■ T CELLS

Reprogramming regulatory T cells

A subset of Foxp3$^+$ regulatory T (T_{reg}) cells is now shown to be capable of acquiring T helper cell activity by downregulating expression of the transcription factor Eos (*Immunity* **38**, 998–1012).

In an inflammatory environment, T_{reg} cells are phenotypically plastic. They can secrete proinflammatory cytokines and show T helper cell activity. Although some of these T_{reg} cells downregulate the expression of Foxp3, a transcription factor required for suppressive activity, some can maintain Foxp3 expression.

Madhav D. Sharma *et al.* identified a subset of Foxp3$^+$ T_{reg} cells that in an inflammatory environment downregulate Eos, a co-repressor required for Foxp3-mediated T_{reg} cell suppressive activity. These Eos-labile T_{reg} cells upregulated interleukin-2 (IL-2), IL-17 and CD40 ligand and showed T helper cell activity while remaining Foxp3$^+$. IL-6 promoted the downregulation of Eos, whereas overexpression of Eos in T_{reg} cells impaired their reprogramming and T helper cell activity *in vivo*. In tumor-bearing mice, downregulation of Eos was impaired and T_{reg} cell suppressive activity was maintained by indolemaine 2,3-dioxygenase (IDO). Inhibition of IDO promoted T_{reg} cell reprogramming and antitumor immune responses. —*KDS*

■ T CELLS

Bending the rules of restriction

T cells can be categorized according to their expression of the glycoproteins CD4 or CD8 on their cell surface. CD8$^+$ T cells recognize peptides presented by major histocompatibility complex class I (MHCI), whereas CD4$^+$ T cells recognize peptides in the context of MHCII. A new study suggests that this distinction is not absolute by showing that that a simian immunodeficiency virus (SIV) vaccine can elicit SIV-specific CD8$^+$ T cells that recognize MHCII-restricted epitopes (*Science* **340**, 1237874).

Louis Picker and his colleagues had previously reported a potential HIV vaccine strategy that used a recombinant rhesus macaque cytomegalovirus (CMV) vector to express SIV proteins (RhCMV/SIV), which yielded impressive levels of protection in vaccinated rhesus macaques. They noticed, however, that the RhCMV/SIV vectors did not induce canonical CD8$^+$ T cell responses, which the virus is known to escape. In their new work, the authors investigated the nature of the CD8$^+$ T cell responses induced by this vaccine in more depth. They found that the recombinant RhCMV/SIV (strain 68-1 RhCMV/SIV) elicited CD8$^+$ T cell responses that are distinct from those induced by SIV or by a wild-type RhCMV vector expressing SIV proteins. Whereas CD8$^+$ T cells induced by a virus usually focus on only a small number of epitopes, strain 68-1 RhCMV/SIV could elicit more promiscuous CD8$^+$ T cell responses to a broad range of SIV epitopes and, notably, to those presented by both MHCI and MHCII.

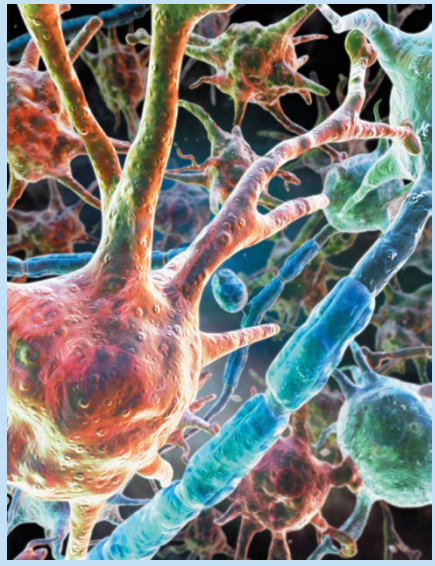
The authors then compared the CD8$^+$ T cell responses induced by strain 68-1 RhCMV/SIV with RhCMV vectors bearing different CMV deletions, allowing them to identify rhesus CMV genes that regulate these responses. As these key CMV genes have human CMV homologs, it may be possible to design vectors that can induce similarly broad T cell responses in humans against HIV and other viruses. Further studies will also be required to dissect the mechanisms by which RhCMV vectors elicit these paradigm-violating T cell responses and to determine whether such T cell responses can be manipulated to create an effective HIV vaccine.—*MS*

ALZHEIMER'S DISEASE

Micrological modulation

Polymorphisms in the gene that encodes the transmembrane protein CD33 have previously been linked to Alzheimer's disease. Now, a new study shows that CD33 affects the ability of microglia to take up amyloid-β, the toxic peptide that accumulates in the brains of individuals with Alzheimer's disease (*Neuron* 78, 631–643).

Ana Griciuc *et al.* found that the *CD33* allele that had previously been shown to protect humans against the disease results in reduced expression of the protein in human brain. When the researchers examined mouse models of the disease, they observed less brain accumulation of amyloid-β if the mice lacked CD33.



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Griciuc *et al.* then showed that compared with brains from healthy people, CD33 expression was increased in microglia within the brains of individuals with Alzheimer's disease. When the authors overexpressed CD33 in microglia in cell culture, the cells were less able to take up amyloid-β from the culture medium compared with control microglia. These findings suggest that inhibition of CD33 could be a potential therapeutic approach to enhance microglial uptake of amyloid-β in Alzheimer's disease. —*EC*

■ CANCER THERAPY

Fueling resistance

A recent study (*Cancer Cell* **23**, 811–825) has uncovered a metabolic adaptation that promotes the growth of therapy-resistant tumor cells and that may also be a targetable vulnerability.

The study broadly characterizes the resistance to chemotherapy of a previously described subpopulation of melanoma cells. This subset of cells within the tumors, which are known to express high levels of the epigenetic modulator JARID1B and to proliferate more slowly than the bulk of the tumor, are enriched after therapeutic regimes that target rapid-growing cells. Alexander Roesch *et al.* now show that this melanoma subset can also thrive under treatment with other anticancer drugs.

The authors surveyed the resistant cell population for potential therapeutic targets in the hope of identifying strategies to fully eradicate tumors and prevent recurrence. They found that, compared with melanoma cells with low expression or knockdown of JARID1B, JARID1B^{high} melanoma cells had an increase in mitochondrial components that corresponded with increased oxygen consumption, suggesting that JARID1B^{high}