Chapter 4
Functions of Myosin Motor Proteins in the Nervous System

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Abstract The myosin superfamily consists of 24 classes of actin-based molecular motors that carry out a diverse array of cellular functions ranging from cell motility and morphology to cytokinesis, signal transduction, membrane trafficking, RNA and protein localization. The development and functioning of the nervous system strongly depends on the proper establishment of complex networks of neurons with highly specialized morphologies and molecular composition. Thus, it is not at all surprising that multiple classes of myosin motors are expressed in the nervous system, including classes I, II, III, V, VI, VII, IX, X, XV, and XVI. This review discusses the current knowledge on myosin functions in both neurons and specific sensory neurons, the hair cells of the inner ear, and the photoreceptors in the eye. The role of myosin II in growth cone motility and neurite outgrowth is the best characterized myosin function in neurons. However, there is increasing evidence that different myosin motors are also involved in protein and organelle trafficking underlying synaptic function. Multiple myosin motors have been localized to hair cells and photoreceptors and associated with genetic diseases; however, a future challenge will be a better characterization of the cellular functions of these various motor proteins.

Keywords Motility · Transport · Contractility · Sensory · Stereocilia

4.1 Introduction

Myosins are molecular motors that use the energy derived from ATP hydrolysis to move along actin filaments. Myosins carry out a large variety of cellular functions including cell movements, maintenance of cell shape, cytokinesis, organelle transport, signal transduction, phagocytosis, membrane trafficking, RNA and

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protein localization, and transcription (Brown and Bridgman 2004, Gillespie and Cyr 2004, Krendel and Mooseker 2005, Sweeney and Houdusse 2007). Over the past 20 years the number of newly identified myosin molecules and classes has increased significantly. The myosin superfamily includes at least 24 classes in species ranging from *Saccharomyces cerevisiae* to *Drosophila* and humans (Berg et al. 2001, Foth et al. 2006). Not all classes are present in each species. The human genome encodes approximately 40 myosin genes grouped into 12 classes (Berg et al. 2001). Since the nomenclature for myosin homologs from different species has been confusing in the past, I am following the system suggested for class I myosins; thus, Myo1a will be used as abbreviation for the myosin Ia protein (Gillespie et al. 2001).

Myosins contain at least one heavy chain with an N-terminal conserved catalytic domain of around 80 kDa, followed by a neck region with one or more putative light chain-binding motifs, sometimes known as the IQ motif (Fig. 4.1).

