This Week in The Journal

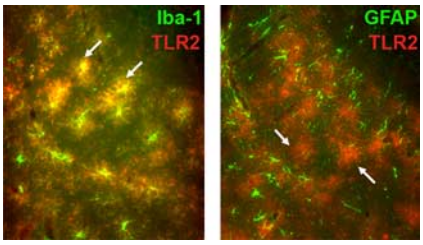
● Cellular/Molecular

TLR2 and Neuroinflammation

Alicia A. Babcock, Martin Wirenfeldt, Thomas Holm, Helle H. Nielsen, Lasse Dissing-Olesen, Henrik Toft-Hansen, Jason M. Millward, Regine Landmann, Serge Rivest, Bente Finsen, and Trevor Owens

(see pages 12826–12837)

When the CNS is injured, microglia spring into action as the agents of the innate immune response. These cells quickly proliferate, call T cells to the site of injury, and kick off a cascade of inflammatory cytokines and chemokines. The response can produce both beneficial and adverse effects. This week, Babcock et al. examined the signals driving this response. In particular, they looked at the functions of two Toll-like receptors (TLRs) in a well characterized model of axonal degeneration. After transection of axons in the entorhinal cortex, transgenic mice lacking TLR2 had reduced expression of cytokines and chemokines, delayed T cell recruitment, and no microglia proliferation. In contrast, mice lacking TLR4 had a normal reaction. Thus, TLR2 signaling appears to be involved in the early microglial response and T cell recruitment to injury but not in the later phases of macrophage recruitment and an astrocytic response.



Photomicrographs of the outer molecular layer of the dentate gyrus after an entorhinal lesion. Microglia labeled with Iba-1 (green; left panel) coexpressed TLR2 (red), as shown by coexpression in two cells (arrows; left panel). Reactive astrocytes stained with anti-GFAP (green; right panel) were not double labeled with anti-TLR2.

▲ Development/Plasticity/Repair

Early Pathfinding and Rhythmic Activity Revisited

M. Gartz Hanson and Lynn T. Landmesser

(see pages 12769–12780)

During early development, motor axons make the way to their targets guided by an array of molecular signposts. Although dogma would have us believe otherwise, it turns out that this early pathfinding is also affected by spontaneous, rhythmic bursts of electrical activity. Hanson and Landmesser hone in on the role of this patterned activity in the developing chick spinal cord. The authors administered *in ovo* an inhibitor of the glycine transporter (sarcosine) during stages 20–30 of chick development. The treatment doubled the frequency of bursting activity in the spinal cord. This change did not affect dorsoventral pathfinding of motor neurons as they exited the spinal cord, the first major pathfinding decision for the developing axons. It did, however, greatly affect subsequent anteroposterior pathfinding. Axons in treated chicks were less able to group into fascicles at the base of the limb and find their ways to their specific muscles.

■ Behavioral/Systems/Cognitive

Perceptual Learning on Listening Tasks

Julia A. Mossbridge, Matthew B. Fitzgerald, Erin S. O'Connor, and Beverly A. Wright

(see pages 12708–12716)

As we are bombarded by sensory information, we have to sort out the relative timing of different events. This week, Mossbridge et al. examined the mechanisms by which we discern the timing of sounds. They tested groups of subjects in two similar tasks: in the first, an order-discrimination task, individuals were asked to determine whether a high or low tone came before the other; and in the second, an asynchrony task, they were asked whether the tones were simultaneous. After the initial tests, one group received training in one task, another group in the other, and the last group received no training at all. When tested later, the trained listeners could do the tasks on which they had been trained better than the untrained subjects. But trained listeners did not generalize their learning to the other task, suggesting that distinct mechanisms underlie order and asynchrony detection. Good listening takes a lot of specific work, it seems.

♦ Neurobiology of Disease

GGA1 and BACE1 Trafficking

Tina Wahle, Dietmar R. Thal, Magdalena Sastre, Andrea Rentmeister, Nenad Bogdanovic, Michael Famulok, Michael T. Heneka, and Jochen Walter

(see pages 12838–12846)

The β-secretase BACE1 initiates the sequential cleavages of β-amyloid precursor protein (APP) that lead to production of β-amyloid (Aβ), the rogue peptide that gets deposited in the brains of patients with Alzheimer's disease (AD). Because understanding how BACE1 functions might have important therapeutic implications, Wahle et al. modified the activity of an adaptor protein involved in trafficking of BACE1, called γ-ear-containing ADP ribosylation factor-binding protein 1 (GGA1). GGA1 was mainly expressed in neurons in control human brain, but also in activated microglia in AD brain. The authors took HEK cells that produced BACE1 and engineered them to express human APP and high levels of either wild-type GGA1 or a dominant-negative mutant form. These cells released less Aβ, suggesting that altering either the amount of, or the function of, GGA1 affected APP processing. GGA1 expression did not alter cellular BACE1 activity, suggesting that modulation of APP processing resulted from altered subcellular trafficking of BACE1.