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Review

Regulation of the enzymatic and motor activities of myosin I

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Abstract

Myosins I were the first unconventional myosins to be purified and they remain the best characterized. They have been implicated in various motile processes, including organelle translocation, ion channel gating and cytoskeletal reorganization but their exact cellular functions are still unclear. All members of the myosin I family, from yeast to man, have three structural domains: a catalytic head domain that binds ATP and actin; a tail domain believed to be involved in targeting the myosins to specific subcellular locations and a junction or neck domain that connects them and interacts with light chains. In this review we discuss how each of these three domains contributes to the regulation of myosin I enzymatic activity, motor activity and subcellular localization.

Keywords: Unconventional myosin; Phosphorylation; Isoleucine–glutamine (IQ) domain

1. Introduction

In 1973 Pollard and Korn reported the discovery of an unconventional myosin, which, unlike all other myosins characterized at that time, was single-headed and did not self-associate into bipolar filaments [1]. They further showed that this protein, *Acanthamoeba* myosin I, expressed actin-activated ATPase activity only in the presence of a ~95 kDa cofactor [2], subsequently identified as myosin I kinase [3]. Despite steady progress in the Korn and Pollard laboratories, it took more than a decade for the unconventional myosin field to gain momentum. As noted from the outset [4] it was essential to demonstrate that myosin I was not merely a proteolytic fragment of conventional myosin. This was conclusively established by Hammer and his colleagues who cloned *Acanthamoeba* myosin IB, and showed that it contained a myosin-like catalytic head of about 80 kDa and a unique tail of about 50 kDa [5,6]. At about the same time the first non-*Acanthamoeba* forms of myosin I were identified, in microvilli of the chicken intestinal brush border [7] and in *Dictyostelium* [8]. By the early 1990s it became clear that multiple forms of myosin I exist and that these are ubiquitously expressed from yeast to human (most recently reviewed in [9]).

With the advent of facile cloning techniques and the expansion of sequence data bases we are now faced with a plethora of actin-dependent motor proteins and a somewhat confusing nomenclature. At present there are fifteen known families of myosin, including the single family of conventional myosins, myosins II [10]. In this review the myosin I subfamily is divided into four classes, which we designate Iα, Iβ, IC and Iγ. In rat these have been termed myr1, myr2, myr3 and myr4, respectively, for myosin I from rat [11]. In some classifications the closely re-

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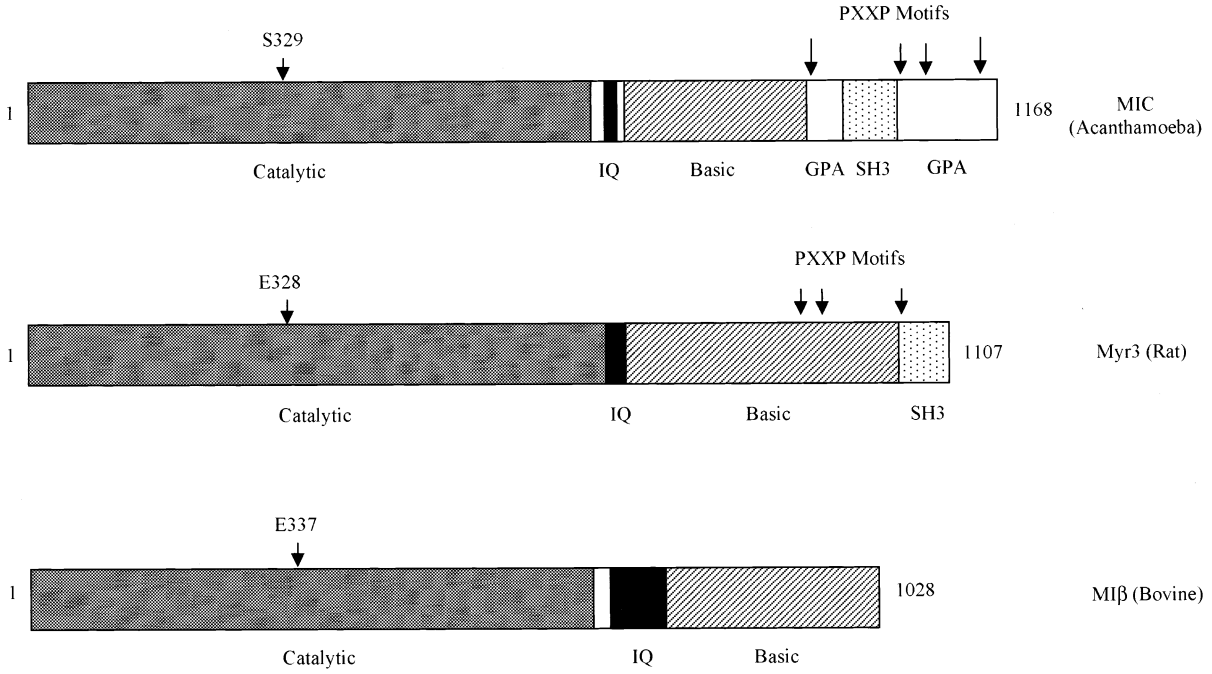

