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Review Article

Microtubules pull the strings: disordered sequences as efficient couplers of microtubule-generated force

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Microtubules are dynamic polymers that grow and shrink through addition or loss of tubulin subunits at their ends. Microtubule ends generate mechanical force that moves chromosomes and cellular organelles, and provides mechanical tension. Recent literature describes a number of proteins and protein complexes that couple dynamics of microtubule ends to movements of their cellular cargoes. These 'couplers' are quite diverse in their microtubule-binding domains (MTBDs), while sharing similarity in function, but a systematic understanding of the principles underlying their activity is missing. Here, I review various types of microtubule couplers, focusing on their essential activities: ability to follow microtubule ends and capture microtubule-generated force. Most of the couplers require presence of unstructured positively charged sequences and multivalency in their microtubule-binding sites to efficiently convert the microtubule-generated force into useful connection to a cargo. An overview of the microtubule features supporting end-tracking and force-coupling, and the experimental methods to assess force-coupling properties is also provided.

Introduction

Cells actively rearrange themselves during the life cycle: vesicles and organelles get transported, membranes get remodelled, chromosomes get separated. Many of these movements are driven by microtubule dynamics, with cell division being the best studied context for microtubule-generated force (reviewed in [1]). Microtubules are 25-nm wide hollow tubes built from α- and β-tubulin heterodimers, and are constantly growing or shortening from their ends through addition or removal of tubulin dimers, respectively. Microtubule dynamics are linked to the nucleotide hydrolysis: GTP-bound tubulin binds to the end of the microtubule and later hydrolyzes GTP to GDP inside the microtubule lattice. If GDP-containing tubulin stochastically crowds out the GTP-tubulin, the microtubule end switches to shortening (reviewed in [2]).

Tubulin dimers and bigger oligomers are bent in solution, but in the microtubule lattice they straighten as they bind to the neighbouring tubulin dimers [3] (Figure 1). Interestingly, the bent shapes of tubulin protofilaments at both growing and shortening microtubules are similar [3] (Figure 1). The microtubule end presents a unique interface in which transitions of tubulin shape from bent (at the end) to straight (in the lattice) and back are coupled to the energy released during GTP hydrolysis. The mechano-chemical link between GTP hydrolysis and dynamics of tubulin protofilaments allows the microtubules to exert force on a cargo with their ends (Figure 1).

Shortening microtubules provide the driving force for chromosome segregation in mitosis [1,5]. Microtubule growth can also generate force (reviewed in [6]) and redistribute membranous networks, such as ER [7–9] or mitochondria [10,11]. Microtubule-generated force is transmitted to the cellular cargoes though microtubule couplers: proteins and protein complexes that harness the energy released during stochastic cycles of microtubule growth and shortening, and convert it into organized motility of cellular cargoes.

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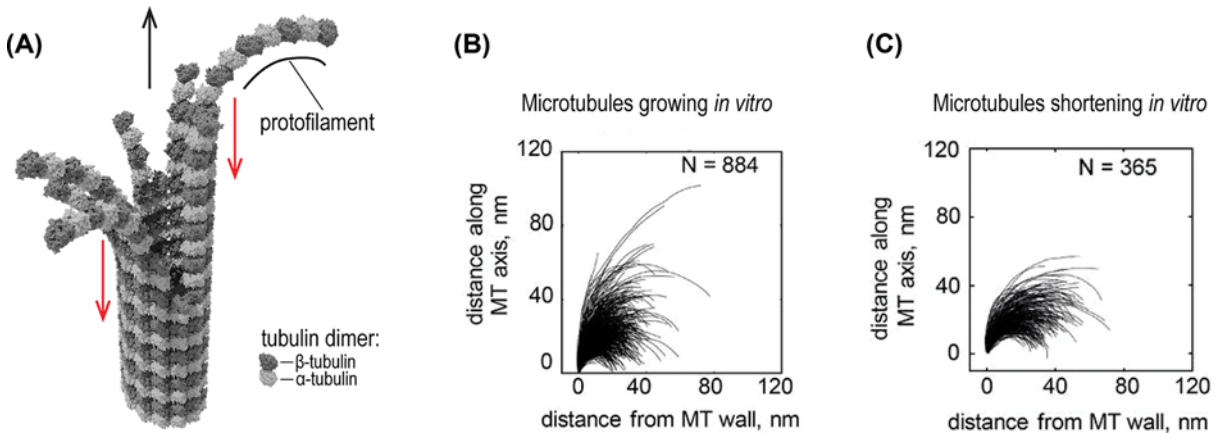

