Are there any diseases associated with KANK proteins? Genetic studies by homozygosity mapping and whole-exome sequencing identified recessive mutations in *KANK1*, *KANK2* and *KANK4* in patients suffering from nephrotic syndrome. A family-based genetic linkage study in patients with cerebral palsy revealed a small genomic deletion spanning the *KANK1* gene. Interestingly, studies of the mode of inheritance revealed that the disease is transmitted through the carrier fathers but not the carrier mothers, suggesting that the *KANK1* gene is imprinted and expressed from the paternal allele. And a homozygous missense mutation in *KANK2* disrupts its binding to SRC and is associated with keratoderma and woolly hair.

Are KANKs essential for development? Genetic loss-of-function studies in mice have only been reported for the *Kank4* gene so far, which revealed normal pre- and postnatal development and a function for artery growth upon ischemic stress.

C. elegans and *Drosophila* harbor a single *Kank* ortholog. Whereas disruption of the *dKank* ortholog in flies is without phenotype, loss of the nematode ortholog, called *VAB-19*, leads to paralysis due to muscle detachment from the epidermis, axon protrusion defects and impaired basement membrane remodeling.

In zebrafish, knockdown of *Kank2* recapitulates a nephrotic syndrome-like phenotype and knockdown of *Kank3* affects tissue morphogenesis and leads to embryonic lethality.

What remains to be explored? Most of our knowledge originates from cell-based studies and human genetics. Loss-of-function studies in mice are restricted so far to KANK4. The extension to the other KANKs will provide important insights as to how individual KANKs orchestrate mammalian embryogenesis and whether they are redundant. So far, most reported KANK functions and binding partners are shared among mammalian KANK orthologs, although it is obvious that both KANK ortholog-specific binding partners and, hence, KANK-specific functions must exist. For example, SRC3/AIB1 seems to interact with KANK2 but not KANK1 (Guo *et al.*; unpublished data).

Genetic studies in humans identified several disease entities associated with KANK family members. Besides these interesting genetic findings, whose molecular contexts are still largely elusive, KANKs also play a role in cancer biology. KANK1 for example, was shown to act as a tumor suppressor in renal cell carcinoma. This observation raises questions such as whether the tumor suppressor function is conserved in all epithelial tumors, how the tumor suppressive function is achieved at the molecular level and whether tumor development, growth as well as progression are affected by KANK1 and other KANK orthologs.

Where can I find out more?

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Max Planck Institute of Biochemistry, Department of Molecular Medicine, Martinsried, Germany.
*E-mail: shguo@biochem.mpg.de

Primer

Microtubule-severing enzymes

Stephanie L. Sarbanes[1], Elena A. Zehr[1], and Antonina Roll-Mecak[1,2,3,*]

One of the most fundamental and enduring myths of human civilization spanning cultures and centuries is that of the serpent-slaying hero. From Indra and Vritra to Thor and Jormungandr, Hercules and the Hydra to Beowulf and the Fireworm, the lore of the extraordinary hero vanquishing some snakish beast has emerged again and again as a symbolic representation of the triumph of Order over Chaos. And yet little could the ancient Greeks or Vedic tribes have imagined, as they used these stories to confront the cosmos and their place in the natural world, that parallel feats were playing out on a much smaller and more intimate scale. In fact, tiny molecular effectors were hard at work in each of their cells wrestling a unique form of writhing beast known as the microtubule into fantastic forms and arrays underlying each of their movements and thoughts. The discovery of a new class of proteins termed microtubule-severing enzymes offered a glimpse into how one derives Order out of Chaos at the level of cells and tissues. In this primer, we familiarize the reader with the story of severing enzymes from their discovery to the present day, highlighting their shared structure and mechanism and the diversity of processes in which they participate.

