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Current Opinion in Cell Biology

Myosin 2 – A general contractor for the cytoskeleton

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Cells derive their shape, and in turn much of their behavior, from the organization of the cytoskeleton. While a myriad of proteins contribute to the regulation and organization of this dynamic structure, two of the principal components are actin filaments, which provide the structure, and myosin motors, which generate the majority of the forces. Here we review recent results on the assembly and kinetics of non-muscle myosin 2, and highlight how the cellular environment modulates local myosin behavior and signaling.

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Current Opinion in Cell Biology 2025, **94**:102522

This review comes from a themed issue on **Cell Architecture (2025)**

Edited by **James Bear** and **Gijsje Koenderink**

For a complete overview see the Issue and the Editorial

Available online xxx

https://doi.org/10.1016/j.ceb.2025.102522

Introduction

Cell architecture is highly influenced by mechanical forces, with the actomyosin cytoskeleton being the dominant player. Inward contractile forces are driven by non-muscle myosin 2 (NM2) motor proteins pulling on actin filaments. These forces are transmitted throughout the cell and to the extracellular environment by the underlying actin network in collaboration with actin-binding proteins (ABPs) to build unique cell architectures. Collectively, decades of research have thus implanted myosin 2 function as a nexus in cell and tissue architecture [1]. In simplified form, signaling pathways with biophysical and biochemical cues dictate the formation of actomyosin networks, which in turn modulate the signaling and biophysical/biochemical environment [2,3] (Figure 1). These actomyosin networks, coupled to adhesions and the membrane [4,5], thus coordinate force production to alter cell shape and dictate cell architecture. Despite this firm establishment of myosin 2's importance, many molecular details of how myosin 2 is modulated and functions to control cell architecture, especially in specialized cells, remain to be uncovered. Here, we explore the spatial organization of myosin 2, while emphasizing recent advances and highlighting open questions in the field.

Note - We have sampled ideas and data from striated and smooth muscle myosin 2 neighbors throughout, while using the term "myosin 2" for readability and simplicity.

Myosin 2 basics

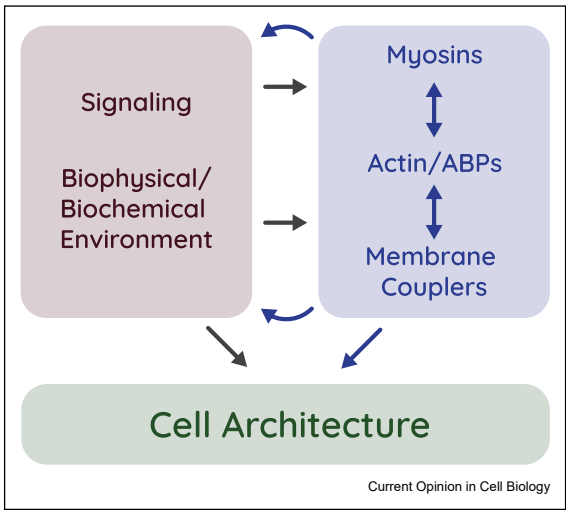
Myosin 2 "monomers" are hexameric ensembles of two myosin heavy chains (MHC), two essential light chains, and two regulatory light chains (RLC). The MHCs contain N-terminal motor domains, light chain-binding neck domains, and extended alpha-helices that dimerize into coiled-coil domains (Figure 2; top right). Humans and other mammals possess three non-muscle MHC genes (MYH9, MYH10, and MYH14) that produce three MHC proteins (MHC 2A, 2B, and 2C) that complex with light chains to generate three NM2 isoforms (NM2A, NM2B, and NM2C). To function, monomers of myosin 2 dynamically assemble into polymeric bipolar filaments with motor domains at opposing ends [1]. These motor domains hydrolyze ATP to produce conformational changes that can apply force to actin. When these myosin filaments encounter actin filaments with opposing polarity, the motors generate a contractile force. Alternatively, when myosin 2s find themselves on unipolar actin arrays, they move processively [6,7]. NM2 isoforms rapidly exchange between the monomer and filamentous state, enabling cells to dynamically modulate their contractile networks within seconds and minutes [8]. This monomer:polymer exchange happens constantly in every cell of the body. To understand myosin 2's contribution to any cellular process, including cell architecture, understanding monomer:polymer exchange and the process by which filaments are dynamically assembled and disassembled is absolutely requisite.