Figure 1. Structure of a dynamic microtubule end

(**A**) A microtubule end is characterized by protofilaments, linear strands of tubulin dimers, bending outward. Shortening microtubule end generates force thanks to the power strokes of individual protofilaments pushing a cargo in the direction of microtubule shortening (red arrows). Microtubule growth can also generate force (black arrow). The microtubule image is produced from coordinates obtained in a coarse-grained molecular dynamics simulation (courtesy of Nikita Gudimchuk [3]), rendered using tubulin structure from [4]. (**B**,**C**) Shapes of tubulin protofilaments obtained from cryo-electron tomographic reconstructions. Whether the microtubules are growing (B) or shrinking (C), the shapes of the tubulin curls at the microtubule ends are not significantly different (reproduced with permission from [3] ©Rockefeller University Press).

Table 1 Length, charge, and amino acid composition of disordered microtubule-binding sequences.

	Length, a.a.	pI	Positive a.a. (RKH, %)	Polar a.a. (GQNS, %)	Hydrophobic a.a. (AVIL, %)	Negative a.a. (DE, %)
Ndc80 human tail	81	10.84	21.0	39.5	16.0	6.2
Ndc80 yeast tail	80	11.88	17.5	36.3	17.5	3.8
CENP-Q tail	67	10.43	31.3	29.9	20.9	9.0
Dam1 C-terminus	189	10.11	20.1	32.3	20.1	11.1
Duo1 C-terminus	68	12.61	23.5	30.9	19.1	0.0
CENP-F C-terminus	221	10.28	17.2	29.0	22.2	9.5
KKT4 linker	258	10.28	12.8	33.3	22.1	5.8
MACF2 Cterminus	43	11.85	27.9	23.3	14.0	4.7
KA7	14	10.78	50.0	0.0	50.0	0.0
XMAP215 linker	82	9.94	17.1	31.7	14.6	7.3
Clasp2 linker	330	10.54	15.2	38.2	25.2	7.9
CENP-E tail	190	9.2	18.4	30.5	19.5	11.1
Abl2 linker	131	4.84	9.9	19.1	26.0	13.0

Abbreviations: CENP, centromere protein; MACF2, microtubule-actin cross-linking factor 2.

In this review, I focus on the ability of microtubule couplers to keep attachment to the microtubule end as it shortens, an activity I will refer to as 'end-tracking'. Persistent, or processive, end-tracking requires that the coupler constantly breaks connections with a protofilament or a microtubule and rebinds again more distal from the initial position of the microtubule end, so multivalency of microtubule-binding sites is important. For many of the couplers described below, the multivalency is provided by the presence of multiple copies of a microtubule-binding protein bound to a cargo. Since the first demonstrations of the end-tracking by purified chromosomes [12], only a few recombinant proteins or protein complexes were shown to support motility with the shortening microtubule ends (summarized in Figure 2). These couplers have a diverse set of microtubule-binding domains (MTBDs), including globular domains with specific folds, completely unstructured microtubule-binding sequences, or combinations of folded and unstructured domains. Two characteristics that seem common to most of microtubule couplers are (1) disordered positively charged sequences (summarized in Table 1), and (2) multiple MTBDs to follow microtubule shortening.

