# The myosin superfamily at a glance

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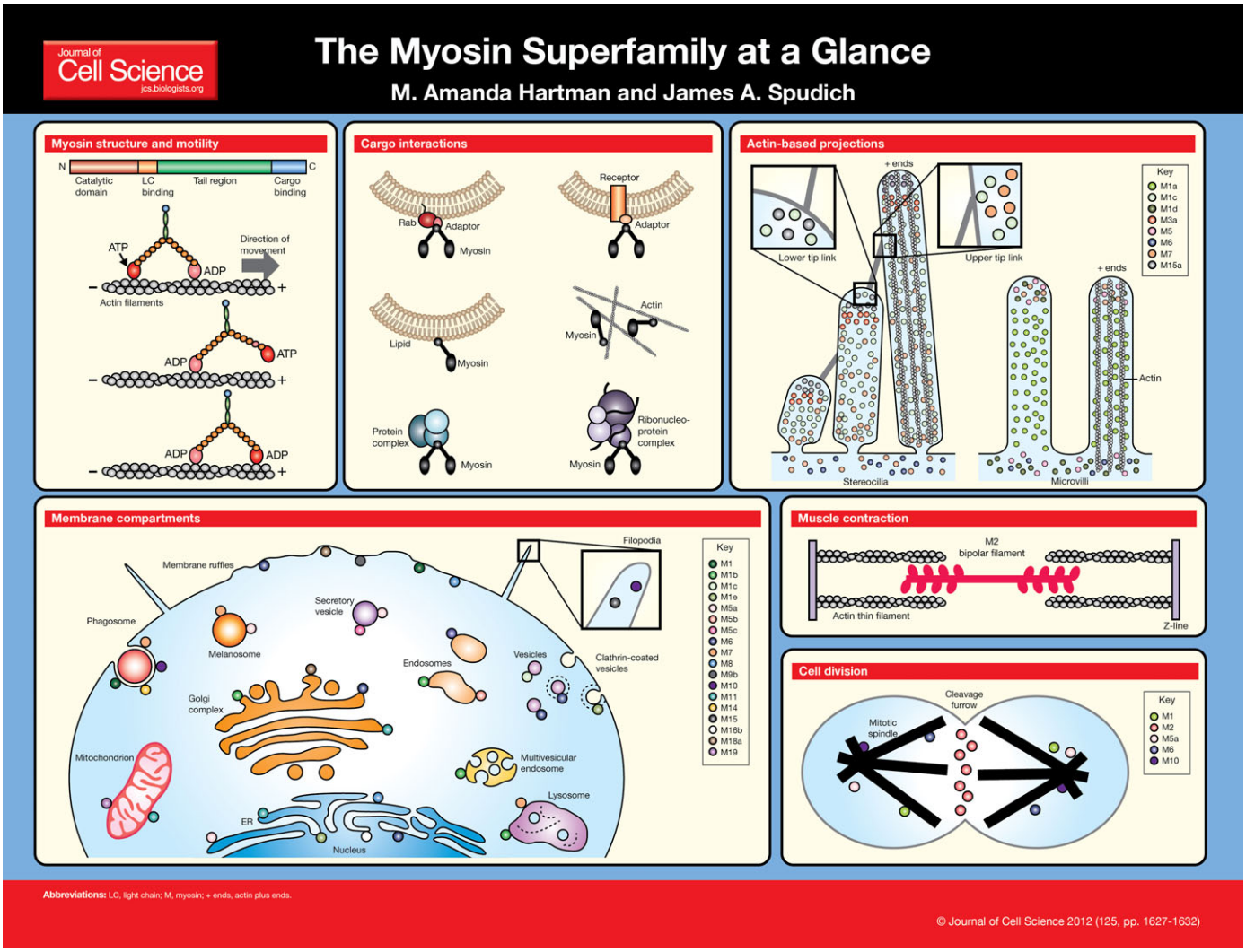
The cytoskeleton is an interconnected network that provides support and organization to cells. In eukaryotes, its main components include actin and microtubules, two types of dynamic filaments. In addition to carrying out structural roles, these filaments act as tracks for the movement of molecular motors that convert chemical energy into mechanical work as they transport and/or anchor organelles, vesicles and other intracellular components. Kinesin and dynein motors both utilize microtubules for transport, whereas myosins – which are the focus of this Cell Science at a Glance article – are the only known actin-based motor proteins (Goode et al., 2000; Hartman et al., 2011; Ross et al., 2008). Different members of the myosin family are typically denoted by roman numerals, such as myosin II and myosin V; to ensure consistency between the accompanying poster and the text, we refer to them here as M2 (or class 2) and M5 (or class 5), respectively.

