The tubulin code: Empowering microtubules

Maria M Magiera

The tubulin code: Empowering microtubules

Maria M. Magiera[a,b]

[a] *Institut Curie, Université PSL, CNRS UMR3348, Orsay, France*

[b] *Université Paris-Saclay, CNRS UMR3348, Orsay, France*

E-mail address: maria.magiera@curie.fr.

Microtubules are essential filamentous components of the cytoskeleton that are present in virtually all eukaryotic cells, where they ensure essential functions: Microtubules establish and maintain cell shape, serve as tracks for the intracellular transport, or build the mitotic and meiotic spindles that segregate genetic material during cell division. Microtubules further form the structural backbone of cilia and flagella, essential organelles that are involved in cell-cell signalling and cell motility.

The history of microtubule research spans more than 150 years. Spindle fibres that we know today are microtubules were first seen in mitotic cells and depicted in 1870s and 80s in drawing by Walther Flemming [1] and Theodor Boveri [2], and were first photographed in dividing worm and sea urchin eggs in 1939 [3]. With the development of transmission electron microscopy approaches in the 1950s, so-called "tube fibres" were identified in the sperm flagella of Sphagnum moss [4], as well as in cilia from several other species [5]. An improvement of fixation methods [6] allowed Myron Ledbetter and Keith Porter to measure the size of those fibres, and to suggest that they may be made from "smaller filamentous units packed together to form the wall of the cylinder" and that these "smaller units […] appear circular in cross-section" [7]. Their analysis of plant cells, together with David Slautterback's analysis of hydra cells brought these authors to propose that the rod-shaped, long, and hollow structures found in mitotic spindles, cilia and flagella and in interphase cells would all be the same structure, which they called for the first time "microtubules" [8, 9].

In 1967, Gary Borisy and Edwin Taylor used colchicine, a well-characterised mitotic-spindle poison, to identify the protein building block of microtubules from sea urchin cells [10, 11]. The Taylor lab further purified this colchicine-binding protein from cilia, sperm tails [12] and brain tissue [13], however it was Hideo Mohri who in 1968 coined its name: "tubulin" [14]. In the following years, biochemical approaches revealed that microtubules were made from dimers of two different tubulin proteins, later known as α- and β-tubulin [15, 16].

The fact that microtubules can assemble into many different structures in cells, and fulfil a wide variety of different functions, together with the emerging notion that more than just two types of tubulin (i.e. α- and β-tubulin) might be present in cells [17], and that tubulin undergoes posttranslational modification [18] led Chandler Fulton and Peter Simpson to propose in 1976 “the multi-tubulin hypothesis” [19]. This hypothesis proposes that tubulin expression from different genes, together with their posttranslational modifications, can generate biochemically divergent microtubule subtypes in cells, which in turn can fulfil distinct functions. Indeed, shortly after, several genes encoding different tubulin variants, aka isotypes, were cloned [20, 21], which immediately suggested that tubulin isotypes could assemble into functionally distinct microtubules. However, subsequent work showing that most tubulin isotypes were functionally interchangeable somehow mitigated the initial excitement in the field [22]. Only the more recent discovery of a large spectrum of disease-causing tubulin mutations [23, 24] was able to reverse this trend, generating a growing interest in the physiological roles of tubulin isotypes.

Microtubule diversity can also be generated by posttranslational modifications of tubulin, such as detyrosination [25], generation of Δ2-tubulin [26], acetylation [27], polyglutamylation [28], polyglycylation [29], polyamination [30], and methylation [31]. The discovery of the enzymes catalysing those modifications ([32], and references within) provided first insights into their physiological importance. For instance, abnormal accumulation of polyglutamylation causes neurodegeneration and vision disorders in mice and humans [33-36], and perturbation of polyglutamylation or polyglycylation was linked to male infertility [37-39], ciliopathies[40] and cancer [41].

