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Focus on glia and disease

A decade ago, glia were the neglected stepchildren of neuroscience. Although glia outnumber neurons by about ten to 1 in the adult human brain, providing support for neurons has traditionally been viewed as their primary function. Glial biology has come into its own recently, as researchers have shown that glia are critical for the development of the nervous system and have key roles in various neurodegenerative disorders. Glia regulate brain vasculature and the blood-brain barrier, modulating ischemia and migraines. Moreover, they are important in the repair of neurons after injury and also contribute to neuropathology in neurodegenerative diseases. In this issue, we present a focus on glia and disease, which highlights recent efforts in some of these areas and discusses how advances in understanding glial biology may lead to new treatments.

Multiple sclerosis is caused by the malfunction of glia, specifically by the failure of remyelination by oligodendrocytes. In their perspective, Robert Miller and Sha Mi discuss the molecular mechanisms of demyelination and remyelination. They describe how successful repair after demyelination recapitulates the cell-cell interactions that control myelination during development. By examining the mechanisms that reduce myelination in adult animals, such as glial scarring and the expression of myelination-inhibiting molecules, they identify a variety of therapeutic targets that might allow researchers to intervene at critical stages to reverse demyelination in disease.

Glia are also important in dominantly inherited neurodegenerative diseases, including amyotrophic lateral sclerosis, spinocerebellar ataxia, Parkinson's disease and Huntington's disease. In their perspective, Christian Lobsiger and Don Cleveland discuss how the mutant proteins that cause these disorders can act in glia to release toxic compounds or to reduce their support activities, thus damaging vulnerable neuron types. These effects range from the acceleration of neurodegeneration caused by mutant SOD1 acting in astrocytes and microglia to the direct production of degeneration in Purkinje cells by mutant ataxin-7 that is expressed in Bergmann glia. These findings raise the prospect of treating neurodegenerative diseases by providing healthy glia via transplanted stem, cells rather than by replacing the damaged neurons themselves.

Neuropathic pain is triggered by a normally innocuous stimulus or by no stimulus at all. Glia, immune cells and neurons interact to produce neuropathic pain, explain Joachim Scholz and Clifford Woolf in their review. They describe neuropathic pain as a neuroimmune disorder, involving activation of Schwann cells, microglia and astrocytes in a complex temporal and spatial pattern. Blocking the signaling pathways between neurons and non-neuronal cells may offer new ways to prevent or treat this disorder, but a key challenge for the future will be to differentiate the healthy aspects of pathways that are activated in response to pain-inducing stimuli from those that produce neuropathology.

Local control of blood flow in the brain is important for matching neural activity to the brain's local supply of oxygen and glucose, a process that provides the basis for functional imaging techniques. In their review, Costantino Iadecola and Maiken Nedergaard discuss the mechanisms by which astrocytes regulate microvasculature. Changes in intracellular calcium in astrocytic endfeet regulate vascular tone in the arterioles that they contact. Because synaptic activity is not the only process that influences astrocytic calcium levels and because astrocytes integrate synaptic activity over long time scales, the authors caution that the interpretation of functional brain imaging signals may need to be reevaluated. These results also raise the speculation that astrocytes may participate in cerebrovascular disease.

Astrocytes clearly contribute to one form of cerebrovascular disorder, brain ischemia, which is often caused by stroke. David Rossi, James Brady and Claudia Mohr review the mechanisms by which astrocytes damage and protect neurons that have lost their blood supply. Astrocytic glycogen stores can provide energy to deprived neurons, but can also increase brain damage as a result of lactic acidosis. Release of neurotransmitters such as glutamate from astrocytes can contribute to ischemic brain damage. Because astrocytes are coupled into networks by gap junctions, they are also important in the spread of stroke-induced damage to bystander neurons surrounding the initial injury. Once brain ischemia has begun, it is difficult to deliver drugs to the affected areas, so the authors concentrate on therapeutic agents that could be given to high-risk patients to reduce the damage caused by stroke.

Microglia are the macrophages of the central nervous system. In their review, Uwe-Karsten Hanisch and Helmut Kettenmann describe the complex roles of microglia, which can either protect or damage neurons depending on where and how they are activated. They hypothesize that microglia are chronically engaged in repairing minor insults and that clinical disease is observed only when these repair efforts fail. Microglia respond to a variety of signals suggesting potential disturbance to the structural or functional integrity of the brain. Fully activated microglia are detrimental to neurons, but other stages in the sequence of reactive states may improve neuronal survival by releasing neurotrophic factors or by removing excess glutamate from the extracellular space.

The research described in this focus has made substantial progress toward understanding the role of glia in neuropathology—and by extension the importance of glia in normal brain function. We hope that these articles may inspire further basic and clinical work on these important problems, leading to new treatments for these disorders. Finally, we thank Kalyani Narasimhan, now a Senior Editor at *Nature*, for conceiving and commissioning this focus during her time at *Nature Neuroscience*.

Sandra Aamodt
Editor