SnapShot: Functions of Tubulin Posttranslational Modifications

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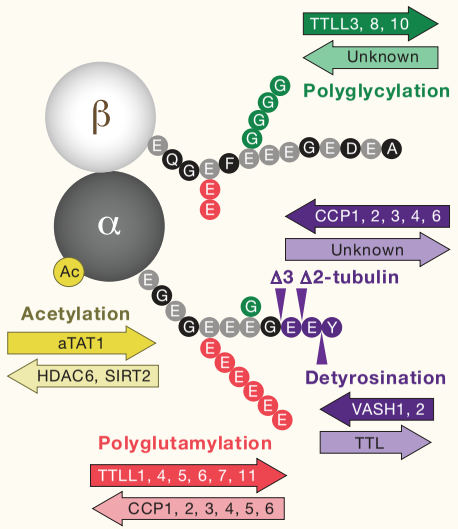
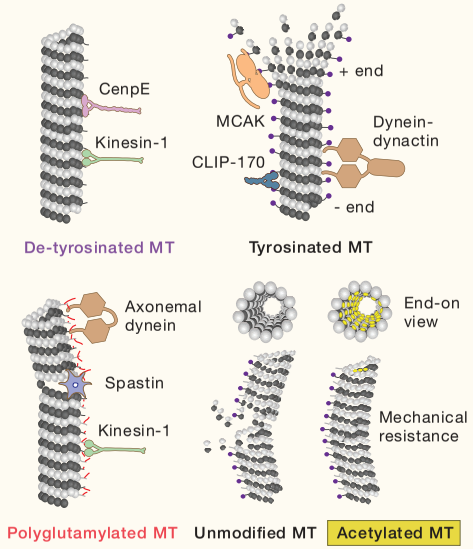
Cell

Tubulin PTMs

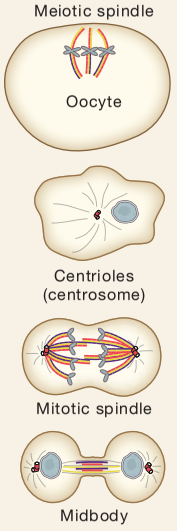


Mechanisms of tubulin PTMs



Functions of tubulin PTMs

Cell division



Detyrosination / Δ2-tubulin

Strongly enriched on centrosomes and selected MTs of the mitotic and meiotic spindles

- Chromosome congression in mitosis
- Non-Mendelian chromosome transmission in female meiosis

Disease link: cancer, poor prognosis for neuroblastoma and breast cancer, potentially linked to many types of cancer via vasohibins

Acetylation (K40)

Enriched on spindle and mid-body MTs

No known function

Polyglutamylation

Strongly enriched on centrioles of centrosomes, enriched on spindle and midbody MTs

- Centrosome integrity

Polyglycylation

Not detected - no known function

Neurons

Detyrosination / Δ2-tubulin

All MTs except in the growth cone

- Timing and extent of neurite outgrowth
- Growth cone organization and pathfinding
- Cortico-thalamic loop formation

Disease link: aberrant neuronal development in mice

Acetylation (K40)

All MTs except in the growth cone

- Axonal transport
- Mechanosensation in touch neurons
- Axonal branching
- Cortical neuron migration
- Regeneration of peripheral neurons

Disease link: axonal loss in Charcot-Marie-Tooth disease, alterations of emotional behavior in mice

Polyglutamylation

Strongly increased during neuronal differentiation, virtually all MTs

- Homeostasis of neurons, e.g., Purkinje, Mitral cells, cerebellar granule cells, thalamic neurons
- Axonal transport and synaptic transmission

Disease link: neurodegeneration in mice

Polyglycylation

Not detected - no known function

Cilia and flagella

Detyrosination / Δ2-tubulin

Strongly enriched on axonemal MTs

No known function

Acetylation (K40)

Strongly enriched on axonemal MTs

- Sperm morphology and motility

Disease link: male subfertility in mice

Polyglutamylation

Strongly enriched on axonemal MTs

- Spermatogenesis and sperm motility
- Ciliary and flagellar motility
- Retinal photoreceptors stability

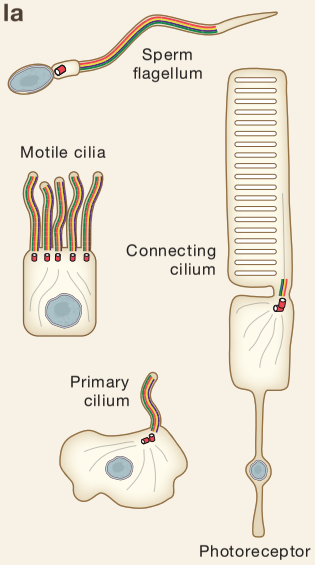
Disease link: vision disorders, male infertility in mice, respiratory diseases in mice

Polyglycylation

Strongly enriched on axonemal MTs of motile cilia and flagella, also on some primary cilia

- Length and stability of primary and motile cilia
- Retinal photoreceptors stability

Disease link: colon cancer, retina degeneration in mice



Platelets

Detyrosination / Δ2-tubulin

Detected on marginal-band MTs

No known function

Acetylation (K40)

Detected on marginal-band MTs

- Megakaryocyte maturation and platelet formation
- Platelet spreading after activation

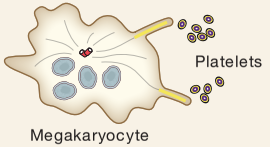
Disease link: thrombocytosis in patients with myeloproliferative neoplasms

