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The Neuroscientist Comments

The axon initial segment: a new target for neuronal injury

Although much is known about neuronal injury as manifested at the cell soma, in perisynaptic regions, and in the axon, the axon initial segment—a functionally important zone where synaptic inputs are integrated and action potentials are initiated—has not been studied as a target of injury. This is somewhat surprising, inasmuch as a rich cytoskeletal network, which should be susceptible to proteolytic injury, is present at the initial segment. Now Schafer and others (2009) present evidence indicating that neuronal injury can induce rapid, reversible, and preferential proteolytic injury of the axon initial segment cytoskeleton, which can occur independently of cell death or distal axonal degeneration. Studying a mouse model of middle cerebral artery occlusion, these investigators observed a remarkable loss of β IV spectrin at the axon initial segment within hours after onset of occlusion. Notably, nodes of Ranvier, which share a similar cytoskeletal organization, were relatively preserved. Similar changes were seen in the initial segments of retinal ganglion cells after optic nerve crush injury. Building upon these observations, these investigators also showed that injury of the axon initial segment is a result of proteolysis of the cytoskeletal proteins ankyrin G and β IV spectrin by the calcium-dependent cysteine protease calpaine. Finally, in a rescue paradigm, these investigators demonstrated that calpaine inhibitors protect the axon initial segment after a variety of insults, both in vitro and in vivo. In demonstrating disruption of the axon initial segment cytoskeleton as a mechanism for neuronal injury, this interesting paper suggests a new target for neuroprotective interventions.

Schafer D, Jha S, Liu F, Akella T, McCullough L, Rasband M. 2009. Disruption of the axon initial segment cytoskeleton is a new mechanism for neuronal injury. J Neurosci 29:13242–54.

Radial glia: activity-dependent control of motility

It is now abundantly clear that radial glia provide a crucial scaffold for cell migration during development of the brain. In this role, radial glial cells help to guide the migration of neurons. To what degree, however, are radial glia influenced by neuronal activity? In a provocative new study, Tremblay and others (2009) have now used multiphoton live imaging of radial glia in the optic tectum of intact *Xenopus* tadpoles in concert with various maneuvers that altered the level of neural activity and sensory stimulation, to show that radial glia can exhibit spontaneous calcium transcients that are modulated by visual stimulation. When viewed by real-time imaging, they found that radial glia can extend and retract multiple filopodial processes within the tectal neuropil over minutes. These radial glial processes interacted with retinotectal synapses and, while the radial glia do not express NMDA receptors, their motility was modulated by NO signaling, downstream of neuronal NMDA receptor activation and visual stimulation. These interesting results show that radial glia in the developing brain can respond to sensory stimulation, both with enhanced calcium transcients and with dramatic changes in structure. The authors note that it will be important, in future experiments, to examine the contributions of structural remodeling and calcium signaling by these glial cells to experience-dependent topographic mapping. It will also be important to determine whether similar sensory stimulation-dependent plasticity occurs in radial glia in the mammalian brain.

Tremblay M, Fugere V, Tsui J, Schohl A, Tavakoli A, Travencolo B, and others. 2009. Regulation of radial glial motility by visual experience. J Neurosci 29:14066–76.

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Gamma oscillations: routing information flow in the hippocampus

Although the occurrence of gamma oscillations within the hippocampus is now well established, their function remains obscure. It has been suggested that gamma oscillations may transiently link distributed cell assemblies while they process related information, a role that might be important for focal attention or memory. Such a "binding mechanism" would require millisecond precision in the activity of spatially distributed cells, so that they fire together. Detailed mechanisms responsible for this coordinated activity, however, are not yet understood. The problem is especially challenging, because gamma oscillations occur with a wide range of frequencies, from about 25 to 150 Hz at different locales and during different time epochs. Now Colgin and others (2009) report, in a study carried out in the rat hippocampus, that gamma oscillations in CA1 have two distinct frequency components, a slow range (~25–50 Hz) and a fast range (~65–140 Hz). The two components are differentially coupled to inputs from the medial entorhinal cortex, a brain region that provides information about the animal's spatial position, and CA3, a subfield within the hippocampus where such information is stored. Interestingly, fast gamma oscillations in CA1 were synchronized with fast gamma oscillations in the medial entorhinal cortex, and slow gamma oscillations in CA1 were synchronized with slow gamma in CA3. Some cells in the medial entorhinal cortex and CA3 were phase-locked to fast and slow CA1 gamma waves. Moreover, the two gamma components occurred during different phases of the CA1 theta rhythm, and often in different theta cycles. The authors interpret their results as suggesting that slow and fast gamma participate in the separation of afferent inputs to CA1 on different phases of theta, a segregation that may be important for avoiding reencoding of previously stored memories and for reliably distinguishing perceptions of ongoing experiences from memories of past ones. Noting that broadband gamma oscillations also occur in other brain areas, the authors also suggest the possibility that the presence of discrete frequency channels within gamma oscillations may be important in interregional communication in many areas within the brain.

Colgin L, Denninger T, Fyhn M, Hafting T, Bonnevie T, Jensen O, and others. 2009. Frequency of gamma oscillations routes flow of information in the hippocampus. Nature 462:353–7.

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