Discovery of microtubule-severing enzymes

Microtubules are polarized polymers that scaffold all eukaryotic cells and organize the chaotic intracellular world. They are composed of αβ-tubulin subunits (heterodimers) that assemble in a head-to-tail fashion into protofilaments, which then interact laterally to form a hollow tube. The ends of this tube fluctuate between phases of polymerization and depolymerization through the addition and loss of these αβ-tubulin subunits. This dynamic behavior of the microtubule ends was originally deemed sufficient to support

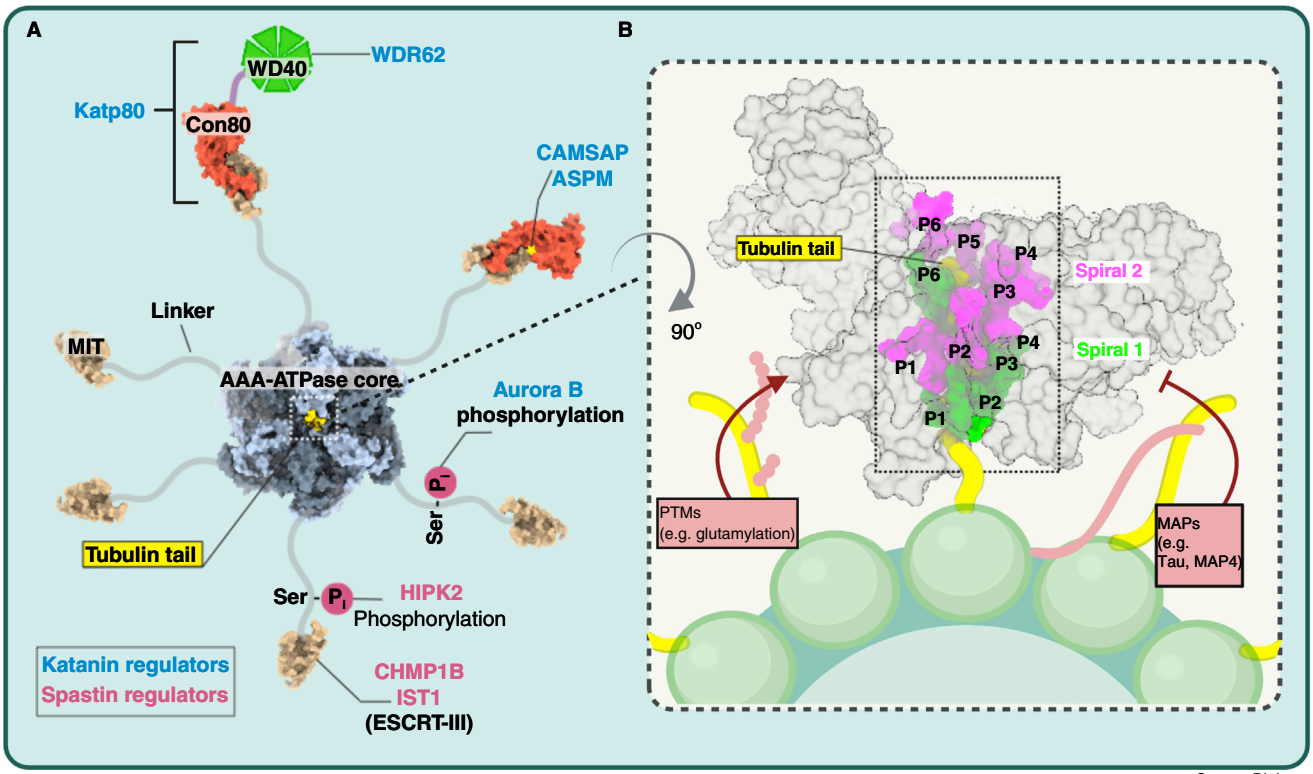

Figure 1. Architecture and regulation of microtubule-severing enzymes.
(A) The severing enzymes spastin and katanin assemble into hexamers with AAA-ATPase domains at their core and flexible arms that recruit effectors for localization and severing activity regulation. (B) An interconnected double spiral in the central pore of the AAA-ATPase core coordinates the tubulin tail and is thought to pull on it to extract tubulin out of the microtubule. Severing is regulated *in cis* by post-translational modifications or *in trans* by MAPs that limit enzyme accessibility.

the organization of microtubules into the complex arrays required to execute their diverse cellular functions.

