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Physiology 20:239-251, 2005. doi:10.1152/physiol.00014.2005

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REVIEWS

PHYSIOLOGY 20: 239–251, 2005; 10.1152/physiol.00014.2005

Myosins: Tails (and Heads) of Functional Diversity

Mira Krendel[1] and
Mark S. Mooseker[1,2,3]
Departments of [1]Molecular, Cellular, and Developmental Biology; [2]Cell Biology; and [3]Pathology, Yale University, New Haven, Connecticut
mira.krendel@yale.edu

The myosin family of actin filament-based molecular motors consists of at least 20 structurally and functionally distinct classes. The human genome contains nearly 40 myosin genes, encoding 12 of these classes. Myosins have been implicated in a variety of intracellular functions, including cell migration and adhesion; intracellular transport and localization of organelles and macromolecules; signal transduction; and tumor suppression. In this review, recent insights into the remarkable diversity in the mechanochemical and functional properties associated with this family of molecular motors are discussed.

Myosins are actin-dependent molecular motors that use the energy of ATP hydrolysis to move along actin filaments. In the past 20 years many novel members of the myosin superfamily have been identified, with 16 new myosin classes joining founding members of this protein family: Myo1 and 2.* Several recent reviews have discussed the myosins' functions, with particular focus on Myo6, Myo1c, and Myo5, and the role of myosins in sensory functions and the nervous system (15, 16, 18, 45, 50, 95, 107). In this review we summarize the latest developments in the myosin field, with the emphasis on newly identified or substantially expanded intracellular functions of myosins.

Myosin Superfamily: Diversity of Structural Motifs and Mechanochemical Properties

Most myosin heavy chains consist of three distinct regions: an NH_2-terminal motor or head domain, responsible for actin binding and ATP hydrolysis; a neck region containing one or more IQ motifs that bind light chains (calmodulin or other members of the E-F hand family of proteins); and a COOH-terminal tail, which is responsible for cargo binding and/or dimerization of heavy chains. Based on the sequence comparison of myosin head domains, the myosin superfamily is currently divided into ~20 classes; myosins within each class are also similar in terms of their tail domain organization. Many of these classes exhibit a broad range of phylogenetic expression, e.g., Myo1, 2, 3, 5, 6, 7 (note, classes 3 and 6 are only expressed in metazoans); Myo8 and 13 are found only in plants; some are expressed only in vertebrates (Myo10 and 16); and the remaining classes have been identified in only one or a few related species (Myo4, 12, 14, 17) (8, 131). The heavy-chain domain structure of the myosins discussed in this review is shown in FIGURE 1.

Tails of some myosins contain heptad repeat sequences that can form α-helical coiled-coils and allow heavy chains to dimerize, resulting in formation of two-headed motors, whereas other myosins do not contain coiled-coil motifs and have either been shown or presumed to be single headed (Table 1). Some myosin tails contain predicted coiled-coil regions, but their dimerization has not been experimentally confirmed. It is also possible that for some myosins their ability to dimerize may be regulated. For example, full-length Myo6 has been shown to be a monomer but its tail contains a predicted coiled-coil motif, and it has been proposed that this myosin may form dimers in the presence of tail-binding proteins or upon phosphorylation (18).

Other regions of the tail, in addition to coiled-coil domains, may contribute to dimerization of heavy chains. For example, dimerization of Myo7a heavy chains, which contain a short predicted coiled-coil motif, is observed only for full-length constructs, whereas truncated Myo7a constructs containing the coiled-coil region but missing the rest of the tail are monomeric (55). In addition to dimerization motifs, myosin tails also contain a number of conserved protein domains, which are responsible for protein-protein interactions and/or additional functions such as kinase activity or lipid binding. Numerous binding proteins for myosins have been identified, many of which are discussed below, providing important insights

*Please note, for uniformity of nomenclature and due to space concerns, myosins are designated by abbreviations (Myo + Arabic numeral denoting myosin class), except in the case of class V budding yeast myosins, which are referred to as Myo2p and Myo4p, and *Dictyostelium* class I myosins, referred to as MyoA etc., according to accepted nomenclature.

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Table 1. Structural and mechanochemical characteristics of various myosin classes

Myosin	Number of Heads	Processivity	Duty Ratio	Directionality
I	1 (145)	No	Low (34, 93)	Plus
IIa	2 (145)	No	*Low* (64)	Plus
IIb	2	?	*High* (116, 144)	Plus
III	1	*No?* (63)		*Plus* (63)
V	2 (20)	No (106), yes (82)	*Moderate* (i.e., 20%) *to high* (31)	Plus (20)
VI	1 (76) (does contain coiled-coil)	*Yes as a dimer* (90, 110) No as a monomer (76)	*High* (30)	*Minus* (148)
VII	1 or 2?			*Plus* (55)
IX	1	*Yes* (56) Yes (100)	High (100)	Plus (91) *Minus* (56)
X	2?		*Moderate* (i.e., 16%) (65)	Plus (52)
XI (higher plants)	2 (135)	Yes (135)	High (135)	

Processivity and duty ratio are shown only for those myosins for which they have been determined experimentally. Italics denote studies that were performed using recombinant myosin constructs rather than native, tissue-purified proteins. Myosins with question marks under NUMBER OF HEADS indicate presence of predicted coiled-coil domains but for which experimental evidence of oligomerization state is lacking. Numbers in parentheses are references.

into the diversity of myosin functions (see Table 2).

Diversity of myosin function is also manifested through significant differences in the motor properties among members of the myosin family. There are several characteristics of a molecular motor that may determine its ability to perform specific intracellular functions: duty ratio (the proportion of the ATPase cycle that a motor spends strongly attached to its track), processivity (the ability of a motor to make multiple steps without detaching from the track), the amount of force produced during a single ATPase cycle, and the velocity and directionality of the movement along the actin track (see Table 1). Load may also alter the mechanochemical properties of some myosins, as has been shown for Myo6 (2).

Table 2. Myosin-binding proteins

Myosin	Binding Partners
I	Sucrase-isomaltase (139), CARMIL (60)
III	INAD (149)
V	Melanophilin/Slac-2/MyRIP (41, 154), Rab11 (70), Bmf (102), CaM kinase II (23), BERP (36), microtubules (19), kinesin (reviewed in 69), dynein light chain (7), intermediate filaments (103), She3p (11, 78, 129), Vac17p (57)
VI	Dab2, SAP97, GIPC (reviewed in 18), optineurin (118)
VII	Vezatin (68), harmonin (10), sans (Usher1 syndrome protein) (1), melanophilin/Slac-2c/MyRIP (35, 41)
IX	RhoA (99), BIG1 (GEF for Arf1) (117)
X	Integrin (157), Mena/VASP (134), microtubules (147)
XV	Whirlin (6, 32)

Included are proteins for which direct binding has been demonstrated either biochemically or by using the yeast two-hybrid system. CARMIL, capping protein, Arp2/3, and Myo1 linker; INAD, inactivation no afterpotential D; MyRIP, Myo7a- and Rab-interacting protein; BERP, brain-expressed RING finger protein; SAP97, synapse-associated protein 97; GIPC, G_α-interacting protein interacting protein, COOH terminus; GEF, guanine nucleotide exchange factor; VASP, vasodilator-stimulated phosphoprotein.

Highly processive motors, such as vertebrate Myo5a (105), are thought to be well suited to the transport of cargo, e.g., vesicles or protein complexes, along actin filaments, because binding of just a few processive motor molecules is sufficient to deliver the cargo to its destination without detaching from the actin track. Factors determining the ability of a motor to support processive movement include its ability to dimerize and its duty ratio. In a two-headed, high-duty-ratio motor such as Myo5, at least one of the two heads is attached to the actin filament at all times, which results in the ability to move processively in a hand-over-hand fashion (138). If processivity of a motor depends on heavy-chain dimerization, it is possible to envision a regulatory mechanism allowing switching from a two-headed, processive motor to a single-headed, nonprocessive one, as has been proposed for Myo6 (18).

Studies of Myo9b indicate that dimerization of heavy chains is not the only possible mechanism for myosin processivity, because this single-headed motor has also been shown to be processive (56, 100). Processivity of Myo9b may be achieved via an

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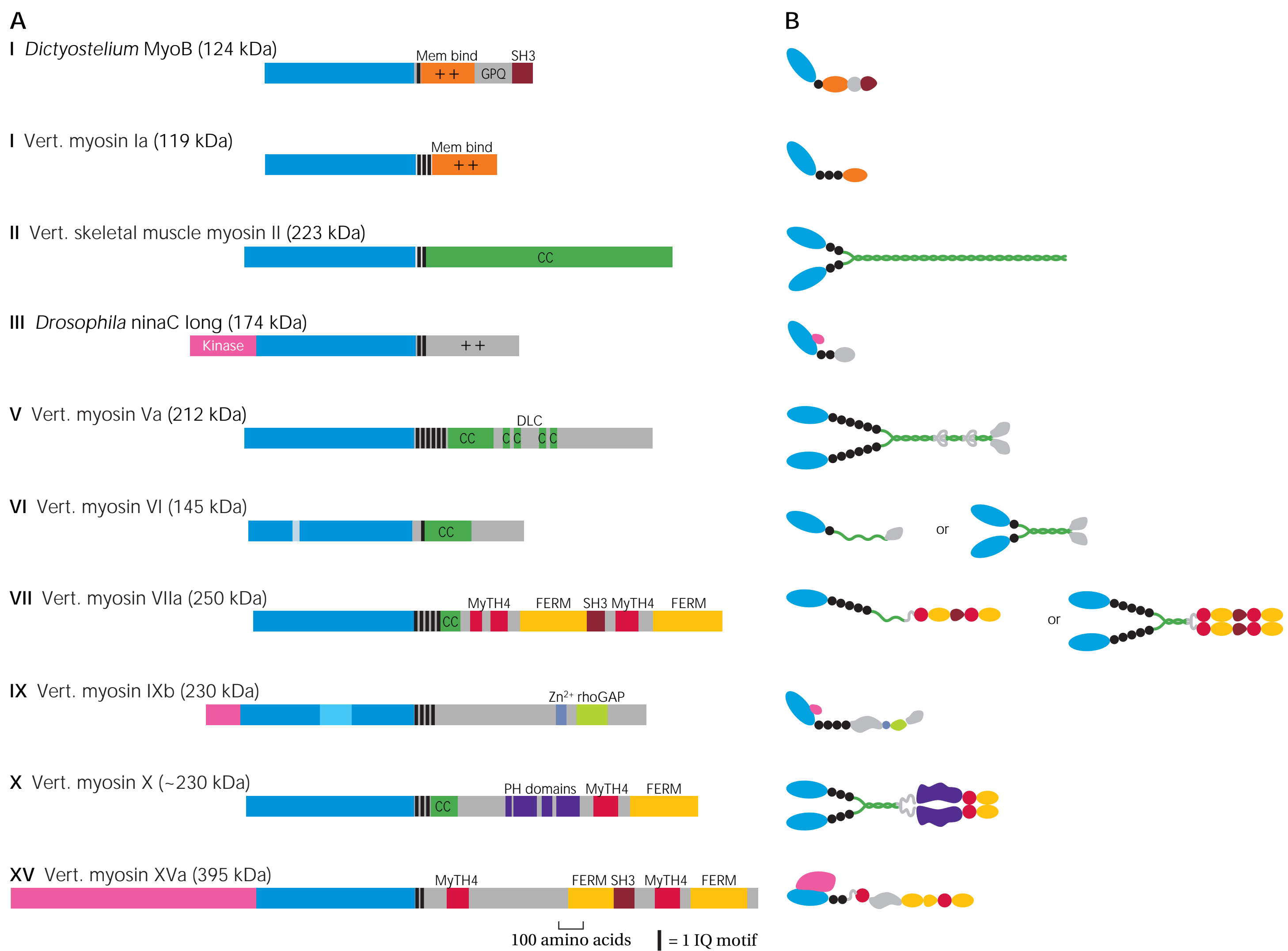

