New twists in actin–microtubule interactions

Morgan L. Pimm[a] and Jessica L. Henty-Ridilla[a,b,*]
[a]Department of Biochemistry and Molecular Biology and [b]Department of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY 13210

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.**

Monitoring Editor
William Bement
University of Wisconsin, Madison

Received: Jul 1, 2020
Revised: Nov 20, 2020
Accepted: Dec 8, 2020

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

DOI:10.1091/mbc.E19-09-0491

*Address correspondence to: Jessica L. Henty-Ridilla (ridillaj@upstate.edu).

Abbreviations used: +Tip, microtubule plus end binding protein; γ-TuRC, gamma-tubulin ring complex; APC, adenomatous polyposis coli; EB1, end-binding protein 1; F-actin, filamentous actin; G-actin, globular actin; GTP, guanosine 5′-triphosphate; KANK, KN motif and ankyrin repeat domain-containing protein; LLPS, liquid-liquid phase separation; MACF, microtubule actin crosslinking factor; MAPK, mitogen-activated protein kinase; MT, microtubule; MTOC, microtubule organizing center; NCK, non-catalytic tyrosine kinase; NPF, nucleation promoting factor; N-WASP, Neural Wiskott-Aldrich Syndrome Protein; SxIP, serine-any amino acid-isoleucine-proline; TPX2, targeting protein for Xklp2.

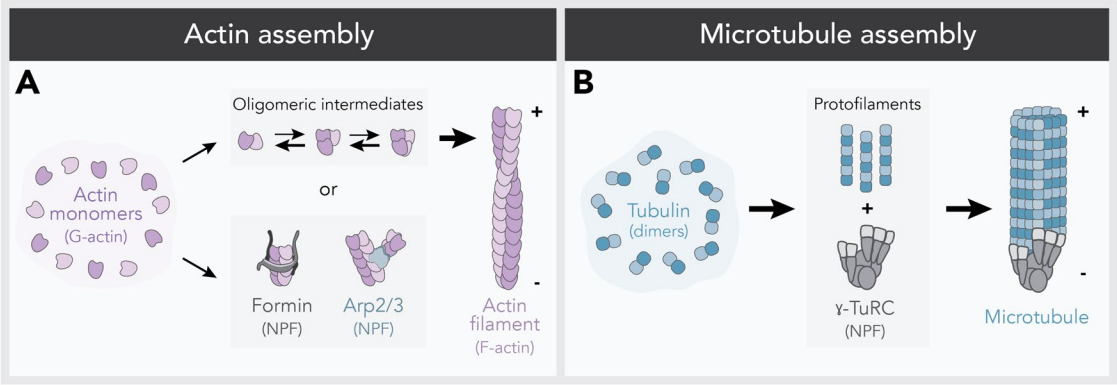

FIGURE 1: Properties of actin and microtubule assembly. (A) Assembly of actin filaments. Actin filaments (F-actin) are assembled from globular monomers (G-actin). Monomers assemble via spontaneous nucleation that is kinetically unfavorable or are assisted by nucleation-promoting factors (NPFs) such as formins or the Arp2/3 complex. (B) Microtubule polymerization. Microtubules require a stable template or NPFs like γ-TuRC to assemble. Dimers of tubulin intrinsically self-assemble to form protofilaments. Protofilaments are arranged on γ-TuRC templates and stabilized by lateral contacts to form microtubules. Polarity of F-actin and microtubules: +, the faster growing plus end; – the slower growing minus end.

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, phoshomyosin, 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; Ricolo and Araujo, 2020). These crosslinking 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 (Schroeder *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 crosslinking 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

