**IN THIS ISSUE…** ***(see article on pp. 664)***

## IFN-γ in Vitiligo, Is It the Fuel or the Fire?

In this issue, Yang et al. (1) report that IFN-γ is produced by cytotoxic $CD8^+$ T cells in vitiligo patient skin lesions and blood, and that IFN-γ directly induces melanocyte apoptosis *in vitro*. Vitiligo is an autoimmune disease that results in depigmentation, or white spots, on the skin, which is due to the loss of melanocytes from the epidermis. Melanocyte specific, $CD8^+$ T cells are increased in the blood of patients with vitiligo compared with healthy controls, their numbers correlate with disease activity, and they are capable of killing melanocytes *in vitro* (2). A study using skin explants from vitiligo patients found that $CD8^+$ T cells from lesional skin were both necessary and sufficient for the induction of apoptosis of melanocytes in non-lesional skin (3), but the mechanism of T-cell-mediated killing of melanocytes is not clear.

IFN-γ and IFN-γ-induced genes are expressed in vitiligo lesional skin (4). Consistent with a previous study (3), Yang et al. (1) report that $CD8^+$ T cells are major producers of this cytokine, and they also found that $CD8^+$ T-cell production of IFN-γ in peripheral blood from patients correlates with disease activity. We, and others, found that IFN-γ is required for depigmentation in mouse models of vitiligo (5, 6), and we further discovered that IFN-γ induces the chemokine CXCL10, which promotes the migration of autoreactive T cells into the skin and to the epidermis (4). Whether IFN-γ is functional beyond the induction of chemokines to recruit T cells to active lesions is not known.

$CD8^+$ T cells are responsible for controlling viral infections and malignancy by killing cells in a targeted, antigen-specific manner. In vitiligo, melanocyte-specific antigens have been identified, including tyrosinase, gp100, MART-1, and others (2, 7). Following antigen recognition, T cells are thought to destroy their targets by initiating apoptosis via Fas-Fas ligand (FasL) signaling, or through the release of cytotoxic granules such as perforin and granzyme that are delivered into the target cell (8). However one study found that $CD8^+$ T cells in a mouse model of uveitis, a disease that targets melanocytes in the eye, were functional even when they could not produce perforin or FasL, suggesting that alternate mechanisms of T-cell-mediated destruction of target cells exist. While perforin and FasL were dispensible, IFN-γ was critical, as IFN-γ receptor (IFNgR)-deficient hosts did not develop uveitis, however the authors did not define the role of IFN-γ in the disease (9).

Two recent studies reported that IFN-γ inhibits melanogenesis (10, 11), and Yang et al. (1) confirm this in their study. However, this cannot be the primary role of IFN-γ in vitiligo, since the disease results from the loss of melanocytes from the epidermis, rather than a decrease in their function (3). More relevant to vitiligo, Yang et al. (1) additionally report that IFN-γ was able to induce apoptosis in melanocytes, and thus IFN-γ-mediated apoptosis may represent an alternative mechanism through which $CD8^+$ T cells kill their targets in vitiligo. However this raises the issue of target cell specificity, as many cell types in the skin could express the IFNgR, yet melanocytes are the primary target in vitiligo. One possibility is that melanocytes express higher levels of IFNgR, as cells that express large amounts of the IFNgR may be more susceptible to IFN-γ-induced apoptosis through rapid activation of STAT1, although this has been studied more in the context of immune cells (12). A more plausible explanation may be that during antigen recognition of target cells by $CD8^+$ T cells, the cells form an immune synapse into which IFN-γ is secreted, which may allow it to reach a very high local concentration, similar to how granzyme/perforin cytotoxicity is targeted. Preferential IFN-γ secretion into the immune synapse has been directly observed in T-cell-target cell conjugates (13).

The findings by Yang et al. (1) may have therapeutic implications, as inhibiting IFN-γ or downstream signaling of the IFNgR could offer new therapies for vitiligo (4). We recently reported that simvastatin, an FDA-approved treatment for hypercholesterolemia, both prevents and reverses vitiligo in a mouse model, and may act by blocking STAT1 activation, which is also required for IFN-γ signaling (14). In summary, IFN-γ is critical for the progression of vitiligo, acting as the fuel to recruit autoreactive $CD8^+$ T cells to the skin through the induction of CXCL10 (4), but Yang et al. (1) introduce the concept that cytotoxic T-cell-derived IFN-γ may directly induce apoptosis in melanocytes as well, therefore potentially also acting as the fire that destroys melanocytes. Future studies using animal models will be helpful to determine how important IFN-γ-induced apoptosis is compared to other mechanisms of cytotoxicity during the progression of vitiligo *in vivo*.

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