Fig. 1. Domain structure of myosins I. GPA: glycine, proline, alanine-rich domain; SH3: Src homology 3 domain; IQ: isoleucine, glutamine motif. Arrows in catalytic domain indicate phosphorylatable or negatively charged residues.

lated myosins Iα and BBMI (brush border myosin I) are grouped separately, giving a total of five subclasses. Myosin IC is the human version of yeast and protozoan myosins I and they are sometimes referred to as 'amoeboid' or 'classical' myosins I. Structurally, myosins I are quite similar to each other. All have N-terminal head domains of ~70–80 kDa containing actin and ATP-binding sites, α-helical neck domains containing from one to six IQ (isoleucine–glutamine) motifs that interact with light chains (often calmodulin molecules) and C-terminal tail domains of varying sizes and considerable sequence diversity. All myosin I tail domains have net positive charges and many have been shown to interact with anionic phospholipids, though sometimes only at low ionic strength [12]. The tails of 'classical' myosins I can be further subdivided into proline-rich segments, Src homology 3 (SH3) domains and, in some cases, ATP-independent actin-binding domains rich in glycine, proline and alanine residues [13–15]. The diversity among myosin I tails is evident in Fig. 1 which shows two classical myosins, *Acanthamoeba* myosin IC and rat myr3, and a non-classical form, bovine myosin Iβ. Fig. 1 highlights another feature that distinguishes vertebrate from lower eukaryotic myosins I: protozoan and yeast myosins have a phosphorylatable residue in the head domains whereas vertebrate forms have negatively charged residues in the corresponding position.

This review focuses on recent advances in the regulation of myosin I enzymatic and motor activities and in the targeting of different forms of myosin I to specific locations in the cell. Regulation can involve interactions or modifications in all three myosin I domains. Phosphorylation in the head domain is required for stimulation of the ATPase activities of lower eukaryotic myosins I by F-actin. The neck domains of myosin I appear to function similarly to the regulatory domains of conventional muscle-type myosins, serving as lever arms to control displacement during the ATPase cycle. The length of this lever arm may be modulated by the presence, absence, or orientation of light chains that interact with the myosin I neck. Finally, it is widely believed that subcellular targeting is determined by interactions involving myosin I tails. In the case of myosin II, the tails self-associate to form bipolar filaments that interact with, and promote the sliding of, actin filaments, as occurs during muscle contraction. The tails of unconven-