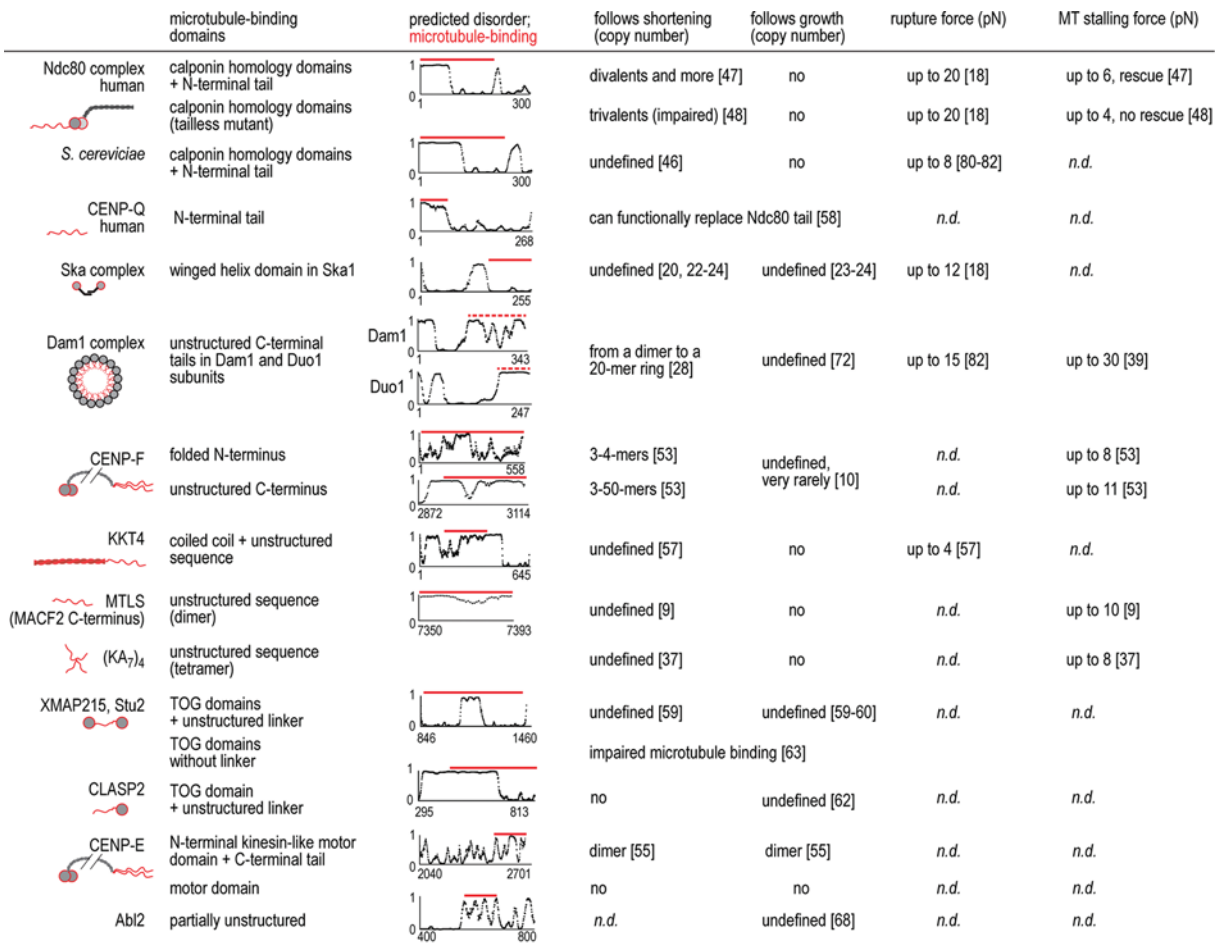

Figure 2. Overview of microtubule end-couplers

(**A**) A summary of end-tracking and force-coupling complexes discussed in the text. Graphs show the probability of disordered sequence from 0 (improbable) to 1 (probable) on y-axis and sequence position on x-axis, as predicted by DISOPRED3 [13]. Red colour denotes the known microtubule-binding regions in the cartoons and on top of the disorder prediction plots. See text for detailed discussion of the differences between the rupture and stalling forces. 'n.d.' equals 'not determined'.

Overview of microtubule couplers

Couplers with folded domains

Ska complex

Any generic microtubule-associated protein, including the ones without end-tracking properties, might occasionally produce motion of a cargo [1]. However, processive tracking of depolymerizing microtubule ends is rare among microtubule-associated proteins with folded MTBDs. To date the only efficient end-tracker that does not require contributions from intrinsically disordered regions is the Ska complex, a metazoan kinetochore component that is loaded onto the microtubule-kinetochore interface late in mitosis and is required for proper segregation of chromosomes [14,15]. SKA123 complex binds microtubules through the C-terminal winged-helix domain of SKA1 [16,17]. SKA3 subunit carries an extensive disordered region, which is however not required for interaction between Ska complex and microtubules [18,19]. The end-tracking ability of Ska complex is attributed to its higher affinity for bent tubulin, which is present at the microtubule ends, compared with straight tubulin in the microtubule lattice [20]. Importantly, affinity for microtubule ends alone is insufficient for end-tracking since the end-bound coupler needs to rebind as the microtubule shortens [21]. Consistently with this, Ska was shown to end-track if oligomerized on the surface of the bead [22]. In the absence of a cargo, fluorescent Ska particles were following both microtubule growth and shortening, however it is unknown if individual molecules of Ska also have this ability [20,23,24]. Enrichment of Ska at the ends of microtubules depended on positively charged amino acids in SKA1 MTBD: K223A,

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R155A and R236A substitutions abolished enrichment of Ska at the both growing and shortening microtubule ends, and K183/184A double substitution preferentially impaired enrichment at growing microtubule ends, while still supporting end-tracking with microtubule shortening [23]. These observations suggest that both affinity to microtubule ends, and potentially presence of multiple copies of Ska are required for efficient end-tracking.

