New twists in actin–microtubule interactions

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ABSTRACT Actin filaments and microtubules are cytoskeletal polymers that participate in many vital cell functions including division, morphogenesis, phagocytosis, and motility. Despite the persistent dogma that actin filament and microtubule networks are distinct in localization, structure, and function, a growing body of evidence shows that these elements are choreographed through intricate mechanisms sensitive to either polymer. Many proteins and cellular signals that mediate actin–microtubule interactions have already been identified. However, the impact of these regulators is typically assessed with actin filament or microtubule polymers alone, independent of the other system. Further, unconventional modes and regulators coordinating actin–microtubule interactions are still being discovered. Here we examine several methods of actin–microtubule crosstalk with an emphasis on the molecular links between both polymer systems and their higher-order interactions.

INTRODUCTION: BASIC PROPERTIES OF ACTIN FILAMENTS AND MICROTUBULES
Actin filaments and microtubules are essential cytoskeletal proteins that act together to endow cells with a foundation for shape, infrastructure for transport, and mechanical forces that drive and direct locomotion and cell division. Altering either system or any of the hundreds of associated regulatory proteins can result in neuropathologies, birth defects, and various cancers. Actin filaments (F-actin) and microtubules intrinsically self-assemble from individual subunits, that is, globular actin monomers (G-actin) or tubulin dimers (Figure 1; Desai and Mitchison, 1997; Pollard and Borisy, 2003; Nogales and Wang, 2006; Rottner et al., 2017; Brouhard and Rice, 2018). Head-to-tail polymerization imparts structural polarity to each polymer and impacts their dynamic properties (Pollard, 2016; van de Willige et al., 2016). For example, specific proteins recognize the fast-growing “plus” ends of F-actin or microtubules to enhance or stabilize polymerization (Galjart, 2010; Bearce et al., 2015; Pollard, 2016; Shekhar et al., 2016). In addition to these fundamental similarities, the property of “dynamic instability” stochastically varies the length of microtubules through oscillating phases of growth and disassembly (Mitchison and Kirschner, 1984). The spontaneous assembly of either F-actin or microtubules is concentration dependent but kinetically unfavorable in cells (Desai and Mitchison, 1997; Pollard and Borisy, 2003). Thus, cells (and many biochemists) employ nucleation proteins that mimic the conformations of assembled polymers to initiate polymerization. Hundreds of regulatory proteins influence properties of cytoskeletal dynamics, including whether F-actin or microtubules are assembled, stabilized, capped, crosslinked, depolymerized, or severed (Pollard, 2016; Bodakuntla et al., 2019). While shared regulatory proteins are an obvious way to coordinate cytoskeletal polymers, most regulators have been characterized for individual F-actin or microtubule dynamics, without the other polymer system. Here we highlight recent cellular and in vitro–based strategies for actin–microtubule crosstalk that include mechanisms that underlie the physical association of both cytoskeletal systems and mechanisms that link both polymers through filament assembly.