The mechanisms generating microtubule diversity by expression of different tubulin isotypes and by posttranslational modifications are today known as the “tubulin code” [K.J. Verhey, J. Gaertig, The Tubulin Code, Cell Cycle 6(17) (2007) 2152-2160]. The recent progress in the understanding of how this diversity is achieved, how it affects microtubule properties and their cellular functions, and how this translates into regulation of biological functions opened up an entirely new perspective on cytoskeletal regulation, and its importance for human health. This special issue gathers in-depth reviews on the relevance of the tubulin code in a variety of biological system written by broad spectrum of experts. Some of them discuss domains in which tubulin diversity was known to be important for a long time, while others highlight fields in which the impact of the tubulin code only begins to emerge. Joachimiak & Wloga discuss how the unicellular prokaryotes became a playground for studying tubulin modifications and modifying enzymes. Guichard et al. review advances in the understanding

of the role of the tubulin code for centrioles, while Gadadhar et al. summarise how tubulin isotypes and posttranslational modifications control sperm development and function. Takashi dissects the emerging roles of tubulin modifications in meiosis, while Sanyal et al. focus specifically on the roles of posttranslational modifications of the α-tubulin C-terminal tails in muscle cells and in neurons. Kimmerlin et al. contribute a comprehensive review on the role of tubulin diversity in platelet functions, and Bieniussa et al. gather growing evidence for the involvement of microtubules in the auditory function. The review from Maillard and colleagues focusses on the spectrum of tubulin mutations linked to neurodevelopmental disorders.

The ambition of this collection is to provide a broad overview of the current knowledge on the role of the tubulin code in different biological settings. It should encourage a broad community of researchers to consider the role of tubulin diversity in their ongoing research and could help revealing similar regulatory principles in different biological systems.

References:

[1] W. Flemming, Beiträge zur Kenntniss der Zelle und Ihrer Lebenserscheinungen, Archiv für mikroskopische Anatomie 18(1) (1880) 151-259.
[2] T. Boveri, Beiträge zur Kenntnis der Nervenfasern, München, 1886.
[3] W.J. Schmidt, Doppelbrechung der Kernspindel und Zugfasertheorie der Chromosomenbewegung, Zeitschrift für Zellforschung und Mikroskopische Anatomie Abt. B Chromosoma 1(1) (1939) 253-264.
[4] I. Manton, B. Clarke, An Electron Microscope Study of the Spermatozoid of Sphagnum, Journal of Experimental Botany 3(9) (1952) 265-275.
[5] D.W. Fawcett, K.R. Porter, A study of the fine structure of ciliated epithelia, Journal of Morphology 94(2) (1954) 221-281.
[6] D.D. Sabatini, K. Bensch, R.J. Barrnett, Cytochemistry and electron microscopy. The preservation of cellular ultrastructure and enzymatic activity by aldehyde fixation, J Cell Biol 17 (1963) 19-58.
[7] M.C. Ledbetter, K.R. Porter, Morphology of Microtubules of Plant Cell, Science 144(3620) (1964) 872-874.
[8] M.C. Ledbetter, K.R. Porter, A "Microtubule" in Plant Cell Fine Structure, J Cell Biol 19(1) (1963) 239-50.
[9] D.B. Slautterback, Cytoplasmic Microtubules. I. Hydra, J Cell Biol 18 (1963) 367-88.
[10] G.G. Borisy, E.W. Taylor, The mechanism of action of colchicine. Binding of colchincine-3H to cellular protein, J Cell Biol 34(2) (1967) 525-33.
[11] G.G. Borisy, E.W. Taylor, The mechanism of action of colchicine. Colchicine binding to sea urchin eggs and the mitotic apparatus, J Cell Biol 34(2) (1967) 535-48.
[12] M.L. Shelanski, E.W. Taylor, Isolation of a protein subunit from microtubules, J Cell Biol 34(2) (1967) 549-54.
[13] R.C. Weisenberg, G.G. Borisy, E.W. Taylor, The colchicine-binding protein of mammalian brain and its relation to microtubules, Biochemistry 7(12) (1968) 4466-79.
[14] H. Mohri, Amino-acid composition of "Tubulin" constituting microtubules of sperm flagella, Nature 217(5133) (1968) 1053-4.