FIGURE 1. **Myosin family of molecular motors**
A: structure of the heavy chains of myosin classes discussed in this review. *B*: schematic representations of myosin structures. Class VI and class VII include myosins that may exist in both a dimeric and a monomeric form. Figure is redrawn from Mermall V, Post PL, and Mooseker MS. Unconventional myosins in cell movement, membrane traffic, and signal transduction. *Science* 279: 527–533, 1998.

electrostatic interaction between actin and a highly basic insert in the Myo9b motor domain, which prevents myosin from diffusing away from an actin filament (56, 100).

Low-duty-ratio motors may be better suited to induce rapid contraction of actomyosin assemblies rather than sustained movement of a cargo along a filament. For these myosins to function efficiently, the probability of their encounters with actin filaments has to be high. This can be achieved by assembling individual myosin molecules into bipolar filaments, as is the case for muscle and nonmuscle Myo2s, or by allowing myosins to act in the regions of high actin-filament concentration, such as brush-border microvilli or the leading edge of the cell, as has been proposed for Myo1s (34, 59). Interestingly, vertebrate nonmuscle Myo2s are represented by both a low-duty-ratio Myo2a (64) and a high-duty-ratio Myo2b (116, 144), both of which may be expressed in the same cell. This may allow Myo2b to perform functions associated with maintenance of cortical tension, whereas Myo2a may be responsible for rapid contractile movements.

Actin filaments possess an inherent polarity, with plus (or barbed) and minus (or pointed) ends. Although most myosins move toward the plus ends of actin filaments, Myo6 has been shown to be a minus-end-directed motor, and Myo9b may move toward both plus and minus ends, which suggests that its directionality may be regulated (see Table 1). Depending on the orientation of actin filaments within a specific intracellular region, plus- or minus-end-directed myosins may be better able to perform specific functions. For example, many types of actin-rich protrusions (filopodia, microvilli of intestinal brush border, inner-ear hair-cell

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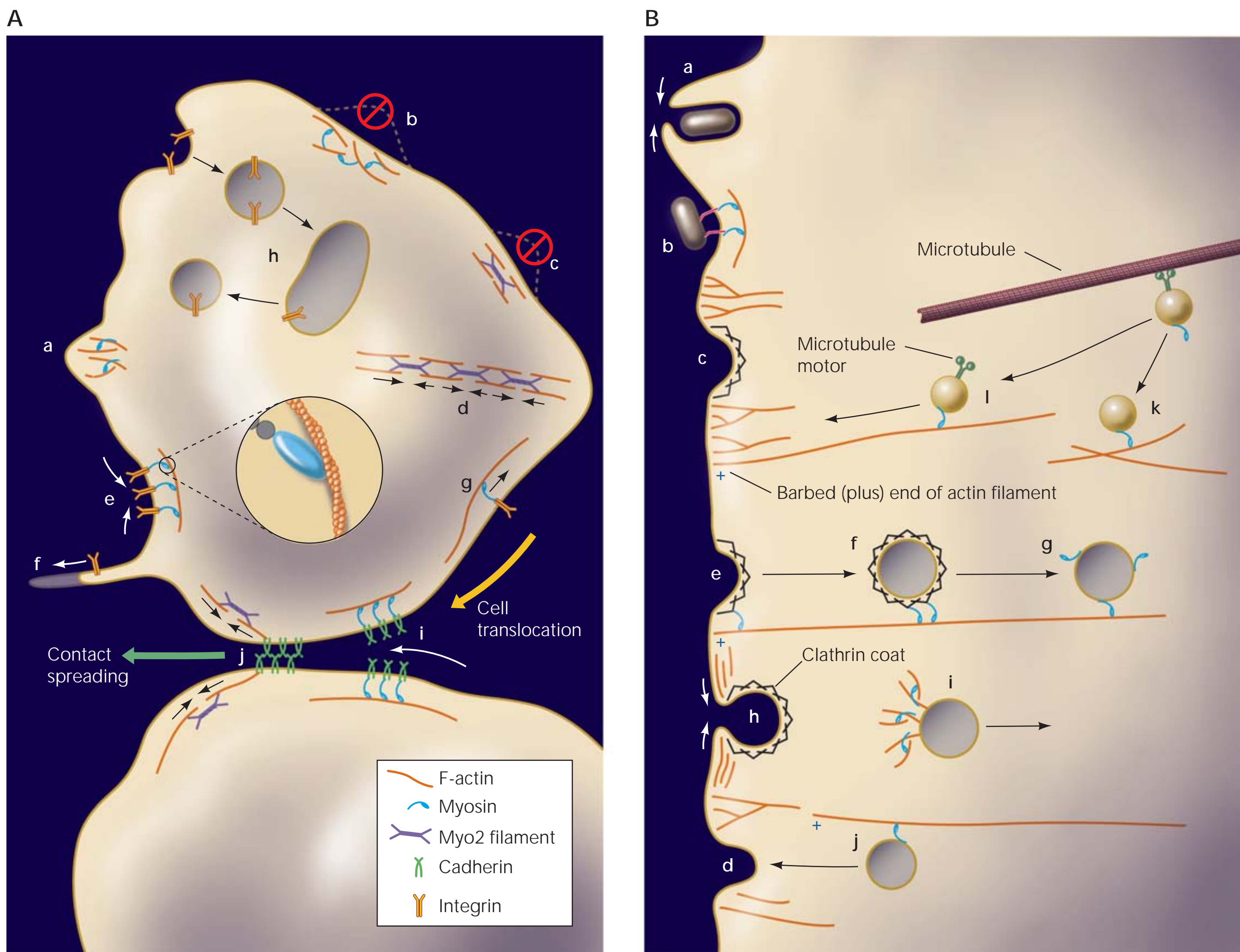

FIGURE 2. **Intracellular functions of myosin motors**
A: myosin functions in cell motility and cell adhesion. *a*, Lamellipodial protrusion driven by actin polymerization, with Myo1 family members contributing to the activation of actin nucleation by the Arp2/3 complex. *b*, Limitation of lateral extension of lamellipodia by Myo1-dependent cortical tension. *c*, Limitation of lateral extension of lamellipodia by Myo2-driven contractility. *d*, Myo2-dependent tail retraction. *e*, Clustering of cell-substrate adhesion receptors. *f*, Elongation of filopodia due to Myo10-dependent transport of integrins or VASP/Mena proteins to the filopodial tip. *g*, Myosin (e.g., Myo10 or Myo2) acting as a clutch coupling cell-substrate adhesion to the forward movement of the cell. *h*, Cell adhesion receptor endocytosis and recycling. *i*, Clustering of cell-cell adhesion receptors. *j*, Myo2-mediated "zippering up" of cell-cell junctions. *B*: roles of myosins in membrane traffic. *a*, Extension of pseudopods during phagocytosis (Myo1, Myo10). *b*, Adhesion of bacteria/food particles to the cell surface during phagocytosis (Myo7). *c–d*, Reorganization of cortical actin to allow invagination of a clathrin-coated pit (*c*) or fusion of an exocytic vesicle with the plasma membrane (*d*) (e.g., by Myo1). *e*, Contribution of a minus-end-directed myosin (e.g., Myo6) to deformation of plasma membrane during clathrin-coated pit formation. *f–g*, Minus-end-directed transport of clathrin-coated (*f*) and uncoated (*g*) vesicles along actin filaments by Myo6. *h–i*, Membrane scission (*h*) and vesicle propulsion (*i*) driven by Arp2/3-regulated actin polymerization with Myo1 contributing to Arp2/3 activation. *j*, Plus-end-directed transport of exocytic vesicles (e.g., by Myo1). *k–l*, Switch between microtubule-dependent and actin-dependent transport, resulting in vesicle capture and anchoring (*k*) or short-range transport along actin filaments (*l*).

stereocilia) contain long bundles of actin filaments oriented with their plus ends toward the membrane. Given this arrangement of actin filaments, a plus-end-directed myosin could be used to deliver proteins or organelles toward the tip of the protrusion, whereas a minus-end-directed motor would be necessary to transport cargo inward or maintain membrane invaginations at the base of the protrusions (112).

