Phospho-Regulation of Soma-to-Axon Transcytosis of Neurotrophin Receptors

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The family of neurotrophins provides one of the best-known examples of target-derived instructive cues that regulate distinct aspects of neuronal development. A key mechanism by which target-derived neurotrophins provides trophic support is by the cell biological processes of endocytosis and retrograde trafficking of their Trk receptors from axonal growth cones to cell bodies. Since Trk receptors are being continuously transported back to the cell bodies, a fundamental question is how neurons replenish these receptors in nerve terminals? Here, we report that retrograde signaling by target-derived nerve growth factor (NGF) is necessary for soma-to-axon transcytosis of TrkA receptors in sympathetic neurons. Activated TrkA receptors are retrogradely transported in signaling endosomes from distal axons to cell bodies, where they are inserted on soma surfaces and promote phosphorylation of resident naive receptors, resulting in their internalization. Endocytosed TrkA receptors are then dephosphorylated by PTP1B, an ER-resident protein tyrosine phosphatase, prior to axonal transport. PTP1B inactivation prevents TrkA exit from soma and causes receptor degradation, suggesting a "gatekeeper" mechanism that ensures targeting of inactive receptors to axons to engage with ligand. In mice, PTP1B deletion reduces axonal TrkA levels and attenuates neuron survival and target innervation under limiting NGF (*NGF^{-/-}*) conditions. These results identify phospho-regulatory mechanisms that underlie a positive feedback loop where target-derived NGF recruits its own receptors to nerve terminals to amplify neuronal responsiveness.