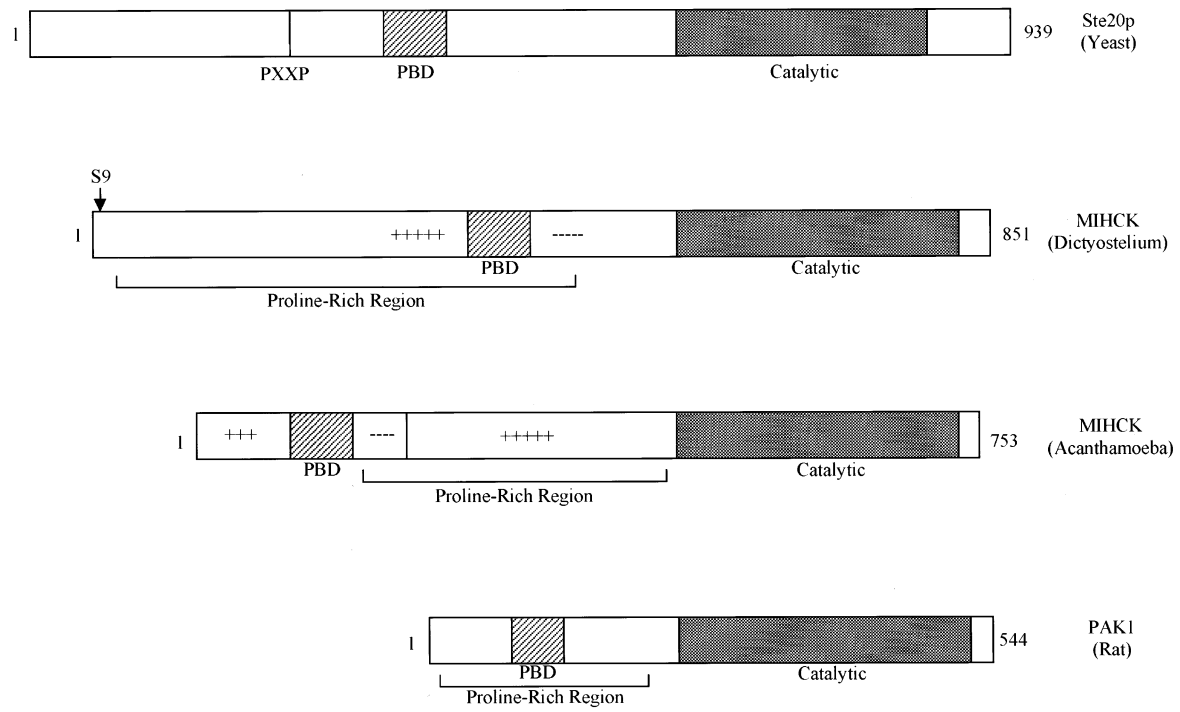

Fig. 2. Structural domain of myosin I kinases and their comparison with PAK and Ste20. PBD-p21 binding domain.

tional myosins have been referred to as 'cargo' domains, for they presumably tether the myosins to the cellular cargo which must be translocated along actin filaments. The great diversity in primary structure of myosin tails is likely to account for specific targeting of the motors, mediated by interactions with distinct myosin I binding proteins.

2. Regulation of myosin I activities by phosphorylation

2.1. Myosin I kinases

We begin our discussion of myosin I regulation with a look at heavy chain phosphorylation, even though it is only in lower eukaryotes that the significance of this modification has been ascertained. The discovery of myosin I kinase nearly coincided with that of myosin I itself, when Pollard and Korn realized that expression of high actin-stimulated ATPase activities of *Acanthamoeba* myosin I required the presence of a 'cofactor' protein [2]. Shortly thereafter the cofactor was recognized as a protein kinase [3] which was subsequently purified to homogeneity from *Acanthamoeba* [16] and *Dictyostelium* [17] and characterized extensively. Both kinases must undergo autophosphorylation for enzymatic activity [18,19]. Negatively charged phospholipids increase the rate of autophosphorylation, thereby also accelerating myosin I phosphorylation. Ca^{2+}-calmodulin inhibits myosin I kinase activity, evidently by competing with phospholipids for a binding site near the amino-terminus of the kinase [19,20].

Interest in these kinases surged when the *Dictyostelium* [21] and *Acanthamoeba* [22] enzymes were found to have sequence similarity to the PAK/Ste20 kinase family, implicated in cell signaling and cytoskeletal reorganization. The two myosin I kinases have many features in common with each other and with the PAK/Ste20 enzymes, but some differences also exist. PAK/Ste20 and myosin I kinases are both activated by Cdc42 and Rac, members of the p21 family of GTP-binding proteins [23]. They have two regions of high sequence similarity: in the catalytic domains, located in the C-terminal halves of the molecules, and within the p21 binding domains (PBDs) found in the N-terminal regulatory domains (Fig. 2). PBDs are approximately 60 amino acid residues in length. The first 14 residues comprize the

