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CELL SCIENCE AT A GLANCE

# Microtubule minus-end regulation at a glance

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## ABSTRACT

Microtubules are cytoskeletal filaments essential for numerous aspects of cell physiology. They are polarized polymeric tubes with a fast growing plus end and a slow growing minus end. In this Cell Science at a Glance article and the accompanying poster, we review the current knowledge on the dynamics and organization of microtubule minus ends. Several factors, including the γ-tubulin ring complex, CAMSAP/Patronin, ASPM/Asp, SPIRAL2 (in plants) and the KANSL complex recognize microtubule minus ends and regulate their nucleation, stability and interactions with partners, such as microtubule severing enzymes, microtubule depolymerases and protein scaffolds. Together with minus-end-directed motors, these microtubule minus-end targeting proteins (–TIPs) also control the formation of microtubule-organizing centers, such as centrosomes and spindle poles, and mediate microtubule attachment to cellular membrane structures, including the cell cortex, Golgi complex and the cell nucleus. Structural and functional studies are starting to reveal the molecular mechanisms by which dynamic –TIP networks control microtubule minus ends.

**KEY WORDS: CAMSAP, Centrosome, Dynein, Gamma-tubulin ring complex, Microtubule, Spindle pole**

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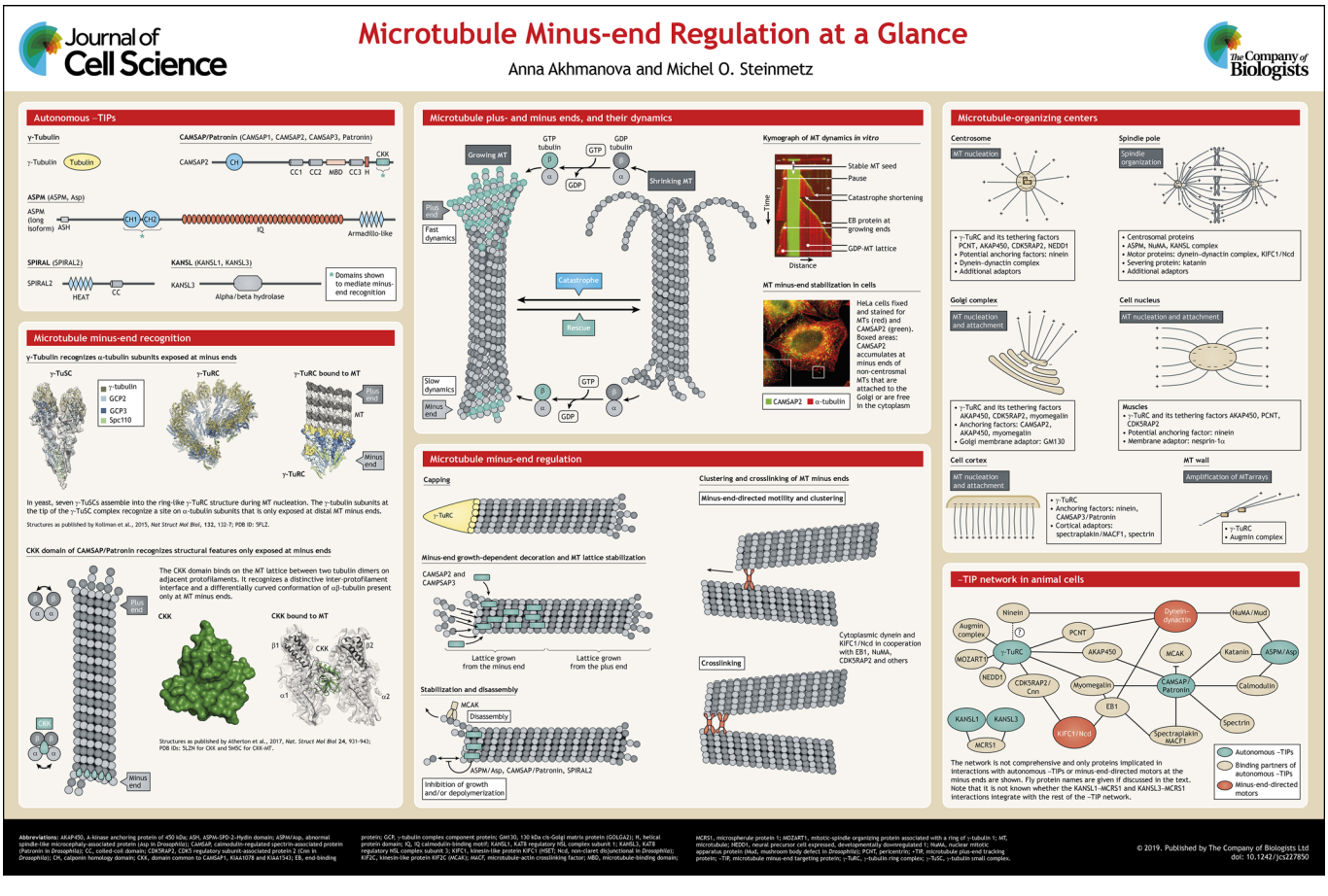
## Introduction