Couplers with only unstructured microtubule-binding sequences

Dam1/DASH complex

One of the first complexes shown to follow microtubule ends autonomously was Dam1/DASH [25]. Dam1 complex is a kinetochore component present in fungi and is essential for viability of *Saccharomyces cerevisiae* [26]. Dam1 oligomerizes into rings around microtubules [27], but can also end-track as smaller, non-ring oligomers [28]. Dam1 and Ska complexes are considered to be functional paralogs, because they are not related and they do not coexist in the same species, while performing the same function of enhancing Ndc80-microtubule attachment in the kinetochore [22,29]. The principal unit of Dam1 is a heterodecamer which binds to microtubules through the protrusion connecting the ring with the microtubule surface [30]. This protrusion is thought to be formed by positively charged disordered C-terminal tails of Dam1 and Duo1 subunits [31–33] (Figure 2 and Table 1), and is crucial for tight binding to microtubule and efficient force-coupling [34], although the contributions from other subunits are also possible [35].

Microtubule-actin cross-linking factor 2 and $(KA7)_4$

Two completely disordered sequences with a net positive charge have been shown to promote microtubule end-tracking and capture microtubule-generated force. One is a peptide containing 43 C-terminal amino acids of human microtubule-actin cross-linking factor 2 (MACF2/dystonin) [36]. MACF2 C-terminal peptide was present in multiple copies on the surface of a quantum dot or a glass bead enabling these cargoes to follow microtubule shortening [9]. $KA7_4$ is a tetravalent particle containing fully synthetic peptide with seven repeats of lysine and alanine [37]. All the three unstructured couplers have been also shown to capture considerable force from shortening microtubule ends [9,37], with Dam1 being the absolute champion thanks to its ring shape, also providing multivalency, and tight binding to the microtubule [38,39] (Figure 2).

Couplers with combinations of folded and unstructured domains

Ndc80 complex

Ndc80 complex is a kinetochore component in majority of eukaryotes and is essential for their viability since it provides the main link between kinetochores and microtubule ends [40,41]. Ndc80's MTBD consists of a folded calponin homology (CH) domain and an unstructured N-terminal tail, both containing positively charged amino acids (Table 1). Ndc80 tail also contains multiple sites for phosphorylation by Aurora B kinase [42,43]; Ndc80 with phosphorylated tail binds microtubules with lower affinity, highlighting the importance of the charge in Ndc80 tail for the kinetochore function [44]. The contribution of multivalency to Ndc80's end-tracking has been appreciated for a decade [45,46], but it was only recently established that as few as two Ndc80 copies joined together are sufficient to end-track, while multiple Ndc80 di- and trivalents bound to glass beads stall and rescue microtubule shortening [47]. In the context of an Ndc80 trivalent the CH-domain is required for stable binding to the microtubule lattice, while the presence of the Ndc80 tail and its overall charge contributes to the trivalent's ability to follow the shortening microtubule ends and to rescue microtubule shortening under force [48].

Centromere protein F

Another example of an efficient coupler is centromere protein F (CENP-F), a component of the corona, a fibrous protein network expanding at the kinetochore at the onset of mitosis [49]. CENP-F regulates interactions between the corona and the microtubules, and is also found at the mitochondria and at the nuclear pores [11,50,51]. Despite its multiple localizations, CENP-F is not essential for viability, and its deletion has a very mild mitotic phenotype [50,52]. CENP-F contains an N-terminal microtubule-binding site with a unique fold and an increased affinity for bent tubulin, and an unstructured positively charged C-terminal tail binding preferentially to straight tubulin [53] (Table 1). When present in multiple copies on the surface of a cargo, both N- and C-terminal MTBDs follow microtubule growth and shortening and capture the force generated by microtubule shortening [10,53].

CENP-E

CENP-E is a potential paralog of CENP-F with a kinesin-like motor domain at the N-terminus and an unstructured positively charged C-terminal tail [49,51] (Table 1). CENP-E is a component of corona and is important for chromosome congression in mitosis [54]. The C-terminal tail is required to retain the CENP-E molecule at the microtubule plus-end if its N-terminal plus-end directed motor domain walks off the microtubule tip [55]. The combination of the motor and the unstructured tail domains allows CENP-E to stay bound to both growing and shortening microtubule ends, but CENP-E's ability to capture microtubule-generated force has not been reported.

