

Central role of glia in disease research

Widening interest in glial involvement in neurological and psychiatric illness is evident from the increasing number and diversity of studies with a focus on glia published in leading journals. Examples of this include recent articles published in *Neurology*, the *Proceedings of the National Academy of Sciences* and all of the papers in this issue of *Neuron Glia Biology*.

Multiple sclerosis (MS) is perhaps the prototypic glial disease, but the disorder is characterized by wide ranging variation in severity and disease progression among individuals. In large part this reflects the relapsing–remitting cycles of autoimmune damage to myelin and its repair, but increasingly, disorders once lumped together under the diagnosis of MS are being isolated as separate diseases with distinct pathophysiological mechanisms. In the process, more diverse roles for glia are being revealed.

Neuromyelitis optica (NMO) is an inflammatory disease that attacks the optic nerve and spinal cord, causing white matter lesions that result in blindness and paralysis. NMO is now seen as distinct from MS, and the most recent evidence supports the hypothesis that the direct target of the disorder is not oligodendrocytes, but rather astrocytes. A *Neurology* paper by Takano *et al.* (2010) reports that glial fibrillary acidic protein (GFAP) in cerebral spinal fluid (CSF) is massively increased in patients with NMO compared to patients with MS. This is consistent with the previous studies linking NMO with anti-aquaporin-4 (AQP4) autoantibodies (Lennon *et al.*, 2005), and the depletion of astrocytic foot processes and loss of AQP-4 (water channel) in pathological studies of MNO patients. This astrocyte-specific biomarker in cerebral spinal fluid can distinguish NMO from MS and it can be used to track the efficacy of treatments (Giovannoni, 2010). Such markers are extremely desirable in monitoring central nervous system (CNS) disease where biopsy is rarely performed. At the same time the results illustrate the interdependence of astrocytes, oligodendrocytes and axons for normal function.

GFAP in the CSF is an indicator of astrocyte damage, but many signals are released from glia to regulate nervous system development, respond to injury and regulate synaptogenesis. Levels of the protein S100 in CSF, for example, showed a similar trend to AQP-4 in NMO and MS patients. S100 protein is secreted from astrocytes and it acts as a neuro-modulator. A study published by Gomez-Casati *et al.* (2010) addresses the question of how the release of signaling molecules from glia that promote synaptogenesis is regulated by signals from neurons. In these studies, signaling by the neuregulin tyrosine kinase receptor (erbB) was eliminated in glial cells in the inner ear of mice by expression of a DN-erbB4 receptor under control of the GFAP promoter. The researchers report that BDNF is the synaptogenic signal produced by nonneuronal cells in the vestibular sensory epithelium in response to the growth factor neuregulin (NRG1), which is provided by sensory neurons.

A promising therapeutic approach in treating many neurodegenerative diseases is cell transplantation, but often transplanted cells behave differently in the adult brain

than during development. Histone modifications are recognized as being important in regulating gene expression during cell differentiation, but the study by Jawerka *et al.* (2010) in this issue reports that HDAC2 regulates neurogenesis differently in the developing and in the adult brain. Their research shows that HDAC2 is required for normal differentiation and survival of adult generated neurons, but it is dispensable in development. In the absence of HDAC2 function in the adult brain, progenitor cells proliferate, suggesting that HDAC2 controls neuronal differentiation by silencing progenitor transcripts to allow full neuronal differentiation. Thus, the epigenetic machinery regulating neurogenesis in the developing and adult brain differs.

Taking an evolutionary approach to study myelin disease, Brösamle (2010) in this issue examined whether myelin proteins that are involved in severe CNS pathology associated with Pelizaeus-Merzbacher disease and spastic paraplegia Type 2 are conserved in early vertebrates. The myelin protein PLP1 is highly conserved between mammals, but less well conserved in lower vertebrates, raising the question of whether certain fish species express PLP1 orthologs at all. Alternatively, the function of PLP1 in CNS myelin may have been taken over by myelin protein zero. A comparison of orthologs of PLP1/DMalpha in 17 fish species supports the conclusion that orthologs of PLP1/DMalpha are retained and they are functionally expressed in most, if not all, species of bony fish. Many of the amino acids in the protein when mutated are associated with CNS pathology, demonstrating conservation of function and the potential of using zebrafish as model organisms for studies of myelin disease.

The role of glia in neurological disease has a long and well-established history, but investigation into possible involvement of glia in psychiatric disorders is a more recent development. Considering the essential function of astrocytes in regulating neurotransmitter at synapses, possible involvement of glia in psychiatric illness seems well founded. Likewise, many treatments for psychiatric illnesses could act in part through effects on glia as they share many of the same neurotransmitter receptors and other membrane proteins as neurons. The study by Zhang *et al.* (2010) in this issue reports that serotonin-specific reuptake inhibitors used for treating depression and other psychiatric conditions, causes serotonin (5-HT_{2B}) receptor transactivation-dependent phosphorylation of ERK1/2 in mouse astrocytes in cell culture. Chronic treatment upregulates mRNA and protein expression of calcium-dependent phospholipase A₂ (cPLA_{2a}). These effects are seen with all five conventional selective serotonin reuptake inhibitors (SSRIs) at therapeutically relevant concentrations. Activation of cPLA_{2a} releases arachidonic acid, which may be directly connected to one of the known biological effects of treatment with SSRI in depressed patients.

Finally, perhaps the most fundamental function of astrocytes is in regulating K⁺ uptake to re-establish resting extracellular K⁺ concentration after neuronal excitation. Peng

et al. (2010) measured and compared the activities of astrocyte and neuron-specific subunits of the Na⁺, K⁺-ATPase (alpha 1, alpha 2 and alpha 3) in mouse cortical astrocytes and cerebellar granule neurons. The study concludes that the high B_{max} and low K⁺ affinity of the Na⁺, K⁺-ATPase endows astrocytes with a high capacity for K⁺ uptake, which is stimulated at elevated [K⁺].

As these diverse studies illustrate, in most nervous system diseases, cell–cell communication between brain cells, both neuronal and non-neuronal, is central.

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