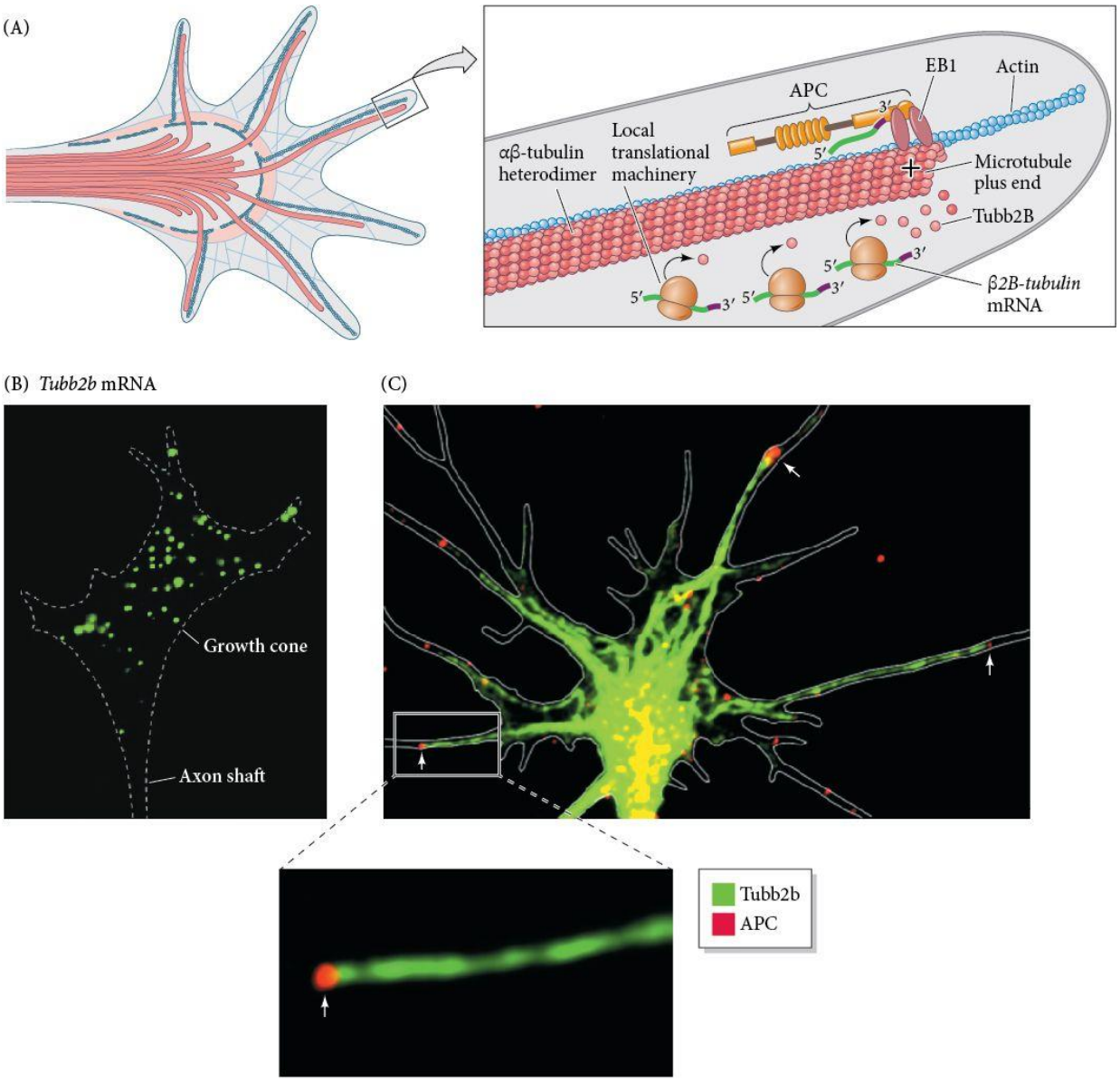
<Further Development 17_10>

# “Plus Tips” and Actin-Microtubule Interactions during Growth Cone Guidance

Regulation of actin filaments and microtubules in the peripheral domain plays an important role in the movement of the growth cone. A complex of proteins that interacts with the distal tip or plus end of the microtubules has been identified and is logically called “microtubule plus-end tracking proteins,” or simply “plus-tip” proteins (+TIPs). Examples are CLASP (*c*ytoplasmic *l*inker *as*sociated *p*rotein) and APC (*a*denomatous *p*olyposis *c*oli), which, based on their level of phosphorylation, can either stabilize and foster extension of the microtubules or disassociate from the microtubules and inhibit axon outgrowth. Plus-tip proteins bind directly to end-binding proteins (EB1/3) at the distal end of the microtubule. End-binding proteins stay in place whether the microtubule is growing or shrinking (Figure 1A, and see Figure 17.23C; Lowery et al. 2010; reviewed in Lowery and Van Vactor 2009; Bearce et al. 2015; Cammarata et al. 2016).

When considering the incredible journey that awaits the growth cone of a young neuron, a certain “supply and demand” problem presents itself. Meeting the demand for a ready supply of proteins at the growth cone, such as tubulin and actin monomers, must be paramount to accomplish the long extension of the axon during pathfinding. As extension proceeds, the growth cone gets farther and farther from the soma and hub of protein generation, suggesting that meeting this demand for protein subunits may get progressively more challenging. However, recent work (Preitner et al. 2014) has shown that transcripts can be housed in the growth cone for onsite translation, and that APC functions to bind and keep transcripts, such as β2b-Tubulin (*Tubb2b*), in position at the distal end of the microtubules. APC also co-localizes with factors that facilitate translation of Tubb2b for rapid microtubule elongation (Figure 1B and C).