In 1991, however, an intriguing phenomenon was observed upon incubation of *Xenopus laevis* egg extracts with microtubules. Within the oocyte, transition from interphase to mitosis requires rapid microtubule disassembly prior to spindle formation. Correspondingly, microtubules incubated in mitotic extracts rapidly depolymerized, while those in interphase extracts did not. Monitoring the fates of individual microtubules in mitotic extracts revealed that they were in fact severed along their lengths and not depolymerized from their ends. Biochemical isolation of the severing activity from sea urchin egg extracts yielded a complex composed of two subunits: a catalytic subunit, p60, and a regulatory subunit, p80, which based on this microtubule-slaying action were named katanin after the Japanese samurai sword, 'katana'. Sequence analysis revealed that the p60 catalytic subunit was an ATPase-associated with various cellular activities (AAA-ATPase) family member, and experiments demonstrated that ATP hydrolysis was required for severing. Two other enzymes purified a decade later — spastin and fidgetin — were similarly shown to possess ATP-hydrolysis-dependent microtubule-severing activity. Spastin had been previously identified through its frequent mutation in patients with hereditary spastic paraplegia (HSP), a disease characterized by gradual degeneration of the corticospinal motor neurons, while a spontaneous mutation in fidgetin in albino mice had been linked with motor abnormalities. By the start of the new millennium, basic biological and genetic studies had thereby converged to define a subfamily of AAA-ATPase microtubule-severing enzymes conserved in a wide range of eukaryotes from ciliates to humans.

Structure and mechanism of action of microtubule-severing enzymes

The discovery that a mere enzyme could dismantle a mesoscopic, stable polymer with a bending rigidity of millimeters came as a surprise. However, recent biochemical reconstitution and structural studies have begun to illuminate the mechanism underlying this feat. All microtubule-severing enzymes have a highly homologous carboxy-terminal AAA-ATPase domain connected through a flexible linker to an amino-terminal microtubule interacting and trafficking (MIT) domain (Figure 1A). Most mechanistic and structural work so far has been performed on spastin and katanin and thus this section focuses on these two enzymes, although the overall structural features of the highly homologous AAA-ATPase domain are shared with fidgetin. The AAA-ATPase domains are essential for severing and hexamerize around the flexible carboxy-terminal tubulin tails that project from the microtubule surface. The enzymes