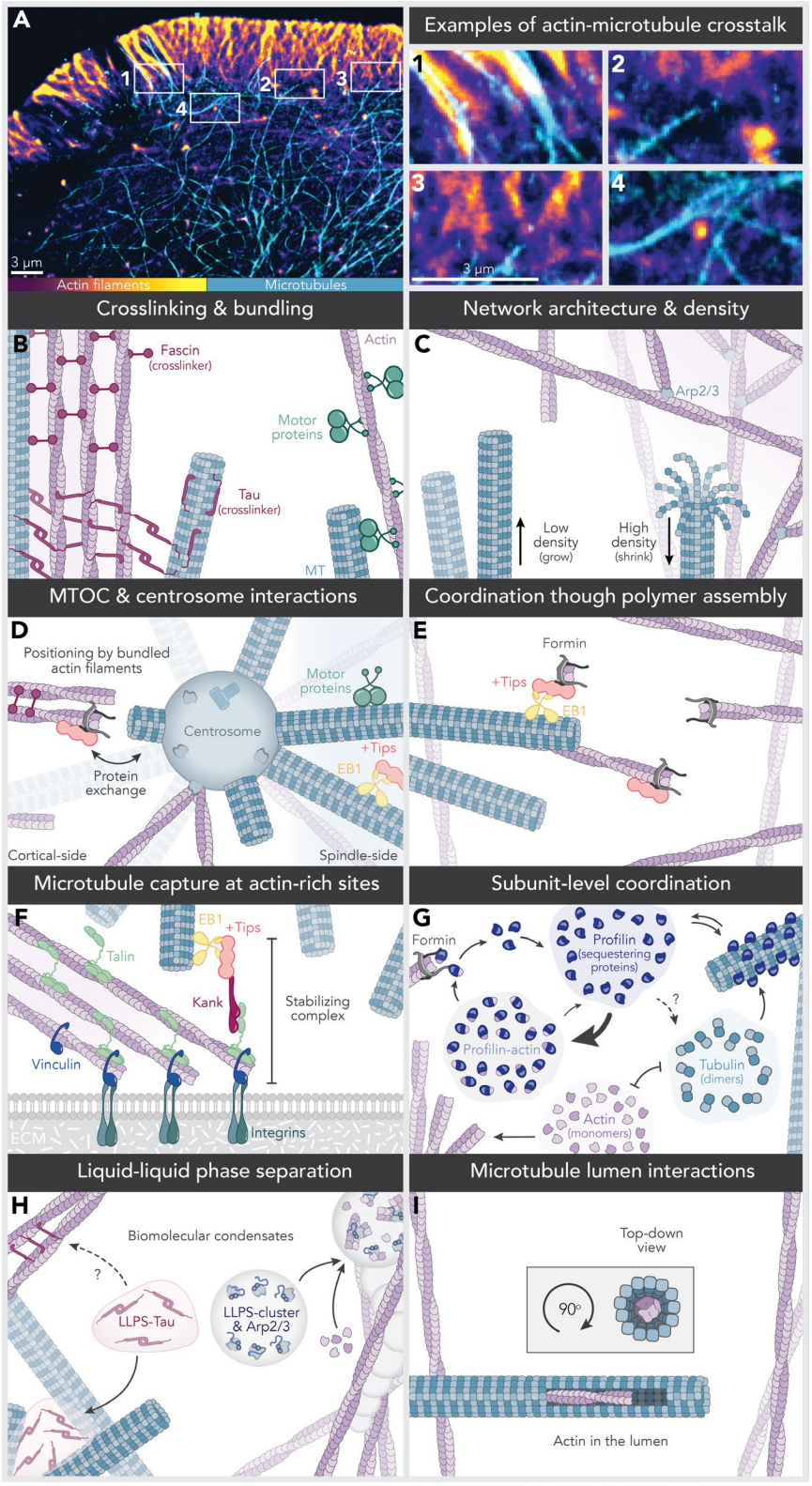

FIGURE 2: Mechanisms of actin–microtubule cross-talk. (A) Stochastic Optical Reconstruction Microscopy (STORM) image of actin filaments (purple-yellow) microtubules (cyan) from a Neuroblastoma-2a cell. Actin filaments are labeled with phalloidin and microtubules are immunolabeled with antibodies conjugated to AlexaFluor dyes. Representative crosstalk mechanisms are highlighted in each inset (right): 1) F-actin crosslinked to microtubules; (2) microtubules unable to penetrate the F-actin–rich cell cortex; (3) actin filaments located at (and possibly growing from) the growing ends of microtubules; (4) endocytic patches likely anchoring microtubules to actin filaments. Scale 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.

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

(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 SxIP motifs (Preciado 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-Johnson *et al.*, 2014; Szikora *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 stabile 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; Ezratty *et al.*, 2009; Machacek *et al.*, 2009; Rooney *et al.*, 2010; Hu *et al.*, 2017; Szikora *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 bespoke 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, acentrosomal 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 ($K_d \approx 60–241$ 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 form 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 enter the microtubule lumen at sites of microtubule damage and repair (Théry and Blanchoin, 2021)? The cross-section of the microtubule lumen is 15 nm, which is barely space to fit 1–2-, 7–8-nm-wide actin filaments—new twists and turns in actin–microtubule crosstalk indeed!