Microtubules are highly dynamic polymeric filaments that are required for a diverse array of essential cellular processes, such as cell division, motility and determination of cell shape. Microtubules participate in these functions by serving as scaffolds for organelle positioning and intracellular transport, and by exerting pulling and pushing forces on different subcellular structures. Microtubules assemble from dimers of α- and β-tubulin that align head-to-tail to form protofilaments, which associate laterally into tubes. This particular arrangement, together with the property that the



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αβ-tubulin heterodimer is asymmetric, leads to the intrinsically polarized microtubule structure comprising two distinct ends (see poster). The end where α-tubulin is exposed (termed the minus end) grows slowly *in vitro*, whereas the opposite end where β-tubulin faces into solution (termed the plus end) grows rapidly (Desai and Mitchison, 1997; Nogales and Wang, 2006). Both microtubule ends can switch between phases of growth and shrinkage, a process that depends on GTP hydrolysis on β-tubulin (Desai, and Mitchison, 1997). In cells, microtubule plus ends are responsible for the formation of the microtubule mass and for dynamic interactions with different subcellular structures. In contrast, the minus ends determine the geometry of microtubule networks because they are often stably anchored at sites where microtubules are nucleated (Akhmanova and Steinmetz, 2015; Martin and Akhmanova, 2018). A number of specific microtubule minus-end regulators have been identified. It is becoming increasingly clear that they represent a structurally and functionally diverse group of factors that control microtubule organization and, thus, play a crucial role in defining cell architecture. In this review and the accompanying poster, we provide an overview of the current knowledge on the structure, interactions and functions of cellular factors that specifically interact with microtubule minus ends, and that regulate their dynamics and organization.

## Structure and dynamics of microtubule minus ends

Microtubule ends differ from the regular microtubule lattice in two main ways. First, the β-tubulin subunit of freshly added tubulin dimers is bound to GTP; such dimers form a stabilizing cap at both growing plus- and minus ends (referred to as 'GTP cap'; see poster). Within microtubule shafts, GTP is hydrolyzed to GDP, which leads to destabilization of the microtubule lattice and, eventually, to microtubule disassembly (Desai and Mitchison, 1997). Second, tubulin protofilaments at plus- and minus ends can have variable lengths and curvatures (Cross, 2019). Similar to plus ends, minus ends switch between periods of growth and shrinkage, albeit at slower rates. Minus ends can also exhibit pausing, a behavior that is not observed at plus ends *in vitro* (Doodhi et al., 2016; Erickson and O'Brien, 1992; Walker et al., 1988). In line with the higher stability of minus ends compared to that of plus ends, removal of the GTP cap by severing leads to the rapid disassembly of plus ends, whereas minus ends are more stable and can readily re-grow (Walker et al., 1989).

