that the secondary Ig gene rearrangement in GC B cells results in the replacement of a preexisting IgV region.

Because the main function of GCs is to allow affinity maturation of the antibody response, it is hard to imagine how random V(D)J recombination can maintain or improve the antigen receptor specificity of GC B cells. Then what is the function of secondary Ig gene rearrangement in GCs? A clue comes from the observation of Kelsoe and colleagues (6) that RAG expression and secondary V(D)J recombination are enriched in $B220^{low}$ relative to $B220^{high}$ GC B cell populations. $B220^{high}$ GC B cells apparently express high-affinity antigen receptors, whereas $B220^{low}$ GC B cells express lower affinity antigen receptors. On the basis of this evidence, they propose that the absence of antigen binding by low-affinity GC B cells triggers RAG expression and secondary V(D)J recombination. In this way, secondary Ig gene rearrangement could rescue GC B cells from apoptosis by allowing them to express new antigen receptors, whereas GC B cells with high-affinity antigen receptors would not be affected. One problem with this hypothesis is that because the antigens held on FDCs are believed to be the primary survival signal for GC B cells (7), it is difficult to explain how random V(D)J recombination can generate high-affinity antigen receptors, allowing GC B cells to bind antigens on FDCs.

In conclusion, the new work clearly demonstrates that mature B cells undergo secondary Ig gene rearrangement in GCs during T cell–dependent immune responses. But we still do not know to what extent secondary Ig gene rearrangement actually contributes to the establishment of the peripheral B cell repertoire. The regulation of RAG expression and V(D)J recombination during primary B lymphopoiesis is largely unknown. Because the molecular controls of the primary and the secondary V(D)J recombination may be similar, the ability to induce V(D)J recombination in GCs and in cell culture may provide insights into the signaling cascade regulating primary V(D)J recombination.

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NEUROSCIENCE

Good Pain, Bad Pain

Michael J. Iadarola and Robert M. Caudle

Pain is never a good thing, right? With this view, investigators in the field of pain research have concentrated on mapping pain pathways and pharmacologically or surgically eliminating pain altogether. But pain also has an important protective function in the preservation of the organism. The problems arise when this "good" pain turns into the "bad" pain that occurs in pathophysiological conditions such as nerve injury, causing debilitating disease. Two reports on pages 275 and 279 of this issue provide significant advances in understanding and counteracting this process (*1*, *2*). Mantyh and colleagues use a ligand-toxin conjugate to specifically kill a population of pain-sensing neurons in the spinal cord, an approach conceptually similar to the use of immunotoxins to kill cancer cells (*3*). Malmberg *et al.* examine nociceptive processes in mice lacking the neuron-specific γ isoform of protein kinase C (PKC). In both cases, only pathological (bad) pain is reduced, leaving good pain functioning.

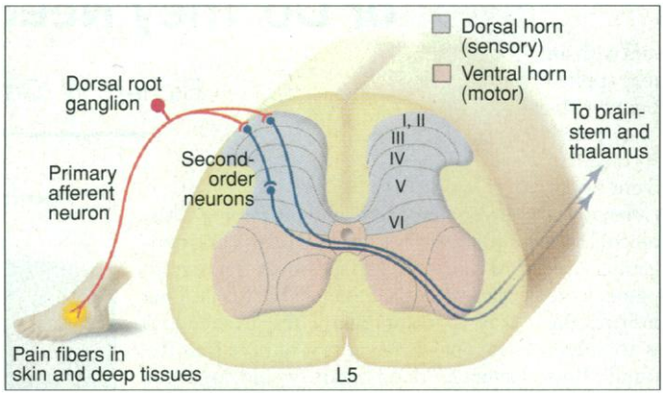

ILLUSTRATION: K. SUTLIFF

Origins of pain.

A striking feature of postinjury and neuropathic pain is that somatosensory signals get mixed up. A normally pleasant light brush on the skin can produce excruciating pain in patients with neuropathic conditions. This painful response to a normally nonpainful stimulus is called allodynia. Furthermore, in these patients the sensations from a mildly painful stimulus are greatly exaggerated (hyperalgesia). Anyone who has been sunburned and steps into a warm shower has an inkling of what this is like.

This hypersensitivity usually serves a protective function after injuries—we don't use a broken arm, and our pain-sensing neural circuits protest vigorously if we try—but usually resolves as the injury heals. However in neuropathic pain disorders, allodynia, hyperalgesia, and spontaneous pain are constant features of life, and this bad pain is often very difficult to treat effectively.

What is less appreciable through personal experience is that persistent pain triggers intense alterations in neuronal gene expression at the very first synaptic processing station for pain: the spinal cord dorsal horn (see the figure). Persistent pain induces changes in neural plasticity at the most fundamental molecular level, altering genes involved in transcriptional control (c-*fos*, c-*jun*, *NGF-IA*) and genes that encode neuropeptides (dynorphin, enkephalin, substance P, NPY) and their receptors (*4*). While a simple pinprick does not induce these changes, 5 or 10 minutes of persistent pain does, and these increases parallel the time course of the peripheral inflammation or pathophysiology. Thus, a transcriptional network is activated in these pain-processing neurons and, if the stimulus is of a sufficient degree and duration, a network of target genes even further downstream is also activated. There are still unknowns about the signal-transduction processes and second-messenger cascades activated by pain in the cytoplasm of these

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cells, and what is known has not yet been used to explore new treatment strategies. The two new reports in this issue fill in some of these gaps in our knowledge.

