αII-spectrin-dependent cytoskeletons are essential for axon function, domain assembly and integrity

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Category: Neuroscience

Spectrins are a family of cytoskeletal proteins that provide structural support of the cell membrane, link membrane-associated proteins to actin and serve as platforms for cell signaling. Spectrins consist of α and β subunits, forming heterotetramers to function as a complex. Among the spectrins, αII-spectrin is the only α-spectrin expressed in the nervous system. αII-spectrin is also implicated in a variety of neurological disorders. Recently, we found that αII-spectrin forms a periodic cytoskeleton and interacts with βIV-spectrin at axon initial segments (AIS) and nodes of Ranvier.

To investigate the functions of αII-spectrin-dependent cytoskeletons, we generated conditional knockout (cko) mice. Loss of αII-spectrin in the central nervous system (CNS) causes profound neurological phenotypes including seizures, aberrant cortical lamination, AIS fragmentation, massive neurodegeneration and perinatal lethality. To more specifically interrogate spectrin functions in axons, we generated peripheral sensory neuron specific αII-spectrin cko mice using *advillin-cre.* We found that large diameter axons preferentially degenerate. By immunostaining, the injury marker ATF3 is observed in dorsal root ganglia (DRG) neurons in cko mice beginning at P10 and increasing with age. Consistent with EM results, $ATF3^{+}$ neurons are mostly large diameter neurons. The preferential degeneration of large diameter neurons caused ataxia due to deficits in proprioception, while nociception remains unaffected. Mutant mice have fewer nodes of Ranvier and sodium channel intensity at nodes is significantly decreased. Paranodal junctions are extensively disrupted. Axon degeneration and disrupted nodes of Ranvier caused decreased nerve conduction velocity in cko mice. Thus, neuronal αII-spectrin is crucial for proper axon function, node of Ranvier assembly and axon integrity.