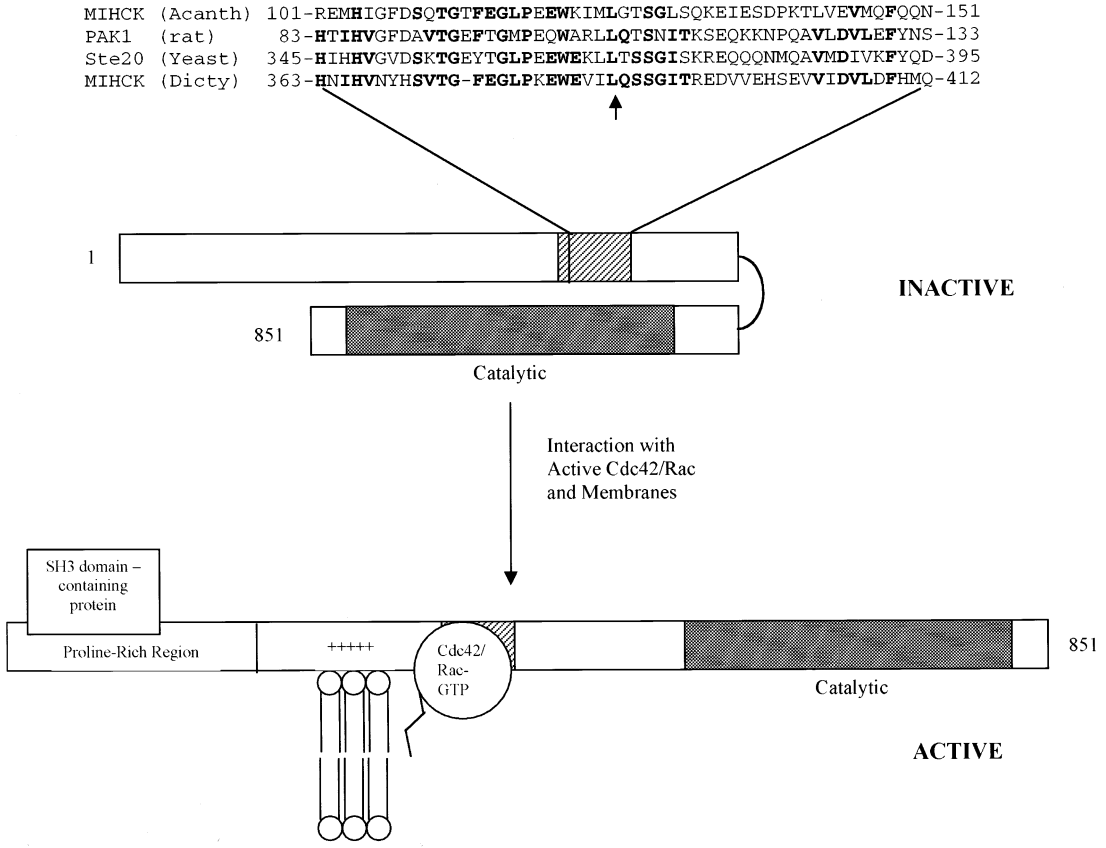

Fig. 3. Hypothetical mechanism of myosin I kinase regulation. The inactive state is maintained by an interaction between the regulatory and catalytic domains. The sequences shown above the scheme represent the putative interaction domain within the PBD (hatched region) that binds to, and inhibits, the catalytic domain. Binding of Cdc42/Rac, negatively charged phospholipids or SH3 domain-containing proteins opens the structure and relieves the autoinhibition).

highly conserved CRIB (Cdc42/Rac interactive binding) motif which, together with the subsequent 15–16 residues, is required for interaction with p21 proteins. Like PAK or Ste20, both myosin I kinases bind Rac/Cdc42 in a GTP-dependent manner, resulting in autophosphorylation and kinase regulation [21,24].

The two myosin I kinases have low sequence similarities outside the PBD and catalytic domains but they share several structural features. Both have proline-rich regions containing multiple PXXP motifs characteristic for binding to Src homology 3 (SH3) domains. These motifs may serve to strengthen interactions with myosins I, many of which contain SH3 domains and to target the kinases to membrane-bound SH3 domain-containing proteins, a mechanism already demonstrated for PAK [25]. Both myosin I kinases also contain clusters of charged amino acids, including a basic region N-terminal to the PBD which mediates phospholipid binding.

Rac/Cdc42 and phospholipids are likely to stimulate myosin I kinase activity by reversing an autoinhibition that results from interactions between the catalytic and regulatory domains of the kinases (Fig. 2). Although the autoinhibitory sites have not yet been identified, their locations can be inferred from studies of PAK/Ste20 regulation. Yeast two-hybrid analysis revealed that the regulatory and catalytic domains of *Schizosaccharomyces pombe* PAK can interact with each other and the site of interaction was localized to the C-terminal portion of the PBD [26] (Fig. 3). This site partially overlaps with the binding site for Rac/Cdc42, which presumably disrupts its inhibitory interaction with the catalytic domain. Zhao et al. [27] provided evidence for the autoinhibition mechanism by showing that a peptide corre-

sponding to residues 83–149 in the regulatory domain blocked PAK activation in vitro and in vivo whereas mutations in residues 101–137 induced constitutive kinase activity. A single point mutation (L107F) in PAK renders the enzyme constitutively active. Leucine 107 is conserved in Ste20 and in *Acanthamoeba* and *Dictyostelium* myosin I kinases and it will be interesting to see whether similar point mutations result in constitutive myosin I kinase activity.

To summarize, available data are consistent with the view that all modes of myosin I kinase activation, whether by binding to phospholipids, to Rac/Cdc42, or by autophosphorylation in the regulatory domain, are due to an opening of the proteins and relaxation of autoinhibition.

2.2. Effects of myosin I phosphorylation

Phosphorylation of *Acanthamoeba* [28] and *Dictyostelium* [8] myosins I by myosin I heavy chain kinase is necessary for activation of their ATPase activities by actin. Presumably this is also true of yeast and *Aspergillus* myosins I but these proteins have not yet been purified or characterized. These lower eukaryotic myosins, as well as metazoan myosin VI, have phosphorylatable serine or threonine residues at conserved positions within their catalytic head domains. Nearly all other myosins have a negatively charged residue at the corresponding position, which resides in a flexible loop believed to be in contact with actin [29]. Apparently, a negative charge, whether contributed by phosphate groups on modified serines or threonines or by aspartyl or glutamyl side chains, is required for acceleration of product release during the ATPase reaction [30]. Only one form of myosin, *Drosophila* myosin IA, violates the so-called 'TEDS rule', i.e. the requirement for T, E, D or S residues in the conserved loop position [31]. However, the consequences of this difference remain to be determined. The effect on the structure of myosin I of a negative charge in the TEDS position must be subtle, since cryoelectron microscopy of a constitutively active *Acanthamoeba* myosin IC mutant (S329E) or an inactive mutant (S329A) revealed no discernible differences in their actin–myosin interfaces [32].

