This Week in The Journal

Astrocytes Can Survive Anaerobically

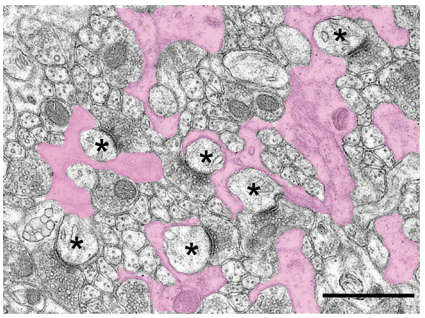
Lotti M. Supplie, Tim Düking, Graham Campbell, Francisca Diaz, Carlos T. Moraes, et al.

(see pages 4231–4242)

A long-standing question in neuroscience is how neurons maintain a constant supply of ATP to fuel synaptic transmission. One hypothesis suggests that uptake of glutamate from synapses stimulates glycolysis in astrocytes, resulting in the production of lactate that is transferred to neurons; lactate is then converted to pyruvate and metabolized to produce ATP in neuronal mitochondria. Although this hypothesis remains controversial, much indirect evidence supports it. Notably, enzymes involved in glycolysis are more highly expressed in astrocytes than in neurons, and the protein that allows pyruvate to enter the Kreb's cycle is actively inhibited in astrocytes, promoting lactate production by these cells (Barros 2013 Trends Neurosci, 36: 396).

Consistent with this work, Supplie et al. report that astrocytes can survive long term without mitochondrial respiration. Whereas inhibiting proteins of the ATP-producing mitochondrial electron transport chain killed cultured neurons, this treatment had no obvious effect on cultured astrocytes. Moreover, when assembly of cytochrome c oxidase—a component of the electron transport chain—was blocked selectively in astrocytes, mice survived more than a year with no apparent increase in astrocyte or neuronal death, no change in astrocyte morphology, and no indication of astrogliosis. Brain lactate levels were elevated in mutant mice, however, suggesting an increase in glycolysis by astrocytes compensated for the loss of aerobic respiration.

These results indicate that astrocytes can survive for long periods depending solely on glycolysis to produce ATP. This is consistent with previous work showing that astrocytes are resistant to hypoxia, and it indicates that astrocytes can export lactate to neurons without suffering from an inadequate energy supply. Whether they do this under normal physiological conditions remains unclear, however, and therefore, debates about the astrocyte–neuron lactate shuttle hypothesis are likely to continue.



Bergmann glial processes (pink) at synapses (asterisks) between parallel fibers and Purkinje cells in the cerebellum of mutant mice appear normal despite disruption of the electron transport chain. Scale bar, 1 μm. See Supplie et al. for details.

Stat3 Helps Maintain Repair Schwann Cells

Cristina Benito, Catherine M. Davis, Jose A. Gomez-Sanchez, Mark Turmaine, Dies Meijer, et al.

(see pages 4255–4269)

The ability of peripheral nerves to regenerate depends on the transformation of Schwann cells distal to the injury from a myelinating phenotype to one that promotes nerve repair. This transformation is driven by upregulation of the transcription factor c-Jun after injury, and it involves downregulation of myelin-specific proteins and upregulation of numerous other proteins. Repair Schwann cells phagocytose their myelin-forming membranes and secrete cytokines that attract macrophages, which assist in debris clearance and promote vascularization. In addition, repair Schwann cells assume an elongated morphology to form tracts that guide regenerating axons, and they secrete growth factors that promote axon growth.

When damaged nerves must regenerate relatively short distances, recovery can be complete within a few weeks. But when long-range growth is required, as sometimes occurs in human injuries, regeneration often fails. This failure is thought to occur because the repair phenotype of Schwann cells decays over time. Finding a way to maintain the repair phenotype for extended periods may therefore improve outcomes from peripheral nerve injuries.

Benito, Davis, et al. have made an important step toward this goal with their discovery that activation of the transcription factor Stat3 is required for maintaining the repair phenotype in Schwann cells after peripheral nerve injury in mice. Although Stat3 was expressed at all stages of Schwann cell development, its phosphorylation (indicating activation) increased dramatically in cut sciatic nerves. Furthermore, although knocking out Stat3 selectively in the Schwann cell lineage did not appear to affect myelin development, it greatly reduced survival of Schwann cells after nerve cut. The increase in Schwann cell death was attributable in part to a failure of Schwann cells to respond to autocrine survival factors, including insulin-like growth factor, which normally activate Stat3. Finally, knocking out Stat3 reduced expression of several markers of repair Schwann cells—including c-Jun—8 weeks after nerve cut, and it reduced expression of neurotrophic factors.

These results suggest that Stat3 activation is required to maintain the repair phenotype that enables Schwann cells to promote peripheral nerve regeneration after injury. Identifying upstream activators of Stat3 and downstream mediators of repair cell survival may inspire the development of treatments that enhance regeneration and restore nerve function after injury in humans.

This Week in The Journal was written by Teresa Esch, Ph.D.