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Role of the actin binding protein eps8 in the formation of filopodia and synaptogenesis

Prof. Michela Matteoli

Istituto di Neuroscienze del CNR, Milano

ABSTRACT OF THE TALK

The regulation of actin-based filopodia by neurotrophins plays a crucial role during neuronal development and synaptogenesis. Here we show that Eps8, an actin-binding and regulatory protein, is enriched in the growth cones and axonal filopodia of developing neurons. Eps8 genetic removal enhances the formation of axonal filopodia, which is inhibited by reintroduction of Eps8 WT, but not an Eps8 capping-defective mutant. We further show that stimulation of hippocampal neurons with Brain-Derived-Neurotrophic-Factor (BDNF) induces MAPK-dependent phosphorylation of Eps8, which dissociates from the actin cytoskeleton, thus mimicking genetic Eps8 removal, and leading to explosive formation of filopodia. Consistently, a phosphoimpaired mutant of Eps8(S624A/T628A) in the MAPK target sites displays increased association to actin-rich structures, is resistant to BDNF-mediated solubilization, and inhibits BDNF-induced filopodia.

The opposite is observed for a phosphomimetic Eps8(S624E/T628E) mutant. Finally, phosphorylation of Eps8 atS624/T628 inhibits the actin barbed ends capping activity of the protein when in a complex with its molecular partner Abi1. Thus, Eps8 directly, through its phosphorylation-dependent capping activity, and indirectly, by competing

with VASP for IRSp53 binding, exerts a crucial role in controlling formation of filopodia during the processes of neuronal development and synaptogenesis.