population-level modeling of behavior and pathology. As a result, macroscopic-scale whole-brain neuroimaging studies, such as the work from Rosenberg *et al.*[2], have a crucial role in bridging the modeling of mechanisms of brain function and pathology to the final outcomes of externally apparent behavior and disease.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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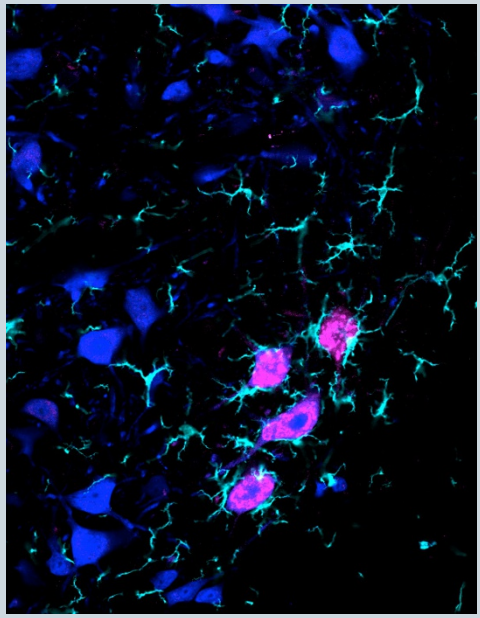
A peripheral messenger for chronic pain



If one steps on the pointy end of a tack, the piercing injury that ensues leads to an acute sensation of discomfort commonly referred to as pain. Pain is usually intense at the time of injury but eventually wanes as tissues heal. When the injury is more serious and tissue damage encompasses nerves, however, pain can become pathological and persist long after tissues have healed. Although nerve injuries can cause long-lasting changes in sensory processing in the periphery, maladaptive changes also occur centrally at the level of the spinal cord. Yet we know relatively little about the mechanisms that connect an injury in the periphery to maladaptive plasticity in the CNS. As reported on page 94 of this issue, Guan and colleagues have now increased our knowledge of this connection by identifying a key set of molecules mediating the influence of the injured state of sensory neurons on cells in the spinal cord.

In what was initially designed as an unbiased exploratory study, the authors performed RNA sequencing on dorsal root ganglia (DRGs) from mice that had received a peripheral nerve injury. One of the RNA species that was greatly upregulated after the induction of neuropathic pain encodes colony-stimulating factor 1, or CSF1, a cytokine involved in the differentiation and proliferation of macrophages and microglia. Given that spinal microglia play a central role in the development of neuropathic pain and that CSF1 can be secreted, this initial observation suggested the possibility that CSF1 could be a trigger for microglial activation and the induction of chronic pain. Of course, this scenario would require that CSF1 be transported to the spinal cord and that microglia have the ability to perceive it. In a subsequent series of experiments, this is exactly what the authors showed. After ligation of the dorsal root between the DRG and the spinal cord, they observed an accumulation of CFS1 at the ligature sites, suggesting that, once expressed, the protein travels along the axons of the sensory neurons toward the spinal cord. In concert, the expression of the CSF1 receptor (CSF1R) increased in microglia in the dorsal horn of the spinal cord. Concomitantly, expression of CSF1 was also upregulated in motor neurons, but only those that had been damaged by the peripheral injury. As can be seen on the accompanying image, the motor neurons (blue) that were injured expressed CSF1 (magenta), and were in close proximity with many of the processes emerging from nearby microglia, which themselves expressed CSF1R (cyan).

Thus, all the elements required for CSF1 to act as a messenger between the peripheral nerves and the spinal cord are in place. But does CSF1 actually contribute to the development of pain? To answer this question, the authors used a two-pronged approach. They showed that deletion of the *Csf1* gene from sensory neurons prevented the activation of spinal microglia that normally follows peripheral injury and the hypersensitivity to mechanical stimulation that is a hallmark of neuropathic pain. In addition, they found that intrathecal injection of CSF1 in uninjured mice was sufficient to both activate microglia and induce chronic pain.

Going a step deeper into the mechanisms, Guan *et al.* also found that DAP12, a transmembrane adaptor protein important for microglial function, was critical for CSF1-induced mechanical hypersensitivity, thus placing it downstream of CSF1. Unexpectedly, although CSF1 stimulated both the activation and proliferation of spinal microglia, DAP12 was required only for its activation. Notably, CSF1 injection could induce pain in mice lacking P2X4, an ATP receptor previously involved in microglia activation and neuropathic pain. This suggests that the CSF1–CSF1R–DAP12 pathway is a key signaling cascade in neuropathic pain but that it acts in parallel to the known ATP–P2X4 pathway.

In sum, the expression of CSF1 represents a pivotal link between peripheral nerve injury and the central mechanisms of neuropathic pain that involve microglia. Microglia are well known to react to various types of injuries in the CNS. In their study, the Basbaum laboratory has identified a key set of factors promoting this activation in the context of neuropathic pain and, in the process, potentially revealed new targets for treating chronic pain. It is tempting to speculate that CSF1 could play a similar role in other conditions that involve an initial insult, such as stroke.

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