

Microtubule dynamics

Rebecca Heald² and Eva Nogales^{1,2}

¹Howard Hughes Medical Institute, and
²Department of Molecular and Cell Biology, University of California, Berkeley, Berkeley, CA 94720, USA
 (e-mail: enogales@lbl.gov)

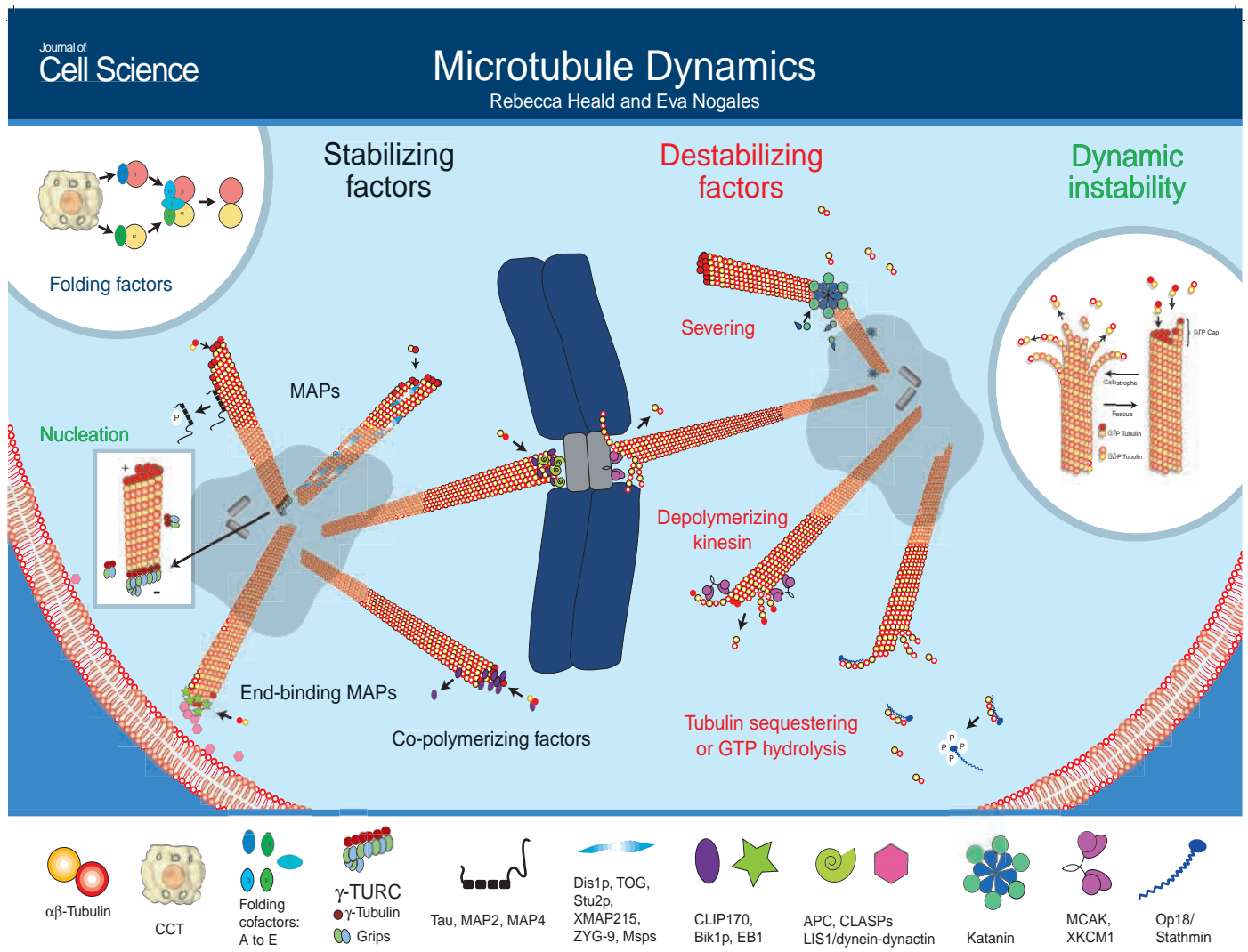
Journal of Cell Science 115, 3-4 (2002)
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Microtubules are highly dynamic and switch stochastically between growing and shrinking phases both in vivo and in vitro. This non-equilibrium behavior, known as dynamic instability, is based on the binding and hydrolysis of GTP at the nucleotide exchangeable site (E-site) in β -tubulin. Only dimers that have GTP

in their E-site can polymerize (red tubulin subunits), but following polymerization this nucleotide is hydrolyzed and becomes non-exchangeable. The GTP-cap model proposes that the body of the microtubule, which comprises GDP-tubulin subunits (pale red), is unstable. The microtubule structure is stabilized by a layer of GTP tubulin subunits at the end that may act to maintain association between protofilaments. When this cap is stochastically lost, the protofilaments peel outward and the microtubule rapidly depolymerizes.

The intrinsic microtubule dynamics are further modified in the cell by interaction with cellular factors that stabilize or destabilize microtubules, which operate

in both spatially and temporally specific ways to generate different microtubule assemblies during the cell cycle. Regulation can occur at many levels: tubulin monomer folding by the chaperonin CCT (chaperonin-containing TCP-1) and the formation of functional dimers by folding cofactors (B and A bind to quasi-native α - and β -tubulin monomers, respectively, whereas C, D and E are involved in the formation and release of the stable tubulin dimer), determine, together with transcriptional control (not shown), the amount of subunits available to polymerize. Nucleation of microtubules occurs primarily at microtubule-organizing centers (MTOCs), which are usually composed of a pair of cylindrical centrioles surrounded by pericentriolar



material containing an isoform of tubulin (γ -tubulin) in a large complex that includes other proteins (collectively known as 'grips') and functions as a nucleating seed: the γ -tubulin ring complex (γ -TuRC).

Microtubule stability is promoted to a large degree by microtubule-associated proteins (MAPs). Classical MAPs, such as MAP2 and Tau, bind to the surface of the microtubule, bridging several tubulin subunits and possibly neutralizing the repulsive negative charge on the microtubule surface. Other MAPs, such as the highly conserved XMAP215/

Stu2p/TOG family, may be enriched on a subset of microtubules. Microtubule-end-binding MAPs, such as CLIP-170 and EB1, may copolymerize with new tubulin subunits, selectively bind to a

special conformation of the microtubule end, and/or serve as attachments for growing or shortening microtubules to kinetochores or cellular membranes through interaction with proteins such as the APC (adenomatous polyposis coli) protein and CLASPs (CLIP-associated proteins). Binding of the dynein-dynactin motor complex, along with proteins such as LIS1, to microtubule ends and cortical sites or the kinetochore also appears to stabilize microtubules.

The microtubule-destabilizing factor katanin functions as a severing factor, generating new ends lacking a GTP cap. Depolymerizing kinesins of the KinI family, such as XKCM1 and MCAK, bind to microtubule ends and distort the microtubule lattice, forcing proto-filament peeling. Op18/Stathmin has

been proposed to act by sequestering tubulin dimers and/or by promoting GTP hydrolysis at the E-site. Thus, microtubule-stabilizing and -destabilizing factors function by a variety of mechanisms and may themselves be regulated both temporally by activation of kinases and phosphatases and spatially through specific localization of factors. For example, phosphorylation of Op18 and some MAPs turns off their activity, and depolymerizing kinesins can be either soluble or bound at the kinetochore.

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Deadline: 31 March 2002