Controlling Microtubule Dynamics and Function with the tubulin code

UMR3348 – Genome integrity, RNA and Cancer

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Highlights

Tubulin polyglutamylation induces neurodegeneration

Tubulin glycylation coordinates sperm swimming

Microtubules, key elements of the cytoskeleton, are 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.

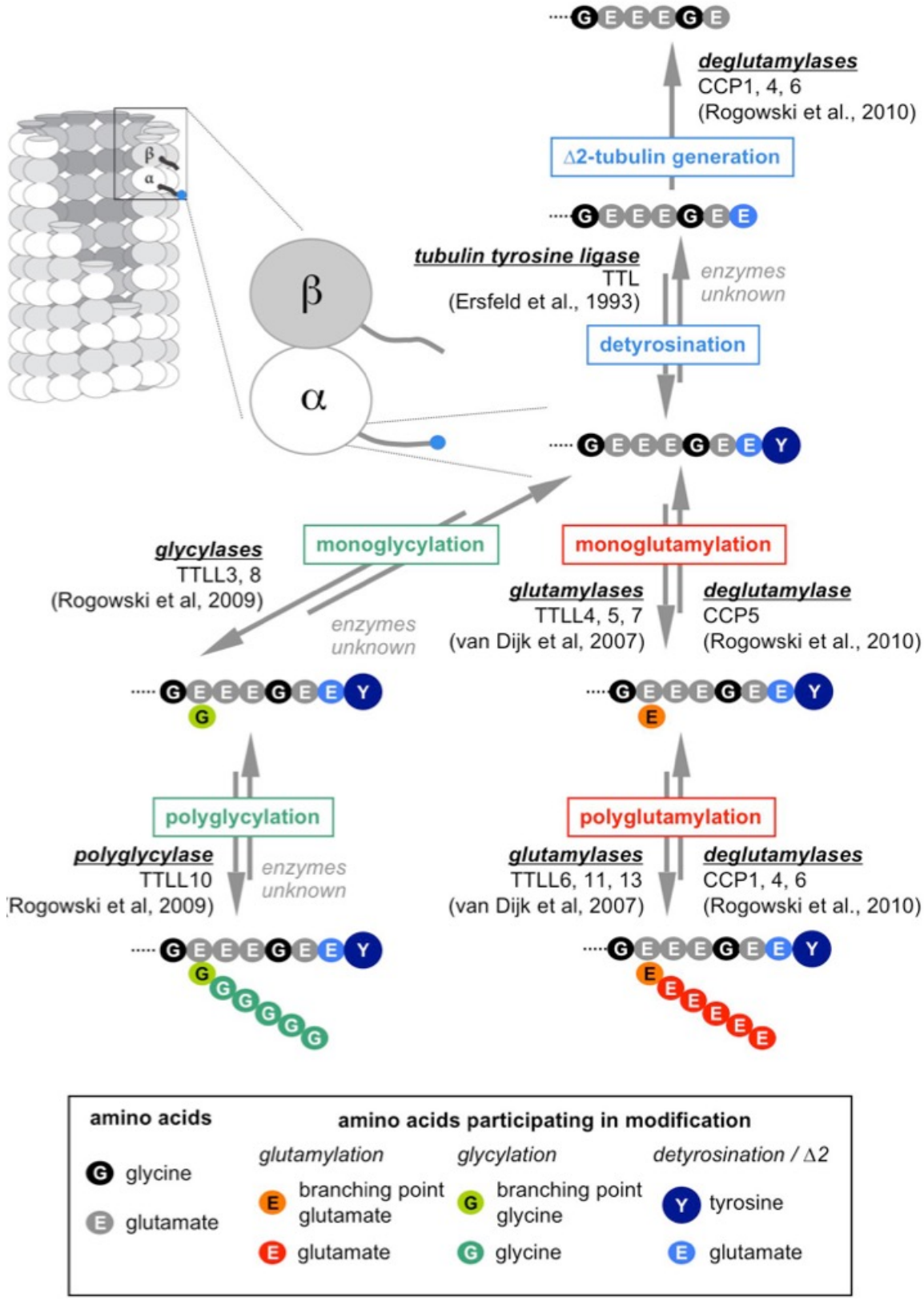
deglutamylases
CCP1, 4, 6
(Rogowski et al., 2010)
Δ2-tubulin generation
tubulin tyrosine ligase
TTL
(Ersfeld et al., 1993)
enzymes unknown
detyrosination
β
α
monoglycylation
monoglutamylation
glycylases
TTLL3, 8
(Rogowski et al, 2009)
enzymes unknown
glutamylases
TTLL4, 5, 7
(van Dijk et al, 2007)
deglutamylase
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 2021

Sudarshan Gadadhar, Gonzalo Alvarez Viar, Jan Niklas Hansen, An Gong, Aleksandr Kostarev, Côme Ialy-Radio, Sophie Leboucher, Marjorie Whitfield, Ahmed Ziyyat, Aminata Touré, Luis Alvarez, Gaia Pigino , Carsten Janke (2021 Jan 8)

Tubulin glycylation controls axonemal dynein activity, flagellar beat, and male fertility

ScienceScience : DOI : 10.1126/science.abd4914

Year of publication 2020

Carsten Janke, Maria M Magiera (2020 Feb 27)

The tubulin code and its role in controlling microtubule properties and functions.
Nature reviews. Molecular cell biology : DOI : 10.1038/s41580-020-0214-3

Year of publication 2019

Satish Bodakuntla, A S Jijumon, Cristopher Villablanca, Christian Gonzalez-Billault, Carsten Janke (2019 Oct 29)
Microtubule-Associated Proteins: Structuring the Cytoskeleton.
Trends in cell biology : 804-819 : DOI : S0962-8924(19)30120-5

Tiziana Giordano, Sudarshan Gadadhar, Satish Bodakuntla, Jonas Straub, Sophie Leboucher, Guillaume Martinez, Walid Chemlali, Christophe Bosc, Annie Andrieux, Ivan Bieche, Christophe Arnoult, Stefan Geimer, Carsten Janke (2019 Feb 7)
Loss of the deglutamylase CCP5 perturbs multiple steps of spermatogenesis and leads to male infertility.
Journal of cell science : DOI : jcs226951

Year of publication 2018

Maria M Magiera, Satish Bodakuntla, Jakub Žiak, Sabrina Lacomme, Patricia Marques Sousa, Sophie Leboucher, Torben J Hausrat, Christophe Bosc, Annie Andrieux, Matthias Kneussel, Marc Landry, André Calas, Martin Balastik, Carsten Janke (2018 Nov 12)
Excessive tubulin polyglutamylation causes neurodegeneration and perturbs neuronal transport.
The EMBO journal. : DOI : e100440

Maria M Magiera, Puja Singh, Carsten Janke (2018 May 31)
SnapShot: Functions of Tubulin Posttranslational Modifications.
Cell : 1552-1552.e1 : DOI : 10.1016/j.cell.2018.05.032