Jump-starting tumor-specific T cells

Vaccination with tumor antigens causes tumor regression in some melanoma patients despite negligible expansion of vaccine-specific T cells. Vaccination may instead result in the expansion of T cells specific for tumor antigens not contained in the vaccine, thus facilitating tumor regression, according to two articles from Pierre Coulie and colleagues on pages 241 and 249.

Tumor-specific T cells can be detected in the blood and the tumors of many melanoma patients, and yet these cells are unable to kill the tumor. What causes the impotence of these T cells is a mystery. Equally mysterious is why vaccination against tumor-specific antigens sometimes causes regression without expanding large numbers of vaccine-specific killer T cells.

Pierre Coulie’s group studied the specificity of antitumor T cell responses in patients vaccinated with a tumor antigen called MAGE-3. In one patient whose tumors regressed after vaccination, the authors found that T cells specific for nonvaccine tumor antigens became detectable or expanded from their prevaccine frequencies. Vaccine-specific T cells became detectable but remained at low frequency. Thus, reinvigoration of existing tumor-specific T cells and activation of new T cells after vaccination does not require large numbers of vaccine-specific T cells.

Although the mechanism underlying this phenomenon remains unknown, Coulie thinks that the few T cells stimulated by the vaccine may change the local environment of the tumor such that existing T cells can be reactivated and new T cells can be recruited.

Rethinking EAE pathogenesis

Th1 cells have long been thought to mediate the pathogenesis of experimental autoimmune encephalitis (EAE), a mouse model for multiple sclerosis. But Langrish et al. now identify a new subset of T cells as the driving force behind brain inflammation in EAE (page 233).

Previous thinking on EAE culprits has focused on Th1 CD4+ T cells and their distinctive product IFN-γ, both of which are found at EAE inflammation sites. But the details were confused by the biology of p40—a subunit shared by both IL-12 (an inducer of Th1 cells) and IL-23. This group showed recently that EAE is suppressed after p40 inactivation because of the loss of IL-23 not IL-12.

The authors now explain the pathogenic effect of IL-23 by showing that this cytokine induces a newly recognized subset of CD4+ T cells, which produces large amounts of IL-17 and IL-6 but very little IFN-γ. These T cells and IFN-γ-producing Th1 cells both invaded the CNS during EAE in wild-type mice, but only IFN-γ-producing Th1 cells were found in the CNS in mice lacking IL-23. Furthermore, T cells cultured in vitro with IL-23, but not those cultured with IL-12, could transfer the disease to naive mice.

How these cells induce disease is not completely understood. IL-17 appears to be a key player, as blocking IL-17 in wild-type mice partially reversed disease.

IL-17 is known to drive the production of inflammatory cytokines from memory T cells, and IL-23 induces proliferation of these cells—both of which may amplify inflammation. Whatever the mechanism, this study appears to exonerate traditional Th1 cells as the main players in the pathogenesis of EAE.