KKT4

Kinetoplastids build a kinetochore that is completely unrelated to any other eukaryote group [56]. However, the principal microtubule-binding protein in trypanosomes, KKT4, shares the pattern with the proteins described above: its microtubule-binding site contains an unstructured positively charged sequence and a folded helical domain (Table 1). This domain combination enables KKT4 to follow shortening microtubule in single-molecule conditions in the absence of force, and against the opposing force when multiple copies of KKT4 are bound to a bead [57].

Potential end-couplers with disordered microtubule-binding sequences

CENP-Q

A component of human kinetochore, was shown to bind microtubules through its N-terminal unstructured sequence [58]. Chromosome congression defects caused by the deletion of CENP-Q^{1-67} could be rescued by fusion of $NDC80^{1-80}$ instead. These observations suggest functional similarity between the N-terminal tails of Ndc80 and CENP-Q, but it remains to be tested whether CENP-Q can follow microtubule shortening on its own, and whether folded domains contribute to CENP-Q's interaction with microtubules.

TOG-domain proteins

Conserved globular TOG-domains bind to the very ends of bent tubulin protofilaments at the microtubule tip. TOG-domain proteins enhance microtubule growth, like homologous proteins XMAP215 (*Xenopus laevis*) and Stu2 (*S. cerevisiae*) [59,60], or stabilize microtubule ends, like CLASP proteins [61,62]. However, at least in the case of XMAP215, the efficient binding to the microtubule requires an unstructured positively charged linker between TOG4 and TOG5 [63] (Table 1). Beads coated with multiple copies of XMAP215 could be transported by growing microtubule ends against a small opposing force [64], but it is unknown whether XMAP215 captures the force released during microtubule shortening. Stu2, a budding yeast homolog of XMAP215, plays an important role at the kinetochore-microtubule interface by enhancing the sensitivity of purified kinetochores to tension [65].

Another protein in this group is Abl2 tyrosine kinase, which can phosphorylate XMAP215 and CLASP [66,67], and was shown to interact with microtubules directly and sometimes follow the growing microtubule ends [68]. Microtubule-binding of Abl2 requires a central unstructured region that is not positively charged, contrary to all other examples described above. Finally, it should be mentioned that XMAP215 was shown to follow shortening microtubule ends, but it was not shown for CLASP or Abl2, and their force-coupling properties are also unclear.

Microtubule features supporting end-tracking and force capture

The shortening ends of microtubules are characterized by tubulin protofilaments bending outward in a shape resembling 'ram's horns' and generating power strokes as microtubule disassembles [69,70] (Figure 1A). One of the force-coupling models discussed in the literature proposes that the couplers bind bent tubulin with high affinity to transform the power strokes into processive motion of the cargo [21,71] (Figure 3A). Indeed, some of the couplers described above bind bent tubulin preferentially, like Ska, N-terminus of CENP-F or CLASP [20,53]. However, not all proteins that have this property follow microtubule shortening, while many efficient force-couplers bind preferentially to the straight tubulin lattice in bulk biochemical assays, like Ndc80 [20], C-terminus of CENP-F [53] or Dam1, which follows microtubule ends thanks to its increased affinity for GTP-tubulin [72].

The relation between the affinity for bent tubulin and the end-coupling properties is further complicated by the observations that tubulin protofilaments at the growing microtubule ends are as bent as at the shortening ones [3] (Figure 1). If specific affinity is the only feature necessary for the end tracking, the couplers should follow the growing ends as efficiently as the shortening ones. While this bidirectional tracking has been observed for XMAP215 [59], and to a lesser extent for Ska [23,24], other couplers with preference for bent tubulin are unidirectional: N-terminus of CENP-F moves with the shortening microtubules [53] with rare exceptions [10], while Stu2 and a single TOG-domain

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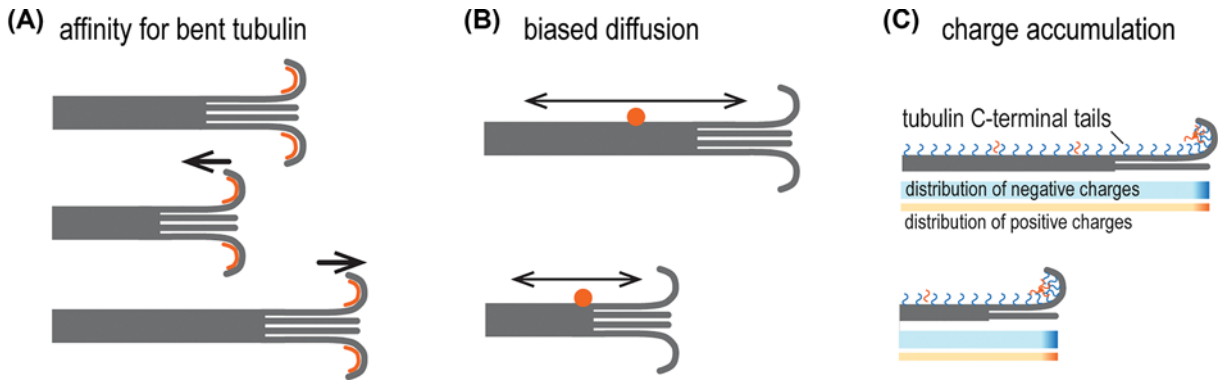

