Cytokine-robbing cells

Transferring tumor-specific T cells is not enough to fight disease, according to Gattinoni et al. on page 907, because endogenous cells steal necessary activating cytokines. This limits the ability of the transferred cells to launch an antitumor attack in mice.

Elimination of the body’s lymphocytes followed by infusion of tumor-specific CD8+ T cells has recently been shown to help destroy established tumors in humans. Studies in mice have suggested that irradiation works in two ways. The depletion of host cells creates empty space, which the transferred cells can fill by homeostatic proliferation. The depletion also rids the host of regulatory T (T reg) cells, which would otherwise dampen the function of the transferred antitumor cells.

Gattinoni and colleagues now add a new wrinkle to this story. They confirmed that tumor-specific T cells combated aggressive skin tumors more effectively in irradiated mice than in nonirradiated controls. To the authors’ surprise, the antitumor T cells increased to equivalent numbers in both mice. The cells transferred into the depleted mice, however, became more activated and secreted more cytokines.

The increased activation was not due to depletion of T reg cells, as irradiation boosted antitumor responses in mice lacking these cells. Rather, the immune depletion freed up activating cytokines, such as interleukin-7 and -15, which were being consumed by endogenous cells. Thus, supplementing tumor-specific T cell transfers with activating cytokines might improve upon this revolutionary antitumor therapy. JEM

TIM-2 soaks up ferritin

The TIM (T cell immunoglobulin mucin) proteins have emerged as key regulators of allergic and autoimmune diseases due to their influence on T helper (Th)-1 and Th-2 responses. On page 955, Chen and colleagues show that one member of this family, TIM-2, multitasks as a receptor for H-ferritin, a component of the iron storage protein ferritin.

Ferritin was not what the group expected to find when they launched a search for TIM-2 ligands. “Ferritin is not something immunologists think about much,” says senior author William Seaman. Although circulating H-ferritin had been shown to increase during inflammation and to bind to T and B cells, the consequences of these observations were largely unknown.

Chen et al. now show that although TIM-2 is most highly expressed in the liver, the primary iron storage organ, this protein is also found on splenic B cells. TIM-2 expression was particularly high on germinal center B cells that were actively responding to antigenic stimulation. Using a TIM-2 reporter cell line, they showed that a soluble product of activated macrophages bound to TIM-2. That product was H-ferritin. Binding triggered endocytosis of the receptor–ligand pair, suggesting that the interaction was functional.

The authors are now investigating the consequences of the ferritin–TIM-2 interaction. A recent study showed that intracellular H-ferritin is required for the antiapoptotic effect of NF-κB activation in fibroblasts, prompting Seaman to speculate that H-ferritin uptake in activated germinal center B cells might have a similar antiapoptotic effect. JEM

NKT cells reject islets

Reporting on page 913, Yasunami and colleagues show that activation of natural killer T (NKT) cells triggers rejection of transplanted insulin-producing islet cells in mice. These data suggest a possible way to avoid the early loss of islet cells that has stymied an otherwise promising diabetes treatment.

Insulin–dependent diabetes is caused by destruction of the insulin-producing cells in the pancreas by CD4+ T cells. Transplantation of islet cells is an effective way to restore insulin production, but this therapy requires life-long immunosuppression of the patient. And even with immunosuppression, up to half of the transplanted islet cells are rapidly rejected.

Early islet rejection is associated with the production of inflammatory cytokines such as interferon-γ (IFN-γ), but the cell types involved in IFN-γ production and islet cell rejection had not been defined. Yasunami and colleagues now place the blame on NKT cells. NKT cells in mice produced IFN-γ in response to islet cell transplantation. This triggered the production of more IFN-γ by graft-infiltrating neutrophils. In the absence of NKT cells, neutrophils or IFN-γ, the islet cells survived.

Multiple injections with the NKT cell–activating compound α-galactosylceramide also protected against islet rejection, consistent with recent reports suggesting that chronic stimulation of NK cells decreases IFN-γ production. Thus, early inhibition of NKT cells might help protect transplanted islet cells, even before destructive T cells are activated. JEM