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Research report

A conceptual view at microtubule plus end dynamics in neuronal axons

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ABSTRACT

Axons are the cable-like protrusions of neurons which wire up the nervous system. Polar bundles of microtubules (MTs) constitute their structural backbones and are highways for life-sustaining transport between proximal cell bodies and distal synapses. Any morphogenetic changes of axons during development, plastic rearrangement, regeneration or degeneration depend on dynamic changes of these MT bundles. A key mechanism for implementing such changes is the coordinated polymerisation and depolymerisation at the plus ends of MTs within these bundles. To gain an understanding of how such regulation can be achieved at the cellular level, we provide here an integrated overview of the extensive knowledge we have about the molecular mechanisms regulating MT de/polymerisation. We first summarise insights gained from work *in vitro*, then describe the machinery which supplies the essential tubulin building blocks, the protein complexes associating with MT plus ends, and MT shaft-based mechanisms that influence plus end dynamics. We briefly summarise the contribution of MT plus end dynamics to important cellular functions in axons, and conclude by discussing the challenges and potential strategies of integrating the existing molecular knowledge into conceptual understanding at the level of axons.

1. Introduction

Axons are the slender, up-to-a-metre long processes of neurons which form the cables that wire the nervous system. These delicate structures often need to survive for a lifetime, i.e. many decades in humans. Parallel polar, predominantly plus end out oriented, bundles of microtubules (MTs) run all along axons to form their structural backbones and highways for life-sustaining transport (Baas and Lin, 2011). These MT bundles are so densely packed,with MTs being separated by less than 100 nm, that they can only be reliably resolved through electron microscopy (Mikhaylova et al., 2015).

MTs are important at every life stage and for virtually all morphogenetic changes of axons (Penazzi et al., 2016; Prokop, 2013) (Fig. 1). Alterations in MT properties are often linked to developmental and/or intellectual brain disorders, and the precocious decay of MT bundles is seen as an important cause for axon degeneration (Adalbert and Coleman, 2012; Neumann and Hilliard, 2014). MTs are therefore viewed as attractive targets for drug therapies (Baas and Ahmad, 2013; Benitez-King et al., 2004; Eira et al., 2016).

In vitro and *in vivo*, MTs are dynamic, characterised by cycles of endothermic polymerisation, and exothermic depolymerisation (Brouhard, 2015) (Section 3). However, *in vivo*, these dynamics are not left to chance but are controlled by different classes of MT binding proteins (MTBPs) and the proteins they recruit and associate with. Such MT binding and associating proteins regulate polymerisation, severing, depolymerisation, stability, transport and force production, as well as cross-linkage and interaction with other organelles or cell structures (Penazzi et al., 2016; Prokop et al., 2013).

Many of these MTBPs and associated proteins have acknowledged links to brain disorders or other human diseases (Prokop et al., 2013). Although the molecular function of these proteins is often known, this knowledge is usually not sufficient to explain their associated diseases. One key challenge is posed by the fact that MT regulators form complex networks that establish robust and redundant machinery which often responds with surprisingly subtle changes upon mutation of single components. Furthermore, the cytoskeleton is required for virtually every cell function

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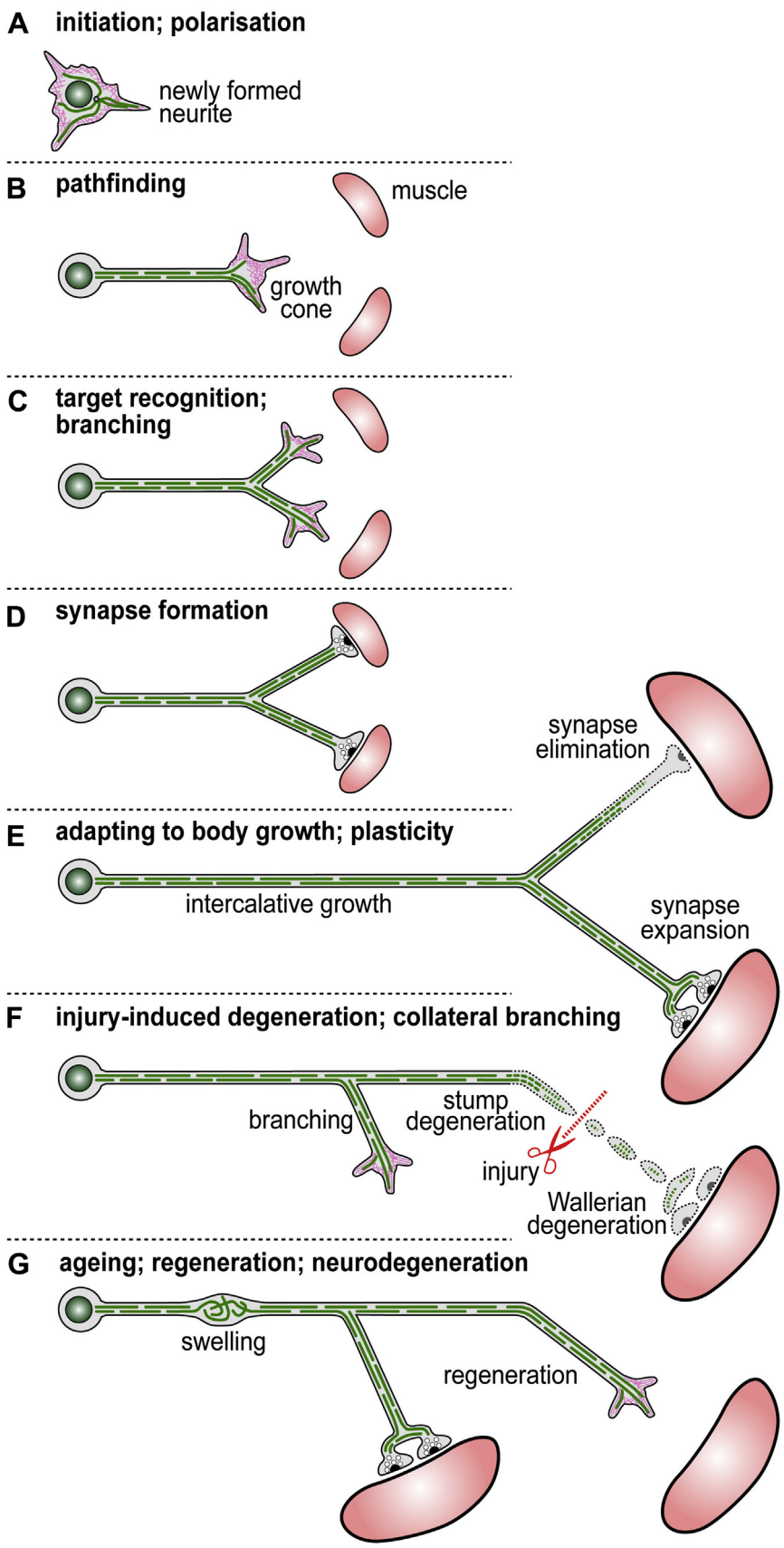

Fig. 1. Life stages of axons. Images show one neuron during its various life stages, with the cell body on the left and axon on the right; MTs are shown as green interrupted lines, actin in magenta and muscles as pink round shapes. The different life stages are indicated in the headings, and the various biological processes associated with those stages are annotated in each figure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)