A +TIP for a smooth trip

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Is there a cellular mechanism for preventing a depolymerizing microtubule track from "slipping out from under" its cargo? A recent study in budding yeast indicates that when a chromosome is transported to the minus end of a spindle microtubule, its kinetochore-bound microtubule plus end–tracking protein (+TIP) Stu2 may move to the plus end to promote rescue; i.e., to switch the depolymerizing end to a polymerizing end. The possibility that other +TIPs may play a similar role in sustaining a microtubule track during vesicular transport deserves investigation.

Microtubule motor proteins such as dynein and kinesins are responsible for transporting cellular cargos along microtubule tracks (Vale, 2003). The net direction and speed of cargo movement, however, are likely to be regulated in a very complicated fashion, especially when a cargo is bound to multiple motors with opposite directionalities (Vale 2003; Mallik and Gross 2004; Levi et al., 2006). The fact that the microtubule track is not very stable further complicates matters. The plus ends of microtubules, which face the cell periphery in most cell types, are highly dynamic, exhibiting alternating periods of polymerization (growth) and depolymerization (shrinkage; Desai and Mitchison, 1997). Such plus end dynamics may be useful for searching and capturing relatively stationary cargos near the cell periphery that need to be transported inward (Vaughan et al., 2002). However, the dynamic nature of the track can also create an obvious problem for the transport process. If a microtubule's rate of shrinkage is greater than the rate of cargo transport, then the microtubule may shrink past an attached cargo, causing its dissociation from the track. Does this happen in cells, or do cells have a mechanism to prevent it?

Although this question has never been directly addressed, a recent study on budding yeast chromosome segregation has shed new light on the issue (Tanaka et al., 2005). In this study, the authors took advantage of a strategy that allowed them to specifically shut off the function of a single kinetochore, thereby preventing it from attaching to a spindle microtubule while, at the same time, permitting other kinetochores to attach to the spindle. After the function of this single kinetochore was switched back on, the behavior of its associated chromosome on a spindle microtubule was subjected to a detailed image analysis.

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Several important insights from this study on chromosome–microtubule interactions during mitosis have been recently reviewed (Bloom 2005), and, thus, only those observations that pertain to cargo transport will be highlighted here. The chromosome was first seen to undergo a lateral interaction with the microtubule followed by minus end–directed transport toward the pole. The mechanism of the minus end–directed transport is not entirely clear, although a member of the kinesin-14 family, Kar3, may be one of the players in this process (Tanaka et al., 2005). During transport, the attached microtubule can undergo shrinkage with a rate higher than that of the minus end–directed chromosome movement (Tanaka et al., 2005); however, it never shrank beyond the position of the cargo. Such exquisite control over the extent of shrinkage appears to rely on a conversation between the cargo and the plus end of the microtubule that is mediated by the microtubule plus end–tracking protein Stu2 (Bloom 2005; Tanaka et al., 2005).

Microtubule plus end–tracking proteins (+TIPs) are a class of proteins that use different structural motifs or specific targeting mechanisms to localize to the dynamic plus ends of microtubules (Carvalho et al., 2003; Akhmanova and Hoogenraad, 2005). Although most +TIPs associate with only the growing ends of microtubules, several +TIPs also localize to the shrinking ends (Carvalho et al., 2003; 2004; Akhmanova and Hoogenraad, 2005; Mennella et al., 2005; Sproul et al., 2005; Molk et al., 2006; Wu et al., 2006). Many +TIPs have been found to impact microtubules by either promoting their growth or promoting dynamic behavior. Stu2 is a member of the XMAP215/TOG/Dis1/DdCP224 family of proteins that have been shown to affect microtubule dynamics in multiple ways depending on different experimental conditions (Ohkura et al., 2001; Popov and Karsenti 2003; Holmfeldt et al., 2004; Akhmanova and Hoogenraad, 2005). In vitro, Stu2 binds to the plus ends of preformed microtubules and promotes catastrophe, which is a switch from growth to shrinkage (van Breugel et al., 2003). In vivo studies using mutants of Stu2, however, indicate that Stu2 promotes microtubule growth (Severin et al., 2001) and the dynamics of both kinetochore and cytoplasmic microtubules (Kosco et al., 2001; Pearson et al., 2003). During anaphase B spindle elongation, Stu2 may antagonize the function of Kip3 (a kinesin-13 family member) to promote the plus end polymerization of overlapping microtubules (Severin et al., 2001). Although it is not fully understood how or why Stu2 is so versatile, it is well recognized that the in vivo interactions among +TIPs are very complicated, and the loss of function of a +TIP in vivo may decrease or increase the accumulation of

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other +TIPs that also regulate microtubule dynamics (Carvalho et al., 2003; 2004; Lansbergen et al., 2004; Akhmanova and Hoogenraad, 2005; Galjart 2005; Komarova et al., 2005).