Figure 3. Microtubule features supporting end-tracking

(**A**) A coupler with increased affinity for bent tubulin should be enriched at the ends of the microtubule, where protofilaments are bent. (**B**) Free diffusion of weakly bound coupler (shown with an arrow) without a specific affinity for microtubule end is biased in the direction of microtubule shortening by the shrinking of the available microtubule lattice. (**C**) Negative charges of the tubulin C-termini are spatially enriched on the inner side of the bent tubulin protofilaments at the microtubule end. This increased density of negative charges at the microtubule end (shown in cyan) retains positively charged microtubule couplers close to microtubule end (shown in orange).

of CLASP2 fused to a positively charged linker follow microtubule growth [60,62]. One possible explanation for this discrepancy is given by an almost 10-fold difference in the growth and shortening speeds of microtubules *in vitro*, which might make the dissociation and re-association rates of the coupling molecules limiting for their processivity.

An alternative model of 'biased diffusion' is used to explain how freely diffusing molecules can promote cargo motion with a shortening microtubule end: the microtubule 'lattice shrinking' biases net movement of a cargo as the microtubule shortens [21,71] (Figure 3B). This model is attractive because it explains how couplers with no affinity to microtubule ends can still follow microtubule shortening. In the absence of an interaction with the end, the couplers moving by biased diffusion do not influence microtubule dynamics. For multivalent couplers like a full Dam1 ring [28] or an Ndc80 oligomer [47] this model becomes less suitable, because the coupler's diffusion is negligibly slow compared with the typical lifetime of a dynamic microtubule. Microtubule depolymerization forces the practically immobile coupler either to move or to detach. Consequently, the shortening microtubule end spends a fraction of the released energy to move such a strongly bound coupler, resulting in a slowdown of the shortening speed [34,47,53], contrary to the predictions of the biased diffusion model [38,46].

Many of the couplers discussed in this review rely in their microtubule binding on the unstructured negatively charged C-termini of tubulin, including the disordered C-termini of CENP-F and Dam1, CENP-E tail and Ndc80 [53,73–75], but not globular MTBD of Ska [16]. One of the most studied couplers, Ndc80, is binding preferentially to straight tubulin lattice in bulk [20], but relies on its positively charged N-terminus to stall and rescue microtubule shortening under force as a multivalent [47,48]. Because Ndc80 multivalents stall microtubule shortening after the microtubule end has generated force, i.e. after the power-stroke generated by tubulin protofilaments, this interaction between Ndc80 and microtubule is unlikely to happen along the stable microtubule lattice, away from the action of microtubule-generated force. Ndc80-mediated rescue and stalling of microtubule shortening suggests that Ndc80 multivalents transiently interact with the tubulin protofilaments under force. This hypothesis is further corroborated by an observation that Ndc80-microtubule connection stiffens during stall, with the stiffness and the stalling force positively correlating [47]. A similar effect, although documented with less detail, is observed for MACF2 C-terminus [9]. Theoretical considerations suggest that the stiffness of the microtubule-kinetochore link is an important parameter to rationalize kinetochore oscillations observed in mitotic cells [76]. Further studies will have to address the nature of the tubulin interface at the shortening microtubule end which mediates the force-dependent stiffening connection to multivalent unstructured couplers. It is attractive to speculate that the binding interface could be formed by an increased density of negatively charged tubulin C-termini on the inner side of tubulin 'ram's horns' (Figure 3C). Positively charged sequences could then be enriched in these negatively charged regions long enough (thanks to multivalency and the presence of additional folded MTBDs) to allow microtubule-generated force to be transmitted to the cargo, or for the opposing force from the cargo to stall microtubule shortening and put tubulin protofilaments in a configuration compatible with rescue and regrowth.