Assembling myosin 2 filaments

Standard model: RLC phosphorylation

The standard model for modulating monomer:polymer exchange, and therefore controlling myosin 2 assembly, is via RLC phosphorylation (Figure 2). Myosin 2 monomers mostly exist in a folded, inactive state, termed the 10S [9,10]. The 10S is stabilized by the motor domains folding back on the tail and docking on one another, known as the interacting heads motif

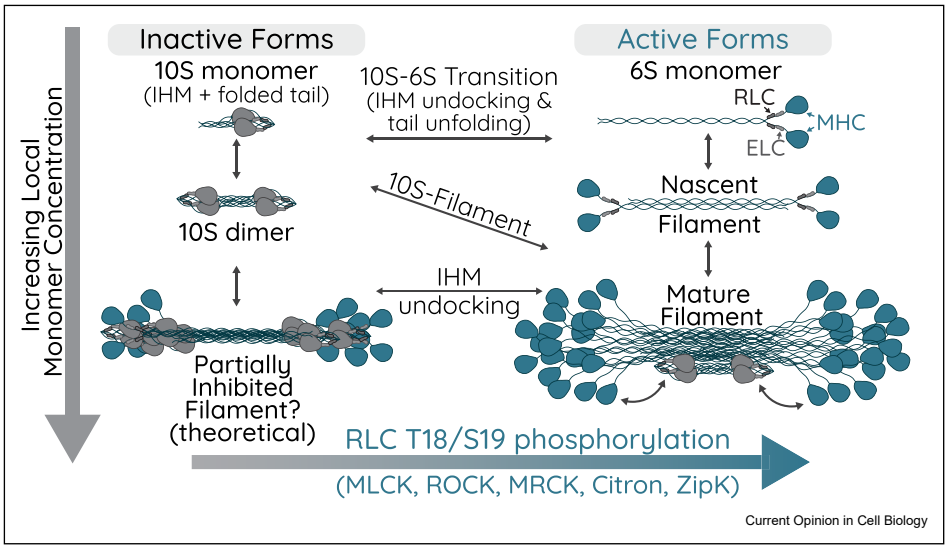
Figure 1



Overview. Numerous signaling pathways nested in biophysical and biochemical environments control and are controlled by the spatiotemporal localization of myosin 2, actin, ABPs, and membrane coupling components (i.e. Ezrin-Radixin-Moesin proteins, cell–cell or cell–matrix adhesions). These reciprocally influence one another to coordinate force production and cell architecture across multiple scales.

(IHM) [11,12], and the tail wrapping around the IHM 10S [13]. These 10S monomers diffuse throughout the cytosol until they are activated to unfold into a 6S monomer via phosphorylation of key residues (Thr18/Ser19) on the RLC [14]. Once unfolded, the heads are free to bind actin and resume the mechanochemical cycle, and the coiled-coil tail domains are available to participate in parallel/antiparallel interactions required for filament assembly [15]. RLC phosphorylation is mediated by various kinases, especially Rho-associated coiled-coil-containing kinases (ROCK) and myosin light chain kinase (MLCK) [16,17]. ROCK is activated downstream of RhoA, which is activated by guanine exchange factors (GEFs) concentrated at the cortex upon external stimuli (e.g. cytokines, chemokines, growth factors). MLCK is activated by calcium/calmodulin in response to multiple upstream stimuli. Numerous additional pathways and kinases (MRCK, ZIPK, citron kinase, PKC, CK2, etc.) impinge on RLC phosphorylation and MHC phosphorylation events, providing a wealth of modulatory mechanisms [1,18]. Together, these phosphorylation mechanisms are key determinants in the subcellular distribution of myosin 2. Yet aside from MLCK, we have a relatively poor understanding of molecular details for most of the kinase–myosin interactions. For example, we do not

