Microtubule +TIPs at a glance
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Microtubules are highly dynamic hollow tubes that are involved in many vital cellular activities, including maintenance of cell shape, division, migration and intracellular transport. They are assembled from heterodimers of α- and β-tubulin that align in a head-to-tail fashion. Microtubules are, thus, intrinsically polar because they contain two structurally distinct ends: a slow-growing minus end, exposing α-tubulin subunits; and a fast-growing plus end, exposing β-tubulin subunits (for a review, see Nogales and Wang, 2006). In mammalian cells, microtubule minus ends are often stably anchored, whereas the plus ends are highly dynamic and stochastically switch between phases of growth and shrinkage, a process that is powered by GTP hydrolysis.

Microtubule plus-end tracking proteins (+TIPs) are a structurally and functionally diverse group of proteins that are distinguished by their specific accumulation at microtubule plus ends (Mimori-Kiyosue et al., 2000; Perez et al., 1999; Schuyler and Pellman, 2001). +TIPs typically target growing but not shrinking microtubule ends; however +TIP association with depolymerizing ends can occur and, in some organisms such as budding yeast, is even quite common. In this Cell Science at a Glance article we review and illustrate the current knowledge of these peculiar proteins, summarize their structural and functional properties, and discuss the proposed molecular mechanisms that they use to track microtubule ends.

Classification of +TIPs
The first reported +TIP was cytoplasmic linker protein of 170 kDa (CLIP-170, officially known as CLIP1) (Perez et al., 1999). Since its discovery, more than 20 different +TIP families have been identified. +TIPs are usually

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**Microtubule +TIPs at a Glance**

**What is a +TIP?**
+TIPs localize to and track dynamic MT plus ends

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**Microtubule +TIP interactions**
Proteins with +TIP/tubulin-binding mechanisms

- Adenovirus +TIP
- Non-autonomous +TIPs
- Kinesin
- GDP-tubulin
- GTP-tubulin
- Liquid lipid

Proteins in motor complexes

- CLIP-170
- CLASP
- APC
- XMAP215
- MCAK

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**Classifications of +TIPs**

**+TIP classification**
- CAP-Gly proteins
- CAP–Gly Coiled coil ZnF
- Other proteins

**+TIP localization**
- +TIP distribution in mitotic interphase cells

**+TIP interactions**
Proteins with +TIP/tubulin-binding mechanisms

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Proteins in motor complexes

- CLIP-170
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- APC
- XMAP215
- MCAK

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**Microtubule +TIP functions**

- Polymerization (GTP-binding, EB)
- Depolymerization (GDP-binding, EB)
- Stabilization (CAP-Gly, CLASP)

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**Introduction to cellular structures**

- Center (CLASP, CLIP, CLIP-170, EB1, dynamic, dynamin, LIP1)
- Actin (EB1, CLASP, CLIP, CLIP-170, Kar9, RhoGEF2, p140Cap)
- Microtubule (CLIP-170, CLASP, MACF, CLIP, CLIP-170, Kar9, Melanophilin)
- Vesicle (CLIP-170, CLASP, APC, MACF)
- Membrane (CLIP-170, CLASP, MACF)

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**Microtubule +TIP plus-end tracking mechanisms**

- 1D lattice diffusion
- 2D diffusion
- Hitchhiking
- Induced release
- Recognition of specific microtubule plus-end structure (3D1)

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**Microtubule +TIPs at a Glance**