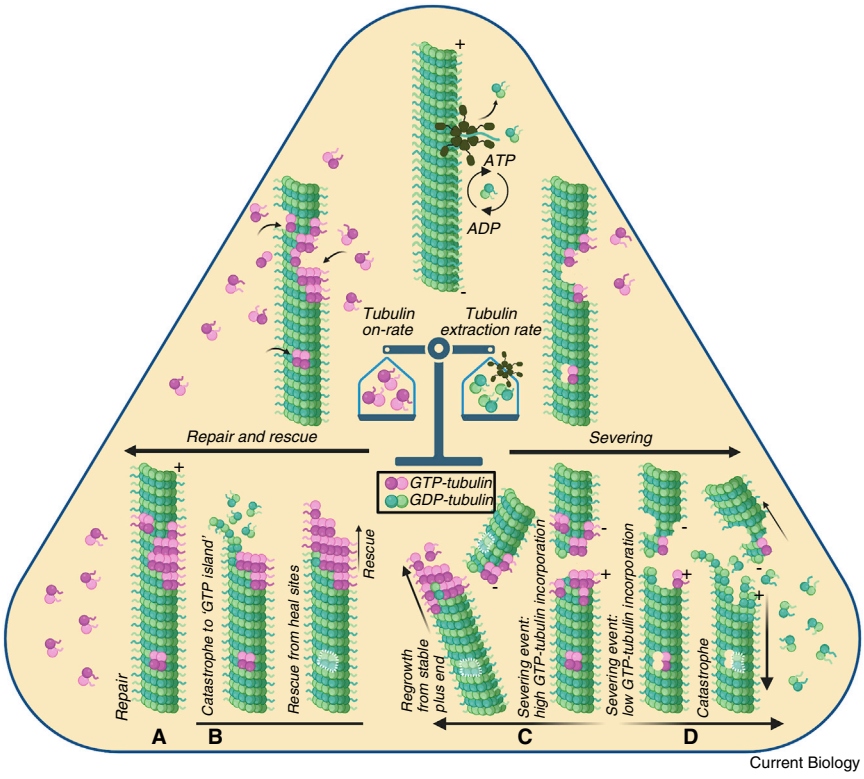

Figure 2. Severing proceeds through repaired lattice intermediates and generates diverse outcomes.
Severing enzymes extract tubulin dimers from the microtubule lattice iteratively to generate nano-damage of varying sizes. If GTP-tubulin replenishment outpaces severing activity, the microtubule lattice is repaired and strengthened by 'GTP islands' (A), which serve preferentially as rescue sites (B). When extraction of tubulin dimers outpaces GTP-tubulin incorporation, a mesoscopic severing event occurs, generating fragments that are either stable and primed for regrowth because of a simultaneously acquired protective layer of GTP-tubulin (C) or undergo depolymerization (D).

engage the electronegative tubulin tails through an intertwined double spiral of two pore loops in the AAA-ATPase core formed of conserved aromatic and positively charged residues (Figure 1B). Both spastin and katanin also interact with the microtubule through a positively charged linker region (Figure 1). ATP hydrolysis triggers conformational changes that are thought to tug on the tubulin tail, ultimately leading to extraction of the tubulin subunit from the microtubule. Visualization of severing intermediates by electron microscopy has indeed revealed that microtubules are peppered along their lengths with holes, representing sites from which tubulin has been removed. It is the accumulation of these tubulin extraction events that ultimately results in full severing. Therefore, although the term 'severing' and katanin's namesake of the samurai sword invoke the swift and decisive slash of a sword cleaving the lattice neatly in two, the actual mechanism is akin to removal of bricks from a tower wall.

The multiple contact points between the severing enzyme and microtubule allow severing to be regulated by diverse post-translational modifications and binding partners (Figure 1A,B). Glutamylation of the carboxy-terminal tubulin tails, for example, modulates binding affinity and severing efficiency. Phosphorylation of katanin in the linker region by Aurora B kinase impairs microtubule binding. Microtubule-associated proteins (MAPs), which coat the microtubule, serve as another means of regulation, blocking access to the microtubule and inhibiting severing, as observed for MAP4 and tau. Meanwhile, regions outside the conserved AAA-ATPase core that vary between each severing enzyme, and even between its isoforms, are responsible for recruiting unique sets of cellular factors (discussed below) to mediate non-overlapping cellular functions (Figure 1A).

Severing proceeds through repaired lattice intermediates generating diverse outcomes

The original microscopy-based assays that led to the discovery of severing enzymes used taxol-stabilized microtubules and missed a key ingredient — soluble tubulin, which is present at micromolar concentrations in the cytoplasm (taxol-stabilized microtubules are stable in the absence of soluble tubulin, and thus a workhorse for biochemical assays in the field). Soluble GTP-tubulin is primarily associated with addition onto the dynamic microtubule plus end, forming a 'GTP cap' that is stabilized against depolymerization and that gradually hydrolyzes or converts to GDP-tubulin upon integration into the lattice. Exposed GDP-tubulin lattice depolymerizes spontaneously. However, recent work showed that the stepwise holes or nanodamage sites that spastin and katanin generate in the microtubule lattice are rapidly filled by the incorporation of GTP-tubulin from solution in a process termed 'repair'. *In vitro* reconstitution experiments demonstrated that these 'GTP islands' can protect the microtubule against depolymerization, as they constitute sites at which 'rescues' (the transition from a depolymerization state to a growth state) preferentially occur (Figure 2A,B).

