Summary

Human thoughts and behaviors result from communication between the cells in our brains, and inside each one of these cells lies an entire world where things are built, packaged, transported, and delivered according to the needs of the cell at any given moment. Contrary to most other cells, a neuron is built to last a lifetime, and as such, the significance of each of its pieces can vary as the neuron progresses from infancy to maturity. The work presented in this thesis describes the way the liprin-α family of proteins, in particular liprin-α1 and liprin-α2, contributes to neuronal development and ultimately synapse function in the hippocampus. We began by examining how the entire liprin-α family (liprin-α1, α2, α3, and α4) was expressed in the brain. While liprin-α2 is expressed at high levels in the hippocampal neurons, we found very little liprin-α1 in the brain, although it is the predominant liprin-α in the rest of the body. From there, we investigated the importance of liprin-α2 as a component of the LAR signaling pathway that is critical for axon development in immature hippocampal neurons. We found that LAR acts through liprin-α2 to control axon growth and regulates axon branching through a liprin-α2-independent pathway. We described a novel link between LAR and the actin cytoskeleton via cortactin and suggest that liprin-α2 connects LAR to microtubules by interacting with p140Cap and EB3. Following axon outgrowth, neurons begin to develop an extensive dendritic tree. Here, we identified the mechanism by which liprin-α1 is degraded by CaMKII and the proteasome, explaining its low expression in the nervous system. Furthermore, liprin-α1 degradation is necessary for proper dendrite development, as the introduction of stably expressed liprin-α1 results in dysfunctional LAR trafficking, impaired dendrite growth, abnormal dendritic tree shape, and decreased synapse density. Finally, we examined the ways in which liprin-α1 and liprin-α2 differentially affect presynaptic function in mature neurons. We found that while liprin-α2 was essential for efficient synaptic transmission, liprin-α1 was detrimental to it. This seems to be due to discrepancies in protein binding between the two liprin-αs, and highlights the fact that liprin-α proteins are not functionally redundant in mammalian neurons. These experiments represent a considerable step towards understanding liprin-α function in the brain, and provide the basis for future study of liprin-α as well as neuronal development and synapse function in general.

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