When the first synapses in the pain pathway are stimulated, they release a bouillabaisse of neuroactive substances from their presynaptic terminals: glutamate, calcitonin gene–related peptide, substance P, and substance K. One of the most provocative consequences of this release is that the NK-1 receptor (which binds substance P), located on the plasma membrane of the second-order neurons, is rapidly internalized upon noxious stimulation (5) (see the figure). The robustness of this internalization suggested a means to biochemically manipulate the second-order nociceptive neurons: make them internalize something interesting. Coauthors Wiley and Lappi coupled substance P to the cytotoxin saporin, which inactivates protein synthesis, thus producing a selective, receptor-targeted toxin for SP-receptor expressing neurons (6). A single injection of the toxin-ligand conjugate into the cerebrospinal fluid bathing the spinal cord kills the substance P receptor–expressing neurons in the superficial lamina I of the spinal cord. The toxic effect did not extend to substance P receptor–expressing cells located deeper in the cord, possibly because the substance P ligand portion of the hybrid molecule is susceptible to degradation by a dipeptidyl carboxypeptidase in the spinal fluid, thereby limiting tissue penetration and duration of ligand-toxin uptake.

When the treated rats were tested with an acute noxious stimulus, radiant heat applied to the hindpaw, they exhibited normal withdrawal latencies; the good pain was spared. But in an experimental hyperalgesia model in which capsaicin (the active ingredient in hot chili pepper, which causes primary afferent C-fibers to release substance P) was injected into the hindpaw, the toxin-ligand treatment reduced pathological pain. In this model the massive release of substance P sensitizes the second-order spinal cord neurons to subsequent mechanical and thermal stimuli. Rats treated with the toxin-ligand showed a reduced behavioral output as a result of the capsaicin injection and reduced hyperalgesia and allodynia in response to subsequent thermal and mechanical stimuli. These results are not specific to the pain model used. In another model of neuropathic pain that also causes abnormal activation of nociceptive primary afferents—chronic constriction of the sciatic nerve—an amidated substance P–diphtheria toxin fusion protein decreases allodynia and hyperalgesia (7). Thus, bad pain is attenuated by two different toxin-ligand molecules.

In the second report, the authors analyzed mice lacking the enzyme PKCγ, revealing a potential role in establishing allodynia and hyperalgesia for another set of second-order spinal cord neurons, in a dorsally located but distinct spinal layer (lamina IIi) from the SP receptor cells in lamina I. In this study, the PKCγ mutant mice displayed an attenuation of behavioral hyperalgesia and changes in spinal cord neuropeptide and receptor levels in animals experiencing pain from both nerve injury and from inflammation. Thus, these experiments identify both a specific neuronal population and the signal transduction pathway (PKCγ-coupled phosphorylation) involved in development of the neuropathic pain state.

What wider possibilities are presaged by these studies? First, they highlight the idea of pain state–specific therapies, drugs that block the development of hyperexcitability in postinjury and chronic pain states, but leave perception of acute pain intact. Second, they predict an emerging dichotomy in therapeutic strategies for chronic neural disorders. Development of an inhibitor for PKCγ will likely conform to the traditional approach to drugs: a small organic molecule with oral bioavailability. This contrasts sharply with biologically based treatments such as noci-toxins, implantation of genetically engineered cells and tissue-engineered devices (8), or gene therapy approaches to pain control, whereby viral vectors delivered to the spinal cord (9) can be used to confer an "analgesic" phenotype to the spinal cord. Both approaches focus on controlling pain at the spinal level. Such spinal anesthesia is particularly effective, because once pain signals reach the brain, there are multiple routes to conscious perception (*10*). Thus, noci-toxins and gene transfer are on the horizon as treatments for severe chronic pain.

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GEOLOGY

Do Continents Part Passively, or Do They Need a Shove?

Richard W. Carlson

Every once in a while in geologic history, fissures form in Earth's continental crust and pour forth prodigious quantities of basalt (*1*) (Fig. 1). One way to comprehend the tremendous scale of such events is to note that the average "flood basalt" would cover the area bounded by New York City, Cleveland, Atlanta, and Charleston with a slab of basaltic magma over a kilometer thick, burying the Appalachian Mountains to form a broad flat plateau over most of the eastern United States.

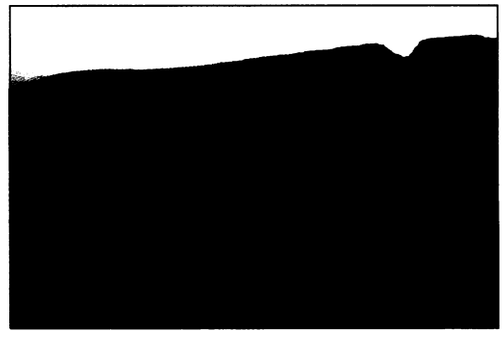

Fig. 1. Flood basalt. A 2-km-thick section of the Columbia River basalts in the Grande Ronde River valley of eastern Washington.

Why such events occur has been a focus of investigation since the recognition of their huge scale. Some flood basalts, such as the Paraná-Etendeka Province of South America, are clearly connected with the opening of major ocean basins (*2*). Others, such as the Deccan Province of India, are associated with linear tracks of continuing volcanism believed to be caused by the melting of plumes of hot material rising from the deep mantle (*3*) (see Fig. 2). These associations have created a "chicken and the egg"

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