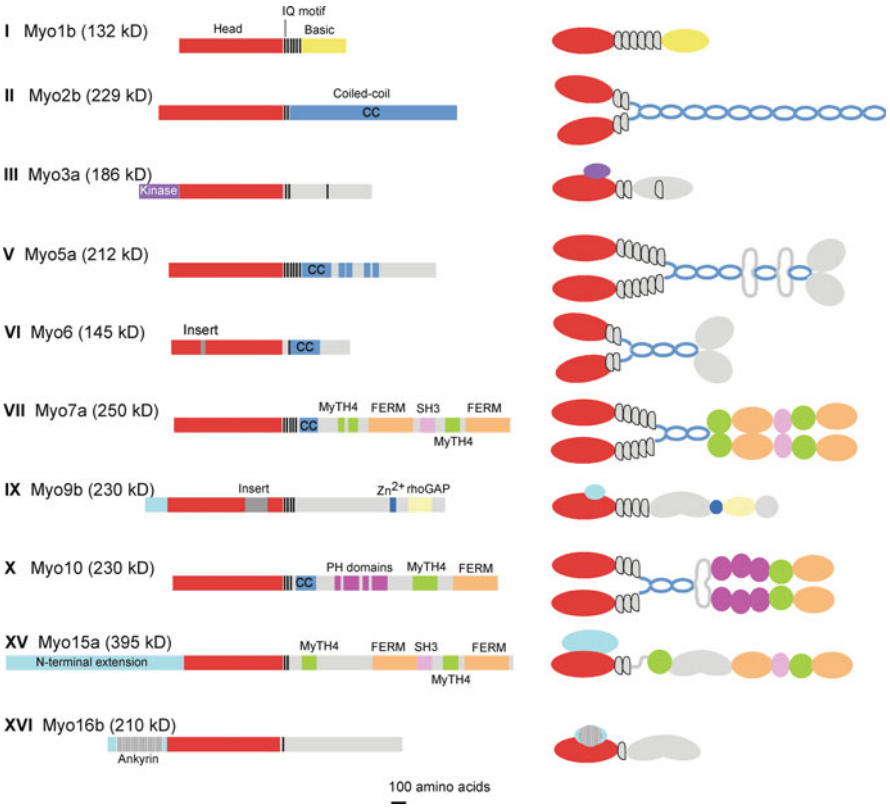

Fig. 4.1 Structures of myosins in the nervous system. Domain organization of the myosin heavy chains represented in the nervous system. Domains are *color coded* and discussed in the text. The *blue* coiled-coil tail domains allow dimerization. The *right panel* shows schematics of the corresponding myosin structures as either single- or double-headed motors. Myo6 and Myo7a can exist in both monomer and dimer form. Light chains (*grey ellipsoids*) are indicated based on the number of IQ motifs. Figure was modified from Krendel and Mooseker (2005)

The most conserved residues of the IQ motif conform to the consensus sequence IQxxxRGxxxRK (Cheney and Mooseker 1992). The following C-terminal tail contains specific domains for cargo binding or heavy chain dimerization that results in a double-headed motor. Class II myosins have been termed as "conventional myosins" since they were discovered first and their role in muscle contraction has been extensively characterized. Beginning with *Acanthamoeba* myosin I (Myo1) (Pollard and Korn 1973), all newly characterized myosins with a structure different from Myo2 have been classified as "unconventional myosins" (Cheney and Mooseker 1992, Mooseker and Cheney 1995). The classes of the myosin superfamily are mainly defined by differences in the head structure. More recently a novel myosin classification scheme has been proposed that is based on the combinations of various tail domains (Fig. 4.1; Richards and Cavalier-Smith 2005). For a more detailed discussion of the diversity of structural motifs and related functions, I refer to several recent articles and reviews (Berg et al. 2001, Krendel and Mooseker 2005, Richards and Cavalier-Smith 2005, Foth et al. 2006).

Structural diversity among myosin heavy chains evolved not only in the tail region but also in the N-terminal head region, resulting in different motor properties, such as number of heads, processivity, duty ratio, and directionality (Krendel and Mooseker 2005). The duty ratio indicates the proportion of the ATPase cycle that the motor spends strongly bound to the actin filament, while the processivity is a measure for how long the motor can walk on the track without detaching (Fig. 4.2). Motors involved in organelle transport such as Myo5 have a higher processivity compared to motors mediating actomyosin contractility such as Myo2 (Mehta et al. 1999). The majority of myosin motors walk toward the barbed end (Fig. 4.2). Myo6 is the only myosin that has been widely accepted as pointed end-directed motor (Wells et al. 1999).

This book chapter provides an overview on the numerous functions of the 10 classes of myosin motor proteins identified in the nervous system to date, classes I, II, III, V, VI, VII, IX, X, XV, and XVI. For some of these myosins (e.g., classes IX and XVI), the functions have not been well characterized in the nervous system. In the first part, I will discuss the functions of myosins in neurons, focusing on classes

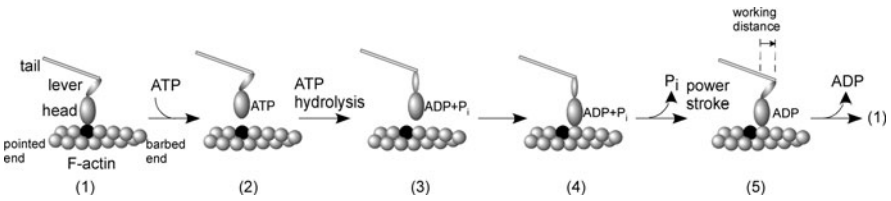

Fig. 4.2 ATPase cycle and actin binding of myosin motors. (*1*) In the absence of ATP, myosin binds tightly to F-actin. (*2*) ATP binding to the head weakens the affinity for actin and causes the motor to detach. (*3*) ATP hydrolysis results in the recovery stroke that moves the head forward. (*4*) The ADP/P_i state rebinds to the actin filament. (*5*) Following the release of phosphate, the power stroke moves the lever forward. Then ADP is released and the cycle begins again at a new position on the actin filament

I, II, V, and VI. In the second part, I will summarize the different myosin motor functions in the best-studied sensory cells, the hair cells of the inner ear, and the photoreceptors in the eye.