Figure 2



Myosin 2 states and assembly mechanisms. The hexameric myosin 2 "monomer" consists of two MHCs, two ELCs, and two RLCs (top right). The canonical pathway of myosin 2 assembly travels clockwise from the folded, inactive 10S monomer (top left) to the unfolded, active 6S monomer. This transition is mediated by phosphorylation of the RLC (Thr18/Ser19), and enables 6S monomers to build nascent filaments or assemble into existing ones. Alternatively, 10S monomers and dimers may associate with existing filaments prior to activation (diagonal 10S-Filament), or possibly generate filamentous structures with inactive motors that can then be activated. A fully inactive filament with all motors in the IHM state is unlikely, but partially active/inactive intermediates are potentially occurring in cells.

know whether these kinases act on the myosin 2 monomer, filament, or both, nor do we understand the spatiotemporal kinetics of kinase activation relative to filament assembly.

The molecular readout of monomer:polymer equilibrium is the assembly, maintenance, and disassembly of myosin 2 filaments to spatiotemporally coordinate contractility and cell architecture. Surprisingly, there are key molecular gaps at all stages of this process.

Assembly pathways

Most graphical abstracts of myosin 2 assembly suggest the folded 10S monomer converts into the extended 6S monomer prior to entering into a filament (clockwise from the 10S in Figure 2) [19,20]. While this pathway is certainly probable, proving it in cells is challenging. Although the 6S is observed via EM [21], it is likely a transient state that needs to assemble into a filament or risk returning to the 10S.

Alternative pathways have recently been suggested. Korn and colleagues observed 10S dimers and tetramers associating with filaments during in vitro assembly (diagonal in Figure 2) [22]. If the 10S associates with filaments prior to unfolding, this could create a more favorable local environment for any 10S–6S intermediates and the eventual 6S itself. As the 10S unfolds and the electrostatic regions along the tail are exposed, the molecule is already in a favorable filamentous environment to provide stable incorporation.

Biophysics of assembly

While signaling via phosphorylation is undeniably important in regulating assembly, spatial and temporal biophysical factors also influence this process. Specifically, myosin:myosin and actin:myosin interactions play critical roles in tuning assembly dynamics, kinetics, and contractile activity.

Myosin interacts with itself across monomer and filament length scales. It is known that myosin will form stacks of filaments in register [23,24]. The preference for myosin to self-accumulate at smaller length scales is more recent. By coupling a photorecruitable tag to myosin 2 we showed that local cortical enrichment of myosin 2 induces filament assembly and amplification [25]. Notably this assembly included both the recruitable myosin 2 and endogenous myosin 2, indicating that myosin:myosin interactions are crucial for this assembly process. These results also demonstrate that filament assembly and growth can occur independent of upstream signaling if critical concentrations of monomer are locally realized [25], as is seen in vitro.

Once a filament assembles, the affinity for additional myosin continues. Using standard fluorescent candles we counted the number of myosin monomers inside what appeared to be individual filaments and larger clusters in the lamella [25]. This quantitative analysis revealed that presupposed "single" filaments were actually composed of multiple filaments, and that myosin assembly occurs ~100-fold more readily in existing clusters than in de novo nucleation events. Parallel work using pharmacological inhibitors showed that myosin clusters could grow in the absence of ATPase activity [26]. When the motor activity was reactivated, multiple clusters aggregated, increasing the cluster size further. These results suggest initial filament formation is rate-limiting, and that existing filaments are likely acting as templates for additional filament formation. This myosin-mediated myosin assembly is also likely driven by cooperative actin binding, where initial filaments alter actin in a favorable manner for additional myosins to bind and dwell [27,28].

The presence of different myosin isoforms and myosin-binding proteins further alters these dynamics.