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**Abbreviations:** AAA, ATPase family associated with various cellular activities; APC, adenomatous polyposis coli; ART1, Additional requirements for tubulin assembly 1; ATP, adenosine triphosphate; AxTIP, axonal targeting of microtubule plus-end proteins; βTIP, β-tubulin-tethering proteins; CCK, Calmodulin-dependent protein kinase II; CBP, CREB-binding protein; CLIP170, cytoplasmic linker protein of 170 kDa; CLIP-170, cytoplasmic linker protein of 170 kDa; CDK5RAP2, CDK5 regulatory subunit-associated protein 2; CDK5, cyclin-dependent kinase 5; EB1, Ect2-binding protein 1; EBH, EB1 homology domain; GDP, guanosine diphosphate; GTP, guanosine triphosphate; GTPase-activating protein; HSPM, heat-shock protein M; KIF, kinesin family; LIM protein; MCAK, mitotic centromere-associated kinesin; MDA5, myxocystol-type ATPase; MDP1/MAP8, microtubule plus-end protein 1/MAP8-like protein 1; Myo2, myosin II; Ncd, non-claret disjunctional; NIP, non-ionic detergent; PIP, phosphatidylinositol phosphates; PLD, phospholipase D; Protein 150glued; Protein 150glued, protein 150; PtdInsP3, phosphatidylinositol 3-phosphate; RhoGEF2, Rho GTPase-activating-like family member 2; SxIP, Ser-x-Ile-Pro tetrapeptide motif; TM, transmembrane domain; TOG, named after the discovery in human chTOG; WD,Walker domain; ZnF, zinc finger; Zyx, zyxin; +TIP, microtubule plus-end tracking protein; TIP150, +TIP of 150 kDa; 3415

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**Image:** Live image of a human keratinocyte fibroblast expressing EB1-GFP (green) and a +TIP marker (EB1-GFP, arrows). (See poster insert)
multidomain and/or multisubunit proteins that range in size from a few hundred up to thousands of residues. They can be cytoplasmic or membrane bound, and comprise motor and non-motor proteins (for a review, see Akhmanova and Steinmetz, 2008). +TIPS can be classified on the basis of prominent structural elements that enable them to interact with each other and with microtubules; however, in some cases, +TIPS combine features characteristic of several +TIP classes.

End-binding (EB) family proteins contain a highly conserved N-terminal domain that adopts a calponin homology (CH) fold (Korenbaum and Rivero, 2002) and is responsible for microtubule binding (Hayashi and Ikura, 2003). In mammalian EB1 and EB3, a CH domain with the adjacent linker sequence is sufficient for plus-end tracking (Komarova et al., 2009; Skube et al., 2010); however dimerization is important for microtubule plus-end recognition by their yeast homologue Bim1 (Zimniak et al., 2009). The C terminus of EB proteins harbors an \( \alpha \)-helical coiled-coil domain that mediates parallel dimerization of EB monomers (Honnappa et al., 2005; Slep et al., 2005). It further comprises the unique EB homology (EBH) domain and an acidic tail encompassing a C-terminal EEY/F motif, reminiscent of those of \( \alpha \)-tubulin and CLIP-170 (Komarova et al., 2005; Miller et al., 2006; Weisbrich et al., 2007). Notably, plant EB proteins lack the EEY/F motif, and some EB family members, such as EB1e in Arabidopsis thaliana, exhibit a positively charged C-terminus that is responsible for nuclear localization (Komaki et al., 2010). Both the EBH domain and the EEY/F motif enable the EB proteins to physically interact with an array of +TIPS to recruit them to microtubule ends.

The cytoskeleton-associated protein glycine-rich (CAP-Gly) domain is a small globular module that contains a unique conserved hydrophobic cavity and several characteristic glycine residues (Li et al., 2002; Saito et al., 2004). CAP-Gly domains use their hydrophobic cavity to confer interactions with microtubules and EB proteins by specifically recognizing C-terminal EEY/F sequence motifs (Honnappa et al., 2006; Mishima et al., 2007; Weisbrich et al., 2007). Prominent examples are the CLIP proteins and the large subunit of the dynactin complex p150\(^{fc}\). A single CAP-Gly domain of CLIP-170, together with the adjacent serine-rich region, can track growing microtubule ends (Gupta et al., 2009).

