Regulation of actin dynamics by local protein synthesis in neuronal growth cones

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A dynamic actin cytoskeleton is essential for growth cones in order to respond to axon guidance cues in the extracellular environment. These guidance cues initiate intracellular signaling pathways that all seem to converge onto the actin cytoskeleton. Attractive cues promote actin polymerization and cause filapodial extension, whereas repulsive cues cause actin depolymerization and growth cone collapse. Growth cone turning is thought to be the result of an asymmetrical response of the growth cone, causing the growth cone to collapse on one side while extending on the other side. Clearly, such complex growth cone behaviors require fast and adequate control of actin dynamics. We found that the actin-binding protein thymosin β4 is locally synthesized form mRNA that is present in neurites of regenerating neurons in vitro. Thymosin β4 is a monomeric actin-sequestering protein that inhibits actin polymerization and has known functions in the remodeling of neuronal processes. We found that the thymosin β4 transcript is one of the most abundant transcripts in outgrowing neurites that seems to accumulate specifically at turning points. DsRNA inhibition experiments showed that thymosin β4 mRNA knock-down significantly increases the rate of outgrowth, both in intact cells and in isolated neurites, suggesting that local synthesis of thymosin β4 prevents excessive actin polymerization and is required for normal outgrowth. Together, our findings suggest that local induction of thymosin β4 translation may be one of the mechanisms used by growth cones to produce the type of asymmetrical actin cytoskeleton responses that underlie growth cone turning behavior.

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