



Membrane Scaffolds controlling the formation of neuronal branches

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Abstract:

In the neuronal axon during development, localized production of PI(3,4,5)P₃ supports the initiation of F-actin patches, which give rise to filopodia protrusions along the axon shaft. These filopodial protrusions are considered as precursors for axonal branches, as they mature by subsequent invasion and stabilization of microtubules and eventually form the basis of neuronal connectivity in the adult brain. Our project within the SFB958 identified and characterized a PTEN-associated membrane protein scaffold, which spatially organizes plasma membrane phosphoinositide and the cytoskeletal machinery during the process of axon branch formation. The membrane protein scaffold essentially involves PRG2, a transmembrane protein belonging to the lipid phosphate phosphatases/phospho-transferases (LPP) family. We demonstrate that PRG2 controls membrane PI(3,4,5)P₃ and F-actin-rich protrusions in dependence of PTEN (manuscript in preparation). In this proposal, and in preparation for the next funding period, we aim to characterize the cytoskeletal constituents the PTEN-PRG2 scaffold that links to the actin as well as to the microtubule machinery. We aim also to strengthen the analysis into the structural and molecular characteristics of PRG2 multimers, which we can readily isolate from cells and brain tissue. In collaboration with Christian Spahn, we were able to obtain initial PRG structural information and hope to increase this endeavor through X-ray crystallographic and/or Cryo-EM analysis.

References:

- Schrötter S, Leondaritis G, Eickholt BJ. Capillary isoelectric focusing of Akt isoforms identifies highly dynamic phosphorylation in neuronal cells and brain tissue. *J Biol Chem*. 2016 Mar 4 -An W, Jackson RE, Hunter P, Gögel S, van Diepen M, Liu K, Meyer MP, Eickholt BJ.
- Engineering FKBP-Based Destabilizing Domains to Build Sophisticated Protein Regulation Systems. *PLoS One*. 2015 Dec 30;10(12)
- Leondaritis G1, Eickholt BJ2. Short Lives with Long-Lasting Effects: Filopodia Protrusions in Neuronal Branching Morphogenesis. *PLoS Biol*. 2015 Sep 3;13(9):e1002241. doi: 10.1371/journal.pbio.1002241. eCollection 2015. (review)
- Functionally distinct groups of inherited PTEN mutations in autism and tumour syndromes. Spinelli L, Black FM, Berg JN, Eickholt BJ, Leslie NR. *J Med Genet*. 2015 Feb;52(2):128-34.