Receptors against autoimmunity

Men are less prone to autoimmunity than women thanks to the anti-inflammatory effect of male sex hormones. But how these androgens, such as testosterone, exert this effect was a mystery. Dunn and colleagues now report on page 321 that a nuclear hormone receptor that gets boosted by testosterone switches off pro-inflammatory cytokine production in male CD4+ T cells.

Androgens are known to shift the balance from pro-inflammatory Th1 cytokines to anti-inflammatory Th2 cytokines. Thus, a testosterone shot is all it takes to suppress lupus and diabetes symptoms in mice. “The link between androgens and protection against autoimmunity could not be clearer,” says senior author Larry Steinman. “But we still had to figure out how androgens actually instruct T cells to stop attacking the host.”

A good candidate was the nuclear hormone receptor peroxisome proliferator activated receptor (PPAR)-α. Expression of PPAR-α was previously shown to increase in response to testosterone and to be higher in male compared with female hepatocytes. The team now shows that this gender difference extends to T cells and that it affects their inflammatory activities.

The group tested mice with experimental autoimmune encephalitis (EAE), a mouse model of multiple sclerosis (MS). In the male mice, knocking out PPAR-α increased disease severity and expression of pro-inflammatory IFNγ and TNF by CD4+ T cells. In females, EAE was severe and cytokine production high in both wild-type and PPAR-α knock-outs.

The team showed that PPAR-α suppresses the production of IFNγ and TNF by preventing transcription factors NF-κB and c-Fos from binding to the promoters of these cytokine genes.

Steinman’s group is now examining PPAR-α expression in humans. If PPAR-α does show a gender-dependent dichotomy in people, they plan to test a known PPAR-α agonist along with androgen therapy in clinical trials for MS. JEM

Tumor-free heart repair

Tissue regeneration without tumor formation may soon be within reach, at least for heart repair. On page 405, Behfar et al. report that embryonic stem (ES) cells preprogrammed to mature into cardiomyocytes can fix injured hearts in vivo without seeding tumors.

Directing ES cells to become a particular tissue type in vivo is an inefficient process. Consequently, transplanted ES cell populations may give rise to tumors in recipient hosts. Behfar et al. reasoned that delivery of partially differentiated ES cells may result in safe outcome provided that a modulator of differentiation shuts down troublesome tumor pathways.

When ES cells are delivered in vivo, their tumorigenicity is reduced in mice that suffer heart attacks. This is associated with TNF production. But TNF had not been tested for its ability to direct cardiomyocyte differentiation, although ES cells do express receptors for TNF. So the authors wondered whether TNF-driven signaling would be enough to guide cells into a differentiation pathway and thus prevent tumors in ES cell recipient mice.

The team engineered mice to express high levels of TNF in their hearts, and found that the transfer of undifferentiated ES cells did not lead to tumor formation. When ES cells were treated with TNF-induced supernatants in vitro, they not only expressed genes necessary for heart function but also down-regulated oncogenes as they differentiated into cardiac progenitor cells. In mice induced to suffer heart attacks, these cells integrated into heart muscle, repaired scar tissue, and improved heart function.

TNF reduced the risk of tumor development by inducing the secretion of pro-cardiogenic factors including TGFβ. TGFβ also suppresses host immunity and may therefore reduce the likelihood of rejection of ES-derived cells. The effect of this immunosuppression on the weakened heart’s ability to fight infections is not yet clear, so the team plans to test autologous stem cells derived from the host’s own bone marrow. This option may remove the need for immunosuppression and improve the safety of stem cell therapy. JEM