Axonal Transport Of Autophagosomes: Organelle Dynamics Regulate Function

E. Holzbaur[1]*
[1]University of Pennsylvania, Department of Physiology, 638A Clinical Research Building, 415 Curie Boulevard, Philadelphia, PA 19104-6085 USA, holzbaur@mail.med.upenn.edu
* Corresponding Author

Keywords: autophagy, dynein, kinesin, organelle transport.

Abstract

Axonal transport is required to maintain neuronal homeostasis. Homeostasis in neurons is particularly dependent on efficient degradative pathways such as autophagy. We used live-cell imaging to investigate autophagosome dynamics in primary neurons expressing the autophagosome marker GFP-LC3. We find that constitutive autophagosome biogenesis is restricted to the distal end of the axon, and occurs via an ordered pathway of protein recruitment following stereotypical kinetics. Concomitant with autophagosome formation, we observed the engulfment of cargos including mitochondrial fragments and aggregated proteins. Following biogenesis, autophagosomes are robustly transported along the axon by cytoplasmic dynein. As autophagosomes move distally to proximally, they undergo maturation into compartments that are increasingly acidified, and thus can more effectively catalyze the degradation of cargo. Both dynein and kinesin motors are tightly associated with motile autophagosomes, indicating motor activity is tightly regulated. The scaffolding proteins JIP1 and Huntingtin are bound to autophagosomes and regulate their transport. Depletion of either scaffolding protein leads to misregulation of transport, and is sufficient to inhibit autophagosome maturation. Thus, there is a spatially defined pathway for autophagosome biogenesis, cargo engulfment, and cargo degradation in primary neurons, and the regulated transport of this organelle is tightly linked to function.