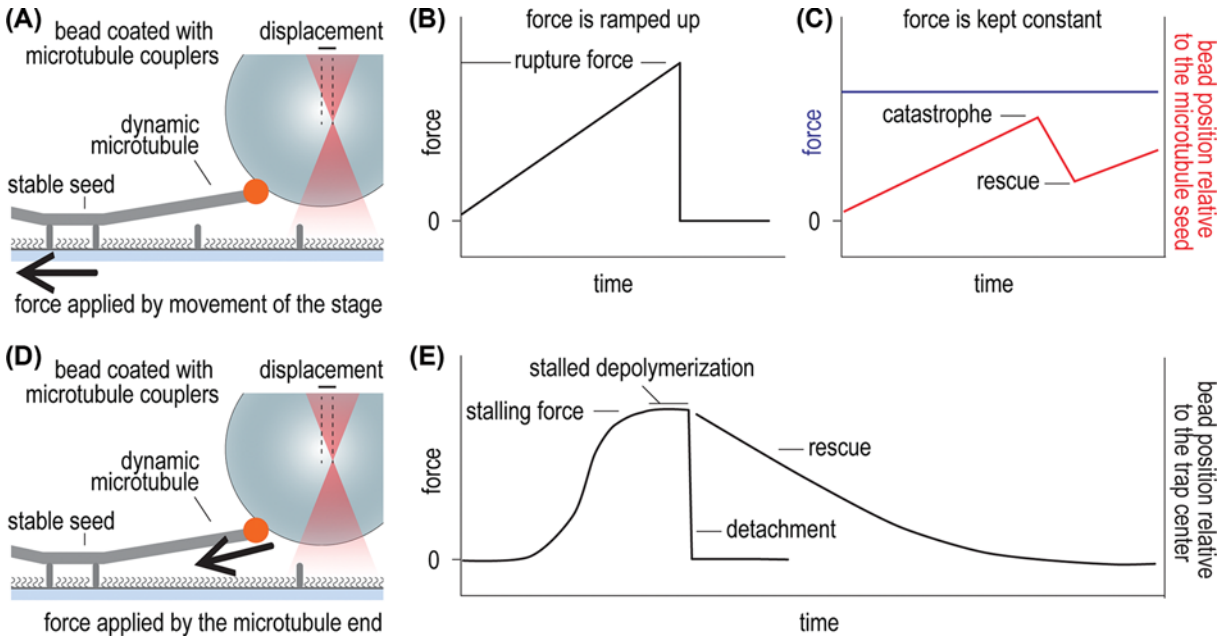

Figure 4. Experimental assays to probe microtubule force-coupling

(**A**) Assays with force applied by the experimenter, usually through a piezo-driven microscope stage. Displacement of the cover-slip-attached microtubule bound to a bead creates a returning force acting toward the centre of the optical trap. The force can be gradually ramped up at a constant speed until the bead-microtubule connection is ruptured (**B**). Alternatively, the force can be kept constant through a feedback loop (**C**, blue line). In a constant force (or 'force-clamp') setup the microscope stage is constantly updated to compensate for the bead movement with the microtubule, so the stage movements can serve as a readout for microtubule dynamics under force (C, red line). (**D**) Assay with force applied by the microtubule end. The optical trap is kept stationary while the bead is displaced by the shortening microtubule end. Bead displacement is calibrated into force. As the microtubule-generated force increases, the bead moves slower against the opposing force from the optical trap, until these forces are equalized and the microtubule shortening is stalled (**E**). After the stall, the bead can detach and microtubule resumes the shortening, or the bead can remain attached and force the microtubule end to switch to growth (rescue). Both of these alternative outcomes are shown in (E).

Capturing the microtubule-generated force

Shortening microtubules generate force thanks to the energy of GTP hydrolysis stored in the tubulin lattice and released in the form of power strokes of tubulin protofilaments bending outward (Figure 1A). Theoretical predictions estimate the maximum force a microtubule could generate in the range of tens of piconewtons [77–79]. The efficiency of a force coupler can be defined as the amount of microtubule-generated force that is transmitted to the cargo. Another parameter that is used to assess a coupler is load-bearing capacity, or the amount of force the coupler can withstand before its connection to microtubule is lost.

While both force-efficiency and load-bearing capacity are important for the couplers' performance, they are estimated using different experimental methods with the same readout expressed in pN (Figure 2A), leading to some confusion in the literature. For the purposes of this review, I discuss the experimental methods in their use to estimate the couplers' force-efficiency. I separate the experimental methods in two groups, one in which a pre-defined force is imposed on the coupler–microtubule connection by the experimenter (Figure 4A–C), and the other in which the force is exerted by microtubule end without any pre-conception of the force magnitude (Figure 4D,E). In all cases however, an integral part of the force-measurement system is a glass or plastic sphere that is held with an optical trap, and interacts with the microtubule through coupling proteins attached to the sphere's surface (Figure 4A,D).