Myosins in Cell Migration and Adhesion

The first member of a myosin superfamily to be described, muscle Myo2, is responsible for muscle contraction, which it powers via the "sliding filament" mode of action (53, 54). In this model, bipolar myosin filaments induce contraction by forcing two sets of actin filaments of opposite polarity to slide toward each other, causing shortening of the

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muscle fibers. Following the discovery that myosins are also present in nonmuscle cells, it was suggested that myosin-dependent contractile activity, similar to that observed in muscle, may also be involved in cell migration and control of cell shape (97). This "sliding-filament" model of cell motility relies on the existence of bipolar myosin filaments and, therefore, can explain only those types of cell motility that involve Myo2, since it is the only known filament-forming myosin. The best examples of nonmuscle sliding-filament-type motility are constriction of the cleavage furrow during cytokinesis (122) and contraction of the apical actin ring associated with adherens junctions in polarized epithelia (51, 61). During cell migration, Myo2 is present in actin stress fibers in the rear of the cell (81, 119) and may be responsible for the forward movement of the cell body and tail retraction. On the other hand, protrusion of the leading edge of the cell is thought to be powered primarily by actin polymerization rather than by myosin-induced contractility (96). However, Myo2-dependent contractility may play an important role in coordination of cell migration and directional motility by preventing formation of lateral pseudopods and limiting pseudopodial/lamellipodial protrusion to the leading edge of the cell.

As an example of the importance of Myo2 in directional movement, a recent study found that Myo2b knockout fibroblasts have numerous, unstable lamellipodia (77) and exhibit high instantaneous velocity and low directional persistence of migration (frequent change of direction). Myo2b appears to be important for limiting formation of lamellipodia to the leading edge of the cell, as well as for sensing mechanical stimuli such as substrate rigidity and pushing/probing forces and for setting direction of migration based on these stimuli. Interestingly, these experiments indicate that Myo2a provides most of the traction forces exerted by a cell on a substrate, whereas the role of Myo2b appears to be to determine/change direction of the traction forces. Myo2b-null cells also exhibit defects in rearward collagen fiber transport along the cell surface and remodeling of 3-D collagen gels (85). Thus, although Myo2b-null cells are able to rapidly, albeit nondirectionally, translocate on two-dimensional substrates, their ability to migrate in 3-D gels, which are more representative of an in vivo environment, may be impaired. Collagen fiber transport occurs via repeated cycles of extension and retraction of lamellipodia that are accompanied by recruitment of Myo2b into extending lamellipodia and rearward movement of Myo2b during retraction. Therefore, Myo2b appears to play an important role in contractile activity of lamellipodia.

Studies in *Dictyostelium* also implicate single-headed, non-filament-forming Myo1 variants in limiting formation of lateral pseudopods. This role is probably accomplished via a mechanism different from that employing Myo2. Myo1 mutants in *Dictyostelium* exhibit decreased velocity of chemotaxis due to increased formation of lateral pseudopods (38, 132). This defect is observed in MyoA, MyoB, and MyoF mutants, with MyoA/MyoB and MyoB/MyoF performing nonredundant functions in cell migration. MyoB also seems to be important for cell response to the waves of chemoattractant cAMP secreted by *Dictyostelium* during starvation-induced cell agreggation and formation of fruiting bodies (38). Since MyoB is known to bind capping protein, Arp2/3, and Myo1 linker (CARMIL), a regulator of the Arp2/3 activity and binding partner of *Dictystelium* capping protein (60, 109), it may influence pseudopod formation by modulating actin nucleation. Myo1 variants may also act as cross-linkers of the cortical actin meshwork to create surface tension that prevents pseudopod extension (28).

Whereas the actin cytoskeleton, both through actin polymerization and actomyosin contractility, provides the main driving force for cell motility, it is also involved in establishment and maintenance of cell adhesion. Cytoplasmic domains of transmembrane cell adhesion receptors (integrins in the case of cell-extracellular matrix contacts and cadherins in the case of cell-cell contacts) interact with actin-binding proteins that link them to actin filaments (49). Due to this close association of adhesion receptors with the actin cytoskeleton, actin-dependent motors are likely to play an important role in cell adhesion. Myosins may bind to cell-adhesion receptors and transport them relative to the actin-rich cortex or to the bulk of actin filaments in the cell body. This can lead to the following outcomes: concentration of adhesion receptors at the leading edge or sites of cell-cell contact assembly (121, 123); formation of clusters of adhesion receptors, which increases the strength of cell adhesion and activates intracellular signaling pathways that promote contact assembly (47, 87, 88); and net forward translocation of the leading edge as a result of rearward transport of adhesion receptors, with myosin acting as a clutch (127). In addition, tension exerted by myosin may promote detachment of adhesion receptors from the substrate in the rear of the cell, which is necessary for efficient translocation (25). Recycling of cell-adhesion receptors, which plays an important role in cell migration and cell adhesion (13, 17), may also involve myosins through their functions in endocytosis and/or exocytosis.

Involvement in cell adhesion has been demonstrated for Myo7 and Myo10, two myosins whose

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tails contain band four-point-one, ezrin, radixin, moesin (FERM) and myosin tail homology 4 (MYTH4) domains. FERM domains typically mediate binding of cytoskeletal proteins to cytoplasmic domains of transmembrane proteins (42), and the FERM domain of Myo10 has been shown to bind integrins (157). Myo10 overexpression enhances formation of filopodia and promotes integrin recruitment into filopodia (157). Myo10 may act as a clutch linking elongating actin filaments to matrix-bound integrins, or it may stabilize filopodia by promoting concentration of integrins at the filopodial tip and establishing strong adhesion to the substrate.

"Myo6 functions are important for maintaining the integrity of cell monolayers and cell shape, possibly due to its role in regulation of E-cadherin stability."

Filopodia induction by Myo10 expression may also depend in part on its involvement in the delivery of Mena/VASP proteins to the cell edge (see below).

The MYTH4- and FERM-domain-containing region of the Myo7a tail binds vezatin (68) and harmonin (10), two proteins that interact with components of cell-cell junctions (cadherins and catenins) and are involved in formation of lateral links between stereocilia in the inner ear hair bundles. Although both vezatin and Myo7a localize to adherens junctions in epithelial cells (125), no overt disruption of adherens junctions assembly has been detected in cells expressing a Myo7a dominant-negative tail construct; however, this construct prevents cadherin-dependent entry of *Listeria* into epithelial cells (125). Sensory defects in Ushers' syndrome (Myo7a, harmonin, and cadherin mutations in humans) have been attributed to defects in formation of links between stereocilia in the inner ear. Therefore, at least some types of cadherin-dependent adhesive interactions in mammalian cells rely on Myo7a functions, and it remains to be determined whether Myo7a also plays a role in modulation of adherens junction organization.

In *Dictyostelium* amoebae, Myo7 appears to function in both cell-cell and cell-substrate adhesion, as well as in attachment of food particles to cell surface receptors during phagocytosis (136). As a result of defects in adhesion, Myo7-null cells are deficient in cell migration (the leading edge loses contact with the substrate for prolonged time periods). Myo7 is also localized to filopodial tips in *Dictyostelium*, and its role in filopodia formation may be analogous to that of Myo10 in mammalian cells.

Another myosin that has been shown to play a role in both cell migration and interactions with cell adhesion proteins is Myo6. In *Drosophila,* Myo6 appears to be necessary for E-cadherin and β-catenin stabilization, which is important for border cell migration in the ovary (43). This function may be related to the role of Myo6 in endocytosis, because endocytosis and recycling of adhesion receptors may be necessary for their proper localization and stability. A recent study has extended research on the role of Myo6 in migration of epithelial sheets in *Drosophila* by implicating it in epithelial cell migration during dorsal closure (86). Myo6 ablation causes a disruption and folding of epithelial sheets; therefore, Myo6 functions are important for maintaining the integrity of cell monolayers and cell shape, possibly due to its role in regulation of E-cadherin stability. Myo6 is also involved in migration of human ovarian carcinoma cell lines; thus its role in cell migration may not be limited to *Drosophila* epithelia (156).

Myo1c has long been known to be involved in the adaptation response in the inner ear hair cells (closure of mechanosensitive ion channels during sustained stimulation) (45). Recently, it has been shown that this motor also interacts with cadherin 23, a component of the tip links between hair cell stereocilia (124). The function for a myosin motor in the process of adaptation is thought to be to transport the channel along the length of deflected stereocilium, which modulates tension applied to the channel. Interaction of Myo1c with cell-adhesion molecules forming tip links suggests that tip-link protein complexes may serve to connect Myo1c to mechanosensitive channels, so that the tip links, together with associated ion channels, may be translocated along the actin bundles in stereocilia. It is important to note that Myo7a may also play a role in adaptation, because electrophysiological studies on hair cells from Myo7a-mutant mice revealed significant defects in the adaptation response (67).

A recent study found that nonmuscle Myo2a is necessary for cell-cell adhesion in mouse embryo (22). Myo2a in normal embryos and embryonic stem cells localizes to cell-cell contacts. Embryos lacking Myo2a die by embryonic day 7.5 and exhibit disorganization of visceral endoderm, an extraembryonic cell layer responsible for nutrient uptake and transport as well as spatial patterning within an embryo (9). These defects can be traced in vitro to the loss of E-cadherin and β-catenin localization to cell-cell junctions, accompanied by the loss of cell-cell attachment (manifested by cell shedding and lack of strong attachment in vitro).

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During establishment of new cell-cell junctions by cultured epithelial cells, Myo2a is associated with contractile arcs of actin filaments that form along the edges of a nascent contact and may promote contact spreading (66). Adhesion defects observed in Myo2a knockouts may be related to decreased contractility of actin bundles during contact formation. Alternatively, Myo2a-mediated tension applied to adherens junctions via apical actin bundles may be necessary for steady-state maintenance of cell-cell contacts.

Myosins and Signal Transduction

As already discussed above for Myo1c and Myo7a, myosins can also play important roles in cell-signaling pathways (reviewed in Ref. 5). Perhaps the most striking examples are Myo9 family members, which contain an active GTPase activation protein (GAP) domain in their tail domain for the G protein Rho (99, 108). Moreover, the GTP exchange factor (GEF) for Arf, BIG1, has recently been identified as a binding protein for Myo9b (117). Overexpression of Myo9 in cultured cells phenocopies expression of dominant-negative Rho (89). Myo9b may play a role in the cytoskeletal remodeling during uptake/infection of cells by the pathogenic bacteria *Shigella* (48). However, for the most part, the functions for Myo9b (for example in regulating Rho-dependent remodeling of the actin cytoskeleton) have yet to be elucidated. It is interesting to note that Myo9b is most highly expressed in highly motile cells such as leukocytes (151). In contrast, however, the other Myo9 in vertebrates, Myo9a, is most highly expressed in brain (21). It will be of great interest to determine if Myo9a is associated with the highly dynamic arrays of actin within synapses (79).

