FoxP3 gets a new gig

On page 1141, the one-trick transcription factor FoxP3 reveals a new function. According to Chang and colleagues, FoxP3 does more than just drive regulatory T (T reg) cell development; it also promotes the proliferation of developing thymocytes.

FoxP3 is required for the development of CD4^+CD25^+ T reg cells, which subdue the activation of conventional T cells and thus protect against chronic inflammation and autoimmunity. Mice and humans that lack FoxP3 develop a spontaneous, multi-organ autoimmune disease that has been primarily attributed to the lack of T reg cells. But one fact suggests that this explanation may be too simple. Irradiated mice that are reconstituted with FoxP3-deficient bone marrow do not develop disease, suggesting that FoxP3 also functions in non-hematopoietic cells.

Chang and colleagues now show that FoxP3 is not exclusive to T cells, but is also expressed in thymic epithelial cells. In mice lacking FoxP3, developing thymocytes were unable to proliferate normally, resulting in thymic atrophy. The proliferation defect was caused by a lack of FoxP3 in thymic stromal cells, rather than in T cells, as normal thymocytes also failed to proliferate in a FoxP3-deficient thymic environment.

How FoxP3 expression on thymic epithelial cells helps drive thymocyte proliferation is unknown. Also unclear is how the proliferation defect contributes to autoimmune disease, although there is a long-standing but poorly understood link between thymic atrophy and T cell–driven autoimmune disease.

CCR5 saves lives

Although West Nile virus (WNV) infections have made headlines in recent years, little is known about how the virus causes disease or how the immune system fights back. On page 1087, Glass and colleagues show that immune cells must invade the central nervous system to combat the virus, and the chemokine receptor CCR5 is their entry ticket into the brain.

WNV is an RNA virus that attacks the brain and can cause meningitis and encephalitis. Although infections with WNV can be fatal, most cases are mild or asymptomatic, suggesting that the immune system is capable of fighting off the virus. But the details of the anti-WNV immune response remain poorly characterized.

Glass and colleagues now show that WNV infection in mice triggers an influx of T cells, natural killer cells and macrophages into the brain in response to local production of chemokines. The influx of cells, which protected the mice against lethal infection, largely depended on the expression of CCR5 on the responding cells. In CCR5-deficient mice, fewer cells gained access to the brain and the infection was uniformly fatal.

To determine whether CCR5 is equally important for combating WNV infection in humans, the authors are now testing whether people who had severe or fatal infections with WNV were more likely to carry the CCR5 deletion mutation. This mutation is best known for its ability to protect against HIV infection, as CCR5 is a cellular coreceptor for HIV.

New target for T regs

The natural killer (NK) cell is a new target for regulatory T (T reg) cell tyranny, according to a study on page 1075. Ghiringhelli and colleagues show that the antitumor activity of NK cells is snuffed out by T reg cells, allowing tumors to grow unchecked.

NK cells are innate immune cells that help destroy NK cell–sensitive tumors, such as melanomas and gastrointestinal tumors, which express activating ligands for these cells. The activation and antitumor functions of NK cells are triggered by the binding of these ligands to the activating receptor NKG2D on the NK cells. In many cancer patients, NK cell activity is hampered by the shedding of NKG2D ligands from tumor cells or by other unknown mechanisms.

This group recently showed that a drug that activates NK cells in patients with gastrointestinal cancer improved their prognosis. They now report that the patients who did not respond to this therapy had increased numbers of circulating T reg cells, whereas the patients who responded did not. The T reg cells from nonresponding patients prevented NK cells from killing tumor cells in vitro.

In mice, transfer of T reg cells blocked the killing capacity of NK cells. This inhibition depended on the expression of membrane-bound TGF-β on the T reg cells, which triggered the down-regulation of NKG2D on the NK cells. Thus TGF-β–induced inhibition of NK cell activation, which normally helps curtail inflammation and prevent autoimmunity, helps certain tumors avoid being recognized by these killer cells.