4.2 Myosins in Neurons

Neurons possess a high degree of polarity, and this enables them to effectively transmit signals in a directed fashion. The initial establishment and the maintenance of the axonal and somatodendritic compartments in neurons depend on both the F-actin and microtubule cytoskeleton (Chapter 5). As discussed in Chapter 2, 3, 5, and 10, specific neuronal compartments such as peripheral domains of growth cones, presynaptic terminals, and dendritic spines are particularly rich in F-actin. While the polarity of the actin filaments in some of these compartments is not completely understood, different myosins have been implicated in growth cone motility, axonal outgrowth, organelle transport, synaptic function, and plasticity.

4.2.1 Class I Myosins

Myo1 is a single-headed, nonfilament-forming motor with a neck domain and a tail. The tail can be short and basic (tail homology 1, TH1 domain) or longer and include an SH3 domain (Fig. 4.1; Mooseker and Cheney 1995, Berg et al. 2001). In humans and mice, eight different class I myosin heavy chain genes have been identified, *Myo1a–Myo1h*, two of which (*Myo1e* and *Myo1f*) are long tailed and include the SH3 domain (Berg et al. 2001). Four of the eight *Myo1* genes are expressed in the nervous system, *Myo1b* (rat myr 1), *Myo1c* (rat myr 2), *Myo1d* (rat myr 4), and *Myo1e* (rat myr 3). Myo1b is widely expressed in the rodent brain and spinal cord (Ruppert et al. 1993, Sherr et al. 1993). Its peak levels of expression occur in the late embryonic and early postnatal stages, declining thereafter. In growth cones of cultured rat superior cervical ganglion (SCG) neurons, Myo1b has been localized close to the upper and lower plasma membrane and on both F-actin bundles and meshwork (Lewis and Bridgman 1996). Thus, Myo1b could have a role in growth cone structure, adhesion, and motility (Fig. 4.3). Although Myo1b is associated with tubulovesicular structures in rat SCG neurons (Lewis and Bridgman 1996) and moves bi-directionally in neurites (Bridgman 1999), there are no functional data to indicate that Myo1b is required for organelle transport in axons.

Myo1c exhibits a wider tissue expression pattern than does Myo1b, but at lower levels in the brain (Wagner et al. 1992, Sherr et al. 1993, Ruppert et al. 1995). Very little Myo1c staining was reported for growth cones of rat SCG neurons (Brown and Bridgman 2003b). However, micro chromophore-assisted laser inactivation (CALI) of Myo1c in chick dorsal root ganglion (DRG) growth cones implicated Myo1c in driving F-actin flow and growth cone motility (Diefenbach et al. 2002). On the other hand, CALI of Myo2b had little effect on retrograde flow (Diefenbach et al. 2002),