## Microtubule nucleation by the γ-tubulin ring complex and associated components

Tubulin addition in cells occurs mainly at microtubule plus ends, whereas microtubule minus ends often remain associated with their original nucleation sites. One reason for this behavior is that the key microtubule nucleator, the γ-tubulin ring complex (γ-TuRC), caps microtubule minus ends by binding to their exposed α-tubulin subunits (reviewed by Kollman et al., 2011; see poster).

In budding yeast, the ring-like γ-TuRC structure assembles during microtubule nucleation from γ-tubulin small complexes (γ-TuSCs) that contain the γ-tubulin complex component proteins 2 and 3 (GCP2 and GCP3, respectively) (Kollman et al., 2015; Kollman et al., 2010). In many other organisms, the γ-TuRC complex is pre-assembled by additional components, including the γ-tubulin-binding proteins GCP4, GCP5 and GCP6. GCPs associate with additional factors, such as Spc110 in yeast, and mitotic-spindle organizing protein associated with a ring of γ-tubulin 1 (MOZART1, officially referred to as MZT1) and neural precursor cell expressed, developmentally downregulated 1 (NEDD1) in mammals (reviewed by Tovey and Conduit, 2018). The microtubule-nucleating activity of γ-TuRC and its localization strongly depend on multiple tethering factors and adaptors, including the mammalian proteins pericentrin (PCNT), A-kinase anchoring protein of 450 kDa (AKAP450, officially known as AKAP9), myomegalin and CDK5 regulatory subunit associated protein 2 (CDK5RAP2; Cnn in *Drosophila* (Tovey and Conduit, 2018). Association of these components with additional molecular scaffolds leads to the clustering of γ-TuRC complexes and microtubule regulators. This assembly process results in the formation of microtubule-organizing centers (MTOCs), such as animal centrosomes, fungal spindle pole bodies and related structures in other organisms (Ito and Bettencourt-Dias, 2018; see poster).

Another γ-TuRC-interacting component is the augmin (HAUS in mammals) complex, comprising eight protein subunits and mediating microtubule nucleation from the lateral surfaces of pre-existing microtubules (Petry et al., 2013; Song et al., 2018). Augmin participates in amplification of parallel microtubule arrays in mitotic spindles, neurons and at the cortex of plant cells (Cunha-Ferreira et al., 2018; Goshima et al., 2008; Sánchez-Huertas et al., 2016; Sánchez-Huertas and Luders, 2015; Yi and Goshima, 2018).

## Proteins specifically targeting free microtubule minus ends

γ-TuRC blocks the exchange of tubulin dimers at minus ends (Wiese and Zheng, 2000); however, not all microtubule minus ends in cells are capped. For example, spindle microtubules slowly disassemble at the minus ends and elongate at the plus ends, a process that leads to the poleward flux of microtubule polymers (Borgal and Wakefield, 2018; Rogers et al., 2005). In interphase, the disassembly of free microtubule minus ends contributes to the turnover of radial centrosomal microtubule arrays (Rodionov et al., 1999).

A number of proteins can interact with dynamic microtubule minus ends and affect their stability; together with γ-TuRC, such specific minus-end targeting proteins were termed −TIPs (Akhmanova and Hoogenraad, 2015). Among these, the members of the calmodulin-regulated spectrin-associated protein (CAMSAP) family in mammals and Patronin in invertebrates have recently received substantial attention (see poster). The ability of these proteins to recognize microtubule minus ends depends on their C-terminal domain common to CAMSAP1, KIAA1078 and KIAA1543 (CKK); however, an autonomous minus-end tracking activity has also been observed for a coiled-coil region of *Drosophila* Patronin (Hendershott and Vale, 2014; Jiang et al., 2014; Atherton et al., 2017). Depending on the family member, CAMSAP/Patronin proteins either track growing microtubule minus ends (CAMSAP1), bind to minus ends to inhibit their growth (*Drosophila* Patronin), or specifically bind to lattice stretches formed by minus-end growth (CAMSAP2 and CAMSAP3) (Hendershott and Vale, 2014; Jiang et al., 2014). While the function of CAMSAP1 is still not clear, CAMSAP2 and CAMSAP3 slow down but do not block minus-end polymerization and form stabilized microtubule stretches that can promote repeated plus-end outgrowth (Hendershott and Vale, 2014; Jiang et al., 2014). CAMSAPs thus stabilize microtubule ends in a manner dependent on minus-end polymerization (Jiang et al., 2014). Whether microtubule minus-end stabilization by Patronin is associated with some tubulin addition at the minus end is currently unclear. In worms and mammals, the activity of CAMSAPs is mainly important for generating non-centrosomal microtubule arrays in differentiated interphase cells, such as epithelial cells or neurons, whereas in *Drosophila*, Patronin regulates minus-end stability both in interphase and mitosis (Chuang et al., 2014; Derivery et al., 2015;

