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IFN-γ Promotes Apoptosis of Melanocytes in Vitiligo

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Dear Editor,

Vitiligo is an immune-mediated inflammatory condition characterized by selective destruction of epidermal and or follicular melanocytes. It is well established that cell-mediated immunity has been implicated in the pathogenesis of this common skin disorder. Although abnormalities in different subpopulations of T cells may play a role in induction and development of vitiligo, great attention has been paid to CD4+ Th1 cells and cytotoxic CD8+ T lymphocytes (CTLs) (1, 2). The significance of both subgroups in vitiligo development is supported by different observations. For instance, CD8+ T cell-mediated melanocyte destruction has been demonstrated in vitiligo. In addition, an increased accumulation of CD8+ T cells in peripheral blood mononuclear cells (PBMCs) and perilesional skin of patients with progressive vitiligo has been reported (1, 3). On the other hand, elevated expression of Th1 cell specific transcription factor (T-bet) and cytokine (IFN-γ) was indicated in PBMCs of patients with vitiligo (2). The exact mechanism by which these cells exert their cytotoxic effects on melanocytes is not well understood. Nonetheless, the results of different laboratory and histological examinations support the hypothesis that apoptosis is an important mechanism for melanocyte disappearance. Apoptosis is a complex process and can be initiated through intrinsic and extrinsic pathways. These pathways are activated by a variety of factors such as cytokines, certain chemicals and other molecular mechanisms. Amongst these factors, cytokines appear to play a pivotal role in promoting apoptotic melanocyte cell death. Cytokines are small secreted proteins that participate in cellular communication and many immunologic functions. Abundant evidence indicated cytokine imbalance (such as IFN-γ, IL-10, IL-17) in the skin and circulation of patients with vitiligo. Therefore, disturbed expression of these molecules may be involved in disease pathogenesis. IFN-γ is a proinflammatory cytokine mainly produced by Th1 lymphocytes, NK cells and CD8+ cytotoxic T cells. This cytokine plays a major role in both innate and adaptive immune response. It can also affect the action of other cytokines in a synergistic or antagonistic manner. The exact function(s) of IFN-γ in the pathology of vitiligo is not known and it may act via different mechanisms. For instance, IFN-γ may participate in the homing of CD8+ T cells to the skin through local induction of chemokines and expression of adhesion molecules on endothelial cells (4). Cytotoxicity via induction of apoptosis has been considered as a major effector mechanism of autoreactive CTLs. Therefore, recruited CD8+ T cells may specifically induce autologous melanocyte apoptosis resulting in disappearance of melanocytes (3). On the other hand, CD4+ Th1 cells (one of the main sources of IFN-γ production) are required for optimal induction of antigen-specific CD8+ T cell effector responses. CD8+ T cells can be considered as a main effector cell of Th1 immunity (5). Therefore, cooperation between CD4+ and CD8+ T cells plays an important role in complete melanocyte clearance. In addition, IFN-γ may influence melanin production. For instance, treatment of melanocytes with IFN-γ resulted in significant suppression of melanin production and reduction of mRNA expression levels of tyrosinase and microphthalmia-associated transcription factor (MITF), which regulates differentiation and development of melanocytes and retinal pigment epithelium (6). Moreover, Natarajan et al. indicated a regulatory role of IFN-γ in skin pigmentation. They showed that IFN-γ signaling impedes maturation of the melanosome, which is a major site for synthesis and storage of melanine (7). Altogether, the actual mechanism of melanocytes killing in the skin of patients with vitiligo has not been definitively determined. Current studies indicate a potential role of Th1 and CTL subpopulations in vitiligo pathology as well as a link between IFN-γ and melanocyte abnormalities in this disease. However, further studies are needed to unravel the exact mode of IFN-γ action. A deeper understanding of these mecha-

nisms would eventually lead to more targeted treatment options associated with better quality of life in patients.

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