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 cofilin 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 cofilin 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.

ACKNOWLEDGMENTS

We are grateful to Marc Ridilla (Repair Biotechnologies), Christina Vizcarra (Barnard College), Maria Holland (University of Notre Dame), Svasti Haricharan (Sanford Burnham Prebys Medical Discovery Institute), George Burslem (University of Pennsylvania), and Ragothaman Yennamalli (Jaypee University) for comments on this manuscript. Research in the Henty-Ridilla laboratory is supported by a Hendrick's pilot grant, Sinsheimer Scholar Award, and NIH R35 award GM133485.

REFERENCES

Adikes RC, Hallett RA, Saway BF, Kuhlman B, Slep KC (2018). Control of microtubule dynamics using an optogenetic microtubule plus end–F-actin cross-linker. J Cell Biol 217, 779–793.

Akhmanova A, Steinmetz MO (2019). Microtubule minus-end regulation at a glance. J Cell Sci 132, jcs227850.

Alberti S, Gladfelter A, Mittag T (2019). Considerations and challenges in studying liquid-liquid phase separation and biomolecular condensates. Cell 176, 419–434.

Ambadipudi S, Biernat J, Riedel D, Mandelkow E, Zweckstetter M (2017). Liquid-liquid phase separation of the microtubule-binding repeats of the Alzheimer-related protein Tau. Nat Commun 8, 275.

Applewhite DA, Grode KD, Keller D, Zadeh AD, Zadeh A, Slep KC, Rogers SL (2010). The spectraplakin Short stop is an actin-microtubule cross-linker that contributes to organization of the microtubule network. Mol Biol Cell 21, 1714–1724.

Banjade S, Rosen MK (2014). Phase transitions of multivalent proteins can promote clustering of membrane receptors. ELife 3, e04123.

Barbier P, Zejneli O, Martinho M, Lasorsa A, Belle V, Smet-Nocca C, Tsvetkov PO, Devred F, Landrieu I (2019). Role of Tau as a microtubule-associated protein: structural and functional aspects. Front Aging Neurosci 11, 204.

Bearce EA, Erdogan B, Lowery LA (2015). TIPsy tour guides: how microtubule plus-end tracking proteins (+TIPs) facilitate axon guidance. Front Cell Neurosci 9, 241.

Bodakuntla S, Jijumon AS, Villablanca C, Gonzalez-Billault C, Janke C (2019). Microtubule-associated proteins: structuring the cytoskeleton. Trends Cell Biol 29, 804–819.

Bouchet BP, Gough RE, Ammon Y-C, van de Willige D, Post H, Jacquemet G, Altelaar AM, Heck AJ, Goult BT, Akhmanova A (2016). Talin-KANK1 interaction controls the recruitment of cortical microtubule stabilizing complexes to focal adhesions. ELife 5, e18124.

Brouhard GJ, Rice LM (2018). Microtubule dynamics: an interplay of biochemistry and mechanics. Nat Rev Mol Cell Biol 19, 451–463.

Cabrales Fontela Y, Kadavath H, Biernat J, Riedel D, Mandelkow E, Zweckstetter M (2017). Multivalent cross-linking of actin filaments and

