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Differential retraction of axonal arbor terminals mediated by microtubule and kinesin motor

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ABSTRACT

Neurons can extend branches from a single axon to send signals to multiple target cells. Axonal arbor morphology must be changed to establish and alternate neuronal wiring properly. For this purpose, the elongation and retraction rate of each terminal in a single axonal arbor are differentially regulated. In addition, competitive growth regulation between 2 neighboring branch processes has been observed. The intracellular systems involved in how neurons differentially regulate growth and stability of axonal branches within the same arbor remain largely unknown. Microtubules play critical roles in the formation and maintenance of axonal morphology, and their functions can be differentially regulated in a region-dependent manner within a single cell. Based on our findings, we propose a microtubule-dependent model that contributes to the differential branch growth in axonal arbors.

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Microtubule dynamics are controlled in a region-dependent manner within the single cell.[1-3] Tubulins that polymerize to form microtubules are known to receive multiple posttranslational modifications. The tyrosination (Tyr) and detyrosination (dTyr) cycle of α-tubulin involves the addition and removal of the carboxyterminal tyrosine residue by the action of tubulin tyrosine ligase (Ttl) and tubulin carboxypeptidase. Acetylation (Ac) and deacetylation in microtubules occurs at lysine 40 in the amino-terminus of α-tubulin, by the activity of an acetyltransferase (αTAT1) and deacetylases (HDAC6, Sirt2).[4] Since these modifications are dependent on the microtubule stability,[2] dTyr and Ac tubulins are enriched in stable microtubules. Previous studies have suggested that kinesin-1 is preferentially recruited on microtubules that contain dTyr and Ac tubulins.[5-7] This molecular regulation contributes to the polarized axonal transport in neurons, as the axonal shaft contains more dTyr and Ac tubulins than dendrites.[6-8]

Neurons continuously change their axonal arbor morphology during development and in adult nervous systems.[9-11] Differential branch growth can be observed in culture,[12-14] indicating the existence of cell-autonomous systems that manipulate arbor morphology in a branch-dependent manner. In addition, enhancing axonal growth at an arbor terminal is often accompanied by the retraction of a neighboring branch terminal[14] (Fig. 1). The mechanisms by which growth of a particular axonal branch affects another branch on the same arbor remains to be clarified.

Microtubules near growth cones are unstable and most of them cause catastrophe, whereas microtubules at the distal region from the terminal are more stable. During neuronal polarization, microtubule turnover becomes slower in longer axonal processes compared with minor processes.[15] When the microtubule turnover of arbor branch pairs is compared in the area proximal to the branching point, it is more stable in the longer process than in the shorter one.[16] Consequently, the ratio of dTyr and Ac of tubulin is higher in longer arbor processes. Thus, microtubules are differentially labeled by tubulin-posttranslational modifications dependent on branch process length within a single axonal arbor.

It is known that a cleaved motor domain of kinesin acts as a constitutively active, and it specifically accumulates in the axonal terminal when expressed in neurons.[7,17,18] Our recent study has revealed that in branched axonal arbors, the kinesin motor domain is

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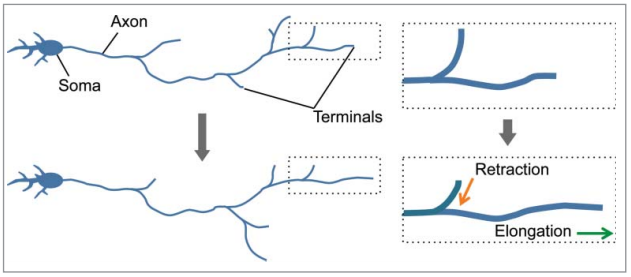

Figure 1. Differential control of branch growth in the same axonal arbor. A schematic representation of a neuron that possesses a branched axon with multiple terminals (top). A pair of axonal terminals is shown in the box with the dashed line (a magnified image is shown on the right). During the rearrangement of the arbor shape, the growth of branches in a single arbor is differentially regulated (bottom). Activation of process elongation on one side of the branch tends to induce the retraction of another process.

preferentially accumulated in longer processes that are enriched with dTyr and Ac tubulins. Because kinesin-mediated transport is required for maintaining axonal morphology,[19,20] kinesin sorting in the axonal arbor may contribute to the differential regulation of axonal terminals. Indeed, axonal retraction is significantly lower at the branched arbor terminal, where more kinesin signals are detected.[16] Moreover, local inhibition of kinesin increased the retraction at the same axonal process.[16] From these observations, we propose the following model for the intracellular molecular system that contributes to the differential regulation of arbor branch length (Fig. 2). At an axonal branching point, kinesin is preferentially recruited to the longer process because it is enriched with stable microtubules that contain dTyr and Ac tubulins. Accumulation of kinesin-1 mediated axonal transport stabilizes the process by inhibiting the retraction, thus the process tends to be longer than a neighboring branch process. This event provides positive feedback to kinesin-1-dependent transport, since microtubule stability and subsequent tubulin modification is affected by the change in process length.[15] In contrast, kinesin-1 mediated accumulation of cargo molecules on one side of the branch process results in the deprivation of molecules in the neighboring process, and causes the retraction. Thus, this model could explain the mechanisms of how competitive growth between 2 neighboring branch processes occurs.

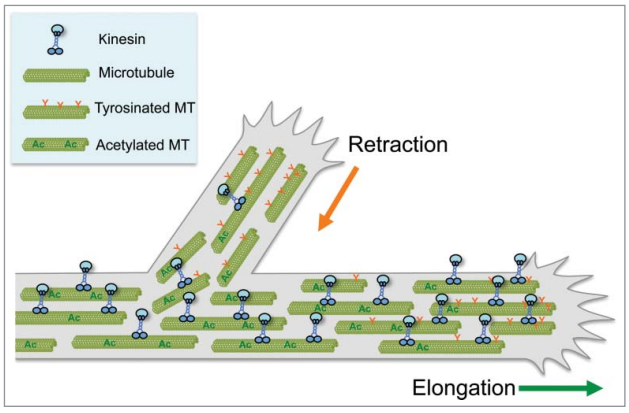

Figure 2. A model for the intracellular system that contributes to the differential growth control of an axonal branch. At an axonal branching point, kinesin-1 is preferentially sorted into longer processes that contains microtubules (MT) enriched with dTyr and Ac tubulins. Accumulation of kinesin-1 and its cargo at the terminal inhibit the retraction, whereby the process becomes longer. At the same time, deprivation of kinesin-1 in another process causes retraction.

Abbreviations

Ac	acetylation
DTyr	detyrosination
MT	microtubules
Tyr	tyrosinon

Disclosure of potential conflicts of interest

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