The myosin superfamily is a large and diverse protein family, and its members, which are grouped into many classes (Foth et al., 2006; Odronitz and Kollmar, 2007), are involved in a number of cellular pathways (Krendel and Mooseker, 2005; Woolner and Bement, 2009). We first describe the basics of myosin mechanoenzymology and motility. Next, we discuss myosin–cargo interactions and present a summary of the roles of myosin proteins in cells, focusing on actin-based projections and the endomembrane system. Finally, we provide an overview of the diseases associated with myosin mutations and our perspective on the future of the myosin field. In order to provide a general overview of the myosin family, we will not be able to discuss some aspects of the vast and important literature on myosins. For example, we will not focus on the large body of literature on yeast myosins, as it deserves a rather long review on its own.

## Myosins are mechanoenzymes

Myosins contain actin- and ATP-binding sites in their conserved catalytic head domains. Conformational changes associated with nucleotide binding,




*(See poster insert)*

hydrolysis and product release are crucial for the productive motility of myosin enzymes. In the absence of nucleotide and in the ADP-bound state, the head interacts strongly with actin. By contrast, when ATP or ADP bound to inorganic phosphate (ADP-$P_i$) bind to the catalytic domain, the affinity of the myosin head for actin is drastically lower. Thus, association of myosin with its filamentous track is regulated by the ATPase cycle. Myosins vary in the rate at which they use ATP and in how long per ATPase cycle they are in the strongly bound state (duty ratio). Some motor proteins, such as M2, have low duty ratios, and each myosin head spends little time in association with actin. Others, such as M5, move processively for many steps before detaching – a characteristic that results from a high duty ratio (Howard, 1997).

Muscle and non-muscle M2, both of which are the conventional members of the myosin superfamily, form bipolar filaments that consist of dozens of myosin molecules. M5 and other unconventional myosins do not form such bipolar thick filaments. Some unconventional myosins, such as M5, have two heads and can take many steps along an actin filament as a single molecule. In these cases, the ATPase cycles of the two identical heads are staggered, such that at least one head is strongly bound to actin at any time. Following the binding of ATP, the rear head dissociates from the filament, which allows the front head to undergo a lever arm swing, thereby propelling the rear head forward. After the hydrolysis of ATP and the release of phosphate, the former rear head attaches to actin in its new front position (De La Cruz and Ostap, 2004).

The changes in nucleotide state are associated with large movements, such as the 36-nm step taken by M5. These movements are enabled by the myosin lever arm, which amplifies the conformational changes in the catalytic domain to generate step sizes that directly depend on the length of the lever arm. In most myosins, the lever arm is a region of the heavy chain to which one or more calmodulin or calmodulin-like light chains bind and provide rigidity. In other members of the myosin family, such as M6 and M10, a single α-helix domain in this neck region may also contribute to the step size (Baboolal et al., 2009; Knight et al., 2005; Spudich and Sivaramakrishnan, 2010).

