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The tubulin code in neuronal polarity

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Cells depend on the asymmetric distribution of their components for homeostasis, differentiation and movement. In no other cell type is this requirement more critical than in the neuron where complex structures are generated during process growth and elaboration and cargo is transported over distances several thousand times the cell body diameter. Microtubules act both as dynamic structural elements and as tracks for intracellular transport. Microtubules are mosaic polymers containing multiple tubulin isoforms functionalized with abundant posttranslational modifications that are asymmetrically distributed in neurons. An increasing body of evidence supports the hypothesis that the combinatorial information expressed through tubulin genetic and chemical diversity controls microtubule dynamics, mechanics and interactions with microtubule effectors and thus constitutes a 'tubulin code'. Here we give a brief overview of tubulin isoform usage and posttranslational modifications in the neuron, and highlight recent progress in understanding the molecular mechanisms of the tubulin code.

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Introduction

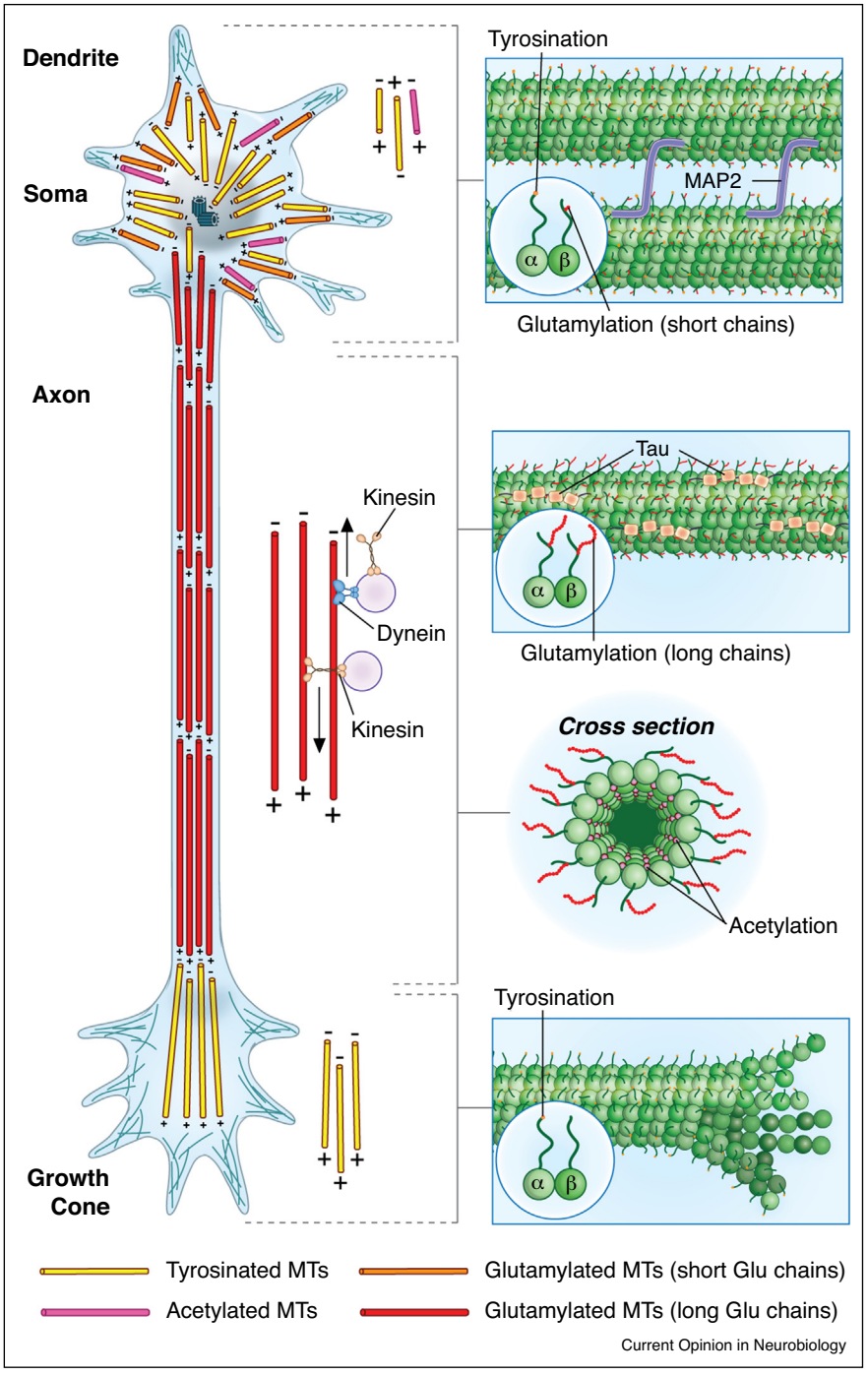
The highly polarized architecture of the neuron underlies its ability to integrate and transmit information. The microtubule cytoskeleton provides not only structural scaffolding for the neuron but also participates in active functional polarization [1]. Microtubules are non-covalent polymers composed of αβ-tubulin heterodimers. Despite their common building block, they give rise to cellular structures with distinct architectures ranging from the transient bipolar mitotic spindle, to the highly complex neuronal microtubule arrays or the stable nine-fold symmetric axonemes in cilia and flagella. This diversity in cellular organization is reflected in the genetic and chemical diversity of the αβ-tubulin dimer through the expression of multiple α-tubulin and β-tubulin isoforms as well as chemically diverse and abundant posttranslational modifications that are temporally and spatially regulated [2•]. This diversity is especially high in neurons, which use multiple tubulin isoforms with abundant posttranslational modifications. The genetic and chemical diversity of the αβ-tubulin dimer was hypothesized to regulate intrinsic microtubule properties such as their dynamics as well as the recruitment and activity of motors and microtubule-associated proteins (MAPs) and thus constitute a 'tubulin code' [3,4]. How the cell writes and reads the tubulin code has largely remained a mystery, but the advent of new tools for *in vitro* and *in vivo* manipulation and imaging has once again brought this fundamental problem into focus. We give a brief overview of microtubule cytoskeleton organization in neurons and the role of the tubulin code in defining neuronal asymmetry, briefly summarize our current knowledge of the tubulin isoform repertoire in the nervous system and highlight key recent advances in dissecting the molecular mechanisms used by cells to read and write the tubulin code.