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Goodwin and Vale, 2010; Jiang et al., 2014; Marcette et al., 2014; Nashchekin et al., 2016; Richardson et al., 2014; Tanaka et al., 2012; Toya et al., 2016; Wang et al., 2013; Yau et al., 2014).

Another protein that can autonomously recognize dynamic microtubule minus ends and inhibit their growth is abnormal spindle-like microcephaly-associated protein (ASPM; Asp in *Drosophila*) (Jiang et al., 2017) (see poster). It localizes to spindle poles and is required for spindle organization, spindle positioning and cytokinesis (Higgins et al., 2010; Saunders et al., 1997; van der Voet et al., 2009; Wakefield et al., 2001). For example, in *Drosophila*, Asp is essential for spindle pole focusing, likely due to its microtubule minus-end binding and crosslinking activities (Ito and Goshima, 2015; Schoborg et al., 2015). In mammals, ASPM affects spindle architecture in more subtle ways, as its activity appears to be somewhat redundant with centrosomal components (Higgins et al., 2010; Jiang et al., 2017; Tungadi et al., 2017). ASPM has been intensively studied because it is encoded by a gene that is frequently mutated in microcephaly, a human brain development disorder (Bond et al., 2002).

Completely different minus-end regulators in vertebrates are components of an interphase chromatin-associated protein complex termed KANSL that contains the KAT8 regulatory NSL complex subunits 1 and 3 (KANSL1 and KANSL3), which can recognize the minus ends of stabilized microtubules (Meunier et al., 2015). The KANSL complex contains another factor, the microspherule protein 1 (MCRS1), which shows no minus-end preference on its own but participates in spindle formation by promoting minus-end stability of kinetochore fibers (Meunier et al., 2015; Meunier and Vernos, 2011). The activity of the KANSL complex on dynamic minus ends *in vitro* has not yet been described.

Plants express the microtubule minus-end regulator SPIRAL2 that is structurally unrelated to the −TIPs described above. This protein autonomously recognizes minus ends, slows down minus-end depolymerization in plant cells and inhibits minus-end dynamics *in vitro* (Fan et al., 2018; Leong et al., 2018; Nakamura et al., 2018). SPIRAL2 also binds to plus ends and affects their dynamics, but this interaction possibly depends on additional binding partners (Fan et al., 2018).

## Minus-end regulators that can interact with both microtubule ends

In addition to the specific minus-end regulators discussed above, a number of proteins show association with both microtubule ends. End-binding (EB; MAPRE) proteins, for example, are classified as microtubule plus-end tracking proteins (+TIPs) based on their localization behavior in cells; however, *in vitro,* EBs autonomously track growing microtubule plus- and minus ends, because they show strong preference for the GTP or GDP-Pi cap (Bieling et al., 2007; Maurer et al., 2012; Zhang et al., 2015). The size of this cap decreases at low microtubule growth rates, and thus under physiological conditions, the actual minus-end accumulation of the EBs, as well as that of the numerous partners they can recruit to microtubule tips, is low (Akhmanova and Steinmetz, 2015).

