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Microtubules are key cytoskeletal elements involved in a large number of functions in eukaryotic cells.

They assemble from a protein dimer of a- and b-tubulin, two highly similar and conserved proteins. Tubulins are subject to a large variety of posttranslational modifications (Fig. 1), which provide a rapid and reversible mechanism to diversify microtubule functions in cells. Our team is studying the mechanisms and functional roles of these modifications by using an interdisciplinary approach.

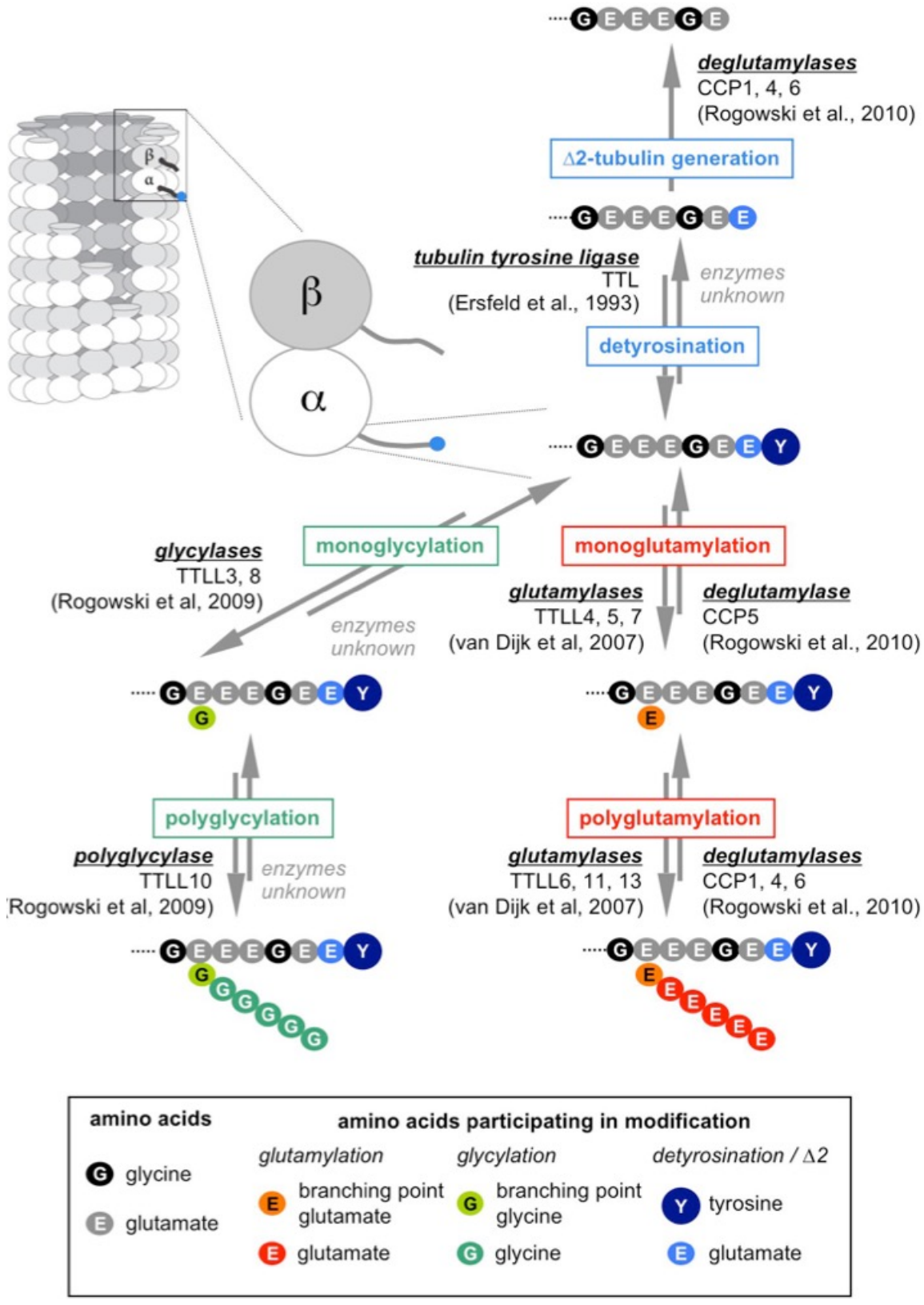
deglutamylases
CCP1, 4, 6
(Rogowski et al., 2010)
Δ2-tubulin generation
tubulin tyrosine ligase
TTL
(Ersfeld et al., 1993)
enzymes unknown
detyrosination
β
α
monoglycylation
monoglutamylation
glycylases
TTLL3, 8
(Rogowski et al, 2009)
enzymes unknown
glutamylases
TTLL4, 5, 7
(van Dijk et al, 2007)
deglutamylase
CCP5
(Rogowski et al., 2010)
polyglycylation
polyglycylase
TTLL10
(Rogowski et al, 2009)
enzymes unknown
polyglutamylation
glutamylases
TTLL6, 11, 13
(van Dijk et al, 2007)
deglutamylases
CCP1, 4, 6
(Rogowski et al., 2010)
amino acids
glycine
glutamate
amino acids participating in modification
glutamylation
branching point glutamate
glutamate
glycylation
branching point glycine
glycine
detyrosination / Δ2
tyrosine
glutamate