Myo3, an unusual myosin containing an active protein kinase domain at its NH_2 terminus (63), has long been implicated in phototransduction in *Drosophila*, including regulation of intracellular localization of calmodulin in *Drosophila* photoreceptors (98). Recent studies show that this myosin is responsible for the transport of two vision-related signaling proteins, arrestin and $G_q\alpha$, from the cell body to the rhabdomeres in *Drosophila* photoreceptors (27, 72). Myo3-dependent transport requires interaction of arrestin with phosphoinositides (72), suggesting that the mechanism of arrestin transport may involve myosin-dependent movement of phosphoinositide-containing vesicles. In addition to interacting with phosphoinositides, the Myo3 tail also binds F-actin (74) and the adapter protein inactivation no afterpotential D (INAD) (149). Disruption of Myo3-INAD interaction leads to a delay in photoreceptor deactivation (149). Genetic studies link human Myo3 with defects in both hearing and vision (33, 142).

In addition to its multiple roles in membrane traffic and cargo transport (see below), Myo5a has been shown to play a role in regulating apoptosis. One of the light chains of Myo5a, dynein light chain 2 (DLC2, which is also a subunit of the microtubule motor dynein), binds proapoptotic protein Bmf and sequesters it to actin filaments. Binding of Bmf to Myo5 is regulated by cell attachment to the extracellular matrix, so that cell detachment leads to the release of Bmf and onset of programmed cell death (102).

Myo18b has recently been implicated as a potential tumor suppressor based on the observations that it exhibits reduced expression in a large number of ovarian tumors; mutations in Myo18b were observed in a subset of these tumors (155).

Myosins in Membrane Traffic

Myosins have been implicated in various types of membrane traffic, including endo- and exocytosis and intracellular transport of a variety of organelles. Unlike microtubules, which serve as tracks for long-range organelle transport, actin filaments typically provide tracks for short-range organelle movements (69, 113). Additionally, in many cell types actin filaments form dense cortical meshworks, which may impede centripetal transport of endocytic vesicles and/or fusion of exocytic vesicles or may serve as a scaffold to which organelles can be anchored by myosins. In agreement with these properties of the actin cytoskeleton, the roles that have been proposed for myosins include transport of endo- and exocytic vesicles through the actin-rich regions, short-range, local delivery of organelles, and capture and retaining of organelles in specific subcellular regions (50, 69, 152). Since the majority of actin filament plus ends are thought to be facing the plasma membrane (26), minus-end-directed myosins may be expected to participate in internalization of endocytic vesicles, whereas plus-end-directed myosins may be involved in exocytosis. However, there are examples of plus-end-directed myosins being involved in endocytosis, suggesting that a subpopulation of actin filaments with the inverse orientation may exist in certain cell types and/or that a different mechanism of internalization may be involved. Additionally, myosins may promote endo- or exocytosis by inducing local reorganization of actin meshworks to allow the passage of vesicles or promote actin-dependent constriction and scission of the necks of membrane pits. Myo1, 5, and 6 family members have long been implicated in membrane traffic (for reviews of earlier work, see Refs. 50, 69, and 153), whereas recent studies have provided evidence for the role of Myo7 and Myo10 in phago-

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cytosis and for involvement of myosins in exocytosis.

Myo6 is well positioned for a role in endocytosis, because its minus-end-directed movement along actin filaments may promote centripetal transport of endocytic vesicles toward early endosomes. Several recent studies have further dissected the role of Myo6 in endocytosis, clarifying its functions in various cell types. Whereas Myo6 in polarized epithelial cells associates with clathrin-coated vesicles and may be involved in transport of endocytic receptors down the surface of microvilli or invagination of clathrin-coated pits (50), in nonpolarized cells Myo6 is recruited to endocytic vesicles following the loss of clathrin coats (3). Displacement of Myo6 using a dominant-negative (headless) construct delays transferrin uptake and slows down centripetal migration of uncoated vesicles and their delivery to pericentriolar endosomes (3). Thus, in nonpolarized epithelial cells, Myo6 may help vesicles traverse dense actin meshworks at the cell periphery. This hypothesis was confirmed using live imaging of green fluorescent protein-Myo6-labeled vesicles, which indicated net inward movement of vesicles, expression of motor-dead Myo6 (which inhibited vesicle migration), and application of actin-depolymerizing drugs (which promoted transferrin trafficking to early endosomes) (4).

Another recent study uncovered the role of the adaptor protein Dab2 in mediating Myo6 recruitment to clathrin-coated vesicles and found that, although interaction of Myo6 with uncoated vesicles does not require Dab2, association of Myo6 with clathrin-coated vesicles can be observed only in cells expressing large amounts of Dab2 (29). The role of Dab2 in Myo6 recruitment and the possibility that this interaction may be regulated, proposed by Dance et al. (29), may explain why in some cell types Myo6 interacts with both clathrin-coated and uncoated vesicles but in others is found only on uncoated vesicles. One specific example of a receptor that is internalized via a Myo6- and Dab-2-dependent endocytic pathway in polarized epithelia is CFTR (128).

> *"Myo6-dependent endocytosis may play an important role in regulation of synaptic plasticity."*

In addition to Dab2, the Myo6 tail also binds two adaptor proteins: G_α-interacting protein interacting protein, COOH terminus (GIPC), which can interact with a variety of transmembrane receptors, and SAP97, which interacts with AMPA-type glutamate receptors at the synapses (50, 94). Myo6 binding to Dab2 is necessary for recruitment of GIPC to clathrin-coated vesicles (29), where GIPC may serve as a scaffold for assembly of signaling complexes associated with the tails of transmembrane receptors. Neurons from Myo6-deficient *Snell's waltzer* mice exhibit defects in AMPA-receptor endocytosis at postsynaptic densities and decreased number of synapses; therefore, Myo6-dependent endocytosis may play an important role in regulation of synaptic plasticity (94). Constitutive endocytosis of transferrin is not impaired in Myo6-mutant mice (94), suggesting that Myo6 is involved only in endocytosis of certain types of receptors in neurons and that this specificity may be mediated by specialized adaptor proteins such as SAP97.

The importance of Myo1 variants in endocytosis was first suggested by studies in *Dictyostelium* amoeba and has recently been emphasized by a study showing that in budding yeast, Myo1 may be directly involved in vesicle scission from the cell membrane (58). This is probably accomplished through Myo1-mediated assembly and reorganization of actin filaments, because Myo1 in both budding and fission yeast has the ability to activate actin nucleation by the Arp2/3 complex and promote assembly of actin filaments at the sites of endocytosis (37, 71, 73). On the other hand, mammalian Myo1 variants do not contain protein domains that could be involved in the activation of the Arp2/3 complex, and therefore in these cells the role of Myo1 in endocytosis may be more indirect, although it is theoretically possible that SH3-domain-containing Myo1s may interact with Arp2/3 through intermediary proteins functionally similar to CARMIL, an Arp2/3 activator and binding partner of the *Dictyostelium* MyoB (60). Interestingly, although a truncated Myo1a construct has been previously shown to inhibit endocytosis in mammalian cells (104), this dominant-negative effect may not reflect the direct involvement of Myo1 family members in endocytosis but instead result from the loss of Myo6 from the apical membrane, similar to that observed in Myo1a knockout enterocytes (137).

The role of Myo5 in vesicular trafficking is well established. There are three isoforms of Myo5 expressed in humans, Myo5a–c (111), and they have been implicated in movement of various types of organelles: melanosomes, phagosomes, smooth ER, endocytic, and recycling vesicles (reviewed in Refs. 69 and 105). Most Myo5-associated organelles also interact with microtubule-dependent motors, and Myo5 activity may counteract fast microtubule-dependent movement of organelles by capturing them at the periphery of the cell and inducing them to undergo short-range

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actin-dependent movements (14, 69, 152). Myo5 isoforms are targeted to their specific cargoes via interactions of their globular tails with various members of the Rab family of small G proteins. Interactions of Myo5 with Rabs may be indirect; for example, interaction between Myo5a and Rab27a, a melanosome-specific protein, is mediated by melanophilin, which binds to both Myo5a and Rab27a (reviewed in Ref. 69). Myo5a, which is predominantly expressed in neurons and melanocytes, plays an important role in regulating melanosome distribution and in organelle transport in neurons (reviewed in Ref. 15). Mutations in Myo5a, Rab27a, and melanophilin are associated in mice with light coat color (due to abnormal pigment distribution) (80, 84, 150) and abnormalities in synaptic function (75) and in humans with Griscelli syndrome, a rare inherited disease that is characterized by defects in hair pigmentation and by neurological and immune system disorders. Detailed genetic characterization of patients with Griscelli syndrome indicates that patients with Myo5a mutations exhibit only neurological symptoms and pigmentation defects, whereas individuals with Rab27a mutations are also characterized by immune system abnormalities (uncontrolled activation of macrophages and lymphocytes) (83, 120). Myo5b has been implicated in recycling of transferrin receptor and muscarinic acetylcholine receptor (70, 141). Expression of dominant-negative Myo5b tail constructs results in perinuclear accumulation of these receptors, as may be expected when centripetal transport by microtubule-dependent motor dynein is not balanced by Myo5 (70, 141). Interestingly, however, a recent study employing a chemical inhibition strategy that locks Myo5b in an inactive, ADP-bound state indicates that this approach to inhibiting Myo5b leads to an opposite result: plasma membrane enrichment of transferrin receptor (101). The authors proposed that the rigor binding of chemically inhibited Myo5b to the actin filaments prevents centripetal transport of endocytic vesicles and promotes accumulation of transferrin receptor at the periphery of the cell. Myo5c is predominantly expressed in epithelial cells, and experiments using Myo5c dominant-negative tail construct implicate this motor in recycling of transferrin receptor but not in its endocytosis (111).