Other proteins, such as members of the microtubule depolymerase kinesin-13 family or the microtubule-severing enzyme katanin, can show preference to microtubule ends possibly because of the increased protofilament curvature present at this location (Asenjo et al., 2013; Jiang et al., 2017). These proteins can either compete or cooperate with specific microtubule minus-end regulators (see poster). For example, the microtubule depolymerase activity of the members of the kinesin-13 family, such as the mitotic centromere-associated kinesin (MCAK; officially known as KIF2C), is counteracted by CAMSAP/Patronin as well as by the KANSL complex (Atherton et al., 2017; Goodwin and Vale, 2010; Meunier and Vernos, 2011). Katanin, on the other hand, can specifically bind to CAMSAPs and ASPM and cooperate with them by inhibiting microtubule minus-end growth (Jiang et al., 2014; Jiang et al., 2017).

Another important microtubule minus-end associated protein is the nuclear mitotic apparatus protein 1 (NUMA1, hereafter referred to as NuMA; known as mushroom body defect, Mud, in *Drosophila*), which acts in complex with cytoplasmic dynein and dynactin (Merdes et al., 1996). NuMA contains a microtubule-binding domain that associates with both microtubule plus- and minus ends *in vitro* (Seldin et al., 2016). In mitotic cells, NuMA can be recruited to freshly severed microtubule minus ends independently of dynein and other known mitotic minus-end regulators and plays a key role in focusing microtubule minus ends at spindle poles (Hueschen et al., 2017). The origin of the microtubule minus-end preference of NuMA is currently unclear.

## Minus-end directed motors in microtubule organization

Microtubule minus-end directed motors, cytoplasmic dynein and members of the kinesin-14 family, such as kinesin expressed in human spleen, embryo and testes (HSET) – officially known as kinesin family member C1 (KIFC1) in mammals and non-claret disjunctional (Ncd) in *Drosophila* – are targeted to minus ends due to their minus-end-directed motor activity (She and Yang, 2017; Tan et al., 2018 and references therein). In cooperation with additional proteins, such as NuMA, EB1 or CDK5RAP2 (Chavali et al., 2016; Goshima et al., 2005; Merdes et al., 1996), these motors can cluster and crosslink microtubule minus ends, an activity that is essential for the formation of a bipolar spindle during cell division (reviewed by Borgal and Wakefield, 2018; Hentrich and Surrey, 2010; Maiato and Logarinho, 2014; Tan et al., 2018). Furthermore, cytoplasmic dynein can bind to different MTOC components involved in microtubule nucleation and anchoring, such as PCNT or ninein (Purohit et al., 1999; Redwine et al., 2017). By doing so, dynein concentrates these factors in the vicinity of minus ends and thereby promotes MTOC formation (Balczon et al., 1999; Burakov et al., 2008; Hori and Toda, 2017).

## Mechanisms of specific microtubule minus-end recognition

In contrast to proteins that interact with both microtubule ends, our understanding of specific minus-end binders is much less advanced. These proteins are supposed to recognize structural features that are only present at minus ends and not at plus ends. One such prominent feature that is only exposed at minus ends is the surface of α-tubulin, which is involved in longitudinal tubulin-tubulin interactions along protofilaments. This surface is recognized by the γ-tubulin subunits of the γ-TuRC complex, which readily explains the specificity of the γ-TuRC towards minus ends (reviewed by Kollman et al., 2011; see poster).

Microtubule plus ends are also distinguished from the minus ends by the distinctive interactions that α- and β-tubulin subunits establish across adjacent protofilament as a result of the polar head-to-tail arrangement of curved αβ-tubulin dimers (reviewed by Brouhard and Rice, 2014). These structural features (i.e. distinct nature of the inter-protofilament interface and the characteristic curvature of protofilaments) are recognized by the globular CKK domain of CAMSAP/Patronin family members, which binds between two tubulin dimers from neighboring protofilaments at minus ends (Atherton et al., 2017) (see poster). The current model is that the tighter interaction of CKK with β-tubulin disfavors binding at microtubule plus ends, while the looser α-tubulin contacts

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preferentially accommodate tubulin curvature at minus ends (Atherton et al., 2017). For other autonomous −TIPs, the mechanisms of minus-end recruitment are currently unknown due to lack of structural information.