Assays with pre-defined force

In a 'rupture force' assay the optically trapped and microtubule-bound bead is subjected to a linearly increasing force until the bead-microtubule attachment breaks (Figure 4A,B). This assay has been used in a number of publications to probe the load-bearing of reconstituted kinetochore complexes [18,80–82] or whole kinetochore particles purified from cells [65,83]. This assay is attractive for its simplicity, however, as long as the amount of exerted force is decided by

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the experimenter, the rupture force assay is not suitable to probe the couplers' ability to capture microtubule-generated force. In a variation of this approach, the force acting on the bead is kept constant while the bead is following the growing and shortening microtubule ends. Constant force, or 'force-clamp' was very valuable to assess the effect of tension on microtubule dynamic parameters, such as the shortening speed or the frequency of switches from growth to shortening (a catastrophe), and from shortening to growth (a rescue) [18,65,83] (Figure 4C).

Assays with microtubule-generated force

To address the coupler's force-transmission experimentally, a shortening microtubule is made to pull on an optically trapped bead coated with coupling molecules; displacement of the bead is calibrated to estimate the force (Figure 4D,E). This assay is characterized by a stationary trap that does not follow microtubule dynamics, like in force-clamp assay. A predictor of the correct estimation of microtubule-generated force is stalling, an equilibrium situation in which the microtubule-generated force is at balance with the returning force exerted by the optical trap on the bead (Figure 4F). The stall can result either in a detachment of the bead from the microtubule, or if there is soluble tubulin present in the assay, in force-dependent rescue [47,48] (Figure 4E). This approach allowed to identify the unstructured N-terminal tail of Ndc80 as the main contributor to the duration of the microtubule stalling by Ndc80 oligomers, and the duration of the stall as a predictor of rescue [48]. Force-clamp assay is also suitable to estimate microtubule stall force by finding the minimal applied force that prevents movement of otherwise processive cargo [83]. However, in the stationary trap assay (Figure 4D,E) the whole range of microtubule-generated forces and coupler movement speeds can be sampled from one measurement [39].

Concluding remarks

Given the abundance of disordered domains in the proteome (reviewed in [84]), specific requirements for a disordered domain to become a microtubule coupler remain to be found. This question is especially interesting because of very poor sequence conservation among the disordered microtubule couplers. Even the N-terminal tail of the evolutionary conserved Ndc80 complex is only poorly conserved across its orthologs [85]. In light of rapid evolution of disordered proteins compared with folded ones (reviewed in [86]) there are open interesting questions: does a specific amino acid sequence matter to make an efficient microtubule coupler? Do coupler sequences co-evolve with tubulin C-terminal tails? Do specific coupler sequences co-occur with specific tubulin post-translational modifications in different cell types or cell cycle phases?

Summary

- Majority of proteins following shortening microtubule ends act as multimers and rely on unstructured positively charged sequences in this activity.
- The unstructured microtubule-biding domains are not conserved in their sequence, but share overall positive charge and amino acid composition.
- High affinity for bent tubulin is not necessary for end-tracking and capture of microtubule-generated force.
- Microtubule stalling and rescue happens through a poorly understood interaction that might stiffen under force.

Competing Interests

The author declares that there are no competing interests associated with the manuscript.

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Abbreviations

Catastrophe, a stochastic switch from microtubule growth to shortening; **CENP**, centromere protein; **CH**, calponin homology; **Coupler**, a protein complex/oligomer that passively binds to microtubule and utilizes microtubule-generated force to move itself or a cargo; **End-tracking**, ability of a coupler to retain its association to the end of the microtubule as the microtubule shortens. The length/duration of end-tracking is also referred to as **processivity**; ER, endoplasmic reticulum; **MACF2**, microtubule-actin cross-linking factor 2; **MTBD**, microtubule-binding domain; Multivalency, coupler's ability to bind microtubules through multiple (similar or different) MTBDs; Optical trap, an instrument to measure forces in the piconewton (pN) range. Features a parallel beam of an infrared laser focused by a microscope objective into a diffraction-limited spot. Glass or plastic spheres (**beads**) are attracted to the centre of the focused beam, and a force is necessary to displace the bead from the trap centre; Protofilament, linear strand of $\alpha\beta$-tubulin dimers attached head to tail; Rescue, a stochastic switch from microtubule shortening to growth; Stall, microtubule shortening that is forcefully slowed down to a pause.

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Essays in Biochemistry (2020) EBC20190078
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