[15] J. Bryan, L. Wilson, Are cytoplasmic microtubules heteropolymers?, Proc Natl Acad Sci U S A 68(8) (1971) 1762-6.
[16] I.N. Feit, R.M. Iverson, L.K. Chu, Appearance of polyribosomes during germination of spores in cellular slime mold Dictyostelium purpureum, Exp Cell Res 65(2) (1971) 439-44.
[17] R.E. Stephens, Structural chemistry of the axoneme: evidence for chemically and functionally unique tubulin dimers in outer fibers, Soc Gen Physiol Ser 30 (1975) 181-206.
[18] H.S. Barra, J.A. Rodriguez, C.A. Arce, R. Caputto, A soluble preparation from rat brain that incorporates into its own proteins (14C)arginine by a ribonuclease-sensitive system and (14C)tyrosine by a ribonuclease-insensitive system, J Neurochem 20(1) (1973) 97-108.
[19] C. Fulton, P.A. Simpson, Selective synthesis and utilization of flagelar tubulin. The multitubulin hypothesis., in: R. Goldman, T.D. Pollard, J.L. Rosenbaum (Eds.), Cell Motility, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1976, pp. 987-1005.
[20] D.W. Cleveland, M.W. Kirschner, N.J. Cowan, Isolation of separate mRNAs for alpha- and beta-tubulin and characterization of the corresponding in vitro translation products, Cell 15(3) (1978) 1021-31.
[21] D.W. Cleveland, M.A. Lopata, R.J. MacDonald, N.J. Cowan, W.J. Rutter, M.W. Kirschner, Number and evolutionary conservation of alpha- and beta-tubulin and cytoplasmic beta- and gamma-actin genes using specific cloned cDNA probes, Cell 20(1) (1980) 95-105.
[22] R.F. Luduena, Are tubulin isotypes functionally significant, Mol Biol Cell 4(5) (1993) 445-57.
[23] S. Chakraborti, K. Natarajan, J. Curiel, C. Janke, J. Liu, The emerging role of the tubulin code: From the tubulin molecule to neuronal function and disease, Cytoskeleton (Hoboken) 73(10) (2016) 521-550.
[24] M.A. Tischfield, G.Y. Cederquist, M.L. Gupta, Jr., E.C. Engle, Phenotypic spectrum of the tubulin-related disorders and functional implications of disease-causing mutations, Curr Opin Genet Dev 21(3) (2011) 286-94.
[25] M.E. Hallak, J.A. Rodriguez, H.S. Barra, R. Caputto, Release of tyrosine from tyrosinated tubulin. Some common factors that affect this process and the assembly of tubulin, FEBS Lett 73(2) (1977) 147-50.
[26] L. Paturle-Lafanechere, B. Eddé, P. Denoulet, A. Van Dorsselaer, H. Mazarguil, J.P. Le Caer, J. Wehland, D. Job, Characterization of a major brain tubulin variant which cannot be tyrosinated, Biochemistry 30(43) (1991) 10523-10528.
[27] S.W. L'Hernault, J.L. Rosenbaum, Chlamydomonas alpha-tubulin is posttranslationally modified by acetylation on the epsilon-amino group of a lysine, Biochemistry 24(2) (1985) 473-8.
[28] B. Eddé, J. Rossier, J.P. Le Caer, E. Desbruyeres, F. Gros, P. Denoulet, Posttranslational glutamylation of alpha-tubulin, Science 247(4938) (1990) 83-85.
[29] V. Redeker, N. Levilliers, J.M. Schmitter, J.P. Le Caer, J. Rossier, A. Adoutte, M.H. Bré, Polyglycylation of tubulin: a posttranslational modification in axonemal microtubules, Science 266(5191) (1994) 1688-1691.
[30] Y. Song, L.L. Kirkpatrick, A.B. Schilling, D.L. Helseth, N. Chabot, J.W. Keillor, G.V.W. Johnson, S.T. Brady, Transglutaminase and polyamination of tubulin: posttranslational modification for stabilizing axonal microtubules, Neuron 78(1) (2013) 109-23.
[31] I.Y. Park, R.T. Powell, D.N. Tripathi, R. Dere, T.H. Ho, T.L. Blasius, Y.-C. Chiang, I.J. Davis, C.C. Fahey, K.E. Hacker, K.J. Verhey, M.T. Bedford, E. Jonasch, W.K. Rathmell, C.L. Walker, Dual Chromatin and Cytoskeletal Remodeling by SETD2, Cell 166(4) (2016) 950-62.
[32] C. Janke, M.M. Magiera, The tubulin code and its role in controlling microtubule properties and functions, Nat Rev Mol Cell Biol 21(6) (2020) 307-326.