Having APC localize mRNA to the growing end of microtubules is like having a constant supply of fuel being pumped into the gas tank of the motorized growth cone. Could CLASP and some of the other seven or more families of +TIPs also sequester transcripts? It is worth investigating. We have only recently realized that regionalized protein synthesis within a cell can be a mechanism for developmental change.




A after C. H. Coles and F. Bradke 2014. *Cell* 158: 245–247. B and C from N. Preitner et al. 2014. *Cell* 158: 368–382.

**Figure 1** APC localizes tubulin mRNA at the plus end of microtubules for spatially targeted translation to fuel growth cone expansion. (A) Schematic showing the localized *Tubb2b* transcript and targeted translation for immediate microtubule elongation at the plus end. (B) Growth cone of a neuronal cell line (white outline) expressing *β2B-tubulin* mRNA (green) as seen by fluorescence in situ hybridization. (C) APC and β2B tubulin (Tubb2b) immunolocalization in the peripheral domain of a neuron from a dissociated rat dorsal root ganglion. APC is co-localized to the tips of Tubb2b-containing microtubules (arrows), seen at higher magnification in the inset.

# Literature Cited

Bearce, E. A., B. Erdogan, and L. A. Lowery. 2015. TIPsy tour guides: how microtubule plus-end tracking proteins (+TIPs) facilitate axon guidance. *Front. Cell. Neurosci*. 9: 241.
PubMed Link

Cammarata, G. M., E. A. Bearce, and L. A. Lowery. 2016. Cytoskeletal social networking in the growth cone: How +TIPs mediate microtubule-actin cross-linking to drive axon outgrowth and guidance. *Cytoskeleton* doi: 10.1002/cm.21272.
PubMed Link

Coles, C. H. and F. Bradke. 2014. Microtubule self-organization via protein-RNA network crosstalk. *Cell* 158: 245–247.
PubMed Link

Lowery, L. A. and D. Van Vactor. 2009. The trip of the tip: Understanding the growth cone machinery *Nature Rev. Mol. Cell Biol.* 10: 332–343.
PubMed Link

Lowery, L. A., H. Lee, C. Lu, R. Murphy, R. A. Obar, B. Zhai, M. Schedi, D. Van Vactor, Y. Zhan. 2010. Parallel genetic and proteomic screens identify Msps as a CLASP-Abl pathway interactor in *Drosophila*. *Genetics* 185(4): 1311-25
PubMed Link

Preitner, N. and 7 others. 2014. APC is an RNA-binding protein, and its interactome provides a link to neural development and microtubule assembly. *Cell* 158: 368–382.
PubMed Link