

■ AUTOIMMUNITY

Defects in DC tolerance

Dendritic cells (DCs) have previously been implicated in the pathogenesis of the autoimmune disease lupus. Blimp-1, a known regulator of B cells and T cells, is now shown to also regulate the immune tolerance function of DCs, providing new insights into the role of these key immune cells in lupus (*J. Exp. Med.* **208**, 2193–2199).

A polymorphism in Blimp-1 was previously identified as risk variant for systemic lupus erythematosus (SLE), indicating that this factor might be important in SLE pathogenesis. By investigating mice in which Blimp-1 had been selectively knocked out in DCs, Sun Jung Kim *et al.* showed that Blimp-1 expression in DCs is required for immune tolerance in female mice, but not in males. DCs lacking Blimp-1 from female mice showed increased production of the proinflammatory cytokine interleukin-6, promoted the induction of follicular T helper cells and enhanced germinal center responses. These mice also developed autoreactive antibodies that carried multiple mutations, consistent with a germinal center response.

Together, these gender-dependent responses to Blimp-1 knockout in DCs are reminiscent of the human lupus phenotype. It will therefore be interesting to investigate how the Blimp-1 polymorphism identified in genome-wide association studies influences Blimp-1 expression and DC function in human studies. —MS

■ ADDICTION

One thing leads to another

Addiction to alcohol or nicotine often precedes the use of cocaine and other illegal substances. A recent study points to the possible neural basis of this phenomenon (*Sci. Trans. Med.* **3**, 107ra109).

Amir Levine *et al.* pretreated mice with nicotine and found that it increased addiction-related behaviors such as conditioned place preference in response to cocaine. This effect was unidirectional; exposing the mice first to cocaine did not affect responses to nicotine.

Mechanistically, the authors found that nicotine enhanced the ability of cocaine to inhibit histone deacetylase, promoting histone acetylation in the nucleus accumbens, a key component of the brain reward system. This priming magnified the effect of cocaine on synaptic plasticity in the accumbens. Indeed, pharmacologically or genetically manipulating histone acetylation correspondingly modified the effects of cocaine on plasticity.

IMMUNOTHERAPY

A safety switch for immunotherapy

Cellular therapies—such as adoptive T cell transfer—are increasingly used to treat hematological malignancies, with encouraging results. But as progress is made in increasing the persistence and activity of the transferred T cells, the risk of serious graft-versus-host disease (GVHD) also increases. Antonio Di Stasi *et al.* now report their clinical test of a ‘suicide gene’ method to delete transferred cells and resolve GVHD in individuals receiving genetically modified T cells for the treatment of leukemia (*N. Engl. J. Med.* **365**, 1673–1683).

Although suicide genes such as the herpes simplex virus thymidine kinase have been previously tested as a safety strategy for adoptive T cell therapies, a faster-acting alternative would be desirable. Therefore, the researchers engineered human T cells to express an inducible suicide protein consisting of human caspase 9 linked to the FK506-binding protein, FKBP12. Cells expressing this transgene are viable but rapidly undergo apoptosis when treated with the dimerizing molecule AP1903.

To test the ability of the suicide gene product to deplete engineered cells in humans, the researchers treated five individuals with leukemia with donor T cells that expressed the fusion protein. Four of the patients developed GVHD in the skin within 42 days after the transplant, and one of these individuals also developed liver GVHD. The four patients were given one dose of AP1903, and, within 30 minutes, more than 90% of the transferred T cells were eliminated from the peripheral blood, and their GVHD symptoms disappeared by 48 hours. And although some transgenic T cells persisted in the treated individuals and expanded after clearance of the dimerizing drug, GVHD did not recur within up to one year of monitoring, and three of the four individuals showed no leukemia relapse.

The results show that an inducible caspase 9 is an effective tool for the rapid and safe elimination of most transferred T cells in the advent of GVHD. The impact of such deletion of adoptively transferred T cells on cancer relapse will now require further study. —AF



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Analyzing epidemiological data, Levine *et al.* showed that cocaine use often occurs in smokers. Moreover, people who initiate cocaine use after they become smokers are most likely to develop cocaine dependence. Decreasing smoking rates might therefore lead to a decrease in cocaine addiction. —JCL

■ NEUROLOGICAL DISORDERS

Serine to the rescue

No effective treatments exist for individuals with hereditary neuropathies. On the basis of recent progress in understanding the cause of one such disorder, hereditary sensory and autonomic neuropathy type 1 (HSAN1), K. Garofalo *et al.* provide initial promising results for a mechanism-based therapy for this rare disease: dietary supplementation with L-serine (*J. Clin. Invest.* doi:10.1172/JCI57549).

HSAN1 is caused by mutations in genes that encode subunits of serine palmitoyltransferase, which catalyzes the first step in sphingolipid

biosynthesis. These mutations loosen the substrate specificity of the enzyme, allowing it to use alanine or glycine rather than serine. This change in substrate results in the production of deoxysphingolipids, which may be neurotoxic. Proceeding from this mechanistic framework, the researchers hypothesized that increasing serine levels might be beneficial. Indeed, dietary supplementation with L-serine in a mouse model of HSAN1 decreased plasma deoxysphingolipid levels and decreased neuropathic symptoms. In 14 individuals with HSAN1, L-serine dietary supplementation also reduced plasma deoxysphingolipid levels.

In view of the short 10-week course of L-serine supplementation, neurological symptoms were not examined in the treated individuals with HSAN1. A larger and longer-term clinical trial will now be needed to test the safety and efficacy of this therapy.—MB

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