## Myosins contribute to muscle contraction and cytokinesis

The first myosin, M2, was discovered 1864 – in Heidelberg by Willy Kühne – in muscle extracts (Kühne, 1864). We now know how this muscle M2, which is localized in the so-called muscle A-bands, works. The conventional class 2 myosins have long coiled-coil domains that allow multimerization to take place. Thus, interactions between charged residues within these dimers mediate the formation of bipolar thick filaments that are responsible for contraction of muscle and cytokinesis. Each bipolar thick filament consists of dozens of myosin molecules that face opposite directions from the midzone of the filament. In muscle, these thick filaments are at the center of the functional unit of the muscle, the sarcomere. The sarcomere also consists of two sets of actin filaments, which are attached at their plus ends to structures at the ends of the sarcomere called Z-lines. All actin filaments are directed with their minus ends toward the center of the sarcomere. The thick myosin filaments and thin actin filaments interdigitate and slide past each other by repetitive interactions between the myosin heads and the actin filaments, resulting in the two Z-lines being pulled closer together. Sarcomeres are attached to each other in series by way of their Z-lines, and the contraction of the sarcomeres, thus, leads to contraction of the entire muscle.

Similarly, non-muscle M2 bipolar thick filaments provide the force of contraction needed to separate the two daughter cells during cytokinesis (Vicente-Manzanares et al., 2009). Additional myosins appear to be involved in cell division; for example, M6 participates in membrane trafficking towards the cytokinetic furrow (Arden et al., 2007). Other myosins localize to the microtubule-based mitotic spindle, which directs the position of the cell division furrow. Human M10 and *Dictyostelium* M1 have been shown to be required for correct spindle formation (Rump et al., 2011; Woolner et al., 2008), and M5a has been found at spindle poles, although its function at this location remains unclear (Espreafico et al., 1998; Wu et al., 1998).

## Unconventional myosins associate with cargoes

The diversity of the myosin superfamily becomes particularly evident in the variety of domains that are found in the C-terminal tail of these proteins. Whereas the catalytic heads share a number of conserved elements, the tail regions of the various myosin classes are highly divergent (Thompson and Langford, 2002). The unconventional myosins possess specific domains in their tail regions that are thought to enable their individual cellular functions through association with adaptors and other binding proteins (Akhmanova and Hammer, 2010).

Myosins localize to a number of intracellular compartments and participate in many trafficking and anchoring events. The recruitment of motor proteins to an organelle or molecular complex is generally the result of the tail binding to a specific adaptor protein. A number of myosin-binding proteins have been discovered, and their identities have often provided information that is essential to understanding the cellular functions of these motor proteins (Akhmanova and Hammer, 2010). Most of these interactions fall into one of several themes, which we discuss below.

One of these themes is the connection between myosins and members of the Rab protein family through adaptor proteins. For example, in melanocytes a complex containing Rab27a, the adaptor protein melanophilin and M5a is involved in directed migration of pigment-containing vesicles in these cells. Also, Rab27a, M7a- and Rab-interacting protein (MyRIP) and M7a have been shown to interact in retinal pigment epithelial cells (Van Gele et al., 2009).

Other myosins are involved in the trafficking of cell surface receptors. For example, M6 associates with the megalin receptor through the adaptor protein GIPC (GAIP interacting protein, C terminus) and, thereby, permits correct targeting of the receptor to the base of microvilli in kidney proximal tubule cells (Naccache et al., 2006). Representing another type of interaction, many class 1 myosins directly associate with lipids instead of binding adaptor proteins, which allows them to function during membrane tension (McConnell and Tyska, 2010). By contrast, certain yeast class 1 myosins have additional actin-binding sites in their tails and contribute to filament nucleation (Kim and Flavell, 2008).

Some myosins are thought to associate with large protein complexes, such as vertebrate M7a (Kussel-Andermann et al., 2000) and *Drosophila* M6 (Finan et al., 2011). In these examples, the myosin

potentially stabilizes its cargo in a certain position or transport the complex to a specific destination. Myosins are also responsible for the directed movement of ribonucleoprotein complexes, such as the movement of protein-bound *ASH1* mRNA, which encodes a transcription factor that ensures mating-type switching in the newly budded daughter cell (Paquin and Chartrand, 2008) by the yeast class 5 myosin Myo4p during budding division.

