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In This Issue

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First responder homeostasis coordinated by LXRs One of the first immune cells to respond to an invading pathogen is the neutrophil. Numbers of these cells are tightly regulated; this means that the release of an enormous number of neutrophils from the bone marrow of a healthy individual every 24 hours must be matched by the clearance of an equivalently large number of senescent cells. Recent studies have identified a feedback loop that regulates neutrophil homeostasis — the phagocytes that clear senescent neutrophils stimulate neutrophil production in the bone marrow by modulating the IL-23/IL-17/G-CSF granulopoietic cytokine cascade. Now, Hong and colleagues have determined that liver X receptors (LXRs) have a role in coordinating this feedback loop (337–347). Gain- and loss-of-function approaches indicated that in mice, LXR was required for the efficient phagocytosis of senescent neutrophils. It was also required for the repression of the IL-23/IL-17/G-CSF granulopoietic cytokine cascade that occurs upon phagocytosis of senescent neutrophils. Neutrophils have been recently implicated in the pathogenesis of systemic lupus erythematosus (SLE). Hong and colleagues therefore suggest that future studies should examine whether dysregulation of the LXR-controlled feedback loop that coordinates neutrophil homeostasis is an early event in animal models of SLE. Sinking your teeth into the problem of spinal cord injury There is no proven reparative treatment for spinal cord injury (SCI), one of […]

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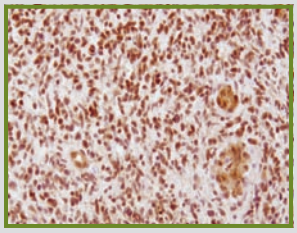
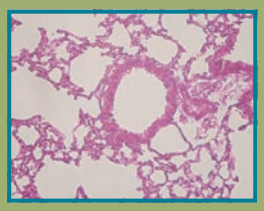
Resisting the effects of chemotherapy



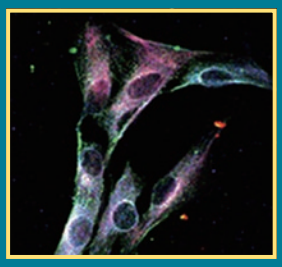
Glioblastoma multiforme (GBM) is the most common and lethal primary brain tumor in adults. For most patients, treatment involves surgery followed by both radiation therapy and chemotherapy with temozolomide (TMZ), a DNA alkylating agent. However, not all GBMs are sensitive to TMZ. This has been linked to high levels of activity of the DNA repair protein O^6-methylguanine–DNA methyltransferase (MGMT); the majority of patients with a methylated *MGMT* promoter show increased responsiveness to TMZ. However, not all such patients respond to TMZ, suggesting that other factors contribute to GBM sensitivity to this chemotherapeutic. In this issue (253–266), Agnihotri and colleagues show that the DNA repair protein alkylpurine–DNA–*N*-glycosylase (APNG) contributes to resistance to TMZ — silencing APNG expression in TMZ-resistant GBM cell lines enhanced TMZ responsiveness, while exogenously expressing the enzyme in TMZ-sensitive GBM lines conferred resistance to TMZ in orthotopic xenograft mouse models. Of clinical significance, high nuclear expression of APNG in clinical samples correlated with poor overall survival. Agnihotri and colleagues therefore suggest that APNG could provide a prognostic marker of responsiveness to TMZ, although this awaits confirmation in predictive and prospective studies.

Alleviating allergy by targeting HRF



Mast cells are considered to play a critical role in the development of allergic diseases such as asthma as a result of their ability to release a diverse array of proinflammatory mediators upon activation by IgE bound to specific antigen. Histamine-releasing factor (HRF) is a protein implicated in certain forms of allergic disease, but it has not been determined whether it has a role in asthma and how it might contribute to the pathogenesis of allergic diseases. In this issue (218–228), Kashiwakura and colleagues show that HRF can bind to the Fab region of a subset of IgE and IgG antibodies, which is the same Ig region that specific antigen binds. Consistent with this, HRF-bound IgE triggered the activation of mouse mast cells in vitro. Moreover, peptides that blocked the HRF/Ig interaction in vitro suppressed airway inflammation and cutaneous anaphylaxis in mouse models of asthma and skin allergy, respectively. As these data indicate that HRF has a proinflammatory role in asthma and skin allergy, Kashiwakura and colleagues suggest that targeting HRF could be of therapeutic benefit in individuals with these conditions.

Sinking your teeth into the problem of spinal cord injury



There is no proven reparative treatment for spinal cord injury (SCI), one of the most common causes of disability in young adults. Developing such a treatment will be hard because repair of SCI requires a multifaceted therapy that promotes axonal regeneration, remyelination, and formation of new synaptic connections. In seeking to rise to the challenge, Sakai and colleagues have found that transplantation of human tooth-derived stem cells into completely transected adult rat spinal cord leads to marked recovery of hind limb function (80–90). Importantly, the tooth-derived stem cells mediated their beneficial effects in several ways. First, they inhibited SCI-induced apoptosis of neurons, astrocytes, and oligodendrocytes (the myelin-forming cells of the CNS). Second, they promoted axonal regeneration by antagonizing inhibitors of axon growth. Last, they replaced lost cells by differentiating into mature oligodendrocytes. The fact that the human tooth-derived stem cells promoted functional recovery in a rat model of SCI via multiple neuroregenerative activities leads the authors to suggest that these cells might provide therapeutic benefit to individuals who have experienced SCI.