Building upon previous research, recent work altering levels of NM2A, NM2B, and NM2C within cells showed that relative levels of these isoforms altered overall assembly, and that NM2B incorporation in particular can limit the contractility of the filament as a whole [29]. We similarly found that NM2B incorporation resulted in reduced myosin 2 processive speeds [7], consistent with in vitro experiments where NM2B slowed filament velocity [6]. Interaction of other proteins with myosin filaments can further impact their self-organization. For example, caldesmon, which binds both actin and myosin, helps regulate the spacing of myosin filaments along stress fibers [30]. Loss of caldesmon leads to poor filament organization and defects in contractility and migration, demonstrating that local organization of myosin filaments impacts larger-scale cellular functions. This is likely not an isolated event as additional novel myosin-binding proteins are continuously being identified that influence myosin 2 [31], including the unconventional myosin 18 [32,33]. Provided many binding partners are multifunctional, the field is recognizing myosin 2 filaments not simply as force producing machines, but as platforms to influence the local proteome and signaling atmosphere.

Collaboration with actin and actin-binding proteins

Actin/ABPs influencing myosin

A dynamic interplay between myosin, actin, and a plethora of ABPs dictates both the local and whole cell architecture. Here, we touch on recent observations of actin and ABPs influencing myosin, and vice versa.

Local actin networks influence myosin 2 assembly. At the leading edge of cells, membrane tension ultimately stalls arp2/3 driven actin polymerization, leading to

collapse of the lamellipodium and compression of the network into transverse arcs [34]. Myosin filament nucleation events in the lamella correlate with these retraction events [23,25]. We speculate that retraction generates a local increase in myosin monomer density by decreasing the pore size in the actin network due to the load applied by the collapsing membrane [35,36]. This local increase in density then allows monomers to overcome the entropic energy barrier required for filament assembly.

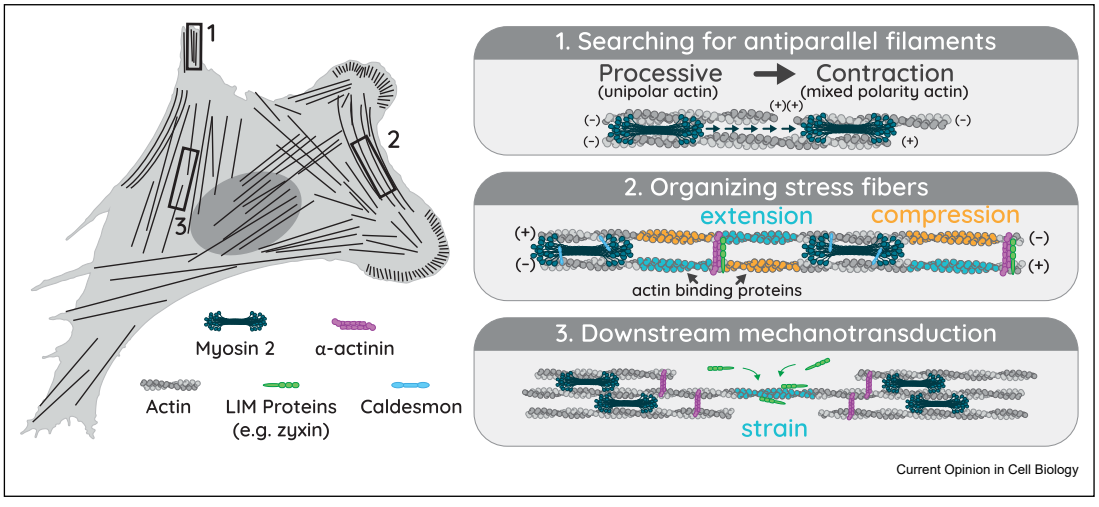
Following assembly, local actin architecture can influence myosin 2 behavior, further impacting macroscopic assembly and organization. The progression of smaller myosin 2 clusters into large clusters and stacks is dependent on actin dynamics [37,38]. Additionally, on unipolar actin filaments, myosin can move processively for microns, with noted differences between NM2 isoforms [6,7]. The processive myosin filament(s) should run until it stochastically falls off actin or it encounters mixed polarity actin, where both motor groups of the bipolar filament can engage with and contract actin (Figure 3). We hypothesize myosin 2 processivity is a mechanism continuously occurring in heterogenous actin networks, enabling filaments to "search" for mixed polarity actin and balance network contractility. The presence of other ABPs can also alter myosin localization. Typically in stress fibers, myosin alternates with alpha-actinin and zyxin [39,40]. These crosslinking proteins hypothetically create local frustrations, leading to local extension and compression of actin filaments within the bundle that ultimately facilitate contraction within the stress fiber (Figure 3) [41].