Stereotyped organization and posttranslational modifications of microtubules in neurons

Microtubules are intrinsically polar polymers. Their minus ends are slow growing while plus ends are fast growing and dynamic. The polarity of microtubule arrays is stereotyped in neurons (reviewed in [5]). Axons contain tiled arrays of microtubules of varying lengths with the plus-end distal to the cell body. Dendrites have arrays of mixed polarities, with many microtubules oriented minus-end distal (Figure 1). While axons extend for long distances and are thin with tightly-bundled parallel microtubules, dendrites are highly branched to serve as effective receptors for the axons with which they synapse, consistent with their greater arborization and mixed polarity microtubule arrays. At the tip of the axon, the growth cone is populated by highly dynamic microtubules with their plus-ends distal (Figure 1).

In addition to this polarization in their organization, microtubules are functionalized with abundant posttranslational modifications that are asymmetrically distributed in the neuron [6,7,8,9••]. These modifications include the reversible removal and addition of a single tyrosine on the C-terminus of α-tubulin (detyrosination/tyrosination), removal of the α-tubulin penultimate glutamate (Δ-2),

Figure 1



Stereotyped distribution of tubulin posttranslational modifications in the neuron. Schematic of a neuron showing the distribution of tubulin modifications in the soma, dendrites, axon and growth cone. Insets show the microtubule surface covered with a lawn of disordered negatively-charged tubulin tails; from top to bottom: (1) microtubules in dendrites are tyrosinated and glutamylated with short glutamate chains; MAP2 concentrates in dendrites and interacts with tubulin tails; (2) microtubules in axons are detyrosinated, glutamylated with long glutamate chains; (3) cross-section of a microtubule showing acetylation on lumenal Lys40; Tau concentrates in axons and interacts with tubulin tails; (4) dynamic microtubules in the growth cone are tyrosinated.