

Spectrin and Lipid Raft Membrane Components Participate in the Pathology of Brain Injury

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Spectrin: Trauma that results in the disruption of cell membrane molecular structure may involve separation of ankyrin from its linkage to membrane proteins and the spectrin network subjacent to the membrane. After membrane disruption, the spectrin may undergo proteolysis by calpain and caspase, which are excessively stimulated by unregulated influxes of Ca^{2+} through neurotransmitter- and voltage-activated channels. The disrupted membrane organization involves various proteins, including ion channels, transporters, receptors, cell adhesion molecules and scaffolding proteins (Bennett & Healy 2008). In various types of trauma, including mechanical, ischemic, hemorrhagic and toxic, spectrin breakdown products are found in the CSF, and the amount is correlated with the extent of brain trauma (Gold et al., 2009). Calpain proteolysis of the axon initial segment cytoskeletal proteins ankyrin and spectrin leads to loss of ion channels and loss of polarity in neurons, which can be prevented by inhibition of calpain (Schafer et al., 2009). Beta-III spectrin is highly expressed in cerebellar Purkinje cells where a critical function is stabilization of the EAAT4 glutamate transporter (see Ch. 17). Mutations in this spectrin gene are the cause of spinocerebellar atrophy type 5, which has been described in an 11-generation kindred descending from President Abraham Lincoln's grandparents and two other families (Ikeda et al., 2006). Mutations in the spectrin and ankyrin families are causes of hereditary spherocytosis and long QT (ankyrin B or sick sinus) syndrome [1].

Lipid rafts are membrane microdomains enriched in sphingolipids and cholesterol, and they contain regulatory proteins, including certain enzymes, receptors, and signaling and transport proteins. Alterations in the composition of membrane lipids associated with lipid rafts

occur as a function of aging and neurodegeneration (Schengrund 2010; Rushworth & Hooper 2010), with possible changes in the function of proteins in the microdomains. Lipid rafts are where the active γ -secretase complexes are located. These complexes are needed to form β -amyloid from amyloid precursor protein (APP) and for the accumulation of amyloid-ganglioside complexes in Alzheimer's disease [6] (see also Ch. 46). Lipid rafts are also loci for conformational conversion of cellular prion to infective prion molecules (see Ch. 50) (Taylor & Hooper 2007) and for phosphorylation of α -synuclein, which accumulates in Parkinson's disease (see Chs. 47, 49) (Zabrocki et al., 2008). Entry of HIV (human immunodeficiency virus) and perhaps other viruses into cells involves interaction of the viruses with receptors in lipid rafts (Carter et al., 2009). Thus, lipid raft components are targets for research into potential therapies for neurodegenerative and viral diseases and for prevention of infection (Cheng et al., 2007).

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