This Week in The Journal

● Cellular/Molecular

Macrophages Can Promote Regeneration . . .

Benoit Barrette, Marc-André Hébert, Mohammed Filali, Kathleen Lafortune, Nicolas Vallières, Geneviève Gowing, Jean-Pierre Julien, and Steve Lacroix

(see pages 9363–9376)

The role of macrophages in recovery from nerve injury is controversial. Some studies show that macrophages improve regeneration, but others show the opposite effect. This week, each side of the controversy gains support. After crushing a peripheral nerve in mice, Barrette et al. locally depleted myeloid white blood cells (both granulocytes and macrophages) that expressed a specific protein. This reduced axonal regeneration and functional recovery. Depletion of myeloid cells in peripheral nerve grafts, which normally permit some regeneration of spinal axons, rendered the grafts unable to support such growth. Additional experiments suggested that myeloid cells normally enhance regeneration by clearing myelin debris (which is likely to contain growth-inhibiting molecules), secreting growth-promoting neurotrophic factors (likely from granulocytes or a subset of macrophages), and stimulating the growth of new blood vessels, which axons often grow along as they regenerate.

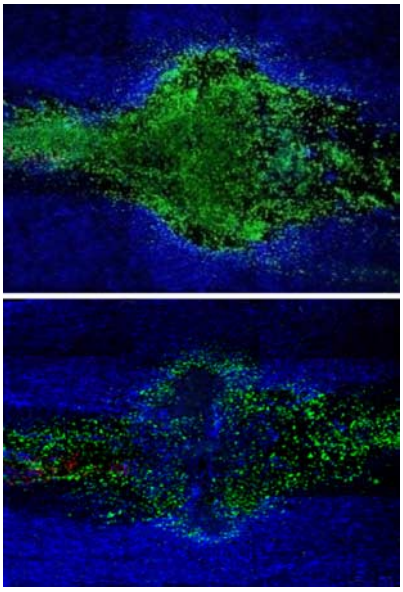
▲ Development/Plasticity/Repair

. . . But Macrophages Can Also Hinder Regeneration

Kevin P. Horn, Sarah A. Busch, Alicia L. Hawthorne, Nico van Rooijen, and Jerry Silver

(see pages 9330–9341)

In contrast to Barrette et al. (above), Horn et al. report that macrophages may hinder regeneration in the spinal cord of rats by promoting axonal retraction. CNS axons normally retract from a site of injury. To examine the role of macrophages in this process, Horn et al. specifically targeted phagocytic cells with toxin enclosed in liposomes. Depleting macrophages after a spinal cord crush did not affect the initial retraction of injured axons, but prevented later retraction that normally occurs after macrophages invade the spinal cord. In vitro studies on dorsal root ganglion neurons revealed that when an activated macrophage contacts a dystrophic axon, the macrophage adheres to and tugs on the axon, pulling it from the substrate and causing retraction. Together, these two studies suggest that whether myeloid cells help or hinder axon regeneration may depend on what type of myeloid cells are present (i.e., what subtypes of macrophages and granulocytes) and where and how macrophages are activated (e.g., by peripheral or CNS cues).



Many macrophages (green) but few astrocytes (blue) were present at a lesion site 7 d after nerve crush (top). Treatment with toxic liposomes greatly reduced the number of macrophages, but astrocytes remained (bottom). See the article by Horn et al. for details.

■ Behavioral/Systems/Cognitive

Histone Deacetylase Inhibitors Eliminate Cocaine Sensitization

Pascal Romieu, Lionel Host, Serge Gobaille, Guy Sandner, Dominique Aunis, and Jean Zwiller

(see pages 9342–9348)

In the nucleus, DNA wraps around histone proteins, which pack the DNA and make it less accessible for transcription. Many transcriptional activators promote histone acetylation, which opens the chromatin structure and helps recruit transcription machinery to the newly accessible genes. Conversely, some gene repressors promote deacetylation of histones. Because drug dependence is mediated partly by changes in gene expression, inhibitors of histone acetylation and deacetylation might prevent the development of drug dependence. Romieu et al. support this hypothesis by showing that administering histone deacetylase inhibitors shortly before giving rats access to cocaine reduced cocaine self-administration and decreased the number of times a rat poked its nose in a hole to receive a dose of cocaine. When control rats receive cocaine daily, their response to a dose increases over time. This increased responsiveness, called sensitization, is thought to promote dependence. Cocaine sensitization was prevented by histone deacetylase inhibitors, suggesting inhibitors may effectively reduce dependence.

♦ Neurobiology of Disease

K_{ATP} Expression Affects Seizure Susceptibility

Libor Velíšek, Jana Velíšková, Ondrej Chudomel, Ka-Lai Poon, Kimberly Robeson, Barbara Marshall, Archana Sharma, and Solomon L. Moshé

(see pages 9349–9362)

Hypoglycemic seizures occur in several diseases, particularly diabetes. In rats (and humans) seizures are induced by excess insulin, which stimulates glucose uptake throughout the body, reducing the amount available to neurons. The substantia nigra pars reticulata (SNR) has been implicated in seizure control: hyperpolarization of SNR neurons is anticonvulsant, whereas increased firing in SNR is proconvulsant. To further investigate the mechanism of hypoglycemic seizures, Velíšek et al. injected insulin into control rats that had fasted overnight. Fasting doubled the probability that insulin would induce a seizure and decreased the latency to seizure. But increased susceptibility in blood glucose levels did not explain the difference. Instead, the proconvulsant effect of fasting was associated with decreased expression of K_{ATP} channels specifically in the SNR. These channels normally open (causing hyperpolarization) only when ATP levels are low (e.g., during hypoglycemia). Decreased K_{ATP} expression prevents hyperpolarization of SNR neurons during hypoglycemia, and thus is proconvulsant.