Myosin influencing actin/ABPs

Reciprocally, the presence and activity of myosin 2 influences actin structure and ABP behavior. Myosin-generated forces can break actin filaments [42—45]. When breakages occur, the load on remaining filaments increases and results in the recruitment of stress fiber repair proteins like zyxin (Figure 3) [46]. Recent works identified additional members of the LIM domain family that participate in this strain-sensing behavior [47,48], making myosin activity a key conduit for downstream mechanotransduction in response to changing myosin architecture. While extreme breakage and repair events are visually notable, similar small-scale events could be happening regularly throughout the network. It is possible that local extensions/compressions of actin within stress fibers even help to recruit zyxin/alpha-actinin and set a macroscopic scale of organization, though this remains to be shown experimentally.

Myosin's impact on actin is not exclusive to producing strain sites. Recent cryo-EM images revealed curved and superhelical morphologies of individual actin filaments under load [49]. Importantly, these structures were seen both in complex sites like focal adhesions and in purified artificial systems. Such changes to actin architecture can

Figure 3



Local architecture affects myosin function and signaling. The cartoon represents a standard fibroblast and the diverse architectures of actin filaments (black lines) that are found throughout the cell, which can each dictate specific myosin behaviors. 1) Along unipolar actin fibers myosin is processive until it encounters mixed polarity fibers which allow it to contract. 2) Within stress fibers, myosin filaments interact with a number of actin-binding proteins (e.g. alpha-actinin and zyxin) and myosin-binding proteins (e.g. caldesmon) likely causing local changes (extension/compression) in the actin filament structure. 3) Myosin-generated forces can cause strain in actin fibers, resulting in the recruitment of the LIM domain protein zyxin - a canonical example of mechanotransduction.

alter the binding kinetics of other ABPs like alpha-catenin [50], and potentially LIM family proteins [51]. Subtle changes in actin architecture induced by myosin may also act at a distance, as multiple ABPs like cofilin[52–54], formin [55,56], and calponin homology domains [57] exhibit altered binding kinetics on tensed filaments. Therefore, there is likely a wide array of actin structural states that are influenced by myosin 2 force production and recognized by a wide array of ABPs. Isolating homogenous populations of these structural states to enable atomistic understanding (e.g. cryoEM) is challenging, but should prove insightful for understanding how these ABPs differentially recognize diverse actin structures to influence cell architecture.

Collectively then, signaling and biophysics alter the reciprocal influence of myosin 2, actin, and ABPs on one another. When coupled with adhesion to the extracellular matrix and membrane/cortex couplers, these interactions ultimately define the cell architecture. While the toolbox of players is materializing, innumerable molecular details remain to be discovered.

Speculation: the auto-inhibited filament

Once assembled, myosin filaments are maintained by steady-state monomer:polymer exchange [26]. While some maintenance is dictated by balanced kinase and phosphatase activity, additional mechanisms are likely at play. One potential mechanism is the existence of autoinhibited motors in the IHM state in NM2 filaments. The IHM was first identified in smooth muscle myosin 2 monomers [11] and subsequently found in filaments in Tarantula [58] and mammalian striated muscles, and into distant relatives [59]. In muscles, it permits motor inactivation without disassembling the entire sarcomere, and then rapid motor activation as needed. This likely contributes to the Frank-Starling Law of the heart and molecular basis of length-dependent activation, where contractile force scales with ventricular filling (more blood in the chamber results in more contraction to push that blood out) [60]. While molecular questions remain, sarcomere stretching potentially destabilizes IHMs, providing more motors for the subsequent systolic contraction [61].

