■ CANCER THERAPEUTIC RESISTANCE

Remodeling tumor niches

Protective tumor microenvironments can induce resistance to otherwise effective antibody-based anticancer therapies. Adding the chemotherapeutic cyclophosphamide to the treatment can render resistant leukemia cells sensitive to immunity-mediated killing by remodeling the tumor cell surroundings in the bone marrow (*Cell* **156**, 560–602, 2014).

Using a humanized mouse model of acute lymphoblastic leukemia treated with alemtuzumab (anti-CD52 antibody), Christian Pallasch and his colleagues have shown that infiltration of cancer cells into the bone marrow creates a specific protective niche that blocks phagocytosis of antibody-targeted tumor cells. An RNAi screen *in vivo* demonstrated that increased expression of certain molecules in leukemic cells inhibits their engulfment by macrophages. In an attempt to overcome resistance, the authors combined cyclophosphamide with the antibody, a strategy that induced a secretory phenotype that triggers release of CCL4, IL-8, VEGF and TNF-α from leukemic cells and almost eliminated disease in the bone marrow. This cytokine secretion increased infiltration of macrophages into the bone marrow niche and their phagocytic activity. Notably, this synergistic effect was also seen in other leukemia mouse models.

Bone marrow biopsies from patients with leukemia confirmed macrophage abundance in the bone marrow after the combination treatment. Although the treatment window during which this combination therapy is effective is very small, the findings suggest conventional therapy could be used to induce innate immune killing and boost efficacy of targeted therapies. —*CP*

■ DISEASES OF THE NERVOUS SYSTEM

Of blood and brain

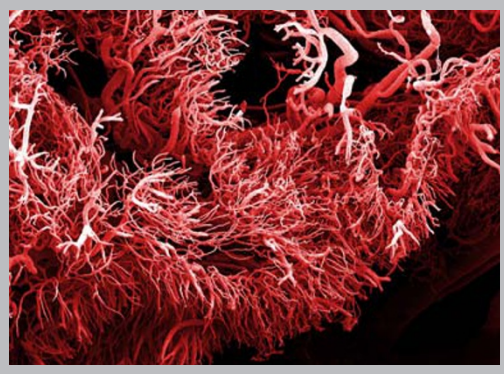
In newborn mammals, the growth of cerebral microvascular networks occurs concurrently with neuronal growth in the brain. Here, Christina Whiteus and her colleagues identify in mice the first direct link between neural activity and microvascular plasticity, demonstrating that overstimulation of neurons in early life results in a near arrest in angiogenesis (*Nature* doi:10.1038/nature12821, 2014).

Chronic neuronal stimulation by exposure to diverse sounds or repetitive whisker stimulation in neonatal mice—but not adult animals—caused a robust reduction in branching and length of vessels in the region of the brain stimulated. The decrease in vascular density was due to reduced proliferation of endothelial cells and impaired vessel sprouting, and it resulted in lack of appropriate oxygenation of the tissue linked to a decrease in neural spine density. Notably, these changes persisted after cessation of overstimulation and were maintained into adulthood. Using mutant mice with a lack-of-function mutation in nitric oxide synthase (NOS) and wild-type mice treated with NOS inhibitors, the authors found that the reduced vascularization was linked to overproduction of nitric oxide by the hyperactive brain cells.

Because neural overstimulation caused by inducing seizures in the neonatal mice also reduced vascularization, the findings suggest that seizure episodes or overstimulation in infants might increase the vulnerability of the brain and potentially predispose to certain pathologies in adulthood. —*HS*

TUMOR ANGIOGENESIS

Tumors fight back with a lectin



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Anti-angiogenic therapy targeting vascular endothelial growth factor (VEGF) is used to treat several types of cancers, but the clinical benefit of this therapy is variable. Gabriel Rabinovich and his colleagues demonstrate that, in mice, tumors resistant to anti-VEGF therapy deploy galectin-1 as a VEGF-mimicking ligand (*Cell* 156, 744–758, 2014).

The researchers found that galectin-1 binds to and signals through the VEGF receptor VEGFR2 on endothelial cells, but only when the receptor is suitably modified by N-glycosylation. Tumors in mice that produced high levels of galectin-1 were resistant to anti-VEGF therapy, and this resistance was overcome by treating the animals with antibodies targeting galectin-1. Resistant tumors challenged with anti-VEGF therapy also reset the glycan composition on the surface of endothelial cells to favor the interaction of galectin-1 with VEGFR2. The authors then showed the impact of the glycosylation pattern on endothelial cells to tumor resistance by implanting sensitive or resistant tumors into mutant mice with altered glycosylation pathways. Deficiency of the glycosyltransferase MGAT5 blocked tumor resistance, whereas deficiency of the sialyltransferase ST6GAL1 conferred resistance.

If galectin-1 promotes tumor resistance to anti-VEGF treatment also in humans, the galectin-1–VEGFR2 interaction could be targeted to increase the efficacy of this treatment. —*MB*

■ INFLAMMATION

HDL beyond cholesterol

High levels of high-density lipoprotein (HDL) in the blood are associated with protection from cardiovascular disease. How HDL also exerts anti-inflammatory properties is now shown in mouse models of acute inflammation—HDL induces expression of ATF3 in macrophages and reduces cytokine production (*Nat. Immunol.* **15**, 152–160, 2014).

Eicke Latz and his colleagues show in a model of acute inflammation that pretreatment of mice with human HDL reduces pro-inflammatory cytokine production and liver injury after exposure to Toll-like receptor (TLR) agonists. These effects seem to be mediated at the transcriptional level, as HDL reduced mRNA expression of cytokines in macrophages incubated with TLR agonists without impairing cytokine secretion. Through microarray analyses, the authors pinpointed the transcriptional regulator ATF3 as the major HDL target in macrophages in culture, whose expression was strongly upregulated in the presence of HDL. The lack of ATF3 in macrophages impaired the anti-inflammatory effects of HDL *in vitro*, and HDL did not protect *Atf3*-deficient mice from TLR-induced inflammation *in vivo*. Moreover, HDL normally promotes reendothelialization after carotid artery injury; this effect of HDL was also impaired in mice lacking ATF3.

Given the broad role of HDL as modulator of TLR responses in macrophages, its effects may be beneficial not only in the context of atherosclerosis and cardiovascular disease but also in other inflammatory diseases. —*KDS*

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