New from NPG

Synthetic lethal metabolic targeting of cellular senescence in cancer therapy

Dörr, J.R. *et al. Nature* <http://dx.doi.org/10.1038/nature12437> (14 August)

In a mouse model of B cell lymphoma, the authors showed that chemotherapy-induced senescence alters the metabolic activity of the senesced cells, allowing these cells to be targeted by drugs that block glucose use or autophagy. These findings indicate that it might be possible to design combination therapies for lymphomas and other tumor types to eliminate senescent cells arising from chemotherapeutic treatment.

A suppressor screen in *Mecp2* mutant mice implicates cholesterol metabolism in Rett syndrome

Buchovecky, C.M. *et al. Nat. Genet.* <http://dx.doi.org/10.1038/ng.2714> (28 July)

By carrying out a mutagenesis suppressor screen in a mouse model of Rett syndrome that lacks methyl CpG-binding protein 2 (*Mecp2*), the authors identified a suppressing mutation in the gene encoding the cholesterol biosynthetic enzyme squalene epoxidase. They showed that there was dysregulation of lipid metabolism in the brains of *Mecp2*-null mice, and they found that statins could improve symptoms in *Mecp2*-mutant mice.

The scavenger receptor SCARF1 mediates the clearance of apoptotic cells and prevents autoimmunity

Ramirez-Ortiz, Z.G. *et al. Nat. Immunol.* <http://dx.doi.org/10.1038/ni.2670> (28 July)

This study shows that dendritic cells, macrophages and endothelial cells use the scavenger receptor SCARF1 to phagocytose dead cells using the complement component C1q. SCARF1-deficient mice showed an accumulation of dead cells in their tissues, which led to the development of a lupus-like disease.

Suppression of eIF2 α kinases alleviates Alzheimer's disease-related plasticity and memory deficits

Ma, T. *et al. Nat. Neurosci.* <http://dx.doi.org/10.1038/nn.3486> (11 August)

Increased phosphorylation of the eukaryotic initiation factor 2 α -subunit (eIF2 α) has been observed in the brains of Alzheimer's disease patients and model mice. Now, these authors show that deletion of the eIF2 α kinases PERK and GCN2 prevents this increased phosphorylation of eIF2 α and ameliorates some of the symptoms in mice that model Alzheimer's disease.

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Epidemiological studies have shown that smoking is a strong risk factor for the development of alcohol dependence, but the neural basis of this interaction has not been fully established. The mesolimbic dopamine system, which includes the ventral tegmental area (VTA) and the nucleus accumbens, mediates our hedonic response to both nicotine and ethanol. Working in rats, William Doyon *et al.* found that pre-exposure to nicotine reduced alcohol-induced dopamine release in the nucleus accumbens, and that this effect was associated with an increase in ethanol self-administration.

Mechanistically, nicotine activated acetylcholine receptors containing the nicotinic $\beta 2$ subunit to stimulate GABA-releasing neurons in the VTA. This led to the inhibition of VTA dopamine neurons and to the reduced release of dopamine in the nucleus accumbens.

The team also found that inhibiting glucocorticoid receptors within the VTA before giving the rats nicotine blocked both the increased inhibition of dopamine neurons and the increased self-administration of alcohol, placing stress hormones upstream of the interaction between both these substances of abuse.—JCL

■ AUTOIMMUNITY

A transcriptional regulator of T cells

Naive T cells need two signals for their activation: an antigen-specific signal through the T cell receptor, and a co-stimulatory sig-

nal via the CD28 receptor. A recent study identifies the transcription factor DEC1 as a regulator of CD4⁺ T cell functions downstream of CD28 signaling, and highlights its role in the development of a T cell-mediated autoimmune disease (*J. Exp. Med.* **210**, 1603–1619).

Marc Martinez-Llordella *et al.* analyzed the transcriptional profile of purified populations of naive CD4⁺ T cells from humans or mice to identify genes regulated by CD28 signaling. Among the genes they identified, the authors homed in on *DEC1*, which encodes a transcriptional factor that is important for the regulation of many early transcripts involved in T cell activation. They then showed that DEC1 was required for efficient T cell activation *in vitro*. CD4⁺ T cells from mice lacking Dec1 showed defects in survival and proliferation that could be corrected by exogenous interleukin-2.

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The authors then examined whether DEC1 has a role in CD4⁺ T cell activation in autoimmune disease using mice with experimental autoimmune encephalomyelitis (EAE, a mouse model of multiple sclerosis). They found that Dec1 was required for EAE development, both by affecting the priming phase of EAE as well as by stimulating production of proinflammatory cytokines in the effector phase of disease. It will be interesting to investigate the role of DEC1 in other autoimmune diseases in future studies, and whether it can be targeted for therapeutic benefit.—MS

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