These examples are only a few of the cargoes discovered for myosin proteins, but many others fall into one of the six general categories described. Because myosin-binding proteins recruit myosins to specific subcellular locations, they enable these motors to associate with their targets. Once targeted to an organelle, vesicle or protein complex, the motor protein can then exert its effects on their movement or anchoring. Through their specific interactions, myosins are able to carry out a number of functions in many different cell types, and their importance is highlighted by their roles in actin-based projections.

## Myosins have roles in actin-based projections

Many myosins localize to membrane extensions, including stereocilia and microvilli, which are supported by large actin bundles. Stereocilia are found in hair cells of the inner ear and contribute to auditory mechanotransduction. Microvilli project from epithelial cells, including those that line the intestines and ducts of the kidneys; particular focus has been placed on examining the roles of myosins in the brush borders of the intestine and kidney, which function in absorption. In both types of structure, actin is oriented such that the plus (barbed) end is at the distal tip (Nambiar et al., 2010). Although all characterized myosins, with the exception of M6 (Wells et al., 1999), move towards the plus end, they are not evenly distributed throughout stereocilia and microvilli; their specific positions at, for example, the base or tip of these projections are likely to be a reflection of their specific functions.

For example, M15a is found at the tip of stereocilia (Belyantseva et al., 2003), whereas M7a is present throughout the length of the stereocilium and possibly concentrated near its base (Hasson et al., 1997; Senften et al., 2006). Each of these two motors associates with several adhesion or scaffolding proteins and contributes to the organization of stereocilia (Nambiar et al., 2010). Although M1c localizes along the length of stereocilia (Schneider et al., 2006), it is thought to function where it is concentrated, i.e. near the cilial tip links – linkages connect neighboring stereocilia and are perturbed by sound waves during the hearing process (Gillespie and Cyr, 2004; Hasson et al., 1997; Steyger et al., 1998). In addition, M7a was recently identified as a component of the upper tip link (Grati and Kachar, 2011). Both M6 and M7a are found below the base of stereocilia (Hasson et al., 1997), and in the case of M6, the myosin protein is thought to ensure correct membrane tension that is required for the maintenance of these projections (Altman et al., 2004; Nambiar et al., 2010). M3a, however, is concentrated below the tip (Schneider et al., 2006), and is involved in transporting the actin-bundling protein espin 1 away from the cell body to ensure correct assembly and elongation of actin (Salles et al., 2009).

Many of the myosins that are found in stereocilia are also found in microvilli of the brush border. Again, M6 is concentrated near the base, as are M5 and M1d (Benesh et al., 2010; Heintzelman et al., 1994). In addition to M5 and M7b, M1d is also present in the tips of microvilli, whereas M1a is present along the entire length of the microvillus (Benesh et al., 2010; Heintzelman et al., 1994). Although the specific functions of each myosin in these projections are less clear than in, for example, stereocilia, they might carry out essential functions in the regulation of actin structure and general cilia organization. Interestingly, it was recently demonstrated that M1a is essential for the shedding of vesicles from microvilli (McConnell et al., 2009; McConnell and Tyska, 2007), which suggests that other myosins also participate in membrane trafficking in cells containing these structures. Indeed, many myosins have been connected to a variety of membrane compartments.

## Myosins organize the endomembrane system

Myosins can be found in nearly any cellular location, where they are thought to link each cargo to the actin cytoskeleton for transport and/or anchoring. For example, type 1 and 6 myosins are associated with endocytic vesicles and endosomes (Chen et al., 2007; Hasson, 2003; Krendel et al., 2007; Puri et al., 2010; Raposo et al., 1999; Salas-Cortes et al., 2005; Wang et al., 2008) and M5b also colocalizes with endosomal compartments (Wang et al., 2008). Both M1b and M7a have been found on lysosomal membranes (Raposo et al., 1999; Soni et al., 2005). By contrast, M10, *Tetrahymena* M14, and *Dictyostelium* M1 and M7 associate with phagocytic cups or phagosomes (Cox et al., 2002; Hosein and Gavin, 2007; Rump et al., 2011; Tuxworth et al., 2001). In addition, M5a and M5c contribute to the exocytosis of dense-core vesicles and secretory granules, respectively (Jacobs et al., 2009; Varadi et al., 2005).