Moreover, the continuous tubulin removal–repair cycle ensures that, when a microtubule is ultimately severed by the enzyme, the newly generated fragment(s) emerge with a higher density of GTP-tubulin at their plus ends that can prevent rapid depolymerization and prime the microtubule for regrowth (Figure 2C). Otherwise, GDP-tubulin plus ends depolymerize spontaneously (Figure 2D). Even when artificially severed with a laser, microtubules first remodeled by severing enzymes through the introduction of GTP-tubulin show higher stability compared to microtubules to which the enzyme is just passively binding. Thus, severing in physiological conditions (and not with taxol-stabilized microtubules) reflects an underlying balance between the rate at which tubulin is removed from the microtubule wall and the rate of GTP-tubulin incorporation, with

both severing and repair existing simultaneously (Figure 2). These GTP-repair sites recruit factors usually associated with the GTP-tubulin-rich microtubule ends (such as plus end binding protein 1, EB1) and thus can be subject to complex additional regulation. Severing enzymes therefore have the capacity to mediate diametrically opposed outcomes — hovering in a yin and yang between depolymerization and amplification of microtubules. The ability to bias and coordinate these intermediate states makes severing enzymes extraordinarily multifaceted microtubule effectors.

The many labors of microtubule-severing enzymes

The katanin-mediated depolymerization of microtubules observed in mitotic egg oocytes marked the origin of the field. However, subsequent studies revealed that severing enzymes have more nuanced or even counterintuitive effects on microtubule arrays, consistent with recent *in vitro* reconstitution experiments. In the Greek myth, each Hydra head severed by Hercules infamously generated two new heads to replace it. However, Hercules recognized that burning of the cut site with a torch prevented regrowth. Similarly, an emerging theme in the determination of severing outcomes *in vivo* is an expanding cast of microtubule-interacting factors capable of localizing or enhancing severing activity or influencing the fate of the resulting severed fragments. These fragments can serve as 'seeds' for amplification of microtubule number and mass. In the subsections below, we explore several examples of how the actions of katanin, spastin and fidgetin are coordinated across organisms, tissues, and developmental stages to craft versatile and varied microtubule architectures and activities.

Construction of cilia and flagella

One of the earliest observed phenotypes linked with mutation of katanin was paralysis of flagella in both *Chlamydomonas* and *Tetrahymena*. Electron microscopy revealed that katanin p80 mutants lacked a distinguishing feature of flagella and motile cilia — the central microtubule pair. Early models proposed that katanin was acting in a depolymerizing capacity to generate a pool of tubulin monomers in the ciliary shaft to nucleate and extend this structure. However, recent work in mammalian ciliated tissues has clarified that it is instead the seed-generating role of katanin that is pivotal for central-pair formation and ciliary function. Katanin severs the elongating outer doublet microtubules that nucleate from the basal body, and the resulting seeds are stabilized by binding of CAMSAP to their minus ends for elongation into the central pair (Figure 3). CAMSAP overexpression leads to an excess number of central microtubules, highlighting the balancing act between severing and local concentrations of regulators. Loss of the central pair is phenocopied in *Tetrahymena* by tubulin mutations that abolish glutamylation, suggesting that this modification serves to localize severing activity during ciliogenesis. Conversely, katanin may also contribute to the dismantling of cilia (Figure 3). Another highly specialized ciliary structure — the mechanosensory organ of the campaniform receptor in *Drosophila* that provides feedback to mechanical strain or pressure — also relies on katanin for its unique organization. In this case, the katanin isoform kat-60L1 generates short microtubule segments that anchor arrays of mechanosensory channels. Its loss leads to sparse and aberrantly long microtubules, fewer active mechanosensory channels, and dramatically reduced flight ability in mutant flies.