There is convincing genetic evidence for the in vivo significance of myosin I phosphorylation. In *Dictyostelium* a double deletion of myoA and myoB impairs growth, pinocytosis and actin organization [33]. These defects are reversed by expression of wild-type myoB but not by mutant S332A which lacks the TEDS phosphorylation site [34]. Likewise, in *Saccharomyces*, expression of wild-type but not the TEDS mutant S357A of Myo3p rescues budding defects caused by deletion of both forms of yeast myosin I [35,36]. Significantly, mutant S357D also rescues the budding defect, demonstrating that a negatively charged residue, as occurs in most vertebrate myosins I, can substitute for phosphoserine or phosphothreonine [36]. The situation is somewhat more complicated in *Aspergillus*. Deletion of *Aspergillus* MYOA results in inhibition of polarized hyphal growth and protein secretion [37]. Expression of non-phosphorylatable TEDS mutant S371A restored all functions lost by MYOA deletion, arguing that this modification is not essential for the cellular activity of the *Aspergillus* enzyme. However, phosphorylation of serine 371 must somehow alter the myosin because cells expressing mutant S371E have increased accumulation of membranes in growing hyphae, perhaps due to an increase in endocytosis [38].

Despite the absence of a phosphorylatable TEDS residue in vertebrate myosins I, it is still possible that these enzymes are subject to regulation by phosphorylation. Myosins Iα (including brush border myosin I), Iβ and Iγ can all be phosphorylated in vitro by protein kinase C (PKC) in yet unidentified sites in the tail domains [39,40]. These modifications apparently do not affect actin-activated ATPase activities but may influence interactions with calmodulin and phospholipid vesicles [39,40]. It is too early to tell whether this type of regulation has physiological significance, but the similarity with neuromodulin [41], in which PKC phosphorylation also reduces affinity for calmodulin at an IQ domain, is intriguing.

3. Regulation of myosin I activity at the 'neck' domain

The junction between head and tail domains of myosin I are extended α-helical structures that interact with light chains, most often calmodulin mole-

cules. There is strong evidence that the ATPase and motor activities of most forms of myosin I are regulated by interactions between light and heavy chains, although the mechanism of regulation is poorly understood.

Myosin I neck domains contain from one to six IQ motifs, α-helical stretches of 20–25 amino acid residues including the consensus sequence (IVL)QXXX-RGXXX(RK)XX(FILVWY) [42]. IQ motifs have been identified in several proteins, including neuromodulin and neurogranin, where they bind to Ca^{2+}-free calmodulin (recently reviewed in [43]). The light chains of vertebrate and yeast myosins I are, in fact, calmodulin molecules and the only sequenced light chain of a protozoan myosin is a calmodulin-like protein containing two potential helix–loop–helix Ca^{2+}-binding domains [44]. In most cases myosin I IQ motifs bind more tightly to apocalmodulin than to Ca^{2+}/calmodulin. An exception is rat myosin Iγ (myr4) which contains two IQ motifs in the neck domain with different affinity for Ca^{2+}: one, the C-terminal, binds calmodulin tightly in the presence of Ca^{2+} and the second, the N-terminal, binds calmodulin more strongly in the absence of Ca^{2+} [45]. The structure of the complex between calmodulin and a myosin I IQ domain has not yet been determined. However, Houdusse et al.[46] have modeled the likely interactions between calmodulin and the first IQ domain of brush border myosin I, based on molecular contacts found in the crystal structure of the scallop myosin regulatory domain. Calmodulin has two high-affinity Ca^{2+}-binding sites in its C-terminal lobe and two low-affinity sites in its N-terminal lobe. The lobes adopt a closed conformation in the absence of Ca^{2+} and an open conformation when Ca^{2+} is bound [47]. According to the model of Houdusse et al. [46], the C-terminal lobe of apocalmodulin adopts a 'semi-open' conformation that can grip the most N-terminal segment of the IQ domain (IQXXXR). The N-terminal (low Ca^{2+}-affinity) lobe of calmodulin binds weakly to the myosin heavy chain. Upon binding Ca^{2+}, the C-terminal lobe changes to an open conformation, reducing its affinity for the N-terminal portion of the IQ domain, leading either to dissociation of calmodulin or its binding to a different set of sites on the IQ motif. This alternative binding mode may be similar to the conventional amphipathic helix interaction that occurs in most proteins that bind preferentially to Ca^{2+}/calmodulin. There is evidence that release of calmodulin is not essential for the regulation of myosin I activity; allosteric changes due to Ca^{2+} ligation of calmodulin are sufficient [48].

Houdusse et al. [46] noted that tandemly repeated IQ motifs of unconventional myosins vary in length from 22 to 36 residues. Thus, calmodulins may adopt different spacings and orientations with respect to each other, perhaps accounting for observed differences in the Ca^{2+} sensitivity of their binding to myosin heavy chains. Variations in IQ domains among the different myosins may also explain the non-uniformity of Ca^{2+} effects on ATPase activities. Ca^{2+} has been reported to stimulate [49,50], inhibit [48,51] or have essentially no effect [52–54] on Mg^{2+}-ATPase activities of myosins I assayed in the presence of actin. In many studies, k_{cat} values of the Mg^{2+}-ATPase reaction are increased by Ca^{2+} both in the absence and the presence of actin. Hence, subtraction of basal activities often result in negligible or even inhibitory effects of Ca^{2+} on actin-activation, even if overall turnover numbers are higher in the presence than in the absence of Ca^{2+}.

While Ca^{2+} has diverse effects on the ATPase activities of myosins I, it invariably inhibits their ability to translocate actin in in vitro motility assays [50,52–54]. By analogy with myosin II, IQ domains are believed to act as lever arms that increase the displacement of the power stroke during myosin motor activity ([55] recently reviewed in [56]). The speed of actin translocation is directly proportional to the length of the lever arm. It is conceivable that Ca^{2+}-induced release or rearrangement of calmodulin light chains alters the myosin I neck in a manner that prevents lever arm movement. In the model of Houdusse et al. [46] the IQ domain–apocalmodulin complex is an elongated structure, with about 30 residues of the IQ motif stabilized by calmodulin, compared to only about 20 residues typically stabilized in targets complexed with Ca^{2+}-calmodulin. This implies that the myosin neck becomes more compact in the presence of Ca^{2+}. Indeed, cryoelectron microscopy and image analysis of brush border myosin I showed that the calcium-induced loss of calmodulin triggers an extensive reorganization of mass within the tail domain whereas the catalytic head domain does not undergo significant changes [57]. In the presence of

calcium, the tail is approximately ovoid with a long axis of 60 Å. In the absence of calcium, however, this domain has more elongated appearance, extending an additional 20 Å.

The in vivo significance of IQ motifs as regulatory elements of myosin I function is currently being examined using molecular genetic approaches. In *Saccharomyces*, receptor-mediated endocytosis of α-mating factor requires calmodulin, although the Ca^{2+}-binding property of calmodulin is not essential for this function [58]. Therefore, proteins which were known to interact with Ca^{2+}-free calmodulin, such as myosin I, were considered likely co-participants in this process. Indeed, endocytosis is blocked in yeast cells lacking both myosin I genes, but can be rescued by expression of Myo5p alone in the double knockouts [59]. Expression of a mutant Myo5p lacking both IQ motifs was also capable of rescuing endocytosis in the double knockouts [60], indicating that the enzyme is functional without a neck domain. This result was interpreted by the author as suggesting that the neck region of Myo5p functions as an autoinhibitory domain and that inhibition is reversed by binding of calmodulin.

In contrast to the *Saccharomyces* results, deletion of the IQ domain of MYOA in *Aspergillus* has a profound impact on the growth of this filamentous fungus. The IQ-deleted mutant strain produced much smaller colonies than cells expressing wild type MYOA and generally induced a variety of morphological defects including thickened cell walls, shorter and wider hyphal compartments and multiple germ tubes [61]. It has been confirmed that MYOA interacts with calmodulin and that the IQ motif is the site of calmodulin binding.

As evident from the above discussion it is still too early to assess the physiological consequences of Ca/calmodulin binding to myosin I. In vivo studies are very limited but in vitro studies, based mainly on motility assays, indicate that Ca^{2+} binding inhibits the motor activity of vertebrate myosin I. If this inhibition also occurs in vivo then these myosins would presumably be inactive when intracellular Ca^{2+} rises to micromolar levels as it does in response to many extracellular stimuli. The precise functions of myosins I will have to be determined before we can understand why their motor activities should be inhibited under cell stimulatory conditions.