Figure 1: Schematic representation of tubulin post-translational modifications The three modifications that directly modify the C-terminal tail of tubulin, their mechanisms and enzymes involved in the modifications are depicted. Polyglutamylation and polyglycylation take place on both, α- and β-tubulin, whereas detyrosination is restricted to α-tubulin.

Our team has identified the enzymes involved in the posttranslational polyglutamylation (*1, 2*), deglutamylation (*3, 4*) and polyglycylation (*5*) of tubulin. Following the discovery of these enzymes, we are now investigating (i) the molecular mechanisms, and (ii) the biological functions of tubulin-modifying enzymes.

Polyglutamylation and polyglycylation take place within the C-terminal tails of the tubulin molecules. These tails are localized at the outer surface of the microtubule (Fig. 1), thus their posttranslational modification is most likely regulating the interactions of microtubules with their multiple binding partners, commonly known as microtubule-associated proteins (MAPs) and molecular motors. So far we have demonstrated that the microtubule-severing protein spastin is regulated by tubulin polyglutamylation (*6*), and that tubulin glycylation stabilizes ciliary axonemes by a yet unknown molecular mechanism (*5, 7*). Our functional studies have demonstrated an important role for both, polyglutamylation and polyglycylation for motile and primary cilia in mammals (*7, 8*), and we have found that polyglutamylation is directly linked to neurodegeneration in mice (*4*). We have further demonstrated a direct link between altered levels of a tubulin glycylase and colorectal cancer development (*8*).

In our ongoing projects, we are using biochemistry, biophysics and structural biology in conjunction with cell and mouse biology to identify the molecular mechanisms by which tubulin posttranslational modifications regulative microtubule behaviour and functions, and which are the cellular and developmental roles of these modifications and the corresponding enzymes. Our functional studies are focussed on the nervous system, cilia and flagella (including spermatogenesis), and cell division. Our team is closely collaborating with clinicians to delineate the implications of tubulin posttranlsational modifications in human pathologies.

Key publications

Year of publication 2018

Maria M Magiera, Puja Singh, Carsten Janke (2018 Jun 2)
SnapShot: Functions of Tubulin Posttranslational Modifications.
Cell : 1552-1552.e1 : DOI : S0092-8674(18)30644-5

Maria M Magiera, Puja Singh, Sudarshan Gadadhar, Carsten Janke (2018 Jun 2)
Tubulin Posttranslational Modifications and Emerging Links to Human Disease.
Cell : 1323-1327 : DOI : S0092-8674(18)30595-6

Year of publication 2017

Renaud Chabrier, Carsten Janke (2017 Dec 21)
The comeback of hand drawing in modern life sciences.
Nature reviews. Molecular cell biology : DOI : 10.1038/nrm.2017.126

Sudarshan Gadadhar, Hala Dadi, Satish Bodakuntla, Anne Schnitzler, Ivan Bièche, Filippo Rusconi, Carsten Janke (2017 Sep 4)
Tubulin glycylation controls primary cilia length.
The Journal of cell biology : 2701-2713 : DOI : 10.1083/jcb.201612050

Kathiresan Natarajan, Sudarshan Gadadhar, Judith Souphron, Maria M Magiera, Carsten Janke (2017 Jun 1)
Molecular interactions between tubulin tails and glutamylases reveal determinants of glutamylation patterns.
EMBO reports : 1013-1026 : DOI : 10.15252/embr.201643751

Montserrat Bosch Grau, Christel Masson, Sudarshan Gadadhar, Cecilia Rocha, Olivia Tort, Patricia Marques Sousa, Sophie Vacher, Ivan Bieche, Carsten Janke (2017 Mar 1)
Alterations in the balance of tubulin glycylation and glutamylation in photoreceptors leads to retinal degeneration.
Journal of cell science : DOI : 10.1242/jcs.199091