Cell division

The meiotic and mitotic bipolar spindle is one of the best-characterized microtubule-based structures, responsible for the elaborate choreography of chromosomal alignment and segregation. In many organisms, both the initial assembly of the spindle, its maintenance, and the transition between the phases are dependent on the interplay between katanin, spastin and fidgetin. *Caenorhabditis elegans* embryos lacking katanin have longer, more sparse microtubules and arrest in meiosis, highlighting katanin's role in generating many short yet stable microtubule fragments for rapid assembly around the microtubule-nucleating meiotic chromatin. By regulating microtubule number and length, katanin also directly regulates spindle size. An Aurora B phosphorylation site present only in *X. laevis* katanin, close to the microtubule-binding interface in the p60 AAA–MIT linker (Figure 1A), inhibits microtubule severing, making *X. laevis* spindles longer than those of *X. tropicalis* (Figure 3). Spindles formed from mixed extracts have intermediate dimensions that scale proportionally with katanin activity. Similarly, *C. elegans* meiotic spindles scale with the severing activity of katanin mutants. In mammals, the adaptor protein WDR62 (Figure 1A) recruits katanin to the spindle, with depletion of either WDR62 or katanin resulting in warped and elongated spindle microtubules (Figure 3). Katanin also interacts through a composite p60–p80 interface with the mitosis-specific adaptor ASPM (Figure 1A), which localizes katanin to the spindle poles. Disrupting this interaction leads to a decrease in astral microtubules and to spindle misorientation (Figure 3). Notably, mutations in both katanin p80 and ASPM cause microlissencephaly in humans, characterized by excessive centriole number and multipolar spindles.

The final stage in mitosis, which encompasses the formation of a narrow cytoplasmic bridge, nuclear envelope resealing and, ultimately, the separation of cells by abscission or cytokinesis, also employs severing enzymes. Via an interaction with IST1 (Figure 1A), a component of the membrane-remodeling ESCRT-III complex, spastin localizes to and dismantles residual microtubules attached to chromatin discs to permit nuclear membrane reformation (Figure 3). In parallel, association with another ESCRT-III component, CHMP1B, along with targeted phosphorylation by HIPK2 (Figure 1A) results in recruitment of spastin to the midbody to break down the stable microtubule bundle bridging the two cells to allow the plasma membrane to reform (Figure 3). In animal cells, katanin also localizes to the midbody where it has been linked to cytokinesis.

Neuronal development and injury

Discovery of spastin through its association with HSP and neurodegeneration immediately tied severing enzymes to neuronal function. Work in zebrafish and *Drosophila* larvae showed that spastin loss causes