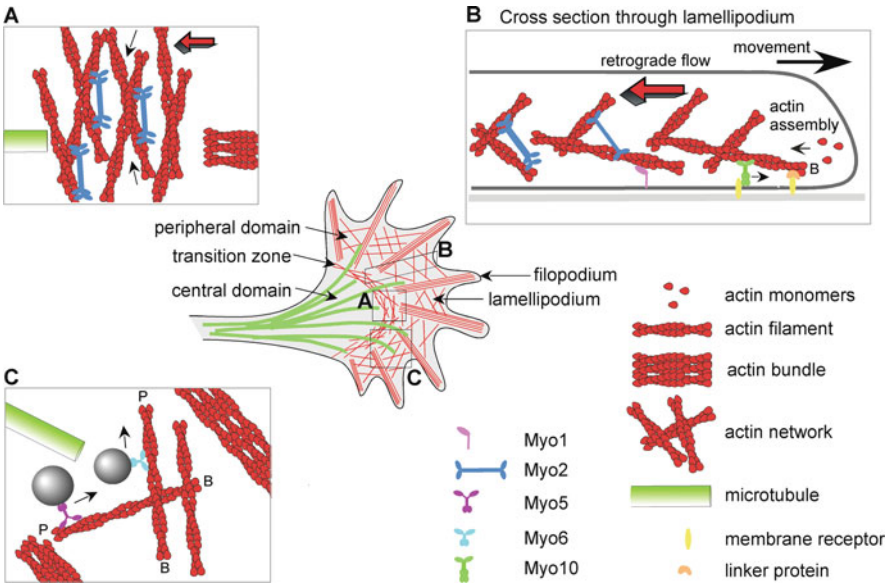

Fig. 4.3 Myosin functions in growth cones. Schematic in the center shows regional organization of the growth cone and the distribution of the actin (*red*) and microtubule (*green*) cytoskeleton. Insets reveal well-described and potential functions of myosin motors. (**A**) In the transition zone, Myo2 forms bipolar filaments mediating network contractions that drive retrograde F-actin flow. (**B**) Cross section through lamellipodium depicting actin networks undergoing retrograde flow. Membrane receptor (*yellow*) and linker protein can couple to actin network. Membrane-bound Myo1 could drive retrograde flow. Receptor-bound Myo10 could move receptor anterogradely or drive retrograde flow. (**C**) Vesicle transport on actin filaments by either Myo5 [barbed (B) end directed] or Myo6 [pointed (P) end directed]

which is at variance with increased retrograde actin flow rates in growth cones from Myo2b knockout mice (Brown and Bridgman 2003b). To better dissect the role of Myo1c and other myosins in growth cone motility, it will be essential to visualize where each motor protein resides relative to the substrate during outgrowth.

While Myo1b and Myo1c are present in axons and growth cones, Myo1d has been localized to neuronal cell bodies and dendrites (Bahler et al. 1994). It is expressed in most parts of the nervous system, and expression levels reach maximal values during adulthood (Bahler et al. 1994). Myo1e has been detected in brain tissue (Stoffler et al. 1995), but not at the subcellular level. Myo1e interacts with both synaptojanin-1 and dynamin in biochemical assays, and expression of the Myo1e tail inhibits receptor-mediated endocytosis in HeLa cells (Krendel et al. 2007). Thus, Myo1e could be involved in actin-dependent membrane turnover and endocytosis at the synapse, particularly since myosin I proteins regulate endocytosis in yeast (Jonsdottir and Li 2004, Sun et al. 2006). In summary, expression patterns and subcellular locations of class I myosins indicate that they may have a role in growth cone motility, organelle transport, and membrane trafficking; however, more

isoform-specific knockdown approaches and high-resolution imaging studies are needed to confirm these potential functions.

4.2.2 Class II Myosins

Myo2 is the conventional double-headed motor protein, comprised of heavy chains that contain two IQ motifs followed by a long coiled-coil tail domain, which allows the formation of bipolar filaments (Fig. 4.1). Nonmuscle Myo2 is present in all eukaryotic cells and involved in essential cellular functions that require sliding of adjacent actin filaments against each other, such as cytokinesis, contraction of the actin ring at adherens junctions, and cell migration. Nonmuscle Myo2 is without doubt the best-studied neuronal myosin motor with well-established functions in neuronal migration, axonal growth, and guidance (Brown and Bridgman 2003a, 2004). Three different nonmuscle Myo2 heavy chains have been identified in vertebrates: Myo2a, Myo2b, and Myo2c (Kawamoto and Adelstein 1991, Golomb et al. 2004). Both Myo2a and Myo2b have overlapping but distinct expression patterns in the nervous system, Myo2b being more abundant than Myo2a (Kawamoto and Adelstein 1991, Itoh and Adelstein 1995). Myo2a and Myo2b are present in cell bodies, axons, and growth cones of cultured rat DRG neurons (Miller et al. 1992). In rat SCG growth cones, Myo2a and Myo2b staining is concentrated in the central and transition domains (Rochlin et al. 1995). The low Myo2c expression levels during development suggest that Myo2c most likely is not involved in neuronal migration or axonal outgrowth (Golomb et al. 2004).