The largest group of +TIPS comprises large and complex, often multidomain, proteins containing low-complexity sequence regions that are rich in basic, serine and proline (basic-S/P) residues. They share the small four-residue motif Ser-x-Ile-Pro (SxIP, where x denotes any amino acid), which is specifically recognized by the EBH domain of EB proteins (Honnappa et al., 2009). Prominent examples of this diverse class of +TIPS are the adenomatous polyposis coli (APC) tumour suppressor, the spectraplakin microtubule-actin-crosslinking factor (MACF) and the mitotic centromere-associated kinase (MCAK). Because SxIP motifs are very short, they can be easily acquired or lost during evolution; for example, CDK5RAP2, a protein implicated in microcephaly, contains an EB1-binding SxIP motif in humans and dogs but not in rodents (Fong et al., 2009).

Proteins with TOG or TOG-like domains (named after their discovery in the protein ch-TOG) include members of the XMAP215/Dis1 family and the CLASPs. Tandemly arranged TOG domains mediate binding to tubulin and are probably responsible for microtubule growth-promoting activity of these proteins (Al-Bassam et al., 2006; Brouhard et al., 2008; Slep and Vale, 2007) (for a review, see Slep, 2009a). Additional domains, such as SxIP motifs in CLASPs, are required for targeting of these proteins to microtubule plus ends and other subcellular sites (Mimori-Kiyosue et al., 2005).

Both microtubule plus- and minus-end-directed motor proteins can track growing microtubule ends. Examples are the yeast kinesins Tea2 and Hip2, the microtubule-depolymerising kinesin 13 MCAK and cytoplasmic dynein (reviewed in Wu et al., 2006). Sequences outside the microtubule-binding motor domains, such as the SxIP motif of MCAK (Honnappa et al., 2009), might be needed for the microtubule tip-tracking behavior of these proteins.

Finally, there are other +TIPS that cannot be grouped in one of the five classes discussed above. A prominent example is the Dam1 complex – an assembly of ten subunits that form rings of 16-fold symmetry (Lampert et al., 2010; Wang et al., 2007) – and which is found in yeast but not in higher organisms. Other examples are the Saccharomyces cerevisiae protein Kar9 (Liakopoulos et al., 2003; Moore and Miller, 2007), and the highly conserved cytoplasmic dynein accessory factor lissencephaly-1 protein (Lis1) (for a review, see Vallee and Tsai, 2006).

**Dynamic +TIP interaction networks**

One hallmark of +TIPS is that they form dynamic interaction networks that rely on a limited number of protein modules and linear sequence motifs, such as the CH, EBH and CAP-Gly domains, and EEY/F and SxIP motifs. These elements mediate the interaction with each other and microtubules, and typically display affinities in the low micromolar range (Gupta et al., 2009; Mishima et al., 2007; Weisbrich et al., 2007).

+TIP proteins are now generally accepted to represent core components of +TIP networks because they autonomously track growing microtubule plus ends independently of any binding partners (Bieling et al., 2008; Bieling et al., 2007; Dixit et al., 2009; Komarova et al., 2009; Zimniak et al., 2009). Moreover, EB proteins directly associate with almost all other known +TIPS and, by doing so, target them to growing microtubule plus ends (for reviews, see Akhmanova and Steinmetz, 2008; Slep, 2009b). SxIP motifs act as a general ‘microtubule tip localization signal’ (MILS) by interacting with the EBH domain of EB proteins (Honnappa et al., 2009). Similarly, EEY/F motifs of EB proteins and \( \alpha \)-tubulin guide CAP-Gly proteins to microtubule tips (Bieling et al., 2008; Dixit et al., 2009). Both the EBH-SxIP and the CAP-Gly-EEY/F interactions have been analyzed to high resolution (Hayashi et al., 2007; Honnappa et al., 2009; Honnappa et al., 2006; Mishima et al., 2007; Plevin et al., 2008; Weisbrich et al., 2007). The two distinct binding modes were revealed through these structures and offer a molecular basis for understanding the majority of known interaction nodes in dynamic +TIP networks.