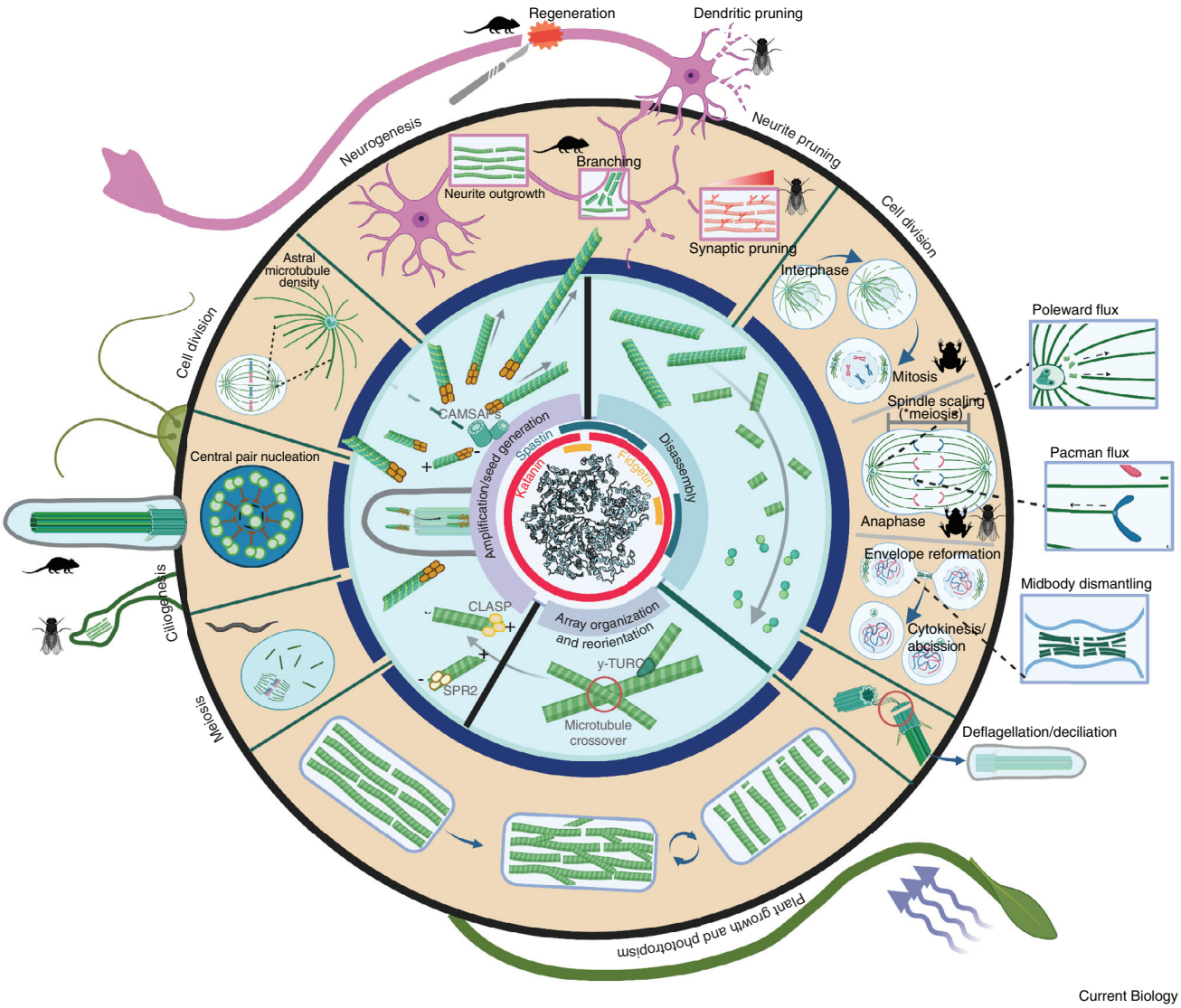

Figure 3. Microtubule-severing enzymes carry out a diversity of processes across organisms, tissues, and developmental stages — breaking down, constructing and reorganizing microtubule arrays.
These functions of severing enzymes are accomplished through either dismantling or amplifying/seed-generating or array-organizing/-reorienting activities mediated by the varied outcomes presented in Figure 2, in combination with protein effectors that localize activity or skew the fate of the resulting fragments (inner ring). Through these modalities, severing enzymes contribute to cilliogenesis, neurogenesis and neuronal regeneration, cell division, and plant growth and responsiveness to environmental stimuli (outer ring) — see reviews in the Further reading section for references to the original studies. The organisms in which these activities have been observed are depicted as black symbols. For an allegorical depiction of severing-enzyme-mediated processes see the Caeretan Hydria from the Getty Museum depicting Herakles and Iolaos slaying the Hydra (https://www.getty.edu/art/collection/object/103VHE). All figures in this primer were prepared with biorender.com.

defects in motor neuron outgrowth, reduced microtubule bundles in the neuromuscular junction and abnormal numbers and arrangement of synaptic boutons. Neuronal development is an intricate act of microtubule organization that encompasses initial neurite outgrowth, specification of a long and stable axon, along with maintenance and plasticity of these neurites to establish functional neural networks. Neurons must therefore coordinate the activity of multiple severing enzymes to carry out these processes. Katanin, poised at the centrosome, is thought to sever and release microtubule fragments, which are stabilized by WDR47 and the minus-end-binding protein CAMSAP, and then transported into the axon for elongation. Indeed, loss of WDR47 resulted in loss of axon specification and decreased microtubule density (Figure 3). In contrast, dorsal root ganglion neurons depleted of spastin were only slightly impaired in primary neurite outgrowth yet formed fewer secondary axonal branches. Spastin, therefore, seems to act downstream of katanin and initial neurite extension to sever microtubules into smaller fragments within the axonal shaft for navigation into finer processes.