Tanaka et al. (2005) identified Stu2 as a rescue (a switch from shrinkage to growth) factor based not on phenotypic studies of Stu2 mutants but, instead, on a direct observation of the relationship between microtubule plus end behavior and Stu2 localization. They found that Stu2 was localized at the plus ends of microtubules emanating from the spindle pole body, and, during periods of microtubule shrinkage, Stu2 levels at the plus ends were decreased. Interestingly, Stu2 was also localized at the unbound kinetochore. When the kinetochore subsequently attached laterally to a spindle microtubule and underwent minus end–directed transport, the Stu2 proteins were transported from the kinetochore to the microtubule plus end. The arrival of Stu2 at the plus end closely correlated to the rescue of the shrinking microtubule (Tanaka et al., 2005). These observations strongly suggest that the Stu2 carried by the kinetochore may serve as a rescue factor for the microtubule track, preventing it from vanishing before the migrating chromosome.

Could such a scenario exist during microtubule-dependent transport of nonchromosomal cargoes during interphase? We do not yet know the answer. However, based on published studies, it seems reasonable to hypothesize that other +TIPs, especially the cytoplasmic linker protein CLIP-170, may function in a manner similar to yeast Stu2 to ensure a safe trip for a minus end–directed cargo. CLIP-170 contains CAP-Gly microtubule-binding motifs at its NH_2 terminus and was initially identified as a protein required for linking endocytic vesicles to microtubules in vitro (Pierre et al., 1992; Rickard and Kreis 1996). Later, CLIP-170 was identified as a founding member of the microtubule plus end–tracking proteins (Perez et al., 1999). The connection between CLIP-170's in vitro endosome–microtubule linking property and its in vivo plus end tracking behavior has not been clearly made. Could an endocytic vesicle use its bound CLIP-170 as a rescue factor to prevent the disappearance of the track on which it is traveling?

CLIP-170 is indeed considered to be a rescue factor in mammalian cells (Komarova et al., 2002a). Komarova et al. (2002b) have found that in cultured CHO and NRK cells, microtubule dynamics seem to be controlled spatially; catastrophe and rescue occur frequently only near the cell periphery. Although the mechanisms behind catastrophe and rescue are not fully understood, protein factors are required for regulating both events in vivo (Desai and Mitchison, 1997). In CHO cells, a dominant-negative form of CLIP-170 that displaces the endogenous CLIP-170 from microtubule plus ends severely reduces the rescue frequency so that microtubules are more likely to shrink all the way back to the microtubule-organizing center (Komarova et al., 2002a). Moreover, both in vivo and in vitro studies suggest that the rescue activity of CLIP-170 is localized to the NH_2 terminus containing the CAP-Gly motifs (Komarova et al., 2002a; Arnal et al., 2004). How CLIP-170 rescues a shrinking end is not clear. CLIP-170 can promote tubulin oligomerization (Diamantopoulos et al., 1999; Arnal et al., 2004), and it is likely that this property serves to increase the local concentration of tubulin substrate, thereby lowering the entropic barrier for the polymerization reaction. CLIP-170 in mammalian cells has only been found at growing plus ends, most likely as a result of copolymerization with tubulin subunits followed by its release from older segments (Diamantopoulos et al., 1999; Perez et al., 1999; Folker et al., 2005). When a microtubule end shrinks, CLIP-170 falls off. Is there a mechanism to get CLIP-170 close to the depolymerizing end and facilitate its function as a rescue factor? Given the proposed function of Stu2 as a rescue factor for spindle microtubules, one may easily imagine a similar scenario in which vesicle-bound CLIP-170 may be transported to the approaching microtubule end to rescue it from further shrinkage.

If vesicle-bound CLIP-170 is transported to the plus end in a manner similar to Stu2, could such transport be mediated by plus end–directed kinesins? Although the kinesin involved in transporting Stu2 toward the microtubule plus end still needs to be identified, detailed image analyses have revealed a role for the Kip2/Tea2 kinesins (members of the kinesin-7 family) in transporting CLIP-170 homologues in fungi (Busch et al., 2004; Carvalho et al., 2004). Bik1 and Tip1 are the CLIP-170 homologues in budding and fission yeasts, respectively, and these proteins are found at microtubule plus ends, where they act as growth-promoting factors or anticatastrophe factors (Berlin et al., 1990; Brunner and Nurse 2000; Carvalho et al., 2004). In both yeasts, the Kip2/Tea2 kinesins bind to and comigrate with the CLIP-170 homologues along the microtubule toward the plus end (Busch et al., 2004; Carvalho et al., 2004). Kinesins have also been implicated in targeting other +TIPs to microtubule plus ends (Jimbo et al., 2002; Maekawa et al., 2003; Zhang et al., 2003; Wu et al., 2006). For example, the mammalian tumor suppressor protein APC (adenomatous polyposis coli) may be targeted to the plus end by KIF3A/KIF3B (a heterotrimeric kinesin II in the kinesin-2 family) as well as by other mechanisms (Jimbo et al., 2002; Nathke 2004; Slep et al., 2005). It will be interesting to see whether a similar transport process for CLIP-170 exists in higher eukaryotic cells. It is possible that such a mechanism would deliver just enough CLIP-170 to the shrinking plus end to initiate rescue. When microtubule growth is resumed, CLIP-170's intrinsic higher affinity for tubulin subunits and lower affinity for the microtubule wall may allow these proteins to "treadmill" on the growing end (Perez et al., 1999; Folker et al., 2005).

