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Regulation of anterograde transcytosis of neurotrophin receptors and its role in health and diseases

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Neurotrophins are one of the best-known examples of target-derived instructive cues that regulate neuronal development. Upon nerve growth factor (NGF) binds to its receptor TrkA at axon terminals, these complexes are internalized and retrogradely transported back to cell bodies. However, how neurons replenish TrkA in nerve terminals remains unknown. We show that retrograde signaling by NGF is necessary for soma-to-axon transcytosis of TrkA. Activated TrkA receptors are retrogradely transported to cell bodies, where they are inserted on soma surfaces and promote phosphorylation of resident naive receptors, resulting in their internalization. Prior to axonal transport, endocytosed TrkA is dephosphorylated by PTP1B to ensure targeting of inactive receptors to axons to engage with ligand. These results identify phospho-regulatory mechanisms of anterograde transcytosis of TrkA, which regulate neuronal sensitivity to NGF. We are now asking whether other membrane proteins are co-transcytosed with TrkA and we identify amyloid-beta precursor protein (APP) as a candidate. The TrkA-APP co-transcytosis regulates NGF functioning and APP metabolism. Since APP and its proteolytic products play an important role in pathogenesis of Alzheimer's disease (AD), NGF-dependent transcytosis might be also related to the onset of AD.