microtubules through the microtubule-associated protein Tau. Nat Commun 8, 1981.
Carter AP, Diamant AG, Urnavicius L (2016). How dynein and dynactin transport cargos: a structural perspective. Curr Opin Struct Biol 37, 62–70.
Case LB, Zhang X, Ditlev JA, Rosen MK (2019). Stoichiometry controls activity of phase-separated clusters of actin signaling proteins. Science 363, 1093–1097.
Chang F, Martin SG (2009). Shaping fission yeast with microtubules. Cold Spring Harb Perspect Biol 1, a001347.
Chapa-Y-Lazo B, Hamanaka M, Wray A, Balasubramanian MK, Mishima M (2020). Polar relaxation by dynein-mediated removal of cortical myosin II. J Cell Biol 219, e201903080.
Coles CH, Bradke F (2015). Coordinating neuronal actin-microtubule dynamics. Curr Biol 25, R677–R691.
Colin A, Singaravelu P, Théry M, Blanchoin L, Gueroui Z (2018). Actin-network architecture regulates microtubule dynamics. Curr Biol 28, 2647–2656.e4.
Copeland SJ, Thurston SF, Copeland JW (2016). Actin- and microtubule-dependent regulation of Golgi morphology by FHDC1. Mol Biol Cell 27, 260–276.
Desai A, Mitchison TJ (1997). Microtubule polymerization dynamics. Annu Rev Cell Dev Biol 13, 83–117.
di Pietro F, Echard A, Morin X (2016). Regulation of mitotic spindle orientation: an integrated view. EMBO Rep 17, 1106–1130.
Dogterom M, Koenderink GH (2019). Actin-microtubule crosstalk in cell biology. Nat Rev Mol Cell Biol 20, 38–54.
Dogterom M, Yurke B (1997). Measurement of the force-velocity relation for growing microtubules. Science 278, 856–860.
Doki C, Nishida K, Saito S, Shiga M, Ogara H, Kuramoto A, Kuragano M, Nozumi M, Igarashi M, Nakagawa H, *et al*. (2020). Microtubule elongation along actin filaments induced by microtubule-associated protein 4 contributes to the formation of cellular protrusions. J Biochem 168, 295–303.
Efimov A, Kharitonov A, Efimova N, Loncarek J, Miller PM, Andreyeva N, Gleeson P, Galjart N, Maia ARR, McLeod IX, *et al*. (2007). Asymmetric CLASP-dependent nucleation of noncentrosomal microtubules at the *trans*-Golgi network. Dev Cell 12, 917–930.
Efimova N, Yang C, Chia JX, Li N, Lengner CJ, Neufeld KL, Svitkina TM (2020). Branched actin networks are assembled on microtubules by adenomatous polyposis coli for targeted membrane protrusion. J Cell Biol 219, e202003091.
Elie A, Prezel E, Guérin C, Denarier E, Ramirez-Rios S, Serre L, Andrieux A, Fourest-Lieuvin A, Blanchoin L, Arnal I (2015). Tau co-organizes dynamic microtubule and actin networks. Sci Rep 5, 9964.
Etienne-Manneville S (2004). Actin and microtubules in cell motility: which one is in control? Traffic 5, 470–477.
Evans RD, Robinson C, Briggs DA, Tooth DJ, Ramalho JS, Cantero M, Montoliu L, Patel S, Sviderskaya EV, Hume AN (2014). Myosin-Va and dynamic actin oppose microtubules to drive long-range organelle transport. Curr Biol 24, 1743–1750.
Ezratty EJ, Bertaux C, Marcantonio EE, Gundersen GG (2009). Clathrin mediates integrin endocytosis for focal adhesion disassembly in migrating cells. J Cell Biol 187, 733–747.
Farhadi L, Ricketts SN, Rust MJ, Das M, Robertson-Anderson RM, Ross JL (2020). Actin and microtubule crosslinkers tune mobility and control co-localization in a composite cytoskeletal network. Soft Matter 16, 7191–7201.
Farina F, Ramkumar N, Brown L, Eweis DS, Anstatt J, Waring T, Bithell J, Scita G, Thery M, Blanchoin L, *et al*. (2019). Local actin nucleation tunes centrosomal microtubule nucleation during passage through mitosis. EMBO J 38, e99843.
Farina F, Gaillard J, Guérin C, Couté Y, Sillibourne J, Blanchoin L, Théry M (2016). The centrosome is an actin-organizing centre. Nat Cell Biol 18, 65–75.
Fletcher DA, Mullins RD (2010). Cell mechanics and the cytoskeleton. Nature 463, 485–492.
Fokin AI, David V, Oguievetskaia K, Derivery E, Stone CE, Cao L, Rocques N, Molinie N, Henriot V, Aumont-Nicaise M, *et al*. (2021). The Arp1/11 minifilament of dynactin primes the endosomal Arp2/3 complex. Sci Adv 7, eabd5956.
Forscher P, Smith SJ (1988). Actions of cytochalasins on the organization of actin filaments and microtubules in a neuronal growth cone. J Cell Biol 107, 1505–1516.
Gaillard J, Ramabhadran V, Neumanne E, Gurel P, Blanchoin L, Vantard M, Higgs HN (2011). Differential interactions of the formins INF2, mDia1, and mDia2 with microtubules. Mol Biol Cell 22, 4575–4587.
Galjart N (2010). Plus-end-tracking proteins and their interactions at microtubule ends. Curr Biol 20, R528–R537.
