

Polarized transport of the ganglioside sialidase protein in morphologically non-polarized neurons is a sufficient signal for axonal fate determination

J.P. Santos Da Silva, C.G. Dotti, J. Abad-Rodriguez, Fondazione Cavalieri Ottolenghi, Univ. of Turin, Orbassano, TO, Italy

Establishment of polarity by segregation of axonal and dendritic territories is crucial for vectorial signal flow in neurons. Although molecules such as the Par3/6 complex, GAP43 and several others are thought to specifically regulate axonal formation, many of the supporting data are equally consistent with such molecules playing a role in overall neurite growth, not only that of the axon. In addition, it remains to be established if axonal fate determination requires such type of qualitative event (i.e. the restriction of a special molecular machinery to only one of the multiple neurites) or if on the contrary it is a simpler quantitative episode (i.e. more, or less, growth promoting/arresting molecules in the different neurites). We here show a series of evidences supporting the view that the preferential delivery and retention in a single growth cone membrane, and thus polarized restriction of highest activity, of a plasma membrane protein, plasma membrane ganglioside sialidase (PMGS), can suffice to produce the molecular changes needed for polarized growth. We show: i) that PMGS is preferentially enriched in the growth cone membrane of a single neurite, although all other growth cones contain discernible levels; ii) that the actin network in the growth cone of the chosen neurite has higher instability directly dependent on the level of activity of PMGS; iii) that activity suppression of PMGS results in neurons lacking the axon and iv) that activity enhancement results in the accelerated growth of the neurite with endogenous PMGS only. Biochemical experiments revealed that PMGS works by blocking the activity of the small GTPase RhoA locally, yet enhances the activities of PI3K and Rac1 via the formation of a complex with TrkA receptors that become highly phosphorylated, leading to a change in the actin-binding activity of the brain-specific actin-regulatory protein Profilin IIa (PIIa) via Rho Kinase (ROCK). These results suggest that axonal determination is the consequence of the higher rate of polarized transport of certain type of membrane proteins, that upon interaction with extrinsic factors can destabilize the submembranous actin cytoskeleton.