Do actin filaments and microtubules interact?
Historically actin filaments and microtubules have been viewed as separate entities, each with their own set of regulatory proteins, dynamic behaviors, and distinct cellular locations. However, classic examples from cells suggest a direct and coordinated relationship, including: striking instances of overlapping localization between F-actin and microtubules in neuronal growth cones (Forscher and Smith, 1988; Suter and Forscher, 2000); microtubule ends probing the actin-rich cellular cortex (Wittmann et al., 2003; Seetharaman and Etienne-Manneville, 2019); and signaling events where microtubules influence...
the formation of specific F-actin arrays and F-actin dynamics reciprocally influence microtubule behaviors (Figure 2A) (Zhou et al., 2002; Suter et al., 2004; Colin et al., 2018; Dogterom and Koenderink, 2019). Recent cellular and biochemical evidence also indicates these polymer systems are fundamentally intertwined (Coles and Bradke, 2015; Dogterom and Koenderink, 2019). Waves of F-actin and microtubule polymerization drive intracellular transport and cell growth in axons (Winans et al., 2016). Elegant superresolution microscopy studies have uncovered linkages between F-actin rings and axonal microtubules mediated through spectrin, phosphomyosin, and ankyrin G protein complexes (Leterrier, 2018; Vassilopoulos et al., 2019). In the test tube, F-actin and microtubules do not directly interact (Griffith and Pollard, 1982; Henty-Ridilla et al., 2016; Farhadi et al., 2020). Instead, additional proteins or complexes that contain binding sites specific for either polymer mediate actin–microtubule crosstalk (Figure 2B). For example, motor proteins, fascin, tau, spectraplakins, microtubule actin crosslinking factor (MACF), and many others, bundle individual polymers (i.e., F-actin–F-actin or microtubule–microtubule) and also directly link F-actin and microtubules (Leung et al., 1999; Krendel et al., 2002; Applewhite et al., 2010; Preciado López et al., 2014; Elie et al., 2015; Villari et al., 2015; Oberhofer et al., 2020; Ricollo and Araujo, 2020). These crosstalk interactions ultimately support the formation of specialized cellular structures including flagella, cilia, microvilli, and filopodia. Bundling of individual polymers also influences several physical properties of cells including cytoplasmic viscosity, diffusion rates, or efficiency of molecular interactions (Fletcher and Mullins, 2010; Dogterom and Koenderink, 2019). Similarly, the direct bundling of microtubules to F-actin explains observations of microtubule growth aligned along actin filaments (Figure 2, A, A1, and B). The proximity of these interactions may facilitate the successful handoff of vesicles between microtubules and F-actin in the transition between long- and short-range modes of transport, or provide mechanical reinforcement to mitigate physical forces required for cell motility (Schoeder et al., 2010; Evans et al., 2014; Preciado López et al., 2014; Bouchet et al., 2016; Oberhofer et al., 2017; Radler et al., 2020). Further, direct linkages between relatively stiff microtubules and flexible F-actin bestows the paired polymers with emergent behaviors that ultimately influence the essential activities of cells, including consequences in the onset and progression of disease (Elie et al., 2015; Cabrales Fontela et al., 2017; Colin et al., 2018; Ricketts et al., 2019; Wang et al., 2019; Farhadi et al., 2020).

**Impact of actin filament network density and geometry on microtubules**

Unlinked F-actin and microtubule networks are flexible and respond to a myriad of physical and molecular signals that promote their incessant assembly or annihilation in cells. However, conventional crosstalk mechanisms that couple F-actin and microtubules tend to promote a transition from this highly dynamic state to one that is more rigid and stable. Preexisting cytoskeletal networks influence the coordination of both F-actin and microtubules. For example, microtubules present at the cell periphery must navigate a crowded Arp2/3 complex–generated meshwork of F-actin at the cell periphery (Figure 2C). This physical mechanism of cytoskeletal crosstalk promotes microtubule catastrophe events by exploiting differences in polymer tensile forces. This “wall” of densely packed cortical F-actin acts as a barrier that obstructs growing microtubules from entering filopodia or the leading edge of mammalian cells (Figure 2, A, A2, and C) (Dogterom and Yurke, 1997; Wittmann et al., 2003; Kueh and Mitchison, 2009; Colin et al., 2018). Microtubules that successfully navigate through the cortical F-actin meshwork become stably aligned or are guided along actin bundles by croslinking factors and orientation-sensitive motor proteins, before rapid disassembly events occur (Huda et al., 2012; Szikora et al., 2017; Svitkina, 2018). Alternatively, microtubules influence actin dynamics through disassembly events that coincide with Rac signals, which trigger F-actin assembly (Etienne-Manneville, 2004; Gupton and Gertler, 2007; Schober et al., 2007; Szikora et al., 2017; Svitkina, 2018; Seetharaman and Etienne-Manneville, 2019). Similarly, actin–microtubule crosstalk at microtubule organizing centers (MTOCs) like the centrosome are tuned by the density of F-actin, where increased F-actin correlates with diminished microtubule arrays in both cell- and biochemistry-based reconstitution assays (Figure 1D) (Inoue et al., 2019; Plessner et al., 2019). In contrast, unbranched F-actin configurations do not trigger frequent microtubule disassembly. Instead, these F-actin structures support the alignment and self-organization of both polymers (Colin et al., 2018; Farhadi et al., 2020). Thus, the geometry of F-actin networks influences microtubule dynamics through physical exchanges that deter net microtubule growth.

