is highly expressed on chronically infected, functionally exhausted CD8$^+$ T cells. PD-1 blockade restores function in exhausted CD8$^+$ T cells and reduces viral load in infected mice.

To investigate the mechanism whereby PD-1 expression is regulated, Rafi Ahmed and his colleagues (*Immunity* **35**, 400–412) examined epigenetic alterations at the *Pdcd1* locus, which encodes PD-1. During acute lymphocytic choriomeningitis virus (LCMV) infection in mice, the *Pdcd1* locus is demethylated in T cells, leading to upregulation of PD-1 expression. These effects, however, are transient, as a reduction in LCMV load is associated with remethylation of the *Pdcd1* locus and reduced PD-1 expression. In T cells chronically infected with LCMV, PD-1 expression is sustained due to prolonged stimulation of the T cell receptor and persistent demethylation of the *Pdcd1* locus. The authors found the same is true in human chronic viral infections: the *PDCD1* locus is demethylated in CD8$^+$ T cells specific to yellow fever virus, Epstein-Barr virus or cytomegalovirus. These results highlight a dynamic mechanism regulating T cell activation in the face of viral infection. —*KDS*

■ CANCER

Metastasis with a little help from MDSCs

Metastatic dissemination can occur early in tumor progression and involves both phenotypic changes in the primary tumor cells as well as modifications in their environment and in the prospective tumor niches. Recent research postulates that immune cells such as myeloid-derived suppressor cells (MDSCs) are subverted in cancer and contribute to metastasis by acclimatizing distant organs for tumor colonization.

A new report (*PLoS Biol.* **9**, e1001162) proposes that MDSCs also have a role earlier in metastasis. Using a mouse model of uveal melanoma that features the characteristic early dissemination properties of this tumor, Toh *et al.* found that MDSCs are recruited by primary tumors and contribute to their growth. In addition, MDSC infiltrates induce phenotypic changes in the tumor cells encouraging a more invasive profile, thus fostering local invasion and dissemination.

The plastic conversion of tumor cells into a migratory phenotype, which is driven by epithelial-mesenchymal transitions, is a cornerstone of metastasis, but its triggers are not firmly established. The findings by Toh *et al.* suggest that MDSCs can stimulate this switch by activating EMT signaling in tumor cells and provide insights into how cells can become metastatic early in tumorigenesis without additional genetic alterations. As early dissemination events are an attractive target to prevent metastasis, it will be of interest to determine whether MDSCs play a similar part in human malignancies. —*VA*

■ IMMUNITY

Stroke slows down iNKTs

Following a stroke, systemic immunity is impaired, leading to increased risk of infection and death. Connie Wong and her colleagues shed new light on the mechanisms of stroke-associated immunosuppression (*Science* **334**, 101–105).

The researchers hypothesized that invariant natural killer T (iNKT) cells in the liver might have a role in sensing damage in distant organs, such as the brain. In a mouse model of stroke, they showed that transient midcerebral artery occlusion (MCAO), followed by reperfusion, was associated with slowed crawling of iNKT cells in the liver vasculature, increased expression of the immunosuppressive cytokine IL-10 and bacterial infection. In contrast, ischemia-reperfusion injury in the hindlimb did not induce these effects.

When Wong *et al.* performed MCAO in iNKT cell–deficient mice, onset of bacterial infection was much sooner, but the brain infarct size was unchanged, indicating that iNKT cells have a key role in protection against infection after stroke. Antibiotic treatment rescued these mice from stroke-associated increased mortality.

But how does injury in the brain alter iNKT cell activity in the liver? The researchers found that administration of noradrenaline mimicked the effects of stroke on hepatic iNKT cell crawling, whereas these effects were blocked by a nonspecific β-adrenergic receptor inhibitor or by activation of iNKT cells by α-galactosylceramide (α-GalCer). Moreover, administration of α-GalCer or of the β-adrenergic receptor inhibitor markedly reduced the severity of bacterial infections in mice after MCAO, indicating that noradrenergic neurotransmitters released during brain injury can undermine systemic immunity by their direct effects on hepatic iNKT cells. The authors suggest that if these findings are extended to humans, a combination of modulating iNKT cell function and antibiotics might be a possible therapeutic strategy to reduce infection and mortality associated with stroke. —*AF*

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New from NPG

Complement factor H binds malondialdehyde epitopes and protects from oxidative stress
Weismann, D. *et al. Nature* **478**, 76–81 (2011).
Malondialdehyde (MDA) is a lipid peroxidation product, the amounts of which are increased in several chronic inflammatory diseases. The authors now show that complement factor H binds MDA and can block macrophage uptake of MDA-modified proteins and MDA-mediated inflammation in mice.

Genome-wide association study identifies a new melanoma susceptibility locus at 1q21.3
MacGregor, S. *et al. Nat. Genet.* doi:10.1038/ng.958 (9 October).

Genome-wide association study identifies three new melanoma susceptibility loci
Barrett, J.H. *et al. Nat. Genet.* doi:10.1038/ng.959 (9 October).
Two genome-wide association studies confirm genetic variants previously associated with melanoma and identify four new melanoma susceptibility loci. The new variants are not associated with pigmentation or nevus density phenotypes, suggesting that they may contribute to melanoma risk through different mechanisms.

***In utero* exposure to cocaine delays postnatal synaptic maturation of glutamatergic transmission in the VTA**
Bellone, C. *et al. Nat. Neurosci.* doi:10.1038/nn.2930 (2 October).
Postnatal maturation of glutamatergic transmission onto dopamine neurons in the ventral tegmental area in mice requires activation of metabotropic glutamate receptor 1 (mGluR1), and cocaine impairs the function of this receptor. Reactivation of mGluR1 *in vivo* rescued synaptic maturation, suggesting that modulating this receptor could be a potential therapeutic option for improving synaptic function in children exposed to cocaine *in utero*.

The kinase LRRK2 is a regulator of the transcription factor NFAT that modulates the severity of inflammatory bowel disease
Liu, Z. *et al. Nat. Immunol.* doi:10.1038/ni.2113 (9 October).
The gene encoding leucine-rich repeat kinase 2 (LRRK2) has been previously implicated as a susceptibility gene for Crohn's disease, and these authors characterize how LRRK2 deficiency might lead to disease pathogenesis in mice. LRRK2 is a negative regulator of the transcription factor NFAT, which is important for regulating immune responses.