A lot of progress has also been made recently with regard to dissecting the role of the class V myosin Myo2p in vacuolar inheritance in yeast. Studies from Weisman and colleagues identified vacuolar protein Vac17p as a receptor for Myo2p and found that Vac17p is proteolytically degraded in the bud following the delivery of the vacuole from the mother cell into the budding daughter cell (57, 130). Degradation of the myosin receptor may serve to ensure one-way flow of myosin cargo as well as provide an additional means of regulation of myosin-dependent intracellular transport. It remains to be determined whether this regulatory mechanism is also utilized in mammalian cells, because it has been suggested that proteolytic degradation of melanophilin may play a role in regulation of melanosome transport (40).

As discussed above, Myo7 and 10 share structural and functional similarities. Both of these myosins have been implicated in phagocytosis (24, 44, 136). The mechanisms underlying defects in phagocytosis in Myo7 mutants in *Dictyostelium* amoeba and in mammalian cells appear to be quite distinct from each other. In *Dictyostelium* Myo7-null cells, the defect in phagocytosis is related to adhesion defects (i.e., lack of adhesion of food particles to the cell surface) (136), whereas in RPE cells from mouse Myo7a mutant (*Shaker-1*) decreased phagocytosis of rod outer segments results from a defect in the centripetal transport of phagosomes that prevents fusion with lysosomes (44). The contribution of Myo10 to phagocytosis appears to result from its role in pseudopod formation by macrophages (24).

Myosins have also been shown to play a role in exocytosis and secretion, possibly by promoting delivery of exocytic vesicles to the plasma membrane and/or inducing reorganization of cortical actin to allow membrane fusion. Myo1c promotes insulin-stimulated exocytosis of glucose transporter GLUT4 in adipocytes (12), whereas Myo2b knockdown using antisense RNA decreases the rate of calcium-stimulated exocytosis in fibroblasts (133). Myo5-mediated transport of exocytic vesicles is involved in chromaffin cell secretion (114) and insulin secretion by pancreatic β-cells (140). Roles for Myo1, Myo2, and Myo6 in delivery of vesicles from the Golgi apparatus to the plasma membrane as well as in structural organization of the Golgi have been proposed by several groups based on the association of these myosins with the Golgi membranes and a decrease in secretion from Golgi to the plasma membrane in *Snell's waltzer* fibroblasts (18, 39, 126). A recent study identified optineurin, a Golgi-associated protein, as a Myo6 binding partner that mediates its interaction with the Golgi apparatus and found that knockdown of optineurin expression leads to disruption of Golgi organization and exocytosis (118).

Myosins in Protein, RNA, and Organelle Localization

In addition to playing important roles in the intracellular transport of membrane-bound organelles, myosins are involved in determining intracellular localization of proteins, multiprotein complexes,

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RNA, and nonmembranous organelles.

Myo1a, a major myosin of the intestinal brush border, has been shown to be involved in localizing sucrase-isomaltase, an intestinal enzyme involved in disaccharide digestion, to the brush border of intestinal epithelial cells (137, 139). The cytoplasmic domain of sucrase-isomaltase binds to the tail of Myo1a. The mechanism responsible for sucrase-isomaltase localization involves interaction of Myo1a with lipid-raft-associated sucrase-isomaltase. Myo1a is also the major calmodulin-binding protein within the brush border and thus by default is required for localization of high concentrations of calmodulin within the microvilli of the brush border, the site of dietary uptake of Ca^{2+}. The brush border cytoskeleton is destabilized in the Myo1a knockout, perhaps because of the loss of microvillar calmodulin and the resultant poor Ca^{2+} buffering that may activate the Ca^{2+}-dependent actin-severing activity of the microvillar core protein villin (137).

Two myosins, Myo5a and Myo10, have recently been shown to interact with microtubules via their tails (19, 147). Myo10-microtubule interaction is important for cortical anchoring of the nucleus and meiotic spindle positioning in *Xenopus* oocytes (147). In addition to directly binding to microtubules, Myo5a also interacts with microtubule-dependent motor kinesin and with intermediate filaments and may serve as a linker between actin-, microtubule-, and intermediate filament-based cytoskeletal systems (69, 103, 146). In another example of coordination between actin and microtubules, Myo2 has been implicated in centrosome separation (115). Cortical contraction that requires Myo2 activity separates and positions centrosomes following nuclear-envelope breakdown. The authors posited that centrosome separation occurs first via activity of dynein motors that interact with the nuclear envelope. Following nuclear-envelope breakdown, final positioning of centrosomes depends on interaction of astral microtubules with the actin-based cell cortex and on cortical Myo2 activity.

As discussed above, Myo10 is involved in transport of integrins and Mena/VASP proteins to the tips of filopodia (134, 157). Both cell-substrate adhesion via integrins and actin filament elongation due to the anticapping activity of Mena/VASP may contribute to the ability of Myo10 to promote formation of filopodia.

In a curious parallel to Myo10's role in filopodia elongation, another MYTH4- and FERM-domain-containing myosin, Myo15a, has been found to be necessary for elongation of stereocilia of the inner ear hair cells (143). The functions of Myo15a in stereocilia elongation involve delivery of a protein called whirlin, which binds to the SH3-MYTH4-FERM-domain-containing region of the Myo15a tail, to the tips of stereocilia, where whirlin may regulate actin dynamics and actin filament elongation (6, 32, 62). In addition to regulation of stereocilia elongation, Myo15a interaction with whirlin may also play a role in cohesion of stereocilia (32).

In addition to protein and organelle localization, class V myosins are also involved in RNA localization. In budding yeast, the class V myosin Myo4p affects the transport and localization of a number of specific mRNAs from the mother cell to the bud via its direct interaction with She3p, one subunit of a multiprotein complex that interacts with specific sequences within the 3′-untranslated region of the transported mRNAs (reviewed in Ref. 46). In neurons, Myo5a has been shown to be part of a polyribosome-associated mRNA/protein (mRNP) complex containing Puralpha, mStaufen, and fragile X protein (92).

Conclusion

Based on the studies summarized above, it has become clear that within a given cell, multiple myosins are expressed with distinct but often overlapping subcellular localizations and potentially overlapping functions. This review highlights the considerable progress made toward unraveling the complexities of myosin functions at the cellular level. However, a major challenge in the future will be to assess how these functions contribute to physiological functions at the tissue, organ, and organism levels in metazoan species, including vertebrates. ■

This work was supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (DK-55389, DK-25387, DK-45735), the Patterson Trust, the American Heart Association, and by a postdoctoral fellowship from the Arthritis Foundation.

References

1. Adato A, Michel V, Kikkawa Y, Reiners J, Alagramam KN, Weil D, Yonekawa H, Wolfrum U, El-Amraoui A, and Petit C. Interactions in the network of Usher syndrome type 1 proteins. *Hum Mol Genet* 14: 347–356, 2005.
2. Altman D, Sweeney HL, and Spudich JA. The mechanism of myosin VI translocation and its load-induced anchoring. *Cell* 116: 737–749, 2004.
3. Aschenbrenner L, Lee T, and Hasson T. Myo6 facilitates the translocation of endocytic vesicles from cell peripheries. *Mol Biol Cell* 14: 2728–2743, 2003.
4. Aschenbrenner L, Naccache SN, and Hasson T. Uncoated endocytic vesicles require the unconventional myosin, Myo6, for rapid transport through actin barriers. *Mol Biol Cell* 15: 2253–2263, 2004.
5. Bahler M. Myosins on the move to signal transduction. *Curr Opin Cell Biol* 8: 18–22, 1996.
6. Belyantseva IA, Boger ET, Naz S, Frolenkov GI, Sellers JR, Ahmed ZM, Griffith AJ, and Friedman TB. Myosin-XVa is required for tip localization of whirlin and differential elongation of hair-cell stereocilia. *Nat Cell Biol* 7: 148–156, 2005.
7. Benashski SE, Harrison A, Patel-King RS, and King SM. Dimerization of the highly conserved light chain shared by dynein and myosin V. *J Biol Chem* 272: 20929–20935, 1997.

Downloaded from physiologyonline.physiology.org on January 16, 2006

8. Berg JS, Powell BC, and Cheney RE. A millennial myosin census. *Mol Biol Cell* 12: 780–794, 2001.

9. Bielinska M, Narita N, and Wilson DB. Distinct roles for visceral endoderm during embryonic mouse development. *Int J Dev Biol* 43: 183–205, 1999.

10. Boeda B, El-Amraoui A, Bahloul A, Goodyear R, Daviet L, Blanchard S, Perfettini I, Fath KR, Shorte S, Reiners J, Houdusse A, Legrain P, Wolfrum U, Richardson G, and Petit C. Myosin VIIa, harmonin and cadherin 23, three Usher I gene products that cooperate to shape the sensory hair cell bundle. *EMBO J* 21: 6689–6699, 2002.

11. Bohl F, Kruse C, Frank A, Ferring D, and Jansen RP. She2p, a novel RNA-binding protein tethers ASH1 mRNA to the Myo4p myosin motor via She3p. *EMBO J* 19: 5514–5524, 2000.

12. Bose A, Robida S, Furcinitti PS, Chawla A, Fogarty K, Corvera S, and Czech MP. Unconventional myosin Myo1c promotes membrane fusion in a regulated exocytic pathway. *Mol Cell Biol* 24: 5447–5458, 2004.

13. Bretscher MS and Aguado-Velasco C. Membrane traffic during cell locomotion. *Curr Opin Cell Biol* 10: 537–541, 1998.

14. Bridgman PC. Myosin Va movements in normal and dilute-lethal axons provide support for a dual filament motor complex. *J Cell Biol* 146: 1045–1060, 1999.

15. Bridgman PC. Myosin-dependent transport in neurons. *J Neurobiol* 58: 164–174, 2004.

16. Brown ME and Bridgman PC. Myosin function in nervous and sensory systems. *J Neurobiol* 58: 118–130, 2004.

17. Bryant DM and Stow JL. The ins and outs of E-cadherin trafficking. *Trends Cell Biol* 14: 427–434, 2004.

18. Buss F, Spudich G, and Kendrick-Jones J. Myosin VI: cellular functions and motor properties. *Annu Rev Cell Dev Biol* 20: 649–676, 2004.

19. Cao TT, Chang W, Masters SE, and Mooseker MS. Myosin-Va binds to and mechanochemically couples microtubules to actin filaments. *Mol Biol Cell* 15: 151–161, 2004.

20. Cheney RE, O'Shea MK, Heuser JE, Coelho MV, Wolenski JS, Espreafico EM, Forscher P, Larson RE, and Mooseker MS. Brain myosin-V is a two-headed unconventional myosin with motor activity. *Cell* 75: 13–23, 1993.