**Coordinating microtubule ends and actin assembly**

Physical interactions and the architecture of cytoskeletal networks classically highlight the vibrant interplay between F-actin and...
microtubules. These observations also underscore why additional crosstalk mechanisms are required to overcome physical obstacles and stabilize actin–microtubule dynamics. Motor proteins directly transport each other along F-actin and microtubules, canoodle on vesicles, and regulate the assembly and stability of their polymer tracks (Heisler et al., 2011; Chapa-Y-Lazo et al., 2020). Dynactin, a cofactor for the microtubule motor protein dynein, contains a capped filament of actin-related proteins (Schroer, 2004; Carter et al., 2016). Once emancipated from capping protein, actin filament polymerization occurs, directly linking microtubule-based motors with F-actin assembly (Fokin et al., 2021). Cells from diverse model systems display many striking actin–microtubule behaviors including some that connect microtubule ends to F-actin through actin assembly mechanisms (Figure 2, A, A3, and E). Following washout of actin disrupting drugs, F-actin regrows from the ends of microtubules in plant cells (Sampathkumar et al., 2011). In fission yeast, complexes of actin and microtubule regulators bars, 3 µm. (B) Crosslinking and bundling. F-actin–microtubule polymer coupling by crosslinking proteins, fascin or tau. (C) Network architecture and density. Dense actin filament networks act as a physical barrier that influences microtubule dynamics. (D) Microtubule organizing center (MTOC) and centrosome interactions. Centrosomes organize and nucleate cytoskeletal polymers, including actin filaments. Fast-growing ephemeral bundles of F-actin emanate from the cell cortex and stabilize the position of the mitotic spindle. This ultimately facilitates changes in actin–microtubule dynamics through the exchange of coregulatory proteins (i.e., formins) from actin bundles to microtubules. (E) Coordination through polymer assembly. Mechanisms using specific microtubule +Tip complexes also coregulate F-actin dynamics. These complexes ultimately organize in vitro and cellular actin–microtubule structures by nucleating actin filaments from the growing ends of microtubules. (F) Microtubule capture at actin-rich sites. Protein complexes present on F-actin capture and stabilize microtubules, particularly at focal adhesions. (G) Subunit-level coordination. Profilin regulates monomeric G-actin and microtubule polymers. Thus, profilin or similar proteins capable of sequestering actin monomers or tubulin dimers may influence actin–microtubule cross-talk through concentration limiting subunit pools. (H) Liquid–liquid phase separation. Biomolecular condensates of tau or liquid–liquid phase-separated (LLPS) clusters of nephrin, Nck, and N-WASP regulate the nucleation of microtubules or actin, respectively. (I) Microtubule lumen interactions. A recently discovered mode of cross-talk where F-actin is present in the microtubule lumen. Abbreviations: F-actin, actin filaments; MT, microtubule; +Tips, microtubule end-binding proteins; MTOC, microtubule organizing center; LLPS, liquid–liquid phase separation.
(i.e., functional homologues of adenomatous polyposis coli [APC], formin, EB1, and others) present on the growing ends of microtubules promote actin polymerization to polarize cells (Chang and Martin, 2009). In neuronal growth cones and at focal adhesions, APC nucleates F-actin networks at microtubule tips (Juanes et al., 2017, 2019, 2020; Efimova et al., 2020). A similar mechanism has been recapitulated in vitro with a minimal set of actin–microtubule binding proteins (Lewkowicz et al., 2008; Swiech et al., 2011; Henty-Ridilla et al., 2016). Studies utilizing protein chimeras or optogenetic strategies further distill the minimal components required for some interactions to conserved tandem calponin-homology domains and SaP motifs (Priciado López et al., 2014; Adikes et al., 2018; van Haren et al., 2018). In a stunning example, the optogenetic release of EB1 from microtubule ends triggers a dramatic reorganization of microtubule networks and a distinct increase in F-actin polymerization (van Haren et al., 2018). This increase in F-actin assembly may involve perturbations to GTP hydrolysis on microtubules, the loss of microtubule stabilizing proteins in complexes with EB1, or the liberation of actin nucleation-promoting factors from microtubule ends and/or sides (Gaillard et al., 2011; Roth-Johnsen et al., 2014; Szkora et al., 2017; van Haren et al., 2018).