4.2.2.1 Myosin II in Neuronal Migration and Cell Adhesion

Myo2b knockout mice have major heart and brain defects and die between embryonic day 14.5 (E14.5) and birth (Tullio et al. 2001). Two recent studies revealed that Myo2 activity is critical early in CNS development for interkinetic nuclear migration of neuronal progenitor cells in both cortex and retina (Schenk et al. 2009, Norden et al. 2009). Aberrant neuronal cell migration in Myo2b knockout mice caused accumulation of facial neurons into the fourth ventricle, resulting in hydrocephalus (Tullio et al. 2001, Ma et al. 2006). Myo2b may have a scaffolding function independent of its functional motor domain, affecting cell adhesion of neuroepithelial cells facing the spinal canal (Ma et al. 2007). Reduced cell adhesion in the Myo2b mutant causes neuroepithelial cells to invade the spinal canal and obstruct cerebrospinal fluid flow. Less is known about in vivo nervous system function of Myo2a, since knockout mice die much earlier (E6.5), probably due to a decreased cell–cell adhesion (Conti et al. 2004). More recently, experiments with the chemical inhibitor blebbistatin have revealed that Myo2 plays a critical role in forward pulling of both the centrosome and the soma during glial-guided neuronal cell migration in vitro and in vivo and that this response is regulated by the cell polarity protein Par6α (Schaar and McConnell 2005, Solecki et al. 2009).

4.2.2.2 Myosin II in Axonal Growth

Both F-actin assembly/disassembly and actomyosin contractility control growth cone motility and axonal outgrowth (Chapters 2 and 3). F-actin assembly in growth cones occurs at the filopodial tips and the leading edge by addition of G-actin to filaments in both polarized bundles and less polarized F-actin networks, respectively (Fig. 4.3). After assembly, F-actin structures undergo retrograde translocation by a process referred to as retrograde F-actin flow, followed by severing and depolymerization in the transition zone (Forscher and Smith 1988, Lin and Forscher 1995, Mallavarapu and Mitchison 1999, Schaefer et al. 2002). What is the driving force of retrograde flow? Initial studies in *Aplysia* growth cones using general myosin inhibition approaches revealed a strong reduction of retrograde flow (Lin et al. 1996). Using a more specific Myo2 inhibitor, blebbistatin, the Forscher lab recently demonstrated that actin flow is reduced by 50% (Medeiros et al. 2006). When actin assembly was blocked in combination with Myo2 inhibition, flow was further reduced, indicating that, in addition to Myo2 activity, actin assembly pushing against the plasma membrane contributes to retrograde flow. All these findings, along with the presence of bipolar Myo2a and Myo2b mini-filaments in the transition zone (Bridgman 2002), suggest that a mechanism similar to the dynamic network contraction model established in fish keratocytes (Svitkina et al. 1997) may drive retrograde flow in growth cones (Fig. 4.3).

What is the role of retrograde flow in cell movement? When retrogradely moving actomyosin networks are linked to extracellular substrates via cell adhesion receptors, flow can be harnessed for forward movement according to the substrate–cytoskeletal coupling model (Fig. 4.3; Mitchison and Kirschner 1988, Suter and Forscher 2000). According to this model, actin flow is specifically reduced in the axis of growth. Simultaneously, there is an increase in both protrusive growth at the leading edge and tension between the growth cone peripheral and central domain, which ultimately pulls the central domain forward. This was experimentally observed in growth cones interacting with specific adhesion protein substrates presented on microbeads (Suter et al. 1998). Consistent with this model, acute Myo2 inhibition results in reduced actin flow, reduced growth cone motility, and increased leading edge advance (Lin et al. 1996, Bridgman et al. 2001, Medeiros et al. 2006), while chronic Myo2 inhibition results in reduced axonal growth and guidance (Wylie et al. 1998, Wylie and Chantler 2001, Turney and Bridgman 2005).

What is known about Myo2a- and Myo2b-specific functions in growth cone motility and axonal growth? Application of Myo2a-specific antisense oligonucleotides to Neuro-2A neuroblastoma cells resulted in reduced neuronal adhesion and reduced lysophosphatidate (LPA)- or thrombin-induced neurite retraction, while neurite length was unaffected (Wylie and Chantler 2001, 2003). Repulsive cues such as LