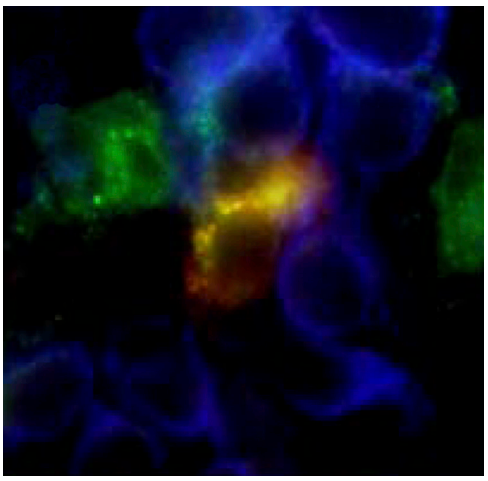
NK cells get helpful



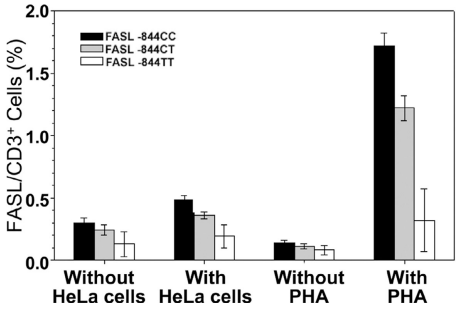
IL-18–conditioned NK cells (yellow) migrate to the T cell (blue) zones of lymph nodes.

On page 941, Mailliard et al. show that natural killer (NK) cells exposed to the cytokine interleukin (IL)-18 commit to a life of helping rather than killing. According to the study, IL-18 creates interferon (IFN)-γ–producing, T helper (Th)-1–promoting NK cells, whereas IL-2 spawns killers.

NK cells are innate immune cells known for their ability to kill transformed or infected cells and to secrete cytokines including IFN-γ. Recently, these cells have been shown to influence the adaptive immune response by interacting with dendritic cells (DCs), thereby triggering either DC maturation or death. But the signals that determine whether NK cells kill DCs or help them mature are not completely understood. Also unknown is whether functionally specialized subsets of NK cells exist or whether individual NK cells are capable of different functions depending on the circumstances.

Mailliard and colleagues now show that IL-18 and IL-2 induce distinct pathways of human NK cell differentiation. IL-18 induced the expression of the chemokine receptor CCR7 on NK cells and the production of IFN-γ, without affecting the ability of the NK cells to kill target cells. IL-2, on the other hand, increased NK cell killing activity but did not induce the expression of CCR7. Interactions between IL-18–conditioned NK cells and DCs increased IFN-γ production by the NK cells and IL-12 production by the DCs, both cytokines that promote Th1 responses.

The authors propose that IL-18–conditioned NK cells would be well suited to migrate to draining lymph nodes after activation in vivo, as lymph node entry depends on CCR7 expression. Once there, these cells might help amplify Th1 responses by interacting with DCs. By contrast, IL-2–conditioned NK cells, which killed DCs in vitro, are more likely to terminate the immune response by eliminating antigen-expressing DCs once the adaptive immune response has done its job. JEM



T cells homozygous for the −844C *FASL* polymorphism express more FASL when activated.

Death receptors in cervical cancer

Death-prone T cells might increase the risk of developing cervical cancer, according to a study on page 967. Sun and colleagues show that women with cervical cancer are more likely to have T cells that are genetically programmed to express high levels of the death-inducing molecule FAS ligand (FASL).

Most cervical cancers are associated with human papillomavirus (HPV) infection. But not all HPV-infected women develop cervical cancer, suggesting that other factors contribute to cancer progression. A recent study linked cervical cancer with a genetic polymorphism in the gene encoding the death receptor FAS, which triggers apoptosis when bound by its ligand FASL. However, these findings are controversial as other studies failed to confirm this association.

Sun and colleagues now find that a naturally occurring polymorphism in the *FASL* promoter was three times more prevalent in Chinese women with cervical cancer than in cancer-free controls. T cells with this single nucleotide polymorphism (−844C) expressed more FASL and were more prone to cell death after stimulation with cervical cancer cells than T cells without the polymorphism (−844T). Although the mechanism remains obscure, the authors suggest that an increased propensity for cell death might limit the ability of tumor-specific T cells to eradicate tumor cells.

The −844C polymorphism was recently found to improve the binding of a transcription factor that helps drive *FASL* gene expression, and to increase FASL protein levels on fibroblasts. In that study, the polymorphism was linked to the autoimmune disease systemic lupus erythematosus (SLE). The link to SLE was postulated to result from increased FAS-mediated cell death, which might facilitate the release of nuclear antigens that are then targeted by the immune response. JEM

Text by Heather L. Van Epps
hvanepps@rockefeller.edu

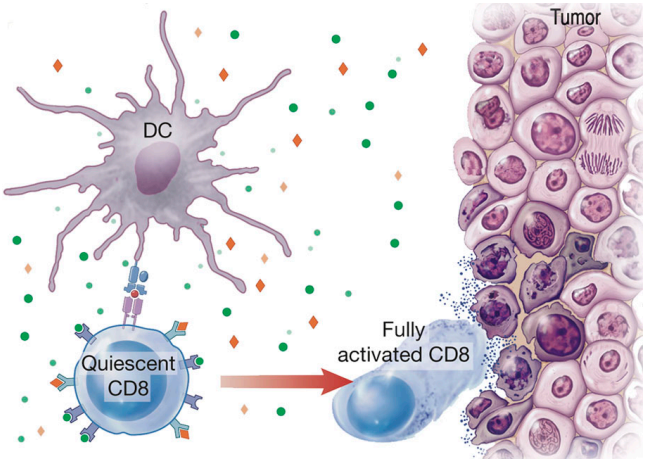
Cytokine-robbing cells

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



Tumor-specific T cells become fully activated in the presence of interleukin (IL)-7 (green dots) and IL-15 (orange diamonds).

NKT cells reject islets

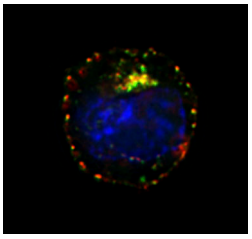
Reporting on page 913, Yasunami and colleagues show that activation of natural killer T (NKT) cells triggers rejection of transplanted insulin-producing islet cells in mice. These data suggest a possible way to avoid the early loss of islet cells that has stymied an otherwise promising diabetes treatment.

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 in 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 NKT 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

TIM-2 soaks up ferritin



H-ferritin (red) binds to TIM-2 (green) and triggers endocytosis of the receptor–ligand pair (yellow).

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