### Microtubule capture at actin-rich sites

The orientation of microtubules is a critical facet of their biological function. To facilitate motor-based vesicular transport in axons, growing microtubule plus ends are positioned outward facing the cell periphery. The arrangement of microtubule ends in dividing cells is critical for both positioning the spindle apparatus and generating the forces required to align and separate chromosomes. To establish and maintain precise microtubule orientations, microtubule ends are captured at membranes or in protein complexes (Figure 2, A, A4, and F). In centrosomes and Golgi complexes, microtubule minus ends are secured and oriented by microtubule nucleation proteins (i.e., γ-TuRC) (Kollman et al., 2010; Gurel et al., 2014; Akhmanova and Steinmetz, 2019). Ultimately this generates arrays with microtubule plus ends radiating outward. Similarly, KN motif and ankyrin repeat domain–containing protein 1 (KANK), talin, and diverse microtubule plus-end binding proteins form complexes to stabilize and capture growing microtubules at focal adhesions (Figure 2F; Kaverina et al., 1998, 1999; Krendel et al., 2002; Krylyshkina et al., 2003; Stehbens et al., 2014; Bouchet et al., 2016; Dogterom and Koenderink, 2019; Juanes et al., 2019; Meiring et al., 2020; Oberhofer et al., 2020).

Microtubules anchored to F-actin bundles are thought to deposit additional proteins important for focal adhesion maturation, although the details and timing of stabilization complex formation are not yet fully resolved. When located near the cell cortex, captured microtubules become exposed to additional cues that regulate F-actin–based protrusions and focal adhesion turnover (i.e., integrin, Rac, Rho, and MAPK signaling pathways; Gupton et al., 2002; Yamana et al., 2006; Ezraty et al., 2009; Machacek et al., 2009; Rooney et al., 2010; Hu et al., 2017; Szkora et al., 2017; Svitkina, 2018; Dogterom and Koenderink, 2019; Seetharaman and Etienne-Manneville, 2019; Doki et al., 2020). Additional high spatial and temporal resolution studies are required to decipher these intricate feedback loops required to coordinate actin and microtubules at focal adhesions.