The EBH-SxIP and CAP-Gly-EEY/F interactions can be regulated by post-translational modifications. Phosphorylation of Ser residues in the vicinity of the SxIP motifs (Honnappa et al., 2009; Kumar et al., 2009; Watanabe et al., 2009) disrupts their interaction with EB proteins, whereas the removal of the C-terminal Tyr of \( \alpha \)-tubulin has a negative effect on the accumulation of CAP-Gly proteins at microtubule tips (Bieling et al., 2008; Peris et al., 2006).

**+TIP tracking mechanisms**

Because +TIPS form complex interaction networks, in-vitro reconstitution studies using purified components are required to determine whether plus-end tracking behavior is an autonomous property of a particular protein. Using this approach, it was shown that some +TIPS can associate with growing microtubule ends in the absence of any additional factors. Autonomous processive microtubule tip tracking, whereby the protein stays bound to the microtubule end during multiple rounds of subunit addition, has been described for XMAP215 (Brouhard et al., 2008). Another example is the yeast Dam1 complex, which continuously tracks both growing and shrinking microtubule ends, possibly by using a form of a diffusion-based mechanism (Lampert et al., 2010). Finally, various EB family members from different species bind to growing but not
shortening plus- and minus ends in vitro (Bieling et al., 2008; Bieling et al., 2007; Dixit et al., 2009; Komarova et al., 2009; Zimniak et al., 2009). Unlike XMAP215, EB proteins exchange rapidly at the microtubule end, undergoing several cycles of binding and unbinding events before the growing microtubule end converts into the mature lattice (Bieling et al., 2007; Dragestein et al., 2008).

It is currently unknown which structural features of the growing microtubule end are recognized by autonomously tracking +TIPs; however, these might include the GTP cap at the end of the freshly polymerized microtubule (Lamping et al., 2010; Zanic et al., 2009) or some specific protofilament arrangement (des Georges et al., 2008; Sandblad et al., 2006) (for a review, see Coquelle et al., 2009). Another attractive idea is that autonomously tracking +TIPs co-polymerize with tubulin subunits and then get released gradually from the mature lattice (Folker et al., 2005); this mechanism has not found support in the in-vitro reconstitution studies using EB and CLIP homologs of fission yeast and vertebrates (Bieling et al., 2007; Bieling et al., 2008; Dixit et al., 2009), but might still apply to some other proteins.

Most +TIPs track the ends of growing microtubules in a non-autonomous manner. STIM1 and CDK5RAP2, for example, hitchhike on microtubule tip-bound EB proteins (Fong et al., 2009; Grigoriev et al., 2008; Honmappa et al., 2009). Others, such as CLIP-170, recognize more complex binding sites that encompass domains of both EB proteins and tubulin (Bieling et al., 2008; Gupta et al., 2010). Because EB proteins rapidly exchange at microtubule tips, accumulation of their partners at microtubule ends is also dynamic, and mostly depends on three-dimensional protein diffusion in the cytosol. However, one-dimensional diffusion along the microtubule lattice might also occur, as is the case for MCAK (Helenius et al., 2006). In the case of STIM1, a transmembrane +TIP, two-dimensional diffusion in the membrane is required to enable accumulation at microtubule tips (Grigoriev et al., 2008).

For EB proteins and their partners that decorate the freshly polymerized microtubule tip, the specificity for microtubule plus ends – as opposed to minus ends – is explained by the fact that, in vivo, minus ends never grow in cells. By contrast, the exclusive accumulation at minus ends is retained on them, either because of interactions with other +TIPs or through their intrinsic autonomous tip-tracking properties (Varga et al., 2009).