Polyglutamylation

Not detected - no known function

Polyglycylation

Not detected - no known function



Myocytes

Detyrosination / Δ2-tubulin

Most MTs

- Mechanotransduction
- Load bearing during cardiomyocyte contraction

Disease link: cardiac arrythmia, contraction-induced injury of muscle cells in Duchenne muscular distrophy

Acetylation (K40)

Most MTs

No known function

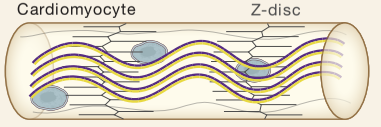
Polyglutamylation

Low levels detected

No known function

Polyglycylation

Not detected - no known function



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Cell

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Introduction

Microtubules (MTs) are essential components of the eukaryotic cytoskeleton. Both MTs and their molecular building blocks, the α-/β-tubulin dimers, are highly conserved throughout evolution, which stands in strong contrast to the myriad of functions to which MTs can adapt. The tubulin code provides a mechanism whereby modulating MT properties allows them to adapt to specific functions in cells. The tubulin code functions by incorporating different tubulin gene products, or isotypes, into the MT lattice or by installing posttranslational modifications (PTMs) on the tubulin units. Here, we present a view of the current understanding of tubulin PTMs and their biological functions.

Tubulin Posttranslational Modifications

Tubulin can be subjected to a large number of PTMs. Most of them can take place on both α- and β-tubulin, although some are restricted to α-tubulin (e.g., detyrosination). Over the past decade, enzymes catalyzing many PTMs of tubulin have been discovered (reviewed in Janke, 2014).

Tubulin detyrosination, a modification that, counterintuitively, consists of the enzymatic removal of a functional moiety—the C-terminal tyrosine of α-tubulin—is catalyzed by enzymes from the vasohibin family (Aillaud et al., 2017; Nieuwenhuis et al., 2017). The reverse reaction—re-addition of the tyrosine or re-tyrosination—is catalyzed by tubulin tyrosine ligase (TTL). After detyrosination, cytosolic carboxypeptidases (CCPs) can further remove glutamate residues to generate Δ2- and Δ3-tubulin. Acetylation of α-tubulin takes place on lysine 40, is catalyzed by aTAT1, and is removed by HDAC6 or SIRT2. Polyglutamylation and polyglycylation are catalyzed by enzymes from the tubulin tyrosine ligase-like (TTLL) enzyme family. Polyglutamylases, as well as polyglycylases, show preferences to either α- or β-tubulin, as well as catalytic specificities, to generate either short or long chains of glutamate or glycine residues, respectively. Deglutamylation is catalyzed by enzymes from the CCP family, whereas no deglycylase has been identified so far (reviewed in Janke, 2014).

Mechanisms of Tubulin Posttranslational Modifications

The location of a modification site on tubulin likely determines the impact of a particular PTM on MT functions. Modifications of the conserved and highly structured tubulin core are expected to alter biophysical properties of the MTs. Indeed, acetylation of lysine 40 has been shown to render MTs more flexible and thus resistant to mechanical stress (Portran et al., 2017). By contrast, modifications localized at the unstructured extreme C-terminal tails of tubulin (gray amino acid chains), which decorate the outer surface of MTs, are likely to differentially regulate the interactions between MTs and specific MAPs. Initial studies have proven this to be the case. Detyrosination, for example, regulates the interaction of a number of motor proteins (e.g., kinesin-1, kinesin-2, CENP-E, kinesin-13, Kif2A) and some plus-end binding (e.g., CLIP170, $p150^{glued}$) proteins with MTs (Peris et al., 2006). No specific mechanism has been so far proposed for Δ2- and Δ3-tubulin variants. Tubulin polyglutamylation, which adds side chains of negatively charged glutamic acid residues, has also been shown to modulate the behavior of kinesin-1 (Sirajuddin et al., 2014) and the flagellar dynein motor (Kubo et al., 2010) on MTs; however, the most striking effect of this modification is the regulation of the MT-severing enzyme spastin (Valenstein and Roll-Mecak, 2016). No molecular mechanism controlled by polyglycylation has been uncovered thus far.

Biological Roles of Tubulin Posttranslational Modifications

In the recent years, an increasing number of functional studies have strongly advanced the understanding of the biological roles of tubulin PTMs. Strikingly, it appears that modifications of tubulin are involved in almost every specialized MT function, either as essential determinants or as subtle regulators. Most of the known tubulin modifications play important roles for cilia and flagella, as they specifically modify the MT-based axoneme (reviewed in Wloga et al., 2017). In neurons, polyglutamylation is important for neuronal survival and the maintenance of synaptic transmission, while detyrosination has been demonstrated to be essential for neuronal development. More subtle functions have been found for detyrosination in the regulation of cell division, where it is important for faithful chromosome segregation in mitosis and generates asymmetry in the meiotic spindles of oocytes. Detyrosination was further implicated in mechanotransduction and load bearing during contractions of cardiomyocytes. Less is known on the physiological role of acetylation (reviewed in Janke and Montagnac, 2017). ATAT1-knockout mice show altered sperm morphology and motility, and some defects in neuronal migration, development, and regeneration, as well as in mechanosensation in touch neurons. Acetylation is so far the only tubulin PTM that has been demonstrated to play a role in blood platelet formation and function.

Implications for Human Health and Disease

Considering that MTs are essential for virtually every mammalian cell, deregulation of tubulin PTMs could result in a range of pathologies. Most potential disease links identified so far stem from observations in mouse models; however, rapidly developing genomic-profiling data have recently provided first direct links between tubulin-modifying enzymes and human pathologies. The emerging links to pathologies are discussed in the accompanying minireview (Magiera et al., 2018).

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