21. Chieregatti E, Gartner A, Stoffler HE, and Bahler M. Myr 7 is a novel myosin IX-RhoGAP expressed in rat brain. *J Cell Sci* 111: 3597–3608, 1998.

22. Conti MA, Even-Ram S, Liu C, Yamada KM, and Adelstein RS. Defects in cell adhesion and the visceral endoderm following ablation of nonmuscle myosin heavy chain II-A in mice. *J Biol Chem* 279: 41263–41266, 2004.

23. Costa MC, Mani F, Santoro W Jr, Espreafico EM, and Larson RE. Brain myosin-V, a calmodulin-carrying myosin, binds to calmodulin-dependent protein kinase II and activates its kinase activity. *J Biol Chem* 274: 15811–15819, 1999.

24. Cox D, Berg JS, Cammer M, Chinegwundoh JO, Dale BM, Cheney RE, and Greenberg S. Myosin X is a downstream effector of PI(3)K during phagocytosis. *Nat Cell Biol* 4: 469–477, 2002.

25. Cox EA and Huttenlocher A. Regulation of integrin-mediated adhesion during cell migration. *Microsc Res Tech* 43: 412–419, 1998.

26. Cramer LP. Organization and polarity of actin filament networks in cells: implications for the mechanism of myosin-based cell motility. *Biochem Soc Symp* 65: 173–205, 1999.

27. Cronin MA, Diao F, and Tsunoda S. Light-dependent subcellular translocation of Gqalpha in *Drosophila* photoreceptors is facilitated by the photoreceptor-specific myosin III NINAC. *J Cell Sci* 117: 4797–4806, 2004.

28. Dai J, Ting-Beall HP, Hochmuth RM, Sheetz MP, and Titus MA. Myosin I contributes to the generation of resting cortical tension. *Biophys J* 77: 1168–1176, 1999.

29. Dance AL, Miller M, Seragaki S, Aryal P, White B, Aschenbrenner L, and Hasson T. Regulation of myosin-VI targeting to endocytic compartments. *Traffic* 5: 798–813, 2004.

30. De La Cruz EM, Ostap EM, and Sweeney HL. Kinetic mechanism and regulation of myosin VI. *J Biol Chem* 276: 32373–32381, 2001.

31. De La Cruz EM, Wells AL, Rosenfeld SS, Ostap EM, and Sweeney HL. The kinetic mechanism of myosin V. *Proc Natl Acad Sci USA* 96: 13726–13731, 1999.

32. Delprat B, Michel V, Goodyear R, Yamasaki Y, Michalski N, El-Amraoui A, Perfettini I, Legrain P, Richardson G, Hardelin JP, and Petit C. Myosin XVa and whirlin, two deafness gene products required for hair bundle growth, are located at the stereocilia tips and interact directly. *Hum Mol Genet* 14: 401–410, 2005.

33. Dose AC and Burnside B. A class III myosin expressed in the retina is a potential candidate for Bardet-Biedl syndrome. *Genomics* 79: 621–624, 2002.

34. El Mezgueldi M, Tang N, Rosenfeld SS, and Ostap EM. The kinetic mechanism of Myo1e (human myosin-IC). *J Biol Chem* 277: 21514–21521, 2002.

35. El-Amraoui A, Schonn JS, Kussel-Andermann P, Blanchard S, Desnos C, Henry JP, Wolfrum U, Darchen F, and Petit C. MyRIP, a novel Rab effector, enables myosin VIIa recruitment to retinal melanosomes. *EMBO Rep* 3: 463–470, 2002.

36. El-Husseini AE, Kwasnicka D, Yamada T, Hirohashi S, and Vincent SR. BERP, a novel ring finger protein, binds to alpha-actinin-4. *Biochem Biophys Res Commun* 267: 906–911, 2000.

37. Evangelista M, Klebl BM, Tong AH, Webb BA, Leeuw T, Leberer E, Whiteway M, Thomas DY, and Boone C. A role for myosin-I in actin assembly through interactions with Vrp1p, Bee1p, and the Arp2/3 complex. *J Cell Biol* 148: 353–362, 2000.

38. Falk DL, Wessels D, Jenkins L, Pham T, Kuhl S, Titus MA, and Soll DR. Shared, unique and redundant functions of three members of the class I myosins (MyoA, MyoB and MyoF) in motility and chemotaxis in *Dictyostelium*. *J Cell Sci* 116: 3985–3999, 2003.

39. Fath KR. Characterization of myosin-II binding to Golgi stacks in vitro. *Cell Motil Cytoskeleton* 60: 222–235, 2005.

40. Fukuda M and Itoh T. Slac2-a/melanophilin contains multiple PEST-like sequences that are highly sensitive to proteolysis. *J Biol Chem* 279: 22314–22321, 2004.

41. Fukuda M and Kuroda TS. Slac2-c (synaptotagmin-like protein homologue lacking C2 domains-c), a novel linker protein that interacts with Rab27, myosin Va/VIIa, and actin. *J Biol Chem* 277: 43096–43103, 2002.

42. Garcia-Alvarez B, de Pereda JM, Calderwood DA, Ulmer TS, Critchley D, Campbell ID, Ginsberg MH, and Liddington RC. Structural determinants of integrin recognition by talin. *Mol Cell* 11: 49–58, 2003.

43. Geisbrecht ER and Montell DJ. Myosin VI is required for E-cadherin-mediated border cell migration. *Nat Cell Biol* 4: 616–620, 2002.

44. Gibbs D, Kitamoto J, and Williams DS. Abnormal phagocytosis by retinal pigmented epithelium that lacks myosin VIIa, the Usher syndrome 1B protein. *Proc Natl Acad Sci USA* 100: 6481–6486, 2003.

45. Gillespie PG and Cyr JL. Myosin-1c, the hair cell's adaptation motor. *Annu Rev Physiol* 66: 521–545, 2004.

46. Gonsalvez GB, Urbinati CR, and Long RM. RNA localization in yeast: moving towards a mechanism. *Biol Cell* 97: 75–86, 2005.

47. Goodwin M and Yap AS. Classical cadherin adhesion molecules: coordinating cell adhesion, signaling and the cytoskeleton. *J Mol Histol* 35: 839–844, 2004.

48. Graf B, Bahler M, Hilpela P, Bowe C, and Adam T. Functional role for the class IX myosin myr5 in epithelial cell infection by *Shigella flexneri*. *Cell Microbiol* 2: 601–616, 2000.

49. Gumbiner BM. Cell adhesion: the molecular basis of tissue architecture and morphogenesis. *Cell* 84: 345–357, 1996.

50. Hasson T. Myosin VI: two distinct roles in endocytosis. *J Cell Sci* 116: 3453–3461, 2003.

51. Hirokawa N, Keller TC 3rd, Chasan R, and Mooseker MS. Mechanism of brush border contractility studied by the quick-freeze, deep-etch method. *J Cell Biol* 96: 1325–1336, 1983.

52. Homma K, Saito J, Ikebe R, and Ikebe M. Motor function and regulation of myosin X. *J Biol Chem* 276: 34348–34354, 2001.

53. Huxley AF and Niedergerke R. Structural changes in muscle during contraction; interference microscopy of living muscle fibres. *Nature* 173: 971–973, 1954.

54. Huxley H and Hanson J. Changes in the cross-striations of muscle during contraction and stretch and their structural interpretation. *Nature* 173: 973–976, 1954.

55. Inoue A and Ikebe M. Characterization of the motor activity of mammalian myosin VIIA. *J Biol Chem* 278: 5478–5487, 2003.

56. Inoue A, Saito J, Ikebe R, and Ikebe M. Myosin IXb is a single-headed minus-end-directed processive motor. *Nat Cell Biol* 4: 302–306, 2002.

57. Ishikawa K, Catlett NL, Novak JL, Tang F, Nau JJ, and Weisman LS. Identification of an organelle-specific myosin V receptor. *J Cell Biol* 160: 887–897, 2003.

58. Jonsdottir GA and Li R. Dynamics of yeast myosin I: evidence for a possible role in scission of endocytic vesicles. *Curr Biol* 14: 1604–1609, 2004.

59. Jontes JD, Milligan RA, Pollard TD, and Ostap EM. Kinetic characterization of brush border myosin-I ATPase. *Proc Natl Acad Sci USA* 94: 14332–14337, 1997.

60. Jung G, Remmert K, Wu X, Volosky JM, and Hammer JA 3rd. The *Dictyostelium* CARMIL protein links capping protein and the Arp2/3 complex to type I myosins through their SH3 domains. *J Cell Biol* 153: 1479–1497, 2001.

61. Keller TC 3rd and Mooseker MS. Ca^{++}-calmodulin-dependent phosphorylation of myosin, and its role in brush border contraction in vitro. *J Cell Biol* 95: 943–959, 1982.

62. Kikkawa Y, Mburu P, Morse S, Kominami R, Townsend S, and Brown SD. Mutant analysis reveals whirlin as a dynamic organizer in the growing hair cell stereocilium. *Hum Mol Genet* 14: 391–400, 2005.

63. Komaba S, Inoue A, Maruta S, Hosoya H, and Ikebe M. Determination of human myosin III as a motor protein having a protein kinase activity. *J Biol Chem* 278: 21352–21360, 2003.

Downloaded from physiologyonline.physiology.org on January 16, 2006

64. Kovacs M, Wang F, Hu A, Zhang Y, and Sellers JR. Functional divergence of human cytoplasmic myosin II: kinetic characterization of the nonmuscle IIA isoform. *J Biol Chem* 278: 38132–38140, 2003.

65. Kovacs M, Wang F, and Sellers JR. Mechanism of action of myosin X, a membrane-associated molecular motor. *J Biol Chem* 280: 15071–15083, 2005.

66. Krendel MF and Bonder EM. Analysis of actin filament bundle dynamics during contact formation in live epithelial cells. *Cell Motil Cytoskeleton* 43: 296–309, 1999.

67. Kros CJ, Marcotti W, van Netten SM, Self TJ, Libby RT, Brown SD, Richardson GP, and Steel KP. Reduced climbing and increased slipping adaptation in cochlear hair cells of mice with Myo7a mutations. *Nat Neurosci* 5: 41–47, 2002.

