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Commentary 3

Mannose-binding lectin (MBL) is one of the infamous foot soldiers that defend the body against micro-organisms in the never-ending 'trench warfare' fought within the body's perimeter. It fights on four different fronts: (1) complement activation; (2) opsonophagocytosis; (3) modulation of inflammatory response; and (4) the promotion of apoptosis (1–3). Poorly equipped or insufficient numbers of soldiers are not capable of operating effectively and allow attacking micro-organisms to infiltrate the body which trigger a series of events resulting in the destruction of the body (autoimmune diseases) as is stated by Werth et al. Cleaning up the battlefield (clearance of the apoptotic cells) after the war between the micro-organisms and the immune-competent cells is one of the soldiers' main functions (4). Inefficient clearance leads to a harmful autoimmune response (5,6).

The MBL infantry plays a role in controlling the body's overreactions represented by proinflammatory cytokines and the clearance of immune response remnants, such as immune complexes and adhesion molecules on inflammatory cells, which often lead to casualties on both sides (7,8).

There have been a number of reports showing associations between MBL deficiency and autoimmune disorders such as systemic lupus erythematosus (SLE), dermatomyositis and cutaneous lupus erythematosus (4,9–11).

In the process of vitiligo, there may be a specific antigenic stimulus which initiates the defensive actions of immune-competent cells in the skin. During these actions, a number of immune-competent skin cells go into apoptosis resulting in alterations of membrane carbohydrates. MBL has the ability to bind to these altered carbohydrates and to facilitate the clearance of apoptotic cells (4,6). Inadequate clearance of the apoptotic cells may cause continuous stimulation of the immune system and antibody production resulting in vitiligous changes in the skin cells (Fig. 1).

It has also been shown that there is insufficient calcium (Ca) uptake in melanocytes and keratinocytes from vitiliginous skin (12,13).

The infantry's (MBL) command and supply chain rely heavily on Ca uptake. We hypothesize that a weak supply and command chain (Ca) and insufficient infantry (MBL) may contribute to undesirable consequences of the war (vitiligo). Therefore, we consider that sufficient numbers of infantry (normal MBL alleles/levels) provide a strong level of protection on the war against vitiligo.

A reduced infantry may also result in a predisposition to attack from specific viral agents such as cytomegalovirus, Epstein–Barr virus, hepatitis E, and of course, the AIDS virus on weakened war fronts (14,15). For example, Grimes et al. identified cytomegalovirus DNA in skin biopsy specimens of patients with vitiligo (16).

All of these notions support the idea that MBL deficiency may play an important role in susceptibility to vitiligo and replacement of deficient MBL may be helpful in combating vitiligo lesions and/or prevent its progression.

Recently, recombinant human MBL (rMBL) has been produced (17) and a phase I study has been designed to evaluate the safety, tolerability, pharmakogenetic and immunogenetic profile of rMBL (18,19). In one of these, this phase I study no adverse effects of intravenous rMBL were observed in healthy but MBL deficient males (18). Protective role of mannose-binding lectin in a murine model of invasive pulmonary aspergillosis was also shown by Kaur et al. (20).

Regarding the protective roles of normal MBL levels in patients with vitiligo, we propose that patients be treated with a topical application of a gel or pomade (name of it can be 'vitiliMBL') containing rMBL which is already available (17). We also consider the addition of Ca to this pomade or/and an increased Ca intake to be even more effective in the treatment of vitiligo.

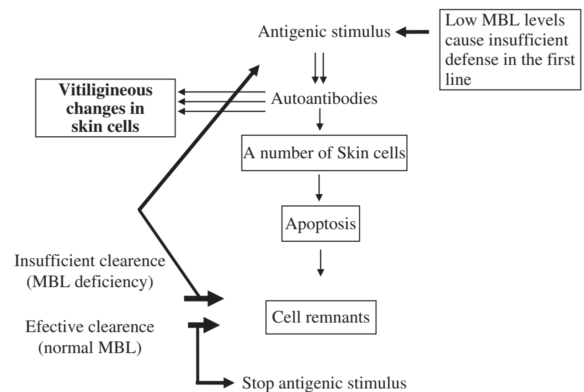

Figure 1. In the aetiopathogenesis of vitiligo, low serum MBL levels may be associated with the impaired defense in the first step of immune response and insufficient clearance of apoptotic cells resulting in autoimmune reactions in the skin cells.

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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

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