Neuronal Polarity in 2011

Neurons appear to be the most highly polarized cell type in our bodies, often exhibiting a very long axon and highly branched dendrites. How neurons establish and maintain their morphological polarity has fascinated neuroscientists from the time of Cajal, but only recently have we begun to understand the molecular mechanisms that establish and maintain neuronal polarity, including both cell-extrinsic signaling and cell-intrinsic cues. In this special issue, we bring together reviews that illuminate the latest findings on how neurons establish and maintain axon and dendrite polarity in organisms ranging from C. elegans to Drosophila to mammals. Some aspects of this field have been recently reviewed (Tahirovic and Bradke, 2009; Rasband, 2010), but the pace is moving so quickly that a current overview is well deserved.

One of the reasons for rapid progress in the neuronal polarity field is its broad relevance to many other critical biological processes. The mechanisms used by neurons are likely to be used, at least in part, by other polarized cells types such as migrating cells, epithelial cells, and cells undergoing asymmetric cell division. In addition, understanding the establishment of axon/dendrite polarity could provide clues for improving regeneration of severed neurons following injury.

The special issue kicks off with a broad historical overview of neuronal polarity research (Baas and Lin, this issue) which highlights the early recognition of the importance of the microtubule cytoskeleton in maintaining neuronal polarity. Microtubule polarity is a major determinant of axon and dendrite differences, due to the polarized transport of specialized cargo to each domain. How microtubule motors accomplish this task, and the identity of some of the cargo they carry, is discussed in the reviews by Namba et al. (this issue) and Stiess and Bradke (this issue). These two reviews focus on mammalian neurons, whereas the following review by Rolls (this issue) explores new findings on microtubules and their motors in maintaining axon/dendrite domains in Drosophila neurons. Although both mammalian and Drosophila neurons use microtubules and their motors for the same ultimate purpose, there are fascinating differences between the systems.

The Rolls review, and the review on the Drosophila axon initial segment (Katsuki et al., this issue) illustrate how Drosophila genetics can be used to investigate neuronal polarity. Undoubtedly this will provide new clues to neuronal polarity in mammals, just as Drosophila research has advanced the study of cell polarity in non-neuronal mammalian cell types. The discovery of molecularly distinct axon domains did not start with the fly however, and Ho and Rasband (this issue) discusses recent findings on the establishment and composition of the mammalian axon initial segment (AIS). Biochemical characterization of the AIS will be difficult, and this is where Drosophila genetics may provide a timely boost.

The next portion of the special issue begins with a description of the role of the evolutionarily-conserved Par protein complex (Par-3, Par-6, atypical protein kinase C) triggering axon formation (Insolera, this issue). The polarized localization of the Par complex is regulated by extrinsic cues, and some of the relevant signaling pathways are described by Yang and Luo (this issue; Wnt signaling) and Shelly and Poo (this issue; LKB1/SAD kinase cascade). These pathways are not specific to mammalian neurons, as shown by the elegant work from the Shen lab on signaling pathways that regulate neuronal polarity in C. elegans (Ou and Shen, this issue).

Although modern era of neuronal polarity research was initiated by the pioneering work of Gary Banker on cultured hippocampal neurons (Banker and Cowan, 1979), many researchers are turning back to testing models in vivo. This includes work in Drosophila and C. elegans (reviewed by Katsuki et al., Rolls, and Ou and Shen in this issue) but also by looking at vertebrate neurons in vivo. The review by Randlett et al. (this issue) discusses findings on retinal ganglion cells when assayed in vivo, highlighting differences between in vivo and in vitro mechanisms. It is still too early to say how much of the basic mechanisms used by cultured neurons will translate to the in vivo setting, but it is likely that there will be differences between in vivo and in vitro, as well as between different types of neurons. Nevertheless, it is essential to start building models based on the rich

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data from in vitro studies, which can be used to develop new hypotheses in vitro and in vivo, and this is the topic of the final review in the issue (Inagaki et al., this issue). It is wonderful to include a modeling review, and it shows how far the field has come since the first review by Craig and Banker over 15 years ago (Craig and Banker, 1994).

Despite the rapid progress over the past few years – including the identification of polarity proteins and signaling pathways, microtubule motors and their cargo, and the introduction of powerful genetic model organisms into the fray – there are still many open questions for postdoctoral fellows and young faculty to explore. What is the composition of the AIS in flies and mammals? Genetic systems may be the best choice for attacking this problem. How much of the neuronal polarity mechanisms discovered in vitro are relevant to neurons developing or regenerating in vivo? This is addressed by Randlett et al. for vertebrate retinal neurons (this issue), as well for Drosophila neurons (Rolls, this issue). In the future, powerful methods for generating marked, mutant neurons can be used in many vertebrates (fish, mouse, chick in particular) and new imaging methods allow unprecedented tracking of these marked neurons in the intact nervous system. We expect to see more work in zebrafish, as this is an ideal system for in vivo analysis of neuronal polarity. Cell polarity mechanisms from other cell types have provided insight into neuronal polarity (e.g. the Par complex), but much more remains to be done in both directions: this is highlighted by the discussion of neuronal polarity mechanisms used by migrating neurons (Govek et al., this issue). Undoubtedly there will be fertile cross-talk between cell types and model organisms as new polarity regulators and mechanisms are discovered. It seems like there has been tremendous progress in the last decade – and there has been! – but the next decade promises to be even more impressive.

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