

■ 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 indoleamine 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 (MHC I), whereas CD4⁺ T cells recognize peptides in the context of MHCII. A new study suggests that this distinction is not absolute by showing 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 canoni-

ALZHEIMER'S DISEASE

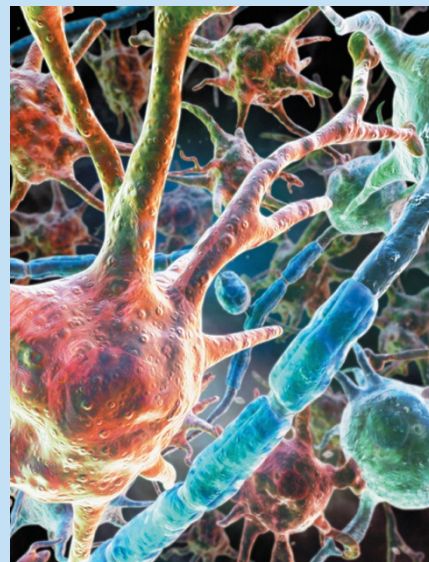
Micrological modulation

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.

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



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cal 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 MHC I 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

■ 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}

cells undergo a metabolic adaptation that may support their growth as well as drug resistance properties.

The researchers then showed that inhibition of the mitochondrial respiratory chain in the resistant population induced cell death. In addition, combining targeting of the mitochondrial respiratory chain with chemotherapy could sensitize the drug's cytotoxic effect in some of the melanoma cell lines studied and reduce tumor growth *in vivo*.

The results support that there is intimate coupling between a tumor cell's proliferative and metabolic states and suggest that compounds that target mitochondrial function currently used in diabetic patients could prevent the development of resistance to cancer therapies. —VA

■ AUTOIMMUNITY

Be more sensitive

Autoantibodies against peptidylarginine deiminases (PADs) may worsen rheumatoid arthritis by increasing the sensitivity of these enzymes for calcium (*Sci. Trans. Med.* **5**, 186ra65).

PADs convert peptidylarginine to citrulline. As citrullinated proteins are effective autoantigens, PADs have been implicated in autoimmune disease. In the case of rheumatoid arthritis, PAD4 is of particular interest, as it is found in synovial fluid. However, PAD4 requires high concentrations of calcium, much higher than those found at the synovium, to work.

Studying samples from patients with rheumatoid arthritis, Erika Darrah *et al.*

identified autoantibodies that recognize both PAD3 and PAD4 and that markedly increase the activity of PAD4. By measuring enzyme kinetics, the authors found that the antibodies increased PAD4's sensitivity for calcium by an order of magnitude. People with arthritis with these autoantibodies had worse disease than those who were negative for them.

Although it remains to be seen whether this mechanism is active *in vivo*, the results of this study disclose an intriguing new mechanism for the generation of citrullinated autoantigens and for the pathogenesis of rheumatoid arthritis. —JCL

■ TUMOR SUPPRESSORS

A new PTEN translational variant

Phosphatase and tensin homolog (PTEN) is a key tumor suppressor that it is mutated in multiple cancer types and antagonizes signaling through the phosphoinositide 3-kinase (PI3K) pathway. A recent study identifies a new secreted variant of PTEN that might have therapeutic utility for cancer (*Science* <http://dx.doi.org/10.1126/science.1234907>).

Benjamin Hopkins *et al.* found an alternative translation start site in the PTEN transcript and showed that this PTEN variant was translated when expressed in cells. Compared with classical PTEN, the alternative PTEN protein (PTEN-Long) had an additional 173 amino acids at its N terminus. The authors detected both forms of PTEN in various human cell lines, including cancer cell lines, but not in those that lacked PTEN. In primary breast tumor tissues, PTEN-Long expression was reduced in the tumors but was higher in the tumor micro-environment than in the tumor or in normal breast tissue.

The researchers then showed that PTEN-Long could be secreted and was present in human plasma and serum. Applied as an exogenous agent, PTEN-Long could block PI3K signaling in cultured cells and was able to regress tumor growth when injected into a number of different mouse xenograft tumor models.

Although further examination of the functions of this alternative PTEN variant is required, the identification of this secreted protein may allow the design of new strategies to restore PTEN to tumor cells. —MS

Written by Victoria Aranda, Eva Chmielnicki, Kevin Da Silva, Juan Carlos López and Meera Swami

New from NPG

Vector transmission regulates immune control of *Plasmodium* virulence

Spence, P.J. *et al. Nature* **498**, 228–231 (2013)

The authors show that transmission of the malaria parasite *Plasmodium chabaudi chabaudi* through its mosquito vector modifies the asexual blood-stage parasite, thus altering host immune responses to *Plasmodium* and parasite virulence.

The perivascular niche regulates breast tumour dormancy

Ghajar, C.M. *et al. Nat. Cell. Biol.* <http://dx.doi.org/10.1038/ncb2767> (2 June)

This study provides new insights into how disseminated tumor cells are kept dormant by showing that in stable microvessels endothelial-derived thrombospondin-1 (TSP1) maintains breast cancer cells in a quiescent state. In sprouting vessels, TSP1 expression decreases, relieving this suppression and stimulating the growth of metastases.

High-density genotyping study identifies four new susceptibility loci for atopic dermatitis

Ellinghaus, D. *et al. Nat. Genet.* <http://dx.doi.org/10.1038/ng.2642> (2 June)

By performing high-density genotyping in thousands of cases and controls, the authors identify four new susceptibility loci for the inflammatory skin disease atopic dermatitis, bringing the total of atopic dermatitis risk loci in European populations to 11.

Nucleation of platelets with blood-borne pathogens on Kupffer cells precedes other innate immunity and contributes to bacterial clearance

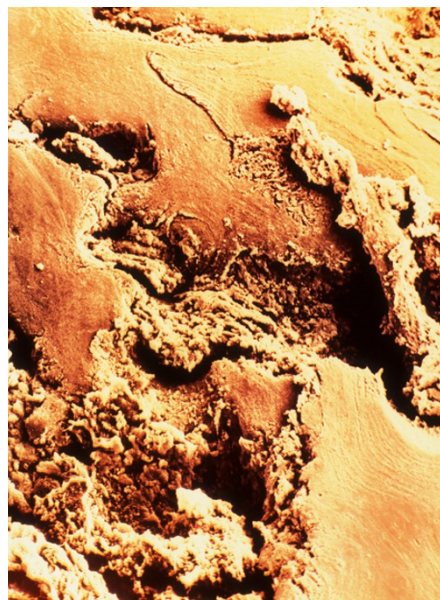
Wong, C.H.Y. *et al. Nat. Immunol.* <http://dx.doi.org/10.1038/ni.2631> (16 June)

The authors show that platelets collaborate with specialized macrophages called Kupffer cells to clear bacteria. This mechanism occurred before recruitment of other innate immune cells and was needed for survival of the mouse host after bacterial infection.

Rett syndrome mutations abolish the interaction of MeCP2 with the NCoR/SMRT co-repressor

Lyst, M.J. *et al. Nat. Neurosci.* <http://dx.doi.org/10.1038/nn.343> (16 June)

The authors identify a new mutational cluster in MeCP2, showing that Rett syndrome mutations in this region prevent the interaction of MeCP2 with the co-repressor complex NCoR/SMRT. Mice with a common Rett syndrome mutation in this domain had severe Rett-like phenotypes.



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