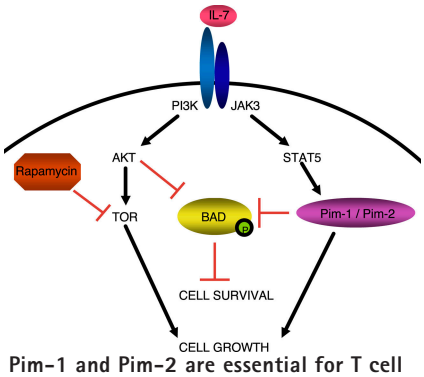
Surviving rapamycin

T cell survival in the face of the immunosuppressive drug rapamycin depends on the expression of prosurvival proteins Pim-1 and Pim-2, according to a report by Fox et al. on page 259. Pim-1 and Pim-2 transmit signals that compensate for those that are wiped out by rapamycin; without the Pim proteins, rapamycin is deadly.

Rapamycin, a drug used to prevent rejection of transplants in humans, blocks the activation of a protein kinase called TOR (target of rapamycin), a component of a T cell signaling pathway that is important for cell survival and activation. Rapamycin works in transplant patients, but treatment of T cells with this drug in vitro or elimination of a signaling protein upstream of TOR in mice has little effect on T cell activation or survival. This paradox, says senior author Craig Thompson, is "rapamycin's dirty little secret." The new work establishes the mechanism behind half of this secret.



Pim-1 and Pim-2 are essential for T cell growth and survival in the presence of rapamycin.

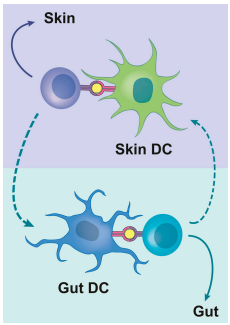
Thompson's group now shows that rapamycin's lack of effect in vitro and in mice is due to the expression of protein kinases Pim-1 and Pim-2, which are activated by growth-promoting cytokines and TCR ligation. T cells lacking both Pim proteins and treated with rapamycin failed in two respects: they did not turn on activation signals in response to TCR ligation and they were unable to respond to cytokine-driven survival signals. Wild-type cells, however, activated the TCR pathway and survived as well as untreated cells. Thus, the Pim proteins provide the only alternative signaling pathway that can bypass the defect inflicted by rapamycin.

The debilitating consequences of lacking Pim-1 and Pim-2 are in part due to an inability to phosphorylate and thus inactivate the proapoptotic protein Bad. Without the Pim proteins, Bad runs rampant. Whether activated Bad is the sole cause of the effects seen in the absence of Pim-1 and Pim-2 is not yet known, but future studies using Bad-deficient mice will reveal if other mechanisms are also at play. Why rapamycin works in patients who have no known defects in the Pim proteins remains a mystery. JEM

DCs redirect T cell traffic

Dendritic cells (DCs) are the master regulators of T cell recirculation, according to a study by Mora et al. on page 303. Memory T cells—thought to be programmed to return to the location in which they first encountered antigen—can be rerouted by an encounter with a DC from another location.

Previous studies have shown that memory T cells express a characteristic array of adhesion molecules and chemokine receptors on their surface that reflect the location of activation and direct their trafficking back to that site. Recently, this group showed that gut DCs, but not spleen or peripheral lymph node DCs, induced the up-regulation of the gut-homing integrin $\alpha4\beta7$ on T cells.



T cell trafficking patterns can be changed after encounter with a dendritic cell from a new location.

Mora et al. now show that these "committed" T cells are not set in their ways. In vitro, T cells stimulated with skin-derived DCs and later restimulated with gut-derived DCs quickly replaced their skin-homing molecules with the gut-homing variety (and vice versa), demonstrating that recirculating T cells simply obey the signals provided by the most recently encountered DC. In vivo, tissue-specific effector–memory T cells can revert to central–memory status, thus acquiring the capacity to home to a variety of second lymphoid tissue where they can encounter new instructions from resident DCs.

This plasticity may be important, points out senior author Ulrich von Andrian, as it would allow the immune system to fight off pathogens that can colonize more than one site. It might also provide a new approach to treating T cell–mediated inflammatory diseases, if harmful T cells can be diverted to an innocuous site. JEM

UV-induced T_{reg} cells

A new study explains how UV exposure induces immunosuppression. Previous studies showed that UV-induced immunosuppression is caused by regulatory T cells (T_{reg} cells). On page 173, Schwarz et al. now show that the development of T_{reg} cells requires DNA damage to DCs called Langerhans cells (LCs).

Mice exposed to UV light are rendered unresponsive to antigens applied to skin because of the induction of T_{reg} cells, which interfere with activation of effector T cells in response to antigen. IL-12, a cytokine produced by LCs, can both prevent the establishment of the unresponsive state and can also reverse established tolerance when provided in combination with antigen stimulation. Schwarz et al. showed in a previous

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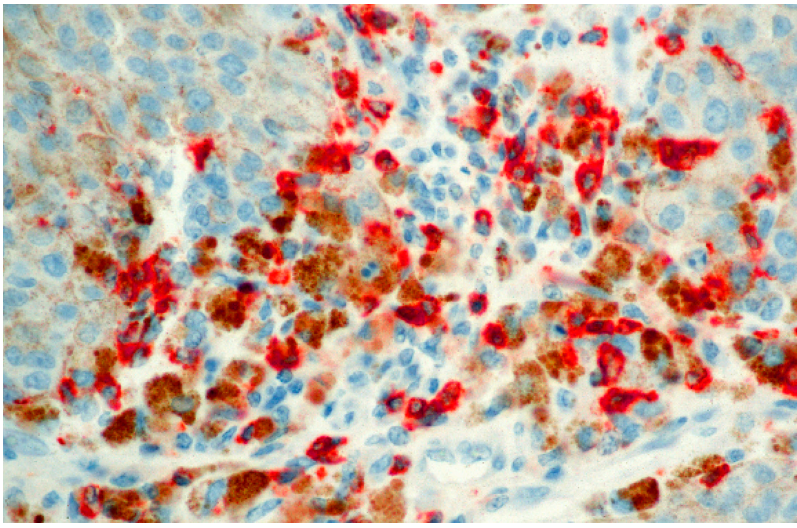
Jump-starting tumor-specific T cells

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. JEM



Tumor-specific T cells (red) infiltrate a tumor after vaccination.

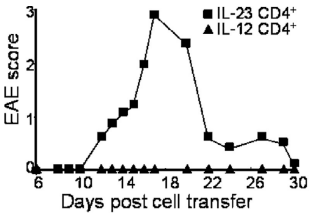
study that IL-12 also promotes DNA repair, but it was unclear how (or if) these functions of IL-12 related to one another.

The group now shows that the prevention of UV-induced immunosuppression relies on DNA repair. Mice that lacked the DNA repair machinery became immunocompromised after UV exposure even after they were given IL-12. In wild-type mice, IL-12 protected against immunosuppression.

Thus, IL-12 interference with immunosuppression appears to be dependent on its induction of DNA repair. The authors suggest that DNA damage may change the costimulatory molecules expressed on LCs, thus altering their stimulatory profile away from effector T cells and toward T_{reg} cells. JEM

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).



$CD4^+$ T cells cultured in vitro with IL-23 (■), but not IL-12 (▲) induce EAE pathogenesis.

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. JEM