association of vitiligo vulgaris with certain HLA class II alleles (13–15) indicates the dominance of peptides binding to these HLA types in inducing immunity. In the lymph nodes, melanocyte-reactive  $CD8^+$  and  $CD4^+$  T cells are activated to proliferate and migrate to the skin, resulting in increased levels of T cells reactive with tyrosinase, gp100 or MART-1 in peripheral blood (16–19), as well as autoanti-



**Figure 1.** Schematic overview of the pathogenesis of vitiligo.

bodies against these antigens (20–22). Moreover, the number of circulating MART-1-reactive T cells expressing CLA in patients with vitiligo correlated with the extent of depigmentation (18).

In perilesional skin, CD8<sup>+</sup> T cells, macrophages and to a lesser extent CD4<sup>+</sup> T cells were found (23,24). Infiltrating CD8<sup>+</sup> T cells expressed skin homing, cutaneous leukocyte-associated antigen (CLA) and T-cell activation markers CD25, perforin and granzyme B (25), and colocalized with disappearing melanocytes. Finally, perilesional melanocyte-reactive CD8<sup>+</sup> cytotoxic T cells were shown to be capable of actively killing melanocytes in autologous skin tissue (J.G. van den Boorn, D. Konijnenberg, T.A.M. Dellelijn, J.P.W. van der Veen, J.D. Bos, C.J.M. Melief, F.A. Vyth-Dreese and R.M. Luiten, unpublished data).

Taken together, the pathogenesis of vitiligo results from changes in biochemical processes in the skin that trigger autoimmunity, which is enhanced by genetic predisposition to autoimmunity.

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## Commentary 6

Vitiligo is the most common depigmenting disorder which is determined by both genetic and environmental factors (1). During the last two decades, however, investigators have focused mainly on the genetics aspects of vitiligo rather than on the environmental side. For example, scholars have not only found more than 10 candidate genes for vitiligo (2–11), but also located several susceptibility genes to vitiligo on chromosomes one, four and six (8,12–15).

At the same time, the evidence base for environmental factors is weak despite the often heard expression that: 'vitiligo, as a complex disease, is affected by both genetic and environmental factors'. In our current post-genomic era, genetics and genomics research is perceived to be 'hot' and epidemiological research to environmental risk factors runs the risk to be undervalued. Especially in the context of complex diseases, it is our duty to investigate all aspects of causation and not only the 'sexy' ones.

Patients with vitiligo often assume that their disease is triggered by an environmental exposure such as sunlight, hair dye or paint (16). From anecdotal evidence (JBL) in clinical practice, we learned that trauma often seems to precede vitiligo as well. In many cases, the initial site of vitiligo is a wounded area.

Gauthier recently proposed the *melanocytorrhagy hypothesis* which may explain this trauma-induced vitiligo

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(17,18). Based on morphologic findings, his theory assumed melanocytorrhagy as the primary defect underlying melanocyte loss and integrated most of the possible triggering/precipitating/enhancing effects of other known factors, such as genetic, autoimmune, neural defections and impaired redox status (19–22).

Despite the well-known nature-nurture debate on the causation of many complex diseases, no paper as yet systematically studied or reviewed environmental risk factors of vitiligo. This is disappointing. Some potential environmental factors were collected in our recently conducted genetic epidemiological study on vitiligo using 3742 patients (1,23). Here, for discussion, we put forward an interesting but yet unpublished finding from this study on the relation between sunlight and vitiligo. We observed that exposure to sunlight might be negatively associated with vitiligo (OR 0.709, 95% CI: 0.453–1.111), especially for women (OR 0.506, 95% CI: 0.263–0.974). This finding is opposite to the experience described above. Today, however, no evidence is available that can prove or disprove the potential protective effect of sunlight on the incidence of vitiligo. It is well known that narrow-band UV-B can be used to treat vitiligo directly (24) and sunlight does accelerate repigmenting during the treatment by PUVA. Could sunlight, perhaps, even exert beneficial effects in vitiligo?