Goode BL, Denis PE, Panda D, Radeke MJ, Miller HP, Wilson L, Feinstein SC (1997). Functional interactions between the proline-rich and repeat regions of tau enhance microtubule binding and assembly. Mol Biol Cell 8, 353–365.
Griffith LM, Pollard TD (1982). The interaction of actin filaments with microtubules and microtubule-associated proteins. J Biol Chem 257, 9143–9151.
Gupton SL, Gertler FB (2007). Filopodia: the fingers that do the walking. Sci STKE 2007, re5.
Gupton SL, Salmon WC, Waterman-Storer CM (2002). Converging populations of F-actin promote breakage of associated microtubules to spatially regulate microtubule turnover in migrating cells. Curr Biol 12, 1891–1899.
Gurel PS, Hatch AL, Higgs HN (2014). Connecting the cytoskeleton to the endoplasmic reticulum and Golgi. Curr Biol 24, R660–R672.
He HJ, Wang XS, Pan R, Wang DL, Liu MN, He RQ (2009). The proline-rich domain of tau plays a role in interactions with actin. BMC Cell Biol 10, 81.
Heisler FF, Loebrich S, Pechmann Y, Maier N, Zivkovic AR, Tokito M, Hausrat TJ, Schweizer M, Bähring R, Holzbaur ELF, *et al*. (2011). Muskelin regulates actin filament- and microtubule-based GABA(A) receptor transport in neurons. Neuron 70, 66–81.
Henty-Ridilla JL, Juanes MA, Goode BL (2017). Profilin directly promotes microtubule growth through residues mutated in amyotrophic lateral sclerosis. Curr Biol 27, 3535–3543.e4.
Henty-Ridilla JL, Rankova A, Eskin JA, Kenny K, Goode BL (2016). Accelerated actin filament polymerization from microtubule plus ends. Science 352, 1004.
Hernández-Vega A, Braun M, Scharrel L, Jahnel M, Wegmann S, Hyman BT, Alberti S, Diez S, Hyman AA (2017). Local nucleation of microtubule bundles through tubulin concentration into a condensed Tau phase. Cell Rep 20, 2304–2312.
Hu Y, Lu J, Xu X, Lyu J, Zhang H (2017). Regulation of focal adhesion turnover in SDF-1α-stimulated migration of mesenchymal stem cells in neural differentiation. Sci Rep 7, 10013.
Huda S, Soh S, Pilans D, Byrska-Bishop M, Kim J, Wilk G, Borisy GG, Kandere-Grzybowska K, Grzybowski BA (2012). Microtubule guidance tested through controlled cell geometry. J Cell Sci 125, 5790–5799.
Inoue D, Obino D, Pineau J, Farina F, Gaillard J, Guerin C, Blanchoin L, Lennon-Duménil A-M, Théry M (2019). Actin filaments regulate microtubule growth at the centrosome. EMBO J 38, e99630.
Jiang H, Wang S, Huang Y, He X, Cui H, Zhu X, Zheng Y (2015). Phase transition of spindle-associated protein regulate spindle apparatus assembly. Cell 163, 108–122.
Juanes MA, Bouguenina H, Eskin JA, Jaiswal R, Badache A, Goode BL (2017). Adenomatous polyposis coli nucleates actin assembly to drive cell migration and microtubule-induced focal adhesion turnover. J Cell Biol 216, 2859–2875.
Juanes MA, Fees CP, Hoeprich GJ, Jaiswal R, Goode BL (2020). EB1 directly regulates APC-mediated actin nucleation. Curr Biol 30, 1–10.
Juanes MA, Isnardon D, Badache A, Brasselet S, Mavrakis M, Goode BL (2019). The role of APC-mediated actin assembly in microtubule capture and focal adhesion turnover. J Cell Biol 218, 3415–3435.
Kaverina I, Krylyshkina O, Small JV (1999). Microtubule targeting of substrate contacts promotes their relaxation and dissociation. J Cell Biol 146, 1033–1044.
Kaverina I, Rottner K, Small JV (1998). Targeting, capture, and stabilization of microtubules at early focal adhesions. J Cell Biol 142, 181–190.
King MR, Petry S (2020). Phase separation of TPX2 enhances and spatially coordinates microtubule nucleation. Nat Commun 11, 270.
Kita AM, Swider ZT, Erofeev I, Halloran MC, Goryachev AB, Bement WM (2019). Spindle–F-actin interactions in mitotic spindles in an intact vertebrate epithelium. Mol Biol Cell 30, 1645–1654.
Kollman JM, Polka JK, Zelter A, Davis TN, Agard DA (2010). Microtubule nucleating γ-TuSC assembles structures with 13-fold microtubule-like symmetry. Nature 466, 879–882.
Krendel M, Zenke FT, Bokoch GM (2002). Nucleotide exchange factor GEF-H1 mediates cross-talk between microtubules and the actin cytoskeleton. Nat Cell Biol 4, 294–301.
Krylyshkina O, Anderson KI, Kaverina I, Upmann I, Manstein DJ, Small JV, Toomre DK (2003). Nanometer targeting of microtubules to focal adhesions. J Cell Biol 161, 853–859.
Kueh HY, Mitchison TJ (2009). Structural plasticity in actin and tubulin polymer dynamics. Science 325, 960–963.
Kunda P, Baum B (2009). The actin cytoskeleton in spindle assembly and positioning. Trends Cell Biol 19, 174–179.
Kwon M, Bagonis M, Danuser G, Pellman D (2015). Direct microtubule-binding by Myosin-10 orients centrosomes toward retraction fibers and subcortical actin clouds. Dev Cell 34, 323–337.

