Seminars in Cell & Developmental Biology 37 (2015) 11–19

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Intrinsically disordered tubulin tails: complex tuners of microtubule functions?

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ARTICLE INFO

Article history:
Available online 13 October 2014

Keywords:
Microtubule
Post-translational modification
Tubulin tyrosine ligase
Molecular motors
Brush polymer
Intrinsically disordered proteins

ABSTRACT

Microtubules are essential cellular polymers assembled from tubulin heterodimers. The tubulin dimer consists of a compact folded globular core and intrinsically disordered C-terminal tails. The tubulin tails form a lawn of densely grafted, negatively charged, flexible peptides on the exterior of the microtubule, potentially akin to brush polymers in the field of synthetic materials. These tails are hotspots for conserved, chemically complex posttranslational modifications that have the potential to act in a combinatorial fashion to regulate microtubule polymer dynamics and interactions with microtubule effectors, giving rise to a "tubulin code". In this review, I summarize our current knowledge of the enzymes that generate the astonishing tubulin chemical diversity observed in cells and describe recent advances in deciphering the roles of tubulin C-terminal tails and their posttranslational modifications in regulating the activity of molecular motors and microtubule associated proteins. Lastly, I outline the promises, challenges and potential pitfalls of deciphering the tubulin code.

Contents

1. Introduction

Microtubules are hollow cylindrical polymers built through the lateral association of protofilaments composed of longitudinally aligned head-to-tail αβ-tubulin dimers ([1,2]; Fig. 1). Microtubules exhibit "dynamic instability" a property that endows them with stochastic growth and shrinkage through the addition or removal of tubulin dimers at their ends [3,4]. The architecture of the microtubule gives it polarity: the minus and plus ends of the microtubule are capped by α-tubulin and β-tubulin subunits, respectively (Fig. 2). The two ends exhibit different behaviors, with the plus end exhibiting higher growth rates and more dynamics. Despite its highly dynamic nature, the microtubule is the most rigid cellular polymer known, exhibiting persistence lengths on the order of a cell's dimension (ranging from hundreds of microns to as much as millimeters; [5–7]). These unique biophysical properties allow

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http://dx.doi.org/10.1016/j.semcdb.2014.09.026
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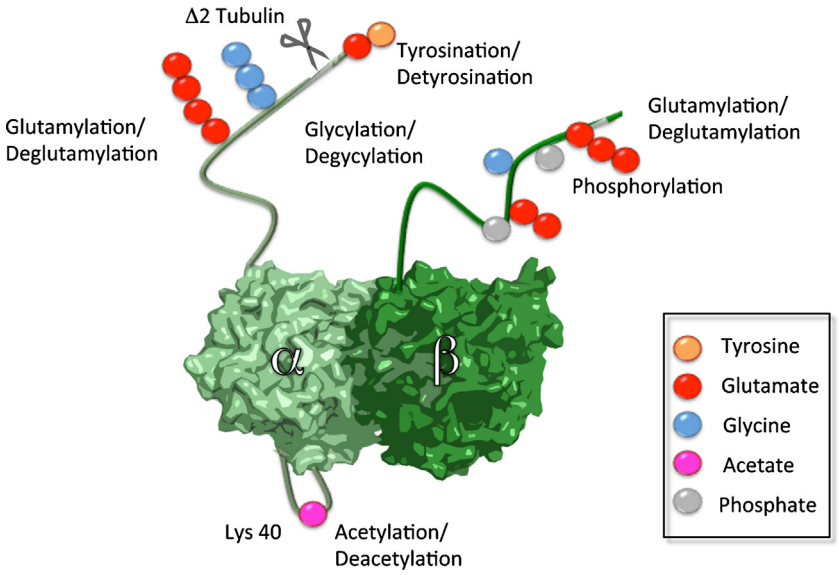

Fig. 1. Structure of the αβ-tubulin dimer. Sites of known posttranslational modifications are indicated by colored spheres (tyrosination, yellow; glutamylation, red; glycylation, cyan; acetylation, magenta; phosphorylation, gray).

