CD11b tunes tolerance

The immune system takes its cues from antigen-presenting cells (APCs) to either go on the offensive against a foreign enemy or to stand down and tolerate a harmless threat. Ehirchiou et al. (page 1519) now report a new mechanism by which APCs power down the immune system: an APC surface receptor suppresses the development of overzealous T helper (Th)-17 cells.

According to dogma, APCs that have only few costimulatory receptors dampen immunity. These APCs can’t give T cells the stimulatory boost they need to become offensive. But some APCs with lots of costimulatory receptors can somehow still keep T cells in low gear.

One APC receptor that might direct this alternative pathway, the authors hypothesized, is CD11b. Mice need this integrin to remove neutrophils and macrophages from infection sites and subdue inflammation. CD11b deficiency also worsens autoimmunity, suggesting that the receptor might enable the immune system to tolerate certain antigens.

The authors studied the effect of CD11b on tolerance by feeding normal and CD11b-deficient mice low doses of ovalbumin (OVA) for a week and then challenging them with high doses of this antigen. The CD11b-deficient mice failed this tolerance test and generated high levels of OVA-specific T cells. Tolerance was restored, however, when these mice were supplied with APCs from normal mice.

The CD11b-deficient mice had high levels of two cytokines, IL-6 and IL-23, which support the growth of Th17 cells, a T cell subset that is associated with allergies and autoimmunity. The mutant mice had almost three times the normal numbers of Th17 cells, suggesting that CD11b suppresses the growth of this dangerous T cell subset and thereby establishes tolerance.

The authors are now investigating whether CD11b signaling directly blocks IL-6/IL-23 production and whether a particular APC subset requires CD11b expression to prevent the development of Th17 cells.

AID overwhelms Polβ in class-switching B cells

The machinery that repairs spontaneous DNA mutations fails when the mutations are purposely induced by an enzyme in activated B cells. Wu and Stavnezer (page 1677) now find that the enzyme wins because it induces too much damage for repair proteins to keep up with.

The spontaneous mutation of cytosine bases to uracils is corrected by a process that removes the wrong bases, cuts the DNA at the empty spots, and reinserts the correct bases. This normally efficient process fails in B cells that are switching from producing IgM to making other classes of antibodies. In these cells, cytosines are converted to uracils by the enzyme activation-induced deaminase (AID). The mutated DNA is cut normally, but the ends then recombine to produce new types of antibodies. Recombination thus occurs at the expense of repair.

The repair failure is blamed on DNA polymerase β (Polβ), whose job is to add back the correct nucleotides. Scientists have proposed that B cells undergoing class switching have too little Polβ or that the damaged DNA sites are not accessible to the enzyme.

But Wu and Stavnezer now show that Polβ is probably as productive in B cells as it is in other cell types. Polymerase levels were normal, and the enzyme found its way to damaged sites. Activated B cells lacking the polymerase had even more mutations—and more recombination events—than usual.

The team needed a new explanation. They hypothesized that recombination happens because AID creates too many damaged sites for Polβ to repair. The absence of Polβ caused a noticeable increase in recombination only in antibody genes with relatively few AID target sequences. Recombination events were abundant, however, in genes with lots of AID targets whether or not Polβ was present. Thus Polβ repairs AID-induced lesions, but can only fix so many.

Activated B cells need their repair machinery to protect themselves from unwanted mutations during antibody gene rearrangement. The authors speculate that, to switch antibody types, B cells thus have to dilute the efficiency of the repair process by gaining more AID targets in antibody genes.
Keeping score of antigraft T cells

Transplanted organs function well in their new home only if they are left alone by the host’s immune system. Now, Codarri et al. (page 1533) have potentially found a way to monitor the health of the new replacements—they identify the T cells that harass grafts in transplant patients.

Unlike grafts that are rejected immediately, those that fail gradually are thought to be rejected in part by CD4+ T cells. But activated CD4+ T cells are difficult to distinguish from the regulatory T (T reg) cells that suppress rejection, as both express CD4 and CD25. Only the T reg cells also express the transcription factor FOXP3, but their sparse numbers are difficult to follow in vivo. FOXP3+ cells express much less IL-7Rα than do other CD4+ T cells. So the team wondered whether IL-7Rα would be a convenient marker to follow activated T cells that enter the grafts.

They now find that CD4+ CD25+ cells expressing high levels of IL-7Rα are abundant in transplant patients. These cells infiltrated the grafts and were able to kill donor cells in vitro. Patients with delayed graft rejection had twice as many of these cells as did stable transplant recipients. Both groups had equal numbers of T reg cells, suggesting that graft rejection is caused by the increased numbers of activated T cells. The authors are now looking at patients to determine whether increases in IL-7Rα-expressing cells can be used to predict transplant rejection. JEM

Neurons need miRNA to survive

Neurons missing their microRNA (miRNA) gradually deteriorate in structure and function, according to Schaefer et al. (page 1553). These bits of RNA prolong neuronal longevity and may keep neurodegenerative diseases at bay.

miRNA—small pieces of RNA generated by the RNA-chopping enzyme called Dicer—strategically shut off genes to allow embryonic cells to differentiate. Because mice that lack Dicer die as embryos, the role of miRNA in vivo has been studied by deleting Dicer only in specific cell types. These studies showed that Dicer—and thus miRNA—is required for both cell differentiation and the survival of some cells. Neurons need miRNA for differentiation, but whether they also need them for survival later was unknown.

Schaefer et al. now find that inactivating Dicer in postmitotic neurons of adult mice eventually kills these cells. The neurons maintained some of their miRNA long after Dicer inactivation and looked and functioned normally. But the reduction in miRNA eventually took its toll. Neuronal signaling malfunctioned, and the cells died off. As cell death progressed, the mice developed symptoms reminiscent of those seen in humans with neurodegenerative disorders. Whether the human disorders are caused by changes in specific miRNA remains to be seen. JEM

Antitumor drug sends new signals

Drugs that collapse the tumor vasculature by increasing the leakiness of tumor blood vessels are a new breed of chemotherapeutic agents, but how they worked was unknown. Now, Roberts et al. (page 1559) have determined the pathway and targets of one such vasculature-disrupting agent (VDA). They find that this drug does more than just increase leakiness.

The VDA called DMXAA works well against several types of human cancers and is currently in phase II clinical trials. But there are no clues from clinical studies to explain why this drug has succeeded where others have failed. Experiments in mice have hinted at its downstream targets: DMXAA prods mouse macrophages to secrete interferon (IFN)-β and other cytokines that promote vessel permeability. IFN-β is also induced by activation of certain pattern recognition receptors (PRRs), such as the Toll-like receptors and the RNA helicases. But Roberts et al. now find that DMXAA’s path to gene induction bypasses all known PRRs. The drug instead potently activates the tank binding kinase (TBK)-1, leading to high levels of an activated transcription factor called IFN regulatory factor (IRF)-3.

Besides IFN-β, IRF-3 also turns on genes that cause the apoptosis and senescence of tumor cells. The functional diversity of the downstream targets of DMXAA might explain the high efficacy of this drug against human cancers. Recombinant IFN-β has been used for years in the clinic to treat a number of malignancies including chronic myelogenous leukemia and malignant melanoma. Thus, Roberts et al. now tie DMXAA to this preeminent tumor-fighting system. JEM