Astrocytes 'feed' memory formation

Astrocytes were initially considered 'extras' in the brain, supporting neurons, the principal actors. But more recent work has suggested that they are involved in cognitive functions such as information processing, signal transmission, and neural and synaptic plasticity. Now these star-shaped cells are moving farther into the spotlight, as new research shows them to be essential in the formation of long-term memory.

Teams led by Cristina Alberini (Mount Sinai School of Medicine, New York, NY) and by Pierre Magistretti (Ecole Polytechnique Fédérale de Lausanne and University of Lausanne-CHUV, Switzerland) collaborated on the studies, which examined hippocampal changes and activities in rats exposed to foot shocks as a model of memory formation. Study development was driven by previous work indicating that learning increased the number of astrocytes in rat brains and that memory in a bead-discrimination exercise in young chicks required glycogenolysis, a process that occurs in astrocytes but not neurons.

Despite this evidence, however, identification and understanding of the mechanisms

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underlying astrocytes' contribution to cognitive functions is lacking. One such mechanism may be metabolic coupling, in which glycogen is broken down by astrocytes to produce lactate, which is transported to neurons to supply energy to meet the metabolic demands of memory formation. Long-term memory, in particular, has high energy demands, as it requires the activation of a cascade of genes and corresponding protein synthesis.

Alberini and Magistretti describe the astrocyte–neuron interaction in an article published in *Cell* (144, 810–823; 2011). They report that learning resulted in an increase in levels of lactate, derived from glycogen in astrocytes, in the rat

hippocampus. Lactate release was essential for formation of long-term memory but not short-term memory. Lactate transport from astrocytes to neurons was also essential for long-term, but not short-term, memory formation: disrupting either the astrocytic or neuronal lactate transporters resulted in amnesia. The amnesia resulting from dysfunctional lactate release or astrocytic transport could be rescued by delivering lactate directly to the rats' brains; however, amnesia resulting from defects in the neuronal lactate transporter could not be rescued by lactate delivery.

The authors conclude that learning leads to astrocytic glycogenolysis and lactate release, and that subsequent astrocyte–neuron lactate transport is essential for long-term memory formation.

Alberini and Magistretti's work helps to shed light on memory formation and may also aid in our understanding and ability to treat memory deficits associated with aging, dementia and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.

Monica Harrington

AN ALTERNATIVE CAUSE OF NEURODEGENERATION

A study in worms has revealed a new potential mechanism for neurodegeneration. The results of the study suggest that susceptibility to neurodegeneration might be increased by a change in the speed of programmed cell death. This increase in the rate of cell death appears to be linked to decreased levels of a protein called progranulin, which is involved with embryogenesis, inflammation and wound healing.

Polymorphisms in the human gene that codes for progranulin are associated with an increased risk of amyotrophic lateral sclerosis, Alzheimer's disease and Parkinson's disease. Research has shown that mutations in the progranulin gene are a major cause of familial frontotemporal lobe degeneration, but the exact role of mutated progranulin in the degeneration has remained unknown.

To explore how progranulin might influence neurodegeneration, Cynthia Kenyon of the University of California, San Francisco and colleagues studied *Caenorhabditis elegans* with mutated progranulin (*Proc. Natl. Acad. Sci. USA* doi:10.1073/pnas.1100650108; published online 28 February 2011). The research team counted the numbers of apoptotic cells in worms at several different developmental stages. They found that worms deficient in progranulin appeared to have fewer dying cells than did wild-type worms.

The researchers then used fluorescent markers to label cells programmed to die in both mutant and wild-type worms. They found that the cells that normally die in wild-type worms also do so in the mutant worms. Further analysis showed that the apoptotic cells were being cleared by phagocytic cells much more quickly in the mutant worms than in the wild-type worms. This increased rate of clearing dying cells explains the reduced numbers of apoptotic cells in mutant worms.

To see whether progranulin might have an effect on apoptotic cell engulfment in mammals, the researchers analyzed peritoneal macrophages from mice lacking progranulin and from normal mice. Macrophages can cross the blood–brain barrier to become indistinguishable from microglia, phagocytic cells that reside in the central nervous system. The macrophages from mice lacking progranulin exhibited increased levels of phagocytosis compared with macrophages taken from normal mice. Though the direct *in vivo* effect of progranulin on microglia remains to be demonstrated in a mouse model, the results from this study suggest a new potential mechanism for neurodegeneration. "If you have a mutation that makes engulfing cells more rabid," Kenyon told *The Scientist*, "then maybe during the normal course of life, a cell that is slightly damaged that would have recovered would now instead be cleared."

Kirsten Dorans