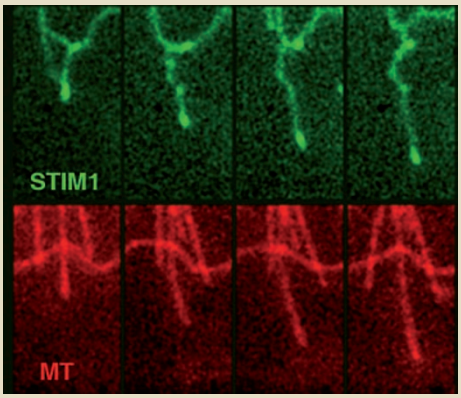
STIM1 tracks growing microtubule ends

The tubular structure of the endoplasmic reticulum (ER) can be modulated by distinct interactions with microtubules: ER tubules can be attached directly to existing microtubules, slide along them through motor activity or associate with the growing plus end of microtubules through the 'tip-attachment complex' (TAC). Akhmanova and colleagues have identified an interaction between the ER membrane resident, stromal interaction molecule 1 (STIM1), and the microtubule plus-end-binding protein EB1, which is required for TAC-mediated ER tubule growth (*Curr. Biol.* **18,** 177-182 2008).

After calcium release from the endoplasmic reticulum, STIM1 translocates to the ER plasma membrane junctions where it activates calcium channels as part of the store-operated calcium entry (SOCE) pathway. Previous work had shown that STIM1 colocalized with α-tubulin, so it was of particular interest when the authors isolated STIM1 in a screen for microtubule plus-end-tracking proteins that bind to EB1. They observed that when a growing microtubule tip encountered the ER membrane, GFP-tagged STIM1 formed a comet-like structure in ER tubules, which then extended together with the microtubule tip. If the connection was lost, the microtubule tip continued to grow but the tubule retracted and the STIM1 comet-like structure disappeared.

Depletion of either STIM1 or EB1 using short interfering RNA led to decreased TAC-mediated ER tubulation without affecting the motor-mediated sliding mechanism. Conversely, increased expression of STIM1 led to an increased frequency of TAC-mediated tubulation. Curiously there was a correlating decrease in ER tubule sliding, perhaps hinting the two tubulation pathways are intrinsically balanced.

Following ER calcium-store depletion, GFP–STIM1 rapidly relocalized from the comet structures to distinct ER punctae, thus preventing it from tracking growing microtubule tips. This suggests that the role of STIM1 in TAC-mediated ER tubulation is disrupted by calcium release from the ER.



Live-cell imaging showing that ER-localized GFP–STIM1 (green) tracks the growing plus-end of microtubules (red), extending the GFP–STIM1-labelled ER tubule.

Previous studies had suggested that the reciprocal may also be true, showing that nocodazole, which depolymerizes microtubules, had a detrimental effect on SOCE; this was rescued in part by overexpression of STIM1. However, in the current study the authors observed no effect on SOCE after disruption of microtubule dynamics by treatment with taxol or when EB1 was depleted. The reasons for the discrepancies between these studies remains unclear but it may be possible that under physiological conditions, microtubule plus-end-tracking by STIM1 and the consequent ER tubulation is important for regulation of calcium uptake.

These findings represent the first identification of a microtubule-plus-end-associated protein that, rather than diffusing freely in the cytosol, is restricted to a membrane. It will be interesting to see whether other plus-end-associating factors exist at the membranes of other organelles.

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