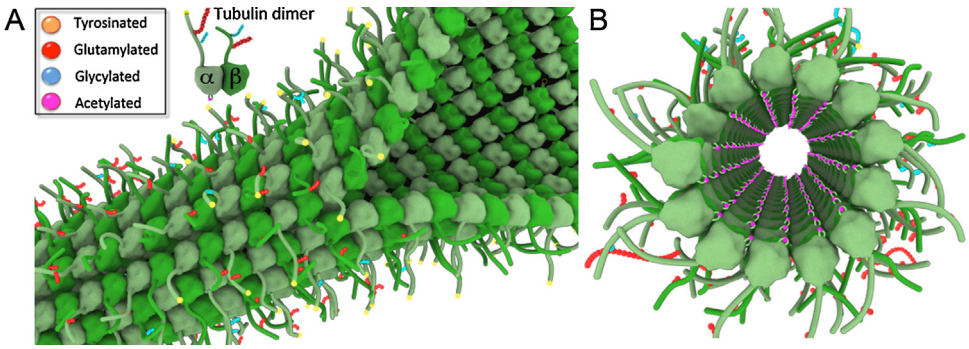

Fig. 2. Microtubules are decorated with posttranslational modifications inside and outside. (A) View of the microtubule exterior surface showing the C-terminal tails decorating the microtubule shaft. Posttranslational modifications are denoted by colored spheres (tyrosination, yellow; glutamylation, red; glycylation, cyan). (B) View of the microtubule lumen. Acetylation at Lys40 is denoted by magenta spheres.

microtubules to perform essential functions in fundamental cellular processes like cell division, differentiation and motility.

2. The tubulin dimer: a versatile building block for cellular infrastructure

Microtubules give rise to complex cellular structures with diverse morphologies and behaviors: the highly dynamic bipolar spindle, the exquisitely complex neuronal array, the disk-shaped marginal band in platelets, and the nine-fold symmetric arrays in cilia and flagella that can beat as fast as 110 Hz [8,9]. All of these structures use the αβ-tubulin heterodimer as their basic building block. The tubulin dimer consists of a compactly folded "body" and disordered, negatively charged α- and β C-terminal tails ([2,10]; Fig. 1). The tubulin body is involved in intimate tubulin–tubulin lattice interactions, while the C-terminal tails decorate the microtubule exterior ([1]; Fig. 2). Not surprising for an essential polymer, most isoform sequence variations and posttranslational modifications are concentrated on the C-terminal tails (~50% sequence identity between tubulin tails, compared to 80–95% for the tubulin body) where subtle changes can potentially tune the biophysical properties of microtubules and their interactions with cellular effectors without interfering with essential polymerization interfaces [11]. This situation is analogous to histones where protomer interfaces have been stringently conserved and sequence variability and posttranslational modifications are concentrated on the positively charged N-terminal tails and give rise to the now widely accepted "histone code" [12]. By analogy to histones, the genetic and chemical complexity of tubulin has been proposed to form the basis of a "tubulin code" [13]. The tubulin C-terminal tails are in close proximity to the binding sites of many motors and microtubule associated proteins (MAPs) and thus can constitute a code that can be read by cytoskeletal effectors [11,13,14].

Humans have eight α-tubulin and seven β-tubulin isoforms [15]. Some of these isoforms are essential for highly specialized cells like sperm, platelets and neurons, consistent with their cell- or tissue-specific expression [16–21]. Many tubulin isoforms can coexist in a given cell type [22] although our understanding of their distribution and roles is still limited. Several studies support the idea that microtubule dynamics can be tuned in cells by varying the relative levels of tubulin isotypes [23,24]. Mutations in various tubulin isoforms have been associated with a broad spectrum of human pathologies ranging from blood clotting to neurological disorders. For example, mutations in βVI, a tubulin isoform most abundant in platelets, have been identified in patients with congenital macrothrombocytopenia [25]. Platelets from these patients are enlarged and spherical due to defects in the assembly of the microtubule marginal band. Mutations in several tubulin isoforms that co-assemble into neuronal microtubules have also been identified in a range of neurological disorders [26–29] and their locations in