The need and presence of a partially inhibited filament in non-muscle cells is theoretical (Figure 2; lower left), but we argue this structure is possible and would enable filament maintenance and rapid tuning of contractility. For example, myosin 2 is a critical component of cell:cell junctions, including intercalated discs [62] in muscle and adherens junctions in epithelia [63]. Pulling by a neighboring epithelial cell requires a responsive contractile event to resist over-extension. While signaling (e.g. calcium-MLCK or Rho-ROCK) mechanisms contribute [64,65], a more rapid activation of myosin 2 motors via IHM destabilization could be a viable alternative. Similar concepts could apply to vascular smooth muscle cells where both smooth muscle and non-muscle myosin 2 isoforms could rapidly respond to luminal pressure increases, supplementing known signaling responses. This autoinhibited filament structure is potentially a transient intermediate, as it has not been detected in studies using purified NM2. However, a binding partner that either stabilizes the IHM or stabilizes the extended coiled-coil tail to prevent IHM interaction to form the 10S monomer, could prolong a transient state in cells. While speculative, this is an enticing hypothesis to consider for more rapid contractile responses.

This concept of a partially active filament further highlights myosin's diverse functional potential. While contractile force generation is oft-cited as myosin 2's primary function, filaments are also potent actin crosslinkers and bundlers. A partially active filament due to some IHM formation might enable crosslinking and bundling but be insufficient for significant actin translocation or meaningful force production. Differentiating between these functions is challenging, but should be considered more often. This is especially true when interpreting data using the small molecule inhibitor, blebbistatin, which places motors in a weak actin-binding state, inhibiting both contractility and actin crosslinking/bundling potential.

Filament disassembly: critically underexplored

The ability to recycle myosin 2 monomers to dynamically re-assemble is crucial throughout cell physiology. However, much less effort has been invested in understanding the disassembly process. This is a critical future direction for the field. One possibility is that simply turning off RLC kinase activity and allowing myosin phosphatase to shift the equilibrium toward the monomer is sufficient. However, a more active down-regulation could be at play. For example, MHC phosphorylation or interaction with S100 family members, especially S100A4, can inhibit assembly or potentially destabilize filaments [1]. In vitro experiments suggest these phosphorylation events and S100 interactions preferentially destabilize NM2A in filaments [66], allowing targeted isoform disassembly and mechanical tuning.

The molecular pathway by which molecules leave a filament is also underexplored. Similar to our considerations of assembly mechanisms, the electrostatic interactions between the tail domains and the conversion into the IHM and 10S are key. Pulling an extended 6S monomer sideways out of an existing filament seems unfavorable, although an unzipping mechanism is possible. Conversely, Korn and colleagues suggested the reversal of their entry pathway, whereby the monomer

folds into the 10S while still in the filament [22]. However, recent work in cardiac myosin 2 demonstrated that the motor domain inhibitor, mavacamten, which favors the IHM state, increased monomer:polymer exchange kinetics without impacting the rate of monomers dissociating from filaments [67]. Therefore, while forming the IHM could be the first step in myosin further folding itself out of a filament, more work is needed.