Leterrier C (2018). The axon initial segment: an updated viewpoint. J Neurosci 38, 2135–2145.
Leung CL, Sun D, Zheng M, Knowles DR, Liem RK (1999). Microtubule actin cross-linking factor (MACF): a hybrid of dystonin and dystrophin that can interact with the actin and microtubule cytoskeletons. J Cell Biol 147, 1275–1286.
Lewkowicz E, Herit F, Le Clainche C, Bourdoncle P, Perez F, Niedergang F (2008). The microtubule-binding protein CLIP-170 coordinates mDia1 and actin reorganization during CR3-mediated phagocytosis. J Cell Biol 183, 1287–1298.
Liu X, Liu X, Wang H, Dou Z, Ruan K, Hill DL, Li L, Shi Y, Yao X (2020). Phase separation drives decision making in cell division. J Biol Chem 295, 13419–13431.
Machacek M, Hodgson L, Welch C, Elliott H, Pertz O, Nalbant P, Abell A, Johnson GL, Hahn KM, Danuser G (2009). Coordination of Rho GTPase activities during cell protrusion. Nature 461, 99–103.
Maier B, Kirsch M, Anderhub S, Zentgraf H, Krämer A (2013). The novel actin/focal adhesion-associated protein MISP is involved in mitotic spindle positioning in human cells. Cell Cycle 12, 1457–1471.
Martin SG, McDonald WH, Yates JR, Chang F (2005). Tea4p links microtubule plus ends with the formin for3p in the establishment of cell polarity. Dev Cell 8, 479–491.
Meiring JCM, Shneyer BI, Akhmanova A (2020). Generation and regulation of microtubule network asymmetry to drive cell polarity. Curr Opin Cell Biol 62, 86–95.
Mitchison T, Kirschner M (1984). Dynamic instability of microtubule growth. Nature 312, 237–242.
Nejedla M, Sadi S, Sulimenko V, de Almeida FN, Blom H, Draber P, Aspenström P, Karlsson R (2016). Profilin connects actin assembly with microtubule dynamics. Mol Biol Cell 27, 2381–2393.
Nogales E, Wang H-W (2006). Structural intermediates in microtubule assembly and disassembly: how and why? Curr Opin Cell Biol 18, 179–184.
Oberhofer A, Reithmann E, Spieler P, Stepp WL, Zimmermann D, Schmid B, Frey E, Ökten Z (2020). Molecular underpinnings of cytoskeletal crosstalk. Proc Natl Acad Sci USA 117, 3944–3952.
Oberhofer A, Spieler P, Rosenfeld Y, Stepp WL, Cleetus A, Hume AN, Mueller-Planitz F, Ökten Z (2017). Myosin Va's adaptor protein melanophilin enforces track selection on the microtubule and actin networks in vitro. Proc Natl Acad Sci USA 114, E4714–E4723.
Paul DM, Mantell J, Borucu U, Coombs J, Surridge KJ, Squire JM, Verkade P, Dodding MP (2020). In situ cryo-electron tomography reveals filamentous actin within the microtubule lumen. J Cell Biol 219, e201911154.
Pimm ML, Hotaling J, Henty-Ridilla JL (2020). Profilin choreographs actin and microtubules in cells and cancer. Int Rev Cell Mol Biol 355, 155–204.
Plessner M, Knerr J, Grosse R (2019). Centrosomal actin assembly is required for proper mitotic spindle formation and chromosome congression. iScience 15, 274–281.
Pollard TD (2016). Actin and actin-binding proteins. Cold Spring Harb Perspect Biol 8, a018226.
Pollard TD, Borisy GG (2003). Cellular motility driven by assembly and disassembly of actin filaments. Cell 112, 453–465.