4. Targeting: a role for the myosin I tail domain

At present there is scant evidence for the regulation of vertebrate forms of myosin I by phosphorylation and there is disagreement concerning their regulation by Ca^{2+} and calmodulin. Thus it is possible that these motors are constitutively active catalytically and that their cellular functions are controlled by targeting them to appropriate subcellular locations and cargo. The mechanism of myosin I targeting is not yet understood. As indicated in Table 1, these myosins have been found in nearly all organelles and, most frequently, in specialized structures at the cell periphery. Although individual myosin types are often found in multiple locations in the same cell, there is enough selectivity to preclude relatively nonspecific targeting mechanisms such as the well-established interactions between myosin I tails and anionic phospholipid headgroups [12]. For example, myosin Iβ is enriched at the plasma membrane but excluded from secretory vesicle membranes in adrenal chromaffin cells (our unpublished observations), even though vesicle membranes are negatively charged and contribute 10 times the available surface area as plasma membranes [62]. Hence, one of the most active areas of current research in myosin I, and other unconventional myosins, is the search for docking proteins or receptors, as well as the search for targeting determinants within the myosin molecules.

In the so-called protozoan class of myosin I (myosin IC in our nomenclature), attention has focused on the role of the SH3 domain, typically found at or near the C-termini of these myosins. Two putative binding partners have been found for myosin I SH3 domains. The first, a soluble protein from *Acanthamoeba* known as Acan125, binds to the SH3 domain of *Acanthamoeba* myosin IC [63] and colocalizes with it to the same intracellular organelles. Acan125 has a proline-rich segment near the C-terminus that includes tandem PXXP motifs characteristic of SH3 domain-binding proteins. In addition, it contains leucine-rich repeats (LRR) found in a variety of signaling proteins [64]. Thus, Acan125 may be an adaptor molecule that links myosin I to a yet unidentified LRR-binding protein, perhaps one which resides on a target membrane [65].

The second putative myosin I 'receptor' is verpro-

Table 1
Subcellular distribution of myosins I

Myosin	Location	References
Acanthamoeba		
Myosin IA	cytoplasm; beneath phagocytic cups on plasma membranes and in small cytoplasmic vesicles	[86]
Myosin IB	plasma membrane; large vacuolar phagocytic membranes	[86]
Myosin IC	contractile vacuolar membranes	[87]
Dictyostelium		
myoB and myoD	lamellipodia; regions of cell–cell contact	[88]
Aspergillus nidulans		
MyoA	cytoplasm; growing hyphal tips (punctate)	[37]
Saccharomyces cerevisiae		
Myo 5p	patches concentrated in buds	[35]
Vertebrate:		
Brush border MI (bovine and avian)	intestinal microvillus	[89]
	Golgi-derived vesicles	[90]
Myosin Iα/myr1	plasma membrane (particularly cell projections); cleavage furrow of dividing cells	[74]
	endosomes and lysosomes	[79]
	neuronal growth cones	[91]
	zymogen granule membranes	[92]
Myosin Iβ/myr2	cell periphery/plasma membrane with some cytoplasmic punctate staining	[74,93]
	nucleus	[94]
	phagocytic cups	[95]
	mitochondria in photoreceptor cells	[96]
	auditory hair cells	[97]
	microvilli of kidney cells	[98]
Myosin IC/myr3 (chicken myosin IB)	cytoplasm and regions of cell–cell contact	[73,99]
	phagocytic membranes	[78]
Myosin Iγ/myr4	membranes in neuronal cell bodies and dendrites	[45]

lin, an actin-binding protein of *Saccharomyces* that contains eleven potential SH3 domain interaction motifs [66,67]. Verprolin was shown to interact both with Myo3p and Myo5p by two-hybrid screening, co-localizes with Myo5p in cortical patches, and co-immunoprecipitates with Myo5p from yeast cell extracts [68]. Although Myo5p patches can form in the absence of verprolin, they no longer localize to sites of polarized cell growth, suggesting that verprolin plays a role in myosin I targeting in yeast.

There is no strong evidence yet for the existence of a binding partner for the SH3 domain of vertebrate myosin IC (myr3). However, this myosin was identified in a yeast two-hybrid screen to find proteins that may interact with the proto-oncogene product c-Cbl [69]. The c-Cbl protein, which contains a proline-rich SH3-domain binding region, is a negative regulator of lymphocyte signaling [70] and is tyrosine phosphorylated upon stimulation of (among others) B-cell and T-cell receptors [71]. Interestingly, the chicken version of myosin IC (called chicken myosin IB), is most highly expressed in lymphoid tissues [72].