Other types of myosin involved in secretion include M1b, M6 and M18a, each of which is found on the Golgi complex (Almeida et al., 2011; Dippold et al., 2009; Spudich and Sivaramakrishnan, 2010). M5a probably transports the peripheral endoplasmic reticulum (ER) to dendritic spines in neuronal cells (Wagner et al., 2011). M9b and many class 1 myosins associate with the plasma membrane (McConnell and Tyska, 2010; van den Boom et al., 2007), and M6 and M18a are found in membrane ruffles (Buss et al., 1998; Hsu et al., 2010). Mammalian M10 and *Drosophila* M15 concentrate in filopodia, which are cellular extensions that are often found at the leading edge of migrating cells. Whereas M10 is involved in filopodial formation, M15 is thought to carry out filopodial transport (Berg and Cheney, 2002; Liu et al., 2008).

Recent data indicate that M19 is responsible for the transport of mitochondria in human cells (Quintero et al., 2009), whereas in maize it seems to be M11 (Wang and Pesacreta, 2004). In *Arabidopsis*, M8 and M11 are responsible for many long-range movements of organelles and are found, for example, on the Golgi, ER and plasma membrane (Sparkes, 2010). In addition, although myosins are generally restricted to the cytoplasm, members of several classes, including M1c, M6 and M16b, have been found in the nucleus and might function there (Woolner and Bement, 2009).

The locations of myosins presented here are certainly not comprehensive, and future work is essential to fully define the subcellular localizations and cargo complexes of myosin motor proteins. Although we have focused on the unconventional members, M2 has also been implicated in numerous functions

**Table 1. Phenotypes associated with myosin mutations**

| Myosin | Organism | Phenotype | Reference |
|---|---|---|---|
| M1a | Human | Deafness | (Donaudy et al., 2003) |
| M1c | Human | Deafness | (Zadro et al., 2009) |
| M31DF (class 1) | Fly | Situs inversus | (Hozumi et al., 2006; Speder et al., 2006) |
| Cardiac muscle M2 | Human | Hypertrophic cardiomyopathy | (Walsh et al., 2010) |
| Cardiac muscle M2 | Human | Dilated cardiomyopathy | (Walsh et al., 2010) |
| Non-muscle M2a | Human | May-Hegglin anomaly | (Kunishima and Saito, 2010) |
| Non-muscle M2a | Human | Deafness | (Kunishima and Saito, 2010) |
| M3a | Human | Deafness | (Walsh et al., 2002) |
| M5a | Human | Griscelli syndrome | (Van Gele et al., 2009) |
| M5b | Human | Microvillus inclusion disease | (Muller et al., 2008) |
| M6 | Human | Deafness | (Melchionda et al., 2001) |
| M6 | Human | Hypertrophic cardiomyopathy | (Mohiddin et al., 2004) |
| M7a | Human | Usher syndrome | (Kremer et al., 2006) |
| M7a | Human | Deafness | (Liu et al., 1997) |
| Crinkled (class 7 myosin) | Fly | Deafness | (Todi et al., 2005) |
| M9a | Mouse | Hydrocephalus | (Abouhamed et al., 2009) |
| M15a | Human | Deafness | (Wang et al., 1998) |
| M18b | Mouse | Heart defects | (Ajima et al., 2008) |

beyond muscle contraction and cytokinesis, such as cell adhesion, rearrangement and cell polarity (Vicente-Manzanares et al., 2009). Determining the extent to which myosins and other motor proteins cooperate to organize cellular contents is an emerging area of research, which may progress further by deducing the phenotypes associated with myosin loss-of-function.