### Microtubule minus-end anchoring to subcellular structures

The most important activity of microtubule minus-end regulators is to form different types of MTOCs (see poster). Among these, the animal centrosome is the best-studied example. It is formed around a pair of microtubule-based cylinders called centrioles, which are surrounded by the pericentriolar matrix (PCM). In addition to γ-TuRC and various proteins that can tether and activate it, the PCM contains proteins that promote microtubule nucleation and growth, such as the microtubule polymerase colonic and hepatic tumor overexpressed gene [chTOG in mammals, officially known as CKAP5; also known as *Xenopus* microtubule-associated protein of 215 kDa (XMAP215)]. PCM also contains microtubule-anchoring factors and proteins that act as a 'glue' between centrosomal components and bridge them to the centriole wall, such as PCNT, and CEP152 and CEP192 (asterless and Spd-2, respectively, in *Drosophila*) (in *Drosophila*) (reviewed by Conduit et al., 2015; Varadarajan and Rusan, 2018). Centrosomes are membrane-free organelles that can be regarded as condensates of PCM proteins that self-assemble around centrioles through multivalent interactions and concentrate tubulin to promote microtubule formation (Woodruff et al., 2017). At least in some cases, such as the very large mitotic centrosomes in worm embryos, where γ-TuRC was shown to be dispensable (Hannak et al., 2002), the function of centrosomes in concentrating proteins rather than the γ-TuRC activity might be key for microtubule nucleation (Woodruff et al., 2017). However, in order to from a radial plus-end-out microtubule array, enhanced microtubule nucleation at the centrosome must be accompanied by stable anchoring of newly generated minus ends. The biochemical basis of this process is still rather obscure. The γ-TuRC-tethering protein NEDD1 is one potential candidate involved in microtubule anchoring at centrosomes as it can tether minus ends to ectopic locations (Muroyama et al., 2016). Another protein frequently implicated in minus-end anchoring at both centrosomes and non-centrosomal sites is ninein (Goldspink et al., 2017; Kowanda et al., 2016; Mogensen et al., 2000; Wang et al., 2015); however, it is unclear whether ninein can recognize γ-TuRC-bound or -free microtubule minus ends.

The same organizing principles likely apply to other MTOCs. For example, the Golgi membranes can recruit γ-TuRC and nucleate microtubules through a complex that consists of AKAP450 and CDK5RAP2 and/or myomegalin, but require a CAMSAP2-AKAP450-myomegalin complex for minus-end anchoring (Rivero et al., 2009; Wu et al., 2016) (see poster). Importantly, even the combination of these two complexes is not sufficient for the MTOC function of the Golgi complex. Additional microtubule-binding proteins such as the +TIPs EBs and cytoplasmic linker associated proteins (CLASPs) are required to nucleate and tether microtubule minus ends at Golgi membranes (Efimov et al., 2007; Yang et al., 2017), suggesting that multiple weak interactions are involved in this process. In epithelial cells as well as in *Drosophila* oocytes, microtubule minus ends are tethered to the actin-rich cell cortex, and depending on the particular system, γ-TuRC-, ninein- or CAMSAP/Patronin-dependent complexes or combinations thereof have been reported (Goldspink et al., 2017; Khanal et al., 2016; Nashchekin et al., 2016; Noordstra et al., 2016; Toya et al., 2016; Wang et al., 2015). A network of γ-TuRC-binding factors and centrosomal proteins – including AKAP450, PCNT and ninein – participates in microtubule minus-end organization at the nuclear envelope of muscle cells (Bugnard et al., 2005; Gimpel et al., 2017; Tassin et al., 1985). Furthermore, in *Drosophila* oocytes γ-tubulin, Mud (NuMA homolog) and Asp participate in organizing the perinuclear MTOC (Januschke et al., 2006; Tissot et al., 2017). Other membrane organelles can also contribute to MTOC formation; for example, mitochondrial derivatives in *Drosophila* spermatids perform an MTOC function that is dependent on γ-TuRC and on a testis-specific non-centrosomal isoform of Cnn (CnnT; Chen et al., 2017). The presence of multicomponent complexes that form through multivalent interactions and exhibit properties of non-membrane-bound protein condensates or phase-separated, liquid droplets might be a general physicochemical feature of MTOCs, including spindle poles in animals (Borgal and Wakefield, 2018) or mitotic MTOCs, such as the polar caps and polar organizers in plants (Yi and Goshima, 2018).