Preciado López M, Huber F, Grigoriev I, Steinmetz MO, Akhmanova A, Koenderink GH, Dogterom M (2014). Actin-microtubule coordination at growing microtubule ends. Nat Commun 5, 4778.
Radler MR, Suber A, Spiliotis ET (2020). Spatial control of membrane traffic in neuronal dendrites. Mol Cell Neurosci 105, 103492.
Ricketts SN, Francis ML, Farhadi L, Rust MJ, Das M, Ross JL, Robertson-Anderson RM (2019). Varying crosslinking motifs drive the mesoscale mechanics of actin-microtubule composites. Sci Rep 9, 12831.
Ricolo D, Araujo SJ (2020). Coordinated crosstalk between microtubules and actin by a spectraplakin regulates lumen formation and branching. Elife 9, e61111.
Rooney C, White G, Nazgiewicz A, Woodcock SA, Anderson KI, Ballestrem C, Malliri A (2010). The Rac activator STEF (Tiam2) regulates cell migration by microtubule-mediated focal adhesion disassembly. EMBO Rep 11, 292–298.
Roth-Johnson EA, Vizcarra CL, Bois JS, Quinlan ME (2014). Interaction between microtubules and the *Drosophila* formin Cappuccino and its effect on actin assembly. J Biol Chem 289, 4395–4404.
Rottner K, Faix J, Bogdan S, Linder S, Kerkhoff E (2017). Actin assembly mechanisms at a glance. J Cell Sci 130, 3427–3435.
Sampathkumar A, Lindeboom JJ, Debolt S, Gutierrez R, Ehrhardt DW, Ketelaar T, Persson S (2011). Live cell imaging reveals structural associations between the actin and microtubule cytoskeleton in *Arabidopsis*. Plant Cell 23, 2302–2313.
Schober JM, Komarova YA, Chaga OY, Akhmanova A, Borisy GG (2007). Microtubule-targeting-dependent reorganization of filopodia. J Cell Sci 120, 1235–1244.
Schroeder HW, Mitchell C, Shuman H, Holzbaur ELF, Goldman YE (2010). Motor number controls cargo switching at actin-microtubule intersections in vitro. Curr Biol 20, 687–696.
Schroer TA (2004). Dynactin. Annu Rev Cell Dev Biol 20, 759–779.
Seetharaman S, Etienne-Manneville S (2019). Microtubules at focal adhesions—a double-edged sword. J Cell Sci 132, jcs232843.
Shekhar S, Pernier J, Carlier M-F (2016). Regulators of actin filament barbed ends at a glance. J Cell Sci 129, 1085–1091.
Stehbens SJ, Paszek M, Pemble H, Ettinger A, Gierke S, Wittmann T (2014). CLASPs link focal-adhesion-associated microtubule capture to localized exocytosis and adhesion site turnover. Nat Cell Biol 16, 561–573.
Suter DM, Forscher P (2000). Substrate-cytoskeletal coupling as a mechanism for the regulation of growth cone motility and guidance. J Neurobiol 44, 97–113.
Suter DM, Schaefer AW, Forscher P (2004). Microtubule dynamics are necessary for SRC family kinase-dependent growth cone steering. Curr Biol 14, 1194–1199.
Svitkina TM (2018). Ultrastructure of the actin cytoskeleton. Curr Opin Cell Biol 54, 1–8.
Swiech L, Blazejczyk M, Urbanska M, Pietruszka P, Dortland BR, Malik AR, Wulf PS, Hoogenraad CC, Jaworski J (2011). CLIP-170 and IQGAP1 cooperatively regulate dendrite morphology. J Neurosci 31, 4555–4568.
Szikora S, Földi I, Tóth K, Migh E, Vig A, Bugyi B, Maléth J, Hegyi P, Kaltenecker P, Sanchez-Soriano N, *et al*. (2017). The formin DAAM is required for coordination of the actin and microtubule cytoskeleton in axonal growth cones. J Cell Sci 130, 2506–2519.