68. Kussel-Andermann P, El-Amraoui A, Safieddine S, Nouaille S, Perfettini I, Lecuit M, Cossart P, Wolfrum U, and Petit C. Vezatin, a novel transmembrane protein, bridges myosin VIIA to the cadherin-catenins complex. *EMBO J* 19: 6020–6029, 2000.

69. Langford GM. Myosin-V, a versatile motor for short-range vesicle transport. *Traffic* 3: 859–865, 2002.

70. Lapierre LA, Kumar R, Hales CM, Navarre J, Bhartur SG, Burnette JO, Provance DW Jr, Mercer JA, Bahler M, and Goldenring JR. Myosin vb is associated with plasma membrane recycling systems. *Mol Biol Cell* 12: 1843–1857, 2001.

71. Lechler T, Shevchenko A, and Li R. Direct involvement of yeast type I myosins in Cdc42-dependent actin polymerization. *J Cell Biol* 148: 363–373, 2000.

72. Lee SJ and Montell C. Light-dependent translocation of visual arrestin regulated by the NINAC myosin III. *Neuron* 43: 95–103, 2004.

73. Lee WL, Bezanilla M, and Pollard TD. Fission yeast myosin-I, Myo1p, stimulates actin assembly by Arp2/3 complex and shares functions with WASp. *J Cell Biol* 151: 789–800, 2000.

74. Les Erickson F, Corsa AC, Dose AC, and Burnside B. Localization of a class III myosin to filopodia tips in transfected HeLa cells requires an actin-binding site in its tail domain. *Mol Biol Cell* 14: 4173–4180, 2003.

75. Libby RT, Lillo C, Kitamoto J, Williams DS, and Steel KP. Myosin Va is required for normal photoreceptor synaptic activity. *J Cell Sci* 117: 4509–4515, 2004.

76. Lister I, Schmitz S, Walker M, Trinick J, Buss F, Veigel C, and Kendrick-Jones J. A monomeric myosin VI with a large working stroke. *EMBO J* 23: 1729–1738, 2004.

77. Lo CM, Buxton DB, Chua GC, Dembo M, Adelstein RS, and Wang YL. Nonmuscle myosin IIb is involved in the guidance of fibroblast migration. *Mol Biol Cell* 15: 982–989, 2004.

78. Long RM, Gu W, Lorimer E, Singer RH, and Chartrand P. She2p is a novel RNA-binding protein that recruits the Myo4p-She3p complex to ASH1 mRNA. *EMBO J* 19: 6592–6601, 2000.

79. Luo L. Actin cytoskeleton regulation in neuronal morphogenesis and structural plasticity. *Annu Rev Cell Dev Biol* 18: 601–635, 2002.

80. Matesic LE, Yip R, Reuss AE, Swing DA, O'Sullivan TN, Fletcher CF, Copeland NG, and Jenkins NA. Mutations in Mlph, encoding a member of the Rab effector family, cause the melanosome transport defects observed in leaden mice. *Proc Natl Acad Sci USA* 98: 10238–10243, 2001.

81. Maupin P, Phillips CL, Adelstein RS, and Pollard TD. Differential localization of myosin-II isozymes in human cultured cells and blood cells. *J Cell Sci* 107: 3077–3090, 1994.

82. Mehta AD, Rock RS, Rief M, Spudich JA, Mooseker MS, and Cheney RE. Myosin-V is a processive actin-based motor. *Nature* 400: 590–593, 1999.

83. Menasche G, Fischer A, and de Saint Basile G. Griscelli syndrome types 1 and 2. *Am J Hum Genet* 71: 1237–1238, 2002.

84. Mercer JA, Seperack PK, Strobel MC, Copeland NG, and Jenkins NA. Novel myosin heavy chain encoded by murine dilute coat colour locus. *Nature* 349: 709–713, 1991.

85. Meshel AS, Wei Q, Adelstein RS, and Sheetz MP. Basic mechanism of three-dimensional collagen fibre transport by fibroblasts. *Nat Cell Biol* 7: 157–164, 2005.

86. Millo H, Leaper K, Lazou V, and Bownes M. Myosin VI plays a role in cell-cell adhesion during epithelial morphogenesis. *Mech Dev* 121: 1335–1351, 2004.

87. Miyamoto S, Akiyama SK, and Yamada KM. Synergistic roles for receptor occupancy and aggregation in integrin transmembrane function. *Science* 267: 883–885, 1995.

88. Miyamoto S, Teramoto H, Coso OA, Gutkind JS, Burbelo PD, Akiyama SK, and Yamada KM. Integrin function: molecular hierarchies of cytoskeletal and signaling molecules. *J Cell Biol* 131: 791–805, 1995.

89. Muller RT, Honnert U, Reinhard J, and Bahler M. The rat myosin myr 5 is a GTPase-activating protein for Rho in vivo: essential role of arginine 1695. *Mol Biol Cell* 8: 2039–2053, 1997.

90. Nishikawa S, Homma K, Komori Y, Iwaki M, Wazawa T, Hikikoshi Iwane A, Saito J, Ikebe R, Katayama E, Yanagida T, and Ikebe M. Class VI myosin moves processively along actin filaments backward with large steps. *Biochem Biophys Res Commun* 290: 311–317, 2002.

91. O'Connell CB and Mooseker MS. Native Myosin-IXb is a plus-, not a minus-end-directed motor. *Nat Cell Biol* 5: 171–172, 2003.

92. Ohashi S, Koike K, Omori A, Ichinose S, Ohara S, Kobayashi S, Sato TA, and Anzai K. Identification of mRNA/protein (mRNP) complexes containing Puralpha, mStaufen, fragile X protein, and myosin Va and their association with rough endoplasmic reticulum equipped with a kinesin motor. *J Biol Chem* 277: 37804–37810, 2002.

93. Ostap EM and Pollard TD. Biochemical kinetic characterization of the *Acanthamoeba* myosin-I ATPase. *J Cell Biol* 132: 1053–1060, 1996.

94. Osterweil E, Wells DG, and Mooseker MS. A role for myosin VI in postsynaptic structure and glutamate receptor endocytosis. *J Cell Biol* 168: 329–338, 2005.

95. Petit C. Usher syndrome: from genetics to pathogenesis. *Annu Rev Genomics Hum Genet* 2: 271–297, 2001.

96. Pollard TD and Borisy GG. Cellular motility driven by assembly and disassembly of actin filaments. *Cell* 112: 453–465, 2003.

97. Pollard TD and Weihing RR. Actin and myosin and cell movement. *CRC Crit Rev Biochem* 2: 1–65, 1974.

98. Porter JA, Yu M, Doberstein SK, Pollard TD, and Montell C. Dependence of calmodulin localization in the retina on the NINAC unconventional myosin. *Science* 262: 1038–1042, 1993.

99. Post PL, Bokoch GM, and Mooseker MS. Human myosin-IXb is a mechanochemically active motor and a GAP for rho. *J Cell Sci* 111: 941–950, 1998.

100. Post PL, Tyska MJ, O'Connell CB, Johung K, Hayward A, and Mooseker MS. Myosin-IXb is a single-headed and processive motor. *J Biol Chem* 277: 11679–11683, 2002.

101. Provance DW Jr, Gourley CR, Silan CM, Cameron LC, Shokat KM, Goldenring JR, Shah K, Gillespie PG, and Mercer JA. Chemical-genetic inhibition of a sensitized mutant myosin Vb demonstrates a role in peripheral-pericentriolar membrane traffic. *Proc Natl Acad Sci USA* 101: 1868–1873, 2004.

102. Puthalakath H, Villunger A, O'Reilly LA, Beaumont JG, Coultas L, Cheney RE, Huang DC, and Strasser A. Bmf: a proapoptotic BH3-only protein regulated by interaction with the myosin V actin motor complex, activated by anoikis. *Science* 293: 1829–1832, 2001.

103. Rao MV, Engle LJ, Mohan PS, Yuan A, Qiu D, Cataldo A, Hassinger L, Jacobsen S, Lee VM, Andreadis A, Julien JP, Bridgman PC, and Nixon RA. Myosin Va binding to neurofilaments is essential for correct myosin Va distribution and transport and neurofilament density. *J Cell Biol* 159: 279–290, 2002.

104. Raposo G, Cordonnier MN, Tenza D, Menichi B, Durrbach A, Louvard D, and Coudrier E. Association of myosin I alpha with endosomes and lysosomes in mammalian cells. *Mol Biol Cell* 10: 1477–1494, 1999.

105. Reck-Peterson SL, Provance DW Jr, Mooseker MS, and Mercer JA. Class V myosins. *Biochim Biophys Acta* 1496: 36–51, 2000.

106. Reck-Peterson SL, Tyska MJ, Novick PJ, and Mooseker MS. The yeast class V myosins, Myo2p and Myo4p, are nonprocessive actin-based motors. *J Cell Biol* 153: 1121–1126, 2001.

107. Redowicz MJ. Myosins and pathology: genetics and biology. *Acta Biochim Pol* 49: 789–804, 2002.

108. Reinhard J, Scheel AA, Diekmann D, Hall A, Ruppert C, and Bahler M. A novel type of myosin implicated in signalling by rho family GTPases. *EMBO J* 14: 697–704, 1995.

109. Remmert K, Olszewski TE, Bowers MB, Dimitrova M, Ginsburg A, and Hammer JA 3rd. CARMIL is a bona fide capping protein interactant. *J Biol Chem* 279: 3068–3077, 2004.

110. Rock RS, Rice SE, Wells AL, Purcell TJ, Spudich JA, and Sweeney HL. Myosin VI is a processive motor with a large step size. *Proc Natl Acad Sci USA* 98: 13655–13659, 2001.

111. Rodriguez OC and Cheney RE. Human myosin-Vc is a novel class V myosin expressed in epithelial cells. *J Cell Sci* 115: 991–1004, 2002.

112. Rodriguez OC and Cheney RE. A new direction for myosin. *Trends Cell Biol* 10: 307–311, 2000.

113. Rogers SL and Gelfand VI. Membrane trafficking, organelle transport, and the cytoskeleton. *Curr Opin Cell Biol* 12: 57–62, 2000.