### Drugs that can perturb microtubule minus ends

Microtubule-targeting agents (MTAs) are among the most important drugs used to treat cancer. It is thought that at low, therapeutically relevant concentrations, MTAs primarily suppress microtubule dynamics by perturbing both microtubule plus- and minus ends (reviewed by Dumontet and Jordan, 2010). Dozens of different chemical classes of MTA are known, and six different tubulin-binding sites – and, accordingly, modes of action – have been described so far (reviewed by Steinmetz and Prota, 2018). Most MTAs target β-tubulin and are, thus, expected to perturb predominantly microtubule plus ends (e.g. paclitaxel, maytansine, eribulin). Other drugs bind simultaneously to both the α- and β-tubulin subunits, either within the tubulin dimer (e.g. colchicine, combretastatin) or in between two longitudinally aligned tubulin dimers (e.g. vinblastine, auristatin). The MTA pironetin, however, binds covalently to a cysteine residue of α-tubulin and causes perturbations of secondary structure elements that are critically involved in longitudinal tubulin-tubulin interactions in microtubules (Prota et al., 2016; Yang et al., 2016). Pironetin, thus, potentially blocks microtubule minus-end growth by inhibiting the addition of tubulin dimers.

Another compound that can affect microtubule minus-end regulation is gatastatin, which binds to γ-tubulin and inhibits microtubule nucleation (Chinen et al., 2015). This property of gatastatin can be exploited in order to dissect the relative importance of γ-TuRC-dependent and -independent nucleation pathways; however, the interpretation of results in cells might be complicated by the fact that this compound also has some affinity for αβ-tubulin (Chinen et al., 2015).

### Perspectives

Genetics and cell biology studies have led to the establishment of a list of −TIPs that control microtubule minus-end organization. However, biochemical and mechanistic studies of −TIPs are lagging behind – even our understanding of the structure and dynamics of microtubule minus ends is limited. Concerted studies have recently identified a number of autonomous −TIPs but this list is likely to be incomplete, especially if one takes into account that specific regulators can be represented by different isoforms with divergent properties. Furthermore, the structural basis of microtubule minus-end recognition, the activity of most of the known −TIPs, and how −TIPs and +TIPs cooperate to regulate microtubule minus ends still need to be defined and represent exciting new areas of future research.

It is also becoming increasingly clear that MTOCs are multicomponent structures formed by dynamic protein networks with multivalent and partially redundant interactions. The concept

of 'phase separation', leading to the generation of liquid-like protein droplets or condensates, turned out to be helpful in describing and understanding the physicochemical principles of MTOC biogenesis (reviewed by Woodruff et al., 2018). Notably, recent work showed that many proteins easily undergo phase separation at high concentrations and in the presence of crowding agents (Woodruff et al., 2018). The current challenge is to assess the physiological relevance of such processes by systematically comparing *in vivo* and *in vitro* experiments, for example, by generating mutants that perturb specific interaction nodes within −TIP networks. The combination of biochemical reconstitutions, structural studies and cell biological assays that employ genetic modifications of −TIPs will eventually lead to a comprehensive understanding of this essential aspect of cell architecture.

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