Theesfeld CL, Irazoqui JE, Bloom K, Lew DJ (1999). The role of actin in spindle orientation changes during the *Saccharomyces cerevisiae* cell cycle. J Cell Biol 146, 1019–1032.
Théry M, Blanchoin L (2021). Microtubule self-repair. Curr Opin Cell Biol 68, 144–154.
van de Willige D, Hoogenraad CC, Akhmanova A (2016). Microtubule plus-end tracking proteins in neuronal development. Cell Mol Life Sci 73, 2053–2077.
van Haren J, Charafeddine RA, Ettinger A, Wang H, Hahn KM, Wittmann T (2018). Local control of intracellular microtubule dynamics by EB1 photodissociation. Nat Cell Biol 20, 252–261.
Vassilopoulos S, Gibaud S, Jimenez A, Caillol G, Leterrier C (2019). Ultrastructure of the axonal periodic scaffold reveals a braid-like organization of actin rings. Nat Commun 10, 5803.
Villari G, Jayo A, Zanet J, Fitch B, Serrels B, Frame M, Stramer BM, Goult BT, Parsons M (2015). A direct interaction between fascin and microtubules contributes to adhesion dynamics and cell migration. J Cell Sci 128, 4601–4614.
Wang K, Sun XH, Zhang Y, Zhang T, Zheng Y, Wei YC, Zhao P, Chen DY, Wu HA, Wang WH, *et al*. (2019). Characterization of cytoplasmic viscosity of hundreds of single tumour cells based on micropipette aspiration. R Soc Open Sci 6, 181707.
Wang JC, Lee JY-J, Christian S, Dang-Lawson M, Pritchard C, Freeman SA, Gold MR (2017). The Rap1–cofilin pathway coordinates actin reorganization and MTOC polarization at the B-cell immune synapse. J Cell Sci, jcs.191858.
Wegmann S, Eftekharzadeh B, Tepper K, Zoltowska KM, Bennett RE, Dujardin S, Laskowski PR, MacKenzie D, Kamath T, Commins C, *et al*. (2018). Tau protein liquid-liquid phase separation can initiate tau aggregation. EMBO J 37, e98049.
Winans AM, Collins SR, Meyer T (2016). Waves of actin and microtubule polymerization drive microtubule-based transport and neurite growth before single axon formation. Elife 5, e12387.
Witke W, Podtelejnikov AV, Di Nardo A, Sutherland JD, Gurniak CB, Dotti C, Mann M (1998). In mouse brain profilin I and profilin II associate with regulators of the endocytic pathway and actin assembly. EMBO J 17, 967–976.
Wittmann T, Bokoch GM, Waterman-Storer CM (2003). Regulation of leading edge microtubule and actin dynamics downstream of Rac1. J Cell Biol 161, 845–851.
Yamana N, Arakawa Y, Nishino T, Kurokawa K, Tanji M, Itoh RE, Monypenny J, Ishizaki T, Bito H, Nozaki K, *et al*. (2006). The Rho-mDia1 pathway regulates cell polarity and focal adhesion turnover in migrating cells through mobilizing Apc and c-Src. Mol Cell Biol 26, 6844–6858.
Zhang X, Vigers M, McCarty J, Rauch JN, Fredrickson GH, Wilson MZ, Shea J-E, Han S, Kosik KS (2020). The proline-rich domain promotes Tau liquid-liquid phase separation in cells. J Cell Biol 219, e202006054.
Zhou F-Q, Waterman-Storer CM, Cohan CS (2002). Focal loss of actin bundles causes microtubule redistribution and growth cone turning. J Cell Biol 157, 839–849.