The regulation of CLIP-170 activity appears to be rather complex. CLIP-170 is most likely phosphorylated by multiple kinases, including FKBP12–rapamycin-associated protein (mTOR; Choi et al., 2002). Although phosphorylation by mTOR/FKBP 12–rapamycin-associated protein may stimulate CLIP-170's microtubule binding, phosphorylation by other kinases may cause CLIP-170 to dissociate from microtubules (Rickard and Kreis 1996; Choi et al., 2002). In vivo, CLIP-170 has a closed conformation that is presumably inactive and an open conformation that may interact with microtubules and dynein regulators such as dynactin (Schroer 2004) and LIS1 (Morris et al., 1998; Lansbergen et al., 2004). It is possible that phosphorylation may regulate the conversion between these two forms, but the specific mechanism and the spatial regulation for this conversion have yet to be resolved. If CLIP-170 is indeed released from

a membranous cargo to move to the plus end in order to serve as a rescue factor, it would be interesting to know when and/or where such a conformational switch occurs. Finally, other proteins may play redundant roles with CLIP-170 in vesicular trafficking, which may explain why a dramatic defect in vesicle/organelle distribution is not detected when the CLIP-170 level is lowered or when the gene is knocked out (Lansbergen et al., 2004; Akhmanova et al., 2005).

+TIPs other than CLIP-170 may play a similar role in rescuing shrinking microtubule tracks. For example, the dynactin complex that links dynein to membranous cargoes and promotes the processive motion of dynein (Schroer 2004) may act as a rescue factor. The $p150^{Glued}$ subunit of dynactin and CLIP-170 both contain CAP-Gly microtubule-binding motifs at their NH2 termini, although $p150^{Glued}$ contains one, whereas CLIP-170 contains two such motifs. Dynactin has been shown to behave as a +TIP facilitating the capture of vesicular cargo for minus end–directed transport (Vaughan et al., 1999; 2002). The head domain of the $p150^{Glued}$ subunit containing the CAP-Gly motif has been shown to promote rescue in vivo in the absence of endogenous CLIP-170, although the effect was much weaker than that caused by the exogenous CLIP-170 head domain (Kamarova et al., 2002a). In vitro studies showed that dynactin may promote nucleation during microtubule assembly (Ligon et al., 2003), which is consistent with it being a potential rescue factor. As shown with CLIP-170, this capacity to bring multiple tubulins together may help to overcome the entropic barrier of the polymerization reaction. Finally, cargo-bound dynactin may also use kinesin to get to the plus end. The $p150^{Glued}$ subunit of dynactin has been shown to interact directly with the COOH terminus of KAP3, a subunit of the heterotrimeric kinesin II (a member of the kinesin-2 family) that also binds to APC (Jimbo et al., 2002; Deacon et al., 2003; Dell 2003). Although this binding is implicated in dynactin's role as a cargo adaptor for kinesin II, it is possible, in theory, that a small amount of dynactin may use this connection to move to the plus end.

The proposed hypothesis that +TIPs may be released from a membranous cargo to rescue a shrinking microtubule track may apply to both minus and plus end–directed transport. In addition, it is important to point out that this hypothesis does not exclude other mechanisms for rescuing long microtubule tracks. Rescue may occur stochastically, and, sometimes, +TIPs may participate in other ways such as mediating microtubule capture by the actin-rich cortex to stabilize the track (Wen et al., 2004; Galjart 2005). In some situations, microtubule dynamics are modulated by the direct binding of membranous cargo to the growing or shrinking plus ends of microtubules (Waterman-Storer and Salmon, 1998).

Currently, the ability of CLIP-170 or other +TIPs to be released from a membranous cargo and to act as a rescue factor for a shrinking microtubule is just a hypothesis. Nevertheless, searching for proteins involved in the communication between a cargo and the approaching shrinking end of its microtubule track is clearly an endeavor worth pursuing.

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