114. Rose SD, Lejen T, Casaletti L, Larson RE, Pene TD, and Trifaro JM. Myosins II and V in chromaffin cells: myosin V is a chromaffin vesicle molecular motor involved in secretion. *J Neurochem* 85: 287–298, 2003.

115. Rosenblatt J, Cramer LP, Baum B, and McGee KM. Myosin II-dependent cortical movement is required for centrosome separation and positioning during mitotic spindle assembly. *Cell* 117: 361–372, 2004.

116. Rosenfeld SS, Xing J, Chen LQ, and Sweeney HL. Myosin IIb is unconventionally conventional. *J Biol Chem* 278: 27449–27455, 2003.

117. Saeki N, Tokuo H, and Ikebe M. BIG1 is a binding partner of myosin IXb and regulates its Rho-GTPase activating protein activity. *J Biol Chem* 280: 10128–10134, 2005.

118. Sahlender DA, Roberts RC, Arden SD, Spudich G, Taylor MJ, Luzio JP, Kendrick-Jones J, and Buss F. Optineurin links myosin VI to the Golgi complex and is involved in Golgi organization and exocytosis. *J Cell Biol* 169: 285–295, 2005.

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119. Saitoh T, Takemura S, Ueda K, Hosoya H, Nagayama M, Haga H, Kawabata K, Yamagishi A, and Takahashi M. Differential localization of non-muscle myosin II isoforms and phosphorylated regulatory light chains in human MRC-5 fibroblasts. *FEBS Lett* 509: 365–369, 2001.

120. Sanal O, Ersoy F, Tezcan I, Metin A, Yel L, Menasche G, Gurgey A, Berkel I, and de Saint Basile G. Griscelli disease: genotype-phenotype correlation in an array of clinical heterogeneity. *J Clin Immunol* 22: 237–243, 2002.

121. Schmidt CE, Horwitz AF, Lauffenburger DA, and Sheetz MP. Integrin-cytoskeletal interactions in migrating fibroblasts are dynamic, asymmetric, and regulated. *J Cell Biol* 123: 977–991, 1993.

122. Schroeder TE. Dynamics of the contractile ring. *Soc Gen Physiol Ser* 30: 305–334, 1975.

123. Sheetz MP, Baumrind NL, Wayne DB, and Pearlman AL. Concentration of membrane antigens by forward transport and trapping in neuronal growth cones. *Cell* 61: 231–241, 1990.

124. Siemens J, Lillo C, Dumont RA, Reynolds A, Williams DS, Gillespie PG, and Muller U. Cadherin 23 is a component of the tip link in hair-cell stereocilia. *Nature* 428: 950–955, 2004.

125. Sousa S, Cabanes D, El-Amraoui A, Petit C, Lecuit M, and Cossart P. Unconventional myosin VIIa and vezatin, two proteins crucial for Listeria entry into epithelial cells. *J Cell Sci* 117: 2121–2130, 2004.

126. Stow JL, Fath KR, and Burgess DR. Budding roles for myosin II on the Golgi. *Trends Cell Biol* 8: 138–141, 1998.

127. Suter DM, Errante LD, Belotserkovsky V, and Forscher P. The Ig superfamily cell adhesion molecule, apCAM, mediates growth cone steering by substrate-cytoskeletal coupling. *J Cell Biol* 141: 227–240, 1998.

128. Swiatecka-Urban A, Boyd C, Coutermarsh B, Karlson KH, Barnaby R, Aschenbrenner L, Langford GM, Hasson T, and Stanton BA. Myosin VI regulates endocytosis of the cystic fibrosis transmembrane conductance regulator. *J Biol Chem* 279: 38025–38031, 2004.

129. Takizawa PA and Vale RD. The myosin motor, Myo4p, binds Ash1 mRNA via the adapter protein, She3p. *Proc Natl Acad Sci USA* 97: 5273–5278, 2000.

130. Tang F, Kauffman EJ, Novak JL, Nau JJ, Catlett NL, and Weisman LS. Regulated degradation of a class V myosin receptor directs movement of the yeast vacuole. *Nature* 422: 87–92, 2003.

131. Thompson RF and Langford GM. Myosin superfamily evolutionary history. *Anat Rec* 268: 276–289, 2002.

132. Titus MA, Wessels D, Spudich JA, and Soll D. The unconventional myosin encoded by the myoA gene plays a role in *Dictyostelium* motility. *Mol Biol Cell* 4: 233–246, 1993.

133. Togo T and Steinhardt RA. Nonmuscle myosin IIA and IIB have distinct functions in the exocytosis-dependent process of cell membrane repair. *Mol Biol Cell* 15: 688–695, 2004.

134. Tokuo H and Ikebe M. Myosin X transports Mena/VASP to the tip of filopodia. *Biochem Biophys Res Commun* 319: 214–220, 2004.

135. Tominaga M, Kojima H, Yokota E, Orii H, Nakamori R, Katayama E, Anson M, Shimmen T, and Oiwa K. Higher plant myosin XI moves processively on actin with 35 nm steps at high velocity. *EMBO J* 22: 1263–1272, 2003.

136. Tuxworth RI, Weber I, Wessels D, Addicks GC, Soll DR, Gerisch G, and Titus MA. A role for myosin VII in dynamic cell adhesion. *Curr Biol* 11: 318–329, 2001.

137. Tyska MJ, Mackey AT, Huang JD, Copland NG, Jenkins NA, and Mooseker MS. Myosin-1a is critical for normal brush border structure and composition. *Mol Biol Cell* 16: 2443–2457, 2005.

138. Tyska MJ and Mooseker MS. Myosin-V motility: these levers were made for walking. *Trends Cell Biol* 13: 447–451, 2003.

139. Tyska MJ and Mooseker MS. A role for myosin-1A in the localization of a brush border disaccharidase. *J Cell Biol* 165: 395–405, 2004.

140. Varadi A, Tsuboi T, and Rutter GA. Myosin Va transports dense core secretory vesicles in pancreatic min6 {beta}-cells. *Mol Biol Cell* (March 23, 2005); 10.1091/mbc.E04-11-1001.

141. Volpicelli LA, Lah JJ, Fang G, Goldenring JR, and Levey AI. Rab11a and myosin Vb regulate recycling of the M4 muscarinic acetylcholine receptor. *J Neurosci* 22: 9776–9784, 2002.

142. Walsh T, Walsh V, Vreugde S, Hertzano R, Shahin H, Haika S, Lee MK, Kanaan M, King MC, and Avraham KB. From flies' eyes to our ears: mutations in a human class III myosin cause progressive nonsyndromic hearing loss DFNB30. *Proc Natl Acad Sci USA* 99: 7518–7523, 2002.

143. Wang A, Liang Y, Fridell RA, Probst FJ, Wilcox ER, Touchman JW, Morton CC, Morell RJ, Noben-Trauth K, Camper SA, and Friedman TB. Association of unconventional myosin MYO15 mutations with human nonsyndromic deafness DFNB3. *Science* 280: 1447–1451, 1998.

144. Wang F, Kovacs M, Hu A, Limouze J, Harvey EV, and Sellers JR. Kinetic mechanism of non-muscle myosin IIB: functional adaptations for tension generation and maintenance. *J Biol Chem* 278: 27439–27448, 2003.

145. Warrick HM and Spudich JA. Myosin structure and function in cell motility. *Annu Rev Cell Biol* 3: 379–421, 1987.

146. Waterman-Storer C, Duey DY, Weber KL, Keech J, Cheney RE, Salmon ED, and Bement WM. Microtubules remodel actomyosin networks in *Xenopus* egg extracts via two mechanisms of F-actin transport. *J Cell Biol* 150: 361–376, 2000.

147. Weber KL, Sokac AM, Berg JS, Cheney RE, and Bement WM. A microtubule-binding myosin required for nuclear anchoring and spindle assembly. *Nature* 431: 325–329, 2004.

148. Wells AL, Lin AW, Chen LQ, Safer D, Cain SM, Hasson T, Carragher BO, Milligan RA, and Sweeney HL. Myosin VI is an actin-based motor that moves backwards. *Nature* 401: 505–508, 1999.

149. Wes PD, Xu XZ, Li HS, Chien F, Doberstein SK, and Montell C. Termination of phototransduction requires binding of the NINAC myosin III and the PDZ protein INAD. *Nat Neurosci* 2: 447–453, 1999.

150. Wilson SM, Yip R, Swing DA, O'Sullivan TN, Zhang Y, Novak EK, Swank RT, Russell LB, Copeland NG, and Jenkins NA. A mutation in Rab27a causes the vesicle transport defects observed in ashen mice. *Proc Natl Acad Sci USA* 97: 7933–7938, 2000.

151. Wirth JA, Jensen KA, Post PL, Bement WM, and Mooseker MS. Human myosin-IXb, an unconventional myosin with a chimerin-like rho/rac GTPase-activating protein domain in its tail. *J Cell Sci* 109: 653–661, 1996.

152. Wu X and Hammer JA 3rd. Making sense of melanosome dynamics in mouse melanocytes. *Pigment Cell Res* 13: 241–247, 2000.

153. Wu X, Jung G, and Hammer JA 3rd. Functions of unconventional myosins. *Curr Opin Cell Biol* 12: 42–51, 2000.

154. Wu XS, Rao K, Zhang H, Wang F, Sellers JR, Matesic LE, Copeland NG, Jenkins NA, and Hammer JA 3rd. Identification of an organelle receptor for myosin-Va. *Nat Cell Biol* 4: 271–278, 2002.

155. Yanaihara N, Nishioka M, Kohno T, Otsuka A, Okamoto A, Ochiai K, Tanaka T, and Yokota J. Reduced expression of MYO18B, a candidate tumor-suppressor gene on chromosome arm 22q, in ovarian cancer. *Int J Cancer* 112: 150–154, 2004.

156. Yoshida H, Cheng W, Hung J, Montell D, Geisbrecht E, Rosen D, Liu J, and Naora H. Lessons from border cell migration in the *Drosophila* ovary: a role for myosin VI in dissemination of human ovarian cancer. *Proc Natl Acad Sci USA* 101: 8144–8149, 2004.

157. Zhang H, Berg JS, Li Z, Wang Y, Lang P, Sousa AD, Bhaskar A, Cheney RE, and Stromblad S. Myosin-X provides a motor-based link between integrins and the cytoskeleton. *Nat Cell Biol* 6: 523–531, 2004.

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