### MTOCs and centrosome-based microtubule–actin interactions

While mitotic spindles are definitively assembled from microtubules, the involvement or even presence of F-actin in spindle assembly is less obvious. Thus, many reports portray F-actin and microtubules as unlinked polymers during cell division. Yet, the direct influence of microtubules on F-actin bundles establishes the position of the spindle and division plane and the timing of cytokinesis by the actin-based contractile ring (Theesfeld et al., 1999; di Pietro et al., 2016; Kita et al., 2019). Actin–microtubule crosstalk occurs at mitotic spindles and centrosomes via two distinct populations of F-actin (Figure 2D). Similar to mechanisms employed at focal adhesions, the first variety of F-actin is somewhat abundant and stably attached to the cell cortex to stabilize the orientation of the mitotic spindle by providing capture sites for the plus ends of astral microtubules (Kunda and Baum, 2009; Maier et al., 2013). Actin-based myosin motors also use this population of F-actin to position the centrosome by pulling on astral microtubules (Kwon et al., 2015). The second be-spoke population of F-actin consists of extremely fast-growing ephemeral actin “fingers” that span the cell cortex (Figure 2D). These actin bundles position the spindle apparatus through the exchange of regulatory proteins from F-actin to microtubules and/or physical nudges (Kita et al., 2019). Intriguingly, the rapid growth rate of the actin “fingers” suggests formin protein complexes stimulate spindle pole F-actin polymerization (Martin et al., 2005; Henty-Ridilla et al., 2016). In synergistic work, branched F-actin networks associated with centrosomes also contribute to the proper alignment and formation of mitotic spindle and the alignment of chromosomes during prometaphase (Farina et al., 2016, 2019; Inoue et al., 2019; Plessner et al., 2019). Genetic or pharmacological disruption of actin filaments generated by the Arp2/3 complex led to defects in mitotic progression (Plessner et al., 2019). These findings complement studies defining MTOCs and centrosomes as organizational hubs for directing F-actin–microtubule interactions in cells and in vitro (Farina et al., 2016, 2019; Inoue et al., 2019). In contrast,acentosomal microtubules nucleated from the Golgi apparatus require formin-derived F-actin polymerization to organize microtubule arrays and further regulate Golgi assembly (Efimov et al., 2007; Gurel et al., 2014; Copeland et al., 2016; Meiring et al., 2020). In sum, MTOCs from multiple sources are microtubule and actin organizing centers.

### Subunit-level coordination of actin and microtubules

Consistent with the convention of studying F-actin and microtubules individually, most proteins that regulate cytoskeletal dynamics have been examined with regard to one polymer or the other. Has this concealed the key properties of actin and microtubule regulation proteins by placing them into specific cytoskeletal factions? Tau is frequently touted as the universal microtubule associated stabilizing protein. Tau also potently binds (K_{D} ≈ 60–241 nM) and bundles F-actin, and efficiently cross-links actin and microtubules together (Figure 2B) (Goode et al., 1997; He et al., 2009; Elie et al., 2015; Barbier et al., 2019). Yet observations detailing the role for tau with F-actin or coordinating actin–microtubule crosstalk are often overlooked in conventional pathophysiological contexts. Similarly, while several studies demonstrate that profilin binds and regulates microtubules, thousands of studies have focused on decoding its roles regulating actin dynamics (Witke et al., 1998; Nejedla et al., 2016; Henty-Ridilla et al., 2017; Pimm et al., 2020). Notably, profilin interacts with microtubules through direct and formin–profilin mechanisms (Witke et al., 1998; Nejedla et al., 2016; Henty-Ridilla et al., 2017). Conversely, pharmacological disruption of F-actin or microtubules shifts the distribution of profilin in favor of the other polymer in cells (Nejedla et al., 2016). In addition, actin monomers (G-actin) and microtubules directly compete for profilin binding (Henty-Ridilla et al., 2017). Altogether these observations suggest a previously unconsidered complex of actin–microtubule crosstalk executed through homeostatic competition of regulatory proteins for limited G-actin and tubulin subunit pools (Figure 2G). Reconsidering the roles of “classic” cytoskeletal regulators with regard to the “other” polymer...
system (or both systems simultaneously) will likely resolve novel behaviors that underpin several actin–microtubule collaborations.