[33] M.M. Magiera, S. Bodakuntla, J. Ziak, S. Lacomme, P. Marques Sousa, S. Leboucher, T.J. Hausrat, C. Bosc, A. Andrieux, M. Kneussel, M. Landry, A. Calas, M. Balastik, C. Janke, Excessive tubulin polyglutamylation causes neurodegeneration and perturbs neuronal transport, EMBO J 37(23) (2018) e100440.
[34] V. Shashi, M.M. Magiera, D. Klein, M. Zaki, K. Schoch, S. Rudnik-Schoneborn, A. Norman, O. Lopes Abath Neto, M. Dusl, X. Yuan, L. Bartesaghi, P. De Marco, A.A. Alfares, R. Marom, S.T. Arold, F.J. Guzman-Vega, L.D. Pena, E.C. Smith, M. Steinlin, M.O. Babiker, P. Mohassel, A.R. Foley, S. Donkervoort, R. Kaur, P.S. Ghosh, V. Stanley, D. Musaev, C. Nava, C. Mignot, B. Keren, M. Scala, E. Tassano, P. Picco, P. Doneda, C. Fiorillo, M.Y. Issa, A. Alassiri, A. Alahmad, A. Gerard, P. Liu, Y. Yang, B. Ertl-Wagner, P.G. Kranz, I.M. Wentzensen, R. Stucka, N. Stong, A.S. Allen, D.B. Goldstein, B. Schoser, K.M. Rosler, M. Alfadhel, V. Capra, R. Chrast, T.M. Strom, E.-J. Kamsteeg, C.G. Bonnemann, J.G. Gleeson, R. Martini, C. Janke, J. Senderek, Loss of tubulin deglutamylase CCP1 causes infantile-onset neurodegeneration, EMBO J 37(23) (2018) e100540.
[35] S. Kastner, I.-J. Thiemann, G. Dekomien, E. Petrasch-Parwez, S. Schreiber, D.A. Akkad, W.M. Gerding, S. Hoffjan, S. Gunes, S. Gunes, H. Bagci, J.T. Epplen, Exome Sequencing Reveals AGBL5 as Novel Candidate Gene and Additional Variants for Retinitis Pigmentosa in Five Turkish Families, Invest Ophthalmol Vis Sci 56(13) (2015) 8045-53.
[36] K. Branham, H. Matsui, P. Biswas, A.A. Guru, M. Hicks, J.J. Suk, H. Li, D. Jakubosky, T. Long, A. Telenti, N. Nariai, J.R. Heckenlively, K.A. Frazer, P.A. Sieving, R. Ayyagari, Establishing the involvement of the novel gene AGBL5 in retinitis pigmentosa by whole genome sequencing, Physiol Genomics 48(12) (2016) 922-927.
[37] P. Vogel, G. Hansen, G. Fontenot, R. Read, Tubulin tyrosine ligase-like 1 deficiency results in chronic rhinosinusitis and abnormal development of spermatid flagella in mice, Vet Pathol 47(4) (2010) 703-12.
[38] T. Giordano, S. Gadadhar, S. Bodakuntla, J. Straub, S. Leboucher, G. Martinez, W. Chemlali, C. Bosc, A. Andrieux, I. Bieche, C. Arnoult, S. Geimer, C. Janke, Loss of the deglutamylase CCP5 perturbs multiple steps of spermatogenesis and leads to male infertility, J Cell Sci 132(3) (2019) jcs226951.
[39] S. Gadadhar, G. Alvarez Viar, J.N. Hansen, A. Gong, A. Kostarev, C. Ialy-Radio, S. Leboucher, M. Whitfield, A. Ziyyat, A. Toure, L. Alvarez, G. Pigino, C. Janke, Tubulin glycylation controls axonemal dynein activity, flagellar beat, and male fertility, Science 371(6525) (2021) eabd4914.
[40] J.E. Lee, J.L. Silhavy, M.S. Zaki, J. Schroth, S.L. Bielas, S.E. Marsh, J. Olvera, F. Brancati, M. Iannicelli, K. Ikegami, A.M. Schlossman, B. Merriman, T. Attie-Bitach, C.V. Logan, I.A. Glass, A. Cluckey, C.M. Louie, J.H. Lee, H.R. Raynes, I. Rapin, I.P. Castroviejo, M. Setou, C. Barbot, E. Boltshauser, S.F. Nelson, F. Hildebrandt, C.A. Johnson, D.A. Doherty, E.M. Valente, J.G. Gleeson, CEP41 is mutated in Joubert syndrome and is required for tubulin glutamylation at the cilium, Nat Genet 44(2) (2012) 193-9.
[41] C. Rocha, L. Papon, W. Cacheux, P. Marques Sousa, V. Lascano, O. Tort, T. Giordano, S. Vacher, B. Lemmers, P. Mariani, D. Meseure, J.P. Medema, I. Bieche, M. Hahne, C. Janke, Tubulin glycylases are required for primary cilia, control of cell proliferation and tumor development in colon, EMBO J 33(19) (2014) 2247-60.