Following initial outgrowth, severing enzymes fine-tune neuronal circuits. In

Drosophila, the katanin isoform kat-60L1 is required to dismantle the microtubules within dendrites of larval sensory neurons in preparation for establishing adult-specific neural connections (Figure 3). At later stages, axonal branches that form functional synapses with other neurons must be reinforced, whereas those that fail to do so must be selectively cleared. In the mammalian neuromuscular junction, loss of spastin leads to a significant delay in synapse elimination (Figure 3). Interestingly, enhanced recruitment of spastin activity to specific neuronal branches may be mediated by activity-dependent polyglutamylation of microtubules (Figure 3). Severing enzymes also act in response to neuronal injury. In the same *Drosophila* sensory neurons in which kat-60L1 drives dendritic pruning, fidgetin responds to dendrite injury by disassembling microtubules in the damaged neurites (Figure 3).

Plant phototropism and tissue morphogenesis

The connection between microtubule severing, cell shape and tissue morphogenesis is most striking in plants where cellulose, which gives plants structure and shape, is patterned on the underlying cortical microtubule cytoskeleton. In *Arabidopsis*, tobacco, rice, and cucumber, aberrant katanin activity leads to less dense, disorganized, net-like microtubule arrays with overly long microtubules and results in defects in the growth and integrity of all organs due to defective cellulose deposition. The microtubule cortical array must also rearrange rapidly in response to hormonal, mechanical and light inputs, and katanin has been implicated in all of these pathways. Direct observation of severing events in *Arabidopsis* cortical arrays revealed that, upon blue-light exposure, katanin localization and severing at microtubule crossovers leads to rapid regrowth of a new microtubule array in a transverse orientation to the original. This guides the anisotropic growth of the plant towards the light. To maintain cortical arrays, katanin also releases microtubules from γ-tubulin ring complexes (γ-TURCs) nucleated from pre-existing microtubules following recruitment by the Msd1/SSX2IP microtubule-anchoring complex (also present in animal cells). Thus, work in plants has shown that katanin works on two fronts to construct microtubule arrays: it generates new microtubule arrays independent of nucleation factors, through microtubule-templated microtubule nucleation, and it synergizes with γ-TURCs to catalyze daughter microtubule release. Analogous mechanisms are likely to operate in other organisms and cell types but have been less amenable to direct visualization due to the density of the microtubule arrays involved.

Conclusions

Through biochemical, structural, and functional studies over the last thirty years, the scientific community has answered many fundamental questions regarding how severing enzymes act to reshape microtubule arrays. However, again like the Lernean Hydra, from each answered question springs several more. Uncovering the mechanistic details of how severing enzymes sculpt microtubule networks in spindles, cilia, or neuronal processes, for example, has been hindered by technical challenges associated with the direct visualization of severing in these dense, highly bundled structures. Now, advances in cellular imaging such as expansion microscopy and cryo-electron tomography coupled with CRISPR-mediated gene editing in diverse organisms and cell types will yield new insights into the interplay of effectors, severing enzymes and their many isoforms, ushering in an exciting next era for the severing-enzyme field.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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[1]Cell Biology and Biophysics Unit, National Institute of Neurological Disorders and Stroke, Bethesda, MD 20892, USA. [2]Biochemistry and Biophysics Center, National Heart, Lung and Blood Institute, Bethesda, MD 20892, USA. [3]Cell Biology and Biophysics Unit, Porter Neuroscience Research Center, National Institutes of Health, Building 35, Room 3B-203, 35 Convent Drive, MSC 3700, Bethesda, MD 20892-3700, USA.

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*E-mail: Antonina@nih.gov