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Commentary 4

I firmly believe that vitiligo is an autoimmune disease in which autoreactive, melanocyte-specific cytotoxic T lymphocytes (CTL) escape central tolerance, break peripheral tolerance and destroy epidermal melanocytes.

The evidence in favour of the autoimmune genesis of vitiligo is highly convincing. Suppression of immune reactivity by various effective treatments suggests that their immunosuppressive mechanism interferes with that which leads to the destruction of melanocytes (1–6). The association of vitiligo with other autoimmune diseases is well known (7–9). The presence of circulating anti-melanocyte antibodies points to a possible involvement of humoral immunity, while the involvement of cellular immunity is indicated by lymphocyte infiltration at the margin of lesions. In particular, the presence of cellular infiltrates *during* the progressive loss of melanocytes from depigmenting vitiligo skin (10) and the detection of T cells *juxtapositionally apposed* to remaining melanocytes (11) demonstrate the early implication of cellular immunity in the pathogenesis of the disease.

Other views, however, exist. Intrinsically increased sensitivity of melanocytes to oxidative stress is said to be pathogenic. This, however, can be no more than a conjecture in the total absence of any experimental demonstration that it is a primary event. Fault can also be found with the postulation of an inappropriate reaction to neuropeptides as the leading cause. Their concentration in vitiligo skin is not sufficient to kill melanocytes, while the time course of their production is such as to rank them as a consequence rather than a cause (12). These and other proposed pathogenetic mechanisms have very little to offer in the way of proof.

The point is 'what immune cells are pathogenic? Melanocyte-specific autoantibodies are certainly present (13–17), but their pathogenic role is a mystery. The patchy distribution of cutaneous depigmentation and the very frequent symmetrical distribution of lesions fit in well with

the view that autoimmune melanocyte destruction is induced by lymphocyte clones with affinities for specific areas of skin (18). We and others (19–21) have demonstrated the presence of high frequencies of melanocyte-specific CTL in the peripheral blood of patients with vitiligo. These autoreactive CTL are functionally intact and kill normal melanocytes *in vitro*. They display high avidity of antigen recognition and express the skin-homing receptor CLA (22). Overall, these findings strongly support an association between the presence of melanocyte-specific CTL and vitiligo, and directly point to their pathogenic role in this disease.

Investigation of the association of vitiligo with melanoma has clarified the role of autoreactive CTL in its development. Identical clonally expanded CTL have been detected in a regressing melanoma and in the vitiligo-like halo surrounding the tumor (23). These and other findings assume that antigen-specific proliferation is involved in the destruction of normal and malignant melanocytes (24–26). Work from our group has contributed to the current opinion that vitiligo T cells demonstrate reactivity to antigens previously recognized as target antigens for T cells infiltrating melanoma tumors (20,22,27). Interestingly, in a comparison with melanoma-derived T cells, vitiligo T cells displayed greater reactivity towards melanoma cells (28).

We believe that high avidity of antigen recognition represents a peculiar property of anti-melanocytic CTL from patients with vitiligo that contributes to their abnormal reactivity (29).

In conclusion, melanocyte-specific CTL with high-affinity T-cell receptors most likely escape clonal deletion in the thymus and enter the circulation. By expressing CLA, they home to the skin where they express type 1 cytokine profiles and mediate melanocyte destruction. The immunological imbalances thus created may be supposed to herald the processes that also initiate a biochemical or neural

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-

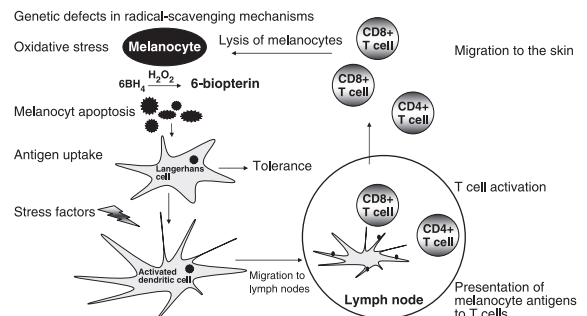


Figure 1. Schematic overview of the pathogenesis of vitiligo.