Myosin 2 in specialized cell architecture

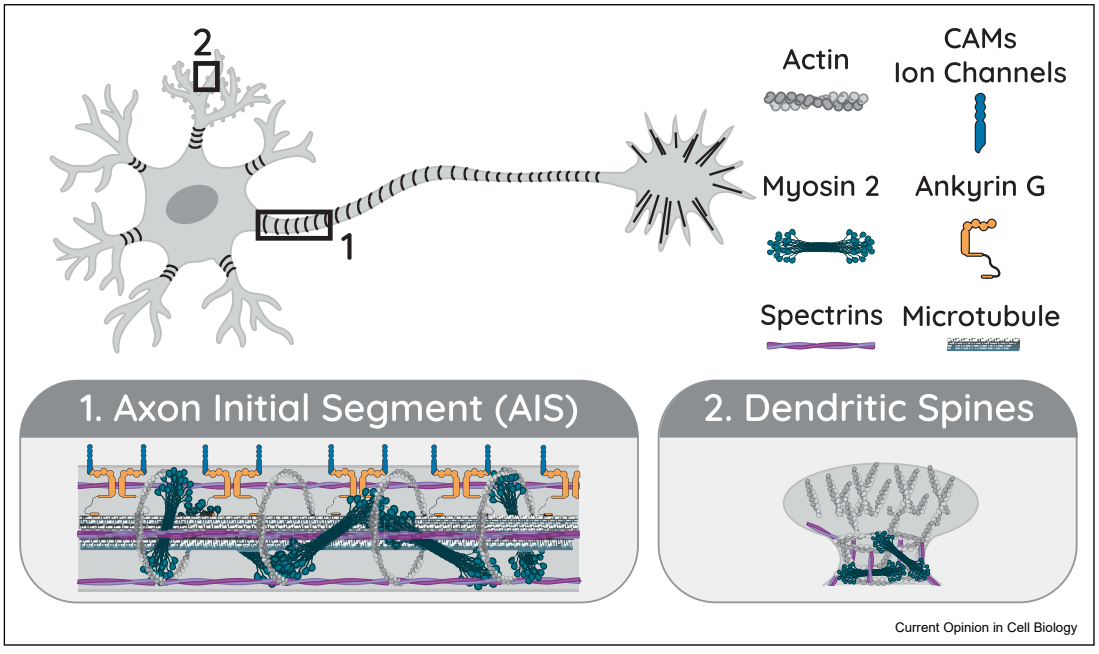
Mechanisms of myosin 2 assembly and its contributions to cell architecture have largely been studied using mesenchymal cells on glass coverslips. However, cells exist in many more complex and specialized architectures. While most model organisms and human tissues have architecturally fascinating cells that depend on myosin 2 [68–70], due to space, we focus here on emerging roles for myosin 2 in neurons.

In contrast to the broad, flat lamella of a fibroblast, neurites (axons and dendrites) are narrow tubes ranging from 0.1 to 10 μm in diameter. All neurites have a core microtubule bundle, which has long been the primary focus of neuronal architecture (Figure 4). However, recent observations in the axon and axon initial segment (AIS; recently reviewed in detail [20]) demonstrate key roles for actomyosin. Here, we briefly explore myosin 2 in growth cones, spines, and axons, where myosin 2's dominant function is to pull on membrane-coupled actin filaments, thus helping define the overall cell architecture.

Growth cones and spines

The path traveled by the growth cone of an extending neurite largely defines its terminal architecture. This protrusion is driven by actin assembly at the leading edge of the growth cone, similar to mesenchymal lamellipodia. Myosin 2 accumulates in the rear of the growth cone where it bundles and organizes actin filaments, limits microtubule intrusion into the anterior growth cone, and helps establish adhesive structures. Simplistically, myosin 2 limits axon protrusion due to its contractile activity and probably actin monomer sequestration, thereby limiting lammelipodia actin assembly similar to studies in migratory epithelial cells [71]. In reality, orchestrated neuronal pathfinding is certainly more complex than simply elongating as fast as possible, and myosin 2's isoform-specific contributions to growth cone architecture and adhesion are unquestionably contributing to overall neuronal cell architecture [72,73].

