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The tubulin code: Empowering microtubules

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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 $\Delta 2$ -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.

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