**Impact of liquid phase separation on actin or microtubules**

Biomolecular condensates or liquid–liquid phase-separated (LLPS) droplets are regulated by properties reminiscent of many cytoskeletal proteins including concentration-dependent formation; the sequestration, localization, and enrichment of proteins; and the generation of forces that deform membranes (Banjade and Rosen, 2014; Hernández-Vega et al., 2017; Alberti et al., 2019). Thus, the principles that underlie this new “phase” in cell biology may also apply to mechanisms of actin–microtubule crosstalk. Indeed, dynamic properties of both microtubules and actin are influenced by LLPS (Figure 2H). Phase transitions are thought to promote mitotic spindle formation by concentrating associated proteins (Jiang et al., 2015; Liu et al., 2020). Confinement or enrichment of cytoskeletal regulation proteins (i.e., tau, TPX2, anillin, and others) and their corresponding building blocks in a biomolecular condensate promotes polymer formation (Figure 2H; Ambadipudi et al., 2017; Hernández-Vega et al., 2017; Bodakuntla et al., 2019; King and Petry, 2020). For example, biomolecular condensates of nephrin–Nck–N-WASP increased the dwell time of N-WASP with the actin filament nucleating Arp2/3 complex to stimulate actin polymerization (Figure 2H; Case et al., 2019). Tau forms liquid droplets capable of binding and reorganizing microtubules in vitro (Ambadipudi et al., 2017; Wegmann et al., 2018; Zhang et al., 2020). Intriguingly, tau-droplet formation uses the same motifs required to bind and cross-link actin filaments (Elie et al., 2015; Ambadipudi et al., 2017; Zhang et al., 2020). However, whether biomolecular condensate-forming proteins with dual affinity for polymers can be used to link actin and microtubule dynamics has not been investigated.

**New directions and concluding remarks**

Mechanisms of actin–microtubule crosstalk require intricate levels of coordination between shared regulatory factors, physical properties, cellular signals, and complex feedback loops. Significant experimental evidence and new tools have recently become available to expand our knowledge of how cytoskeletal polymers respond to and interact with each other. In the test tube, actin filaments and microtubules do not directly interact. Therefore, the coordinated F-actin and microtubules seen in cells is dependent on the presence of coupling molecules, temporal considerations, and the physiological context for each interaction. More actin–microtubule linking mechanisms will be discovered. A surprising recent revelation is the unexpected presence of F-actin inside the microtubule lumen (Figure 2I) (Paul et al., 2020). How does this F-actin get inside? Is the F-actin polymerized in the lumen? Are microtubule protofilaments closed around it? Does the G- or F-actin get inside? Is the F-actin polymerized in the lumen? Are microtubule lumen (Figure 2I) (Paul et al., 2020). Intriguingly, tau-droplet formation uses the same motifs required to bind and cross-link actin filaments (Elie et al., 2015; Ambadipudi et al., 2017; Zhang et al., 2020). How ever, whether biomolecular condensate-forming proteins with dual affinity for polymers can be used to link actin and microtubule dynamics has not been investigated.

Recent discoveries describe new ways to connect actin and microtubule dynamics. Many proteins likely to be involved in actin–microtubule interactions have already been identified and are well characterized with regard to F-actin or microtubules alone. Few studies have addressed whether linked cytoskeletal polymers display emergent properties in vitro or measured the linked activities of both polymers together in cells. Studies that simultaneously monitor dynamic polymers in biomimetic reconstitution assays, may address this gap. In addition to mechanisms that link cytoskeletal polymers, what factors separate F-actin and microtubules? Microtubule disassembly mediated by catastrophe events, rapidly disconnect microtubules from actin structures (Henty-Ridilla et al., 2016). Competitive interactions for binding spots along either polymer or cellular signals could also influence the duration of F-actin and microtubule associations. Alternatively, coupled polymers exposed to specific disassembly factors may unlink F-actin and microtubules. For example, actin disassembly by coflin frees actin-associated polymer-linking proteins to reposition MTOCs at the immunological synapse (Wang et al., 2017). It is unclear whether the F-actin disassembled by coflin is already linked to microtubules or if these observations are another example of reduced F-actin density freeing cellular space for microtubules to polymerize (Farina et al., 2016, 2019; Inoue et al., 2019; Plessner et al., 2019). Research combining live cell experiments with biochemistry, genetic approaches, advanced imaging techniques, and progressive interdisciplinary approaches will bring insights to fully resolve these details.

We direct interested readers to the comprehensive reviews by Dogterom and Koenderink, 2019; Seetharaman and Etienne-Manneville, 2019; Oberhofer et al., 2020.

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