**+TIP functions**

Localization at microtubule ends makes +TIPs ideally suited to control different aspects of microtubule dynamics; for example, by promoting growth through catalyzing the addition of tubulin to microtubule ends (XMAP215) (Brouhard et al., 2008), inducing catastrophes (MCAK) (Kline-Smith and Walczak, 2002) or rescues (CLIP-170) (Komarova et al., 2002), or by stabilizing microtubules at the cell cortex (CLASPs, APC, MACF) (Kodama et al., 2003; Mimori-Kiyosue et al., 2005; Weng et al., 2004) (for reviews, see Heald and Nogales, 2002; van der Vaart et al., 2009). For some +TIPs, the exact effect on microtubule dynamics varies depending on the assay conditions. EB proteins usually promote microtubule dynamics and growth, and suppress catastrophes in cells (Busch and Brunner, 2004; Komarova et al., 2009; Timauer et al., 2002). However, the results of in-vitro experiments with different EB family members have been controversial, because changes in growth and shrinkage rates, induction and suppression of catastrophes, or a complete lack of influence on some or all microtubule dynamics parameters have been reported (Bieling et al., 2008; Bieling et al., 2007; Dixit et al., 2009; Katsuki et al., 2009; Komarova et al., 2009; Manna et al., 2007; Vitre et al., 2008). Taken together, these studies suggest that the regulation of microtubule dynamics is an important +TIP function, but the underlying molecular mechanisms are still poorly understood.

In addition to regulating microtubule dynamics, +TIPs form links between microtubule ends and other cellular structures. For example, they can attach microtubule tips to the cell cortex by binding to plasma-membrane-associated proteins – such as the CLASP–LL5β complex (Lansbergen et al., 2006) – or by interacting with actin fibers to which some +TIPs, such as spectraplakins, can bind directly (Applewhite et al., 2010; Kodama et al., 2003), whereas others (e.g. CLIP-170) might require intermediary factors (Fukata et al., 2002). +TIPs also participate in microtubule-actin crosstalk. The Tea1–Tea4 complex, for example, controls actin polymerization, a process essential for phagocytosis in mammalian cells (Lewkowicz et al., 2008). The EB1 partner RhoGEF2 regulates contractility of epithelial cells in flies (Rogers et al., 2004), and p140Cap acting together with EB3 affects F-actin organization in dendritic spines of neurons (Jaworski et al., 2009). Furthermore, +TIP complexes are used for myosin-based transport of microtubule ends, e.g. Kar9–Myo2 in budding yeast (Liakopoulos et al., 2003).

+TIPS also have an important role in coordinating microtubule attachment and dynamics at mitotic kinetochores – e.g. Dam1, CLIP-170, CLASPs, dynein (for a review, see Maitio et al., 2004) – and participate in the extension of endoplasmic reticulum tubules together with growing microtubule ends (STIM1) (Grigoriev et al., 2008). +TIPs also contribute to loading cargo for minus-end-directed microtubule transport (dynamin, CLIP-170) (Lomakin et al., 2009; Vaughan et al., 2002) and in transporting microtubule ends along other microtubules to promote organization of specialized microtubule arrays, such as mitotic spindles (Goshima et al., 2005) and bipolar microtubule bundles in fission yeast (Janson et al., 2007).

Finally, many +TIPs accumulate at centrosomes and other microtubule organizing centers where they might participate in microtubule nucleation and anchoring (for a review, see Bettencourt-Dias and Glover, 2007). The exact role +TIPs have at the centrosomes awaits to be explored.

**Perspectives**

Growing microtubule ends have emerged as remarkably complex cellular sites where microtubule dynamics can be coordinated with actin polymerization, cargo movement and remodeling of cell membranes. These processes are tightly regulated by a diverse set of proteins that form a dynamic and flexible interaction network. In most cases, the exact role of the microtubule plus-end tracking behavior for +TIP function has not been established and still needs to be examined. Remarkably, some of the key microtubule tip-targeting motifs are very short and simple, and can be acquired easily during evolution. We thus expect that the list of +TIPS is incomplete and that many more protein families showing this peculiar localization behavior will be discovered in the near future.

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