Figure 4



An example of specialized actomyosin structures found in neurons. The cartoon illustrates actin (black lines) distributed in rings along the dendrites and axon protrusions. 1) The Axon Initial Segment (AIS) is characterized by the accumulation of cell adhesion molecules (CAMs) and membrane associated proteins (e.g. Ankyrin G) along with active myosin filaments and spectrin tetramers around a central microtubule bundle. Note that to crosslink neighboring actin rings spaced 185 nm apart, the 300 nm long myosin 2 filaments would need to be angled accordingly. 2) Myosin further accumulates at the base of dendritic spines, helping give them their characteristic mushroom shape. While the localization of myosin to these structures has been well-characterized, there remain numerous open questions about the role myosins play in their formation, and their kinetics and behavior at these sites.

In dendritic spines, myosin 2 is essential for actin dynamics, spine retraction, and spine maturation, where it helps establish the classic mushroom architecture [74,75]. In mature synapses, myosin 2- based tension is critical for firing and plasticity [76,77]. The actomyosin organization at the base of spines may be a structural and functional relative of the actomyosin-spectrin network discussed below [78].

Axon and axon initial segment

The AIS is a specialized 20–60 μm long submembrane domain at the proximal axon crucial for initiating and shaping action potentials, and creating a diffusion barrier and selective cargo transport filter (Figure 4) [79]. The AIS contains the master scaffold protein ankyrin G which organizes and clusters voltage-gated ion channels and cell adhesion molecules, while anchoring itself to the underlying cytoskeleton through spectrin [80] and microtubule [81] binding domains. Advanced light microscopy revealed circumferential axonal actin rings spaced ∼185 nm apart, alternating with a spectrin lattice [82]. This highly organized network, termed the membrane-associated periodic skeleton (or scaffold; MPS), profoundly changed the view of the actomyosin contribution to neuronal architecture [83].

Myosin 2 is found throughout the axon, with a notable increase in active, RLC-phosphorylated myosin 2 in the AIS [84,85]. Static imaging suggests myosin 2 filaments might work on individual actin rings, or crosslink neighboring rings [85,86]. We still know relatively little about the dynamic assembly and maintenance of myosin networks in the axon, due to the requisite resolution to observe them. However, future efforts to understand how actin, spectrin, myosin 2 filaments, and other AIS components are dynamically assembling in the axon and AIS should reveal fascinating and relevant architectural biology.

Myosin 2 function within these structures remains an active area of investigation. Myosin inhibition increases action potential conduction velocity and axonal diameter [86,87]. This latter observation may provide a mechanism to modulate lumen diameter for cargo transport. More recently myosin 2 was suggested to have protective roles during mechanical injury. Transverse mechanical stress to the axon resulted in myosin 2-dependent beading, restricting degeneration-causing calcium transients from spreading along the rest of the axon [88]. Local retraction of the axon was also reported to be coupled directly to glycolysis, suggesting a tight interplay between contractility and metabolism [89]. Notably, most studies testing myosin 2 function relied on small molecule inhibitors, providing temporal but not spatial resolution. Given the diverse roles of myosin 2 throughout neurons, future incorporation of optogenetic approaches to spatially control myosin 2 in the subcellular domain of interest might prove insightful.

Conclusion & future perspectives

As a central player in the cytoskeleton, myosin 2 is clearly well-positioned to act as a force and signaling hub in the cell. Coupled with adhesions and the membrane/cortex, these interactions define not only force production but also the cellular architecture. From general assembly mechanisms to organization into highly specialized structures, the dynamics and activity of myosin 2 play a crucial role in determining many cellular functions. We've highlighted here some of the novel and exciting findings concerning myosin 2 and its many interacting partners. While these findings have no doubt reshaped our understanding of this important motor protein, they've also highlighted how much there is still to discover.

Disclosures

The authors declare no conflict of interest.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

P.W.O. is supported by NIH NIGMS grant R01-GM148644. J.R.B is supported by NIH NIGMS grant R35-GM138183 and R35GM137959-06S2. We thank the reviewers of this work for many helpful suggestions and corrections. We thank all of those who stand up for science.

Data availability

No data was used for the research described in the article.

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