Abstract

A specialized endosomal population mediates Trk, but not EGFR, retrograde signaling.

By

Polyxeni Philippidou

During development, target-derived neurotrophins promote the survival and phenotype of innervating neurons. Neurotrophins exert their effects by initiating Trk signaling cascades at nerve terminals that transmit gene expression changes to the soma. According to the widely accepted signaling endosome model, ligand-bound and activated Trk receptors are endocytosed and retrogradely transported to signal at the soma. However, sustained signaling endosomes are counterintuitive to the classic role of endocytosis in receptor down-regulation and so the mechanisms that dictate their formation and processing have been poorly understood and controversial.

I have developed a novel, multi-faceted approach toward elucidating mechanisms of Trk endosomal signaling. In this approach, Quantum dot-conjugated EGF bound to an EGFR/TrkB chimera or EGF-receptor is tracked by confocal and electron microscopy, along sympathetic axons grown in compartmentalized neuronal cultures that separate axons from soma.

Using this approach, I define the retrogradely transported axonal endosomes of Trk, but not EGFR, as immature multivesicular bodies that avoid lysosomal degradation. These properties of Trk endosomes are dictated by the unique molecular mechanisms that govern their formation and processing that depend principally on the membrane trafficking protein Pincher. Trk, but not EGFR endosomes thereby mediate sustained Erk signaling to gene induction in soma. I further identified the Trk-binding adaptor protein APPL as the critical component that links Trk to Pincher, and disruption of the APPL/Pincher interaction causes rapid lysosomal degradation and eliminates long-term Trk endosomal signaling. I find that the early endosome processor, Rab5, and the Pincher-binding Rab5-effectors, Rabankyrin and Rabenosyn, are also involved in Trk endosomal processing, which is likely to involve a highly specific protein network mediating the unique features of Trk endosomes.

I further show the generality of Trk endosomal signaling in dendrites of hippocampal neurons. Given the essential role of the neurotrophin BDNF in hippocampal plasticity, Pincher-mediated Trk macroendocytosis may thus provide an underlying mechanism for neurotrophin-mediated synaptic plasticity in the central nervous system. An exciting possibility emanating from these studies is that a specialized Trk endosomal population provides the major signaling platform for a broad spectrum of neurotrophin-induced phenotypes.

Date: May 20, 2009
Time: 2:00 pm
Place: Life Sciences, 038
Program: Neuroscience
Dissertation Advisor: Simon Halegoua