### Mutations in myosins can cause disease

Numerous myosin mutations have been linked to disease states and genetic syndromes (Table 1), and myosins are necessary for the process of hearing through their contribution to the structure of to stereocilia (Nambiar et al., 2010). Mutations in M7a can lead to non-syndromic deafness or Usher syndrome, the leading cause of genetic deaf-blindness (Kremer et al., 2006). M5b might transport apical endosomes in brush border cells (Szperl et al., 2011), which could explain the association of mutations in this gene with microvillus inclusion disease (Muller et al., 2008). Furthermore, mutations in M5a are linked to Griscelli syndrome, which is characterized by defects in pigmentation and neuronal malfunction (Van Gele et al., 2009).

Because class 2 myosins are essential for muscle contraction, cell division and other fundamental processes, mutations in the genes encoding these proteins can lead to severe forms of disease. For example, mutations in cardiac M2 can cause cardiomyopathies, which are characterized by malformation and dysfunction of the heart (Walsh et al., 2010). M6 and M18b have also been linked to heart defects, although the molecular basis for these phenotypes is not known (Ajima et al., 2008; Mohiddin et al., 2004). Furthermore, it is unclear what the specific roles for *Drosophila* M1 and mouse M9a are, whose disruption leads to reversal of organ polarity and hydrocephalus, respectively (Abouhamed et al., 2009; Hozumi et al., 2006; Speder et al., 2006).

Although M9b has been linked to a number of intestinal disease states, there is some controversy over these genetic associations. Two studies implicated this motor protein in celiac disease (Monsuur, 2005; Wolters, 2007), but other data indicate that this association is absent in a number of populations (Hunt, 2006; Amundsen, 2006a; Nunez, 2006; Cirillo, 2007; Koskinen, 2008). Furthermore, whereas M9b has been linked to inflammatory bowel diseases (Latiano, 2008; Nunez, 2007; van Bodegraven, 2006; Cooney, 2009), this might not be the case for all cohorts (Amundsen, 2006b), which adds to the debate about the function of this motor protein.

## Perspectives

The molecular basis of energy transduction by the myosin family of molecular motors is reasonably well understood after decades of research using many different approaches. Similarly, the cellular functions of M2 in muscle contraction and cytokinesis can be fairly well described at the molecular level. The cellular roles of other members of the myosin family are beginning to be elucidated, but there is still much work to do in this fruitful research area. It is clear that the ~40 different myosins in a particular cell type are involved in setting up the dynamic layout of the cell. However, the multitude of cargo-binding, structural and regulatory elements that must exist to direct the numerous myosin motor proteins to carry out their various functions inside the cell have not yet been identified and characterized. The field is at the tip of an iceberg with respect to such much-needed biochemical studies, and future research should certainly consider cargo-binding elements of molecular motors as one of the upcoming frontiers in the research of molecular motors.

The time is also ripe to focus on the clinical ramifications of alterations to the actin–myosin contractile system associated with particular disease states. A classic example is the hundreds of sarcomeric protein mutations that, individually, lead to hypertrophic or dilated cardiomyopathy – debilitating diseases that can lead to sudden death. These days, the connection between basic research and its application in the treatment of diseases is much easier to forge in this modern era of genomic biology – and the biotech world is not far behind. A therapeutic approach that directly targets β-cardiac myosin has recently been reported as a potential treatment for congestive heart failure (Malik et al., 2011), a prevalent disease in great need of new therapeutic approaches. The next decade will see much more activity bridging basic science, and clinical and therapeutic approaches to the myosin family of molecular motors.

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A high-resolution version of the poster is available for downloading in the online version of this article at jcs.biologists.org. Individual poster panels are available as JPEG files at http://jcs.biologists.org/lookup/suppl/doi:10.1242/jcs.094300/-/DC1.

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