The evidence that SH3 domains are involved in subcellular targeting is mixed. Strongest support for such a role has emerged from genetic studies in *Saccharomyces*. In normal yeast actin is organized into cables polarized toward the site of bud formation and in punctate cortical patches in the buds. Deletion of Myo3p and Myo5p causes severe defects in polarization of the actin cytoskeleton and, as stated above, in processes such as secretion and endocytosis which depend on the cytoskeleton [35,59]. Whereas expression of wild type Myo5p fully restores these functions, a mutant Myo5p lacking the SH3 domain does so only partially [68]. Moreover, the mutant myosin does not properly localize at sites of polar-

ized cell growth. Similarly, expression in *Dictyostelium* of mutant myoB lacking the SH3 domain fails to rescue defects in growth, endocytosis and cytoskeletal organization in myoA$^-$/myoB$^-$ double mutants [34]. In this case, however, deletion of the SH3 domain did not cause improper localization. Further evidence against the SH3 domain as a targeting determinant is the observation that deletion of the SH3 domain of *Aspergillus* MYOA has no effect on cell growth, morphology, secretion or endocytosis [61]. A similar deletion in rat myr3 also has no affect on its localization to cell–cell junctions in HeLa cells [73]. In *Aspergillus* MYOA the essential portion of the tail is a proline-rich region just beyond the SH3 domain; in myr3 the site required for proper targeting is just prior the SH3 domain, though the catalytic head domain apparently also participates in myosin localization.

The possibility that SH3 domains are involved in regulation of ATPase activity rather than, or in addition to, targeting must also be considered. For example, these domains may be sites of interaction with myosin I kinases which, as mentioned above, contain multiple PXXP motifs. Alternatively, SH3 domains may participate in intramolecular rather than intermolecular interactions, perhaps folding back and binding to proline-rich regions often found in myosin I tails. Indeed, Stoffer and Bahler [48] have shown that a proteolytically truncated myr3 lacking approximately 10 kDa from the C-terminus (including the SH3 domain) expresses a 2–3-fold higher Mg^{2+}-ATPase activity, suggesting an intramolecular, autoinhibitory, mode of regulation similar to that found in some Src family members.

With the exception of human myosin IC/myr3, vertebrate myosins I lack SH3 domains, or other established protein–protein interaction domains. However, it is clear that even in these myosins the targeting determinants are found within the C-terminal tails [74].

Based on kinetic arguments it has been speculated that some forms of myosin I do not bind individually to their cargo but instead must exist as clusters on membrane surfaces [30,75]. Otherwise, given the small portions of the ATPase cycle in which the myosins are strongly attached to actin, the myosins and their cargo would tend to diffuse away before translocation can occur. Interestingly, clusters of approximately 50–100 molecules of myosin Iβ have been visualized by electron microscopy in auditory hair cell stereocilia [76]. The authors of that study suggest that the myosins are gathered together on a putative 'raft' or scaffold molecule that is itself tethered to cargo, in this case ion channels, on the plasma membrane. A multivalent myosin I scaffold or adaptor molecule would allow the translocation of multiple types of proteins, perhaps concentrated in membrane subdomains, by a single class of myosin I.

5. Conclusion

As evident from this and earlier reviews, a great deal is known about myosin I ATPase and contractile activities and their regulation. Unfortunately, our understanding of the functions of myosin I in cells is far less complete. Gene knockout experiments described above have demonstrated a clear connection between the activities of some forms of myosin I and proper organization of the actin cytoskeleton. Because membrane trafficking often depends upon the integrity of the actin cytoskeleton [77] it is difficult to cite clearcut examples of myosin I molecules acting directly as motors for organelle translocation. Thus far, speculations about myosin I functions have been based primarily on their subcellular locations. For example, myosin Iβ is found at both ends of the tip links of auditory hair cell stereocilia, implicating this motor in the movement or gating of ion channels within the plasma membrane [76]. Myosin IC is present on phagosomes, suggesting a role in actin-dependent pinching off of plasma membrane during phagocytosis [78]. Myosin Iα has been localized to endosomes and its participation in endocytosis was recently suggested in mammalian cells using a dominant negative approach [79]. In recent years mutations in several unconventional myosins have been linked to a variety of diseases. Striking examples include the association of myosin III mutations with retinal dysfunction [80,81], myosin V mutations with dilute coat color and neurological defects in mice [82] and myosin VI and VII mutations with deafness and vestibular disorders [83–85]. Thus, elucidation of the functions of myosin I may eventually emerge, not from deliberate interventions (e.g. by gene knockout or overexpression of mutants) but rather from the

unanticipated identification of myosin I gene mutations as etiological factors of known disorders.

6. Note added in proof

Two recent reports demonstrate an interaction between the Arp2/3 complex, involved in actin polymerization on membranes, and an acidic region in the tails of yeast Myo3A and Myo3B [M. Evangelista, B.M. Klebl, A.H.Y. Tong, B.A. Webb, T. Leeuw, E. Leberer, M. Whiteway, D.Y. Thomas, C. Boone, A role for myosin-I in actin assembly through interactions with Vrp1p, Bee1p, and the Arp2/3 complex, J. Cell. Biol. 148 (2000) 353–362; T. Lechler, A. Shevchenko, A. Shevchenko, R. Li, Direct involvement of yeast type I myosins in Cdc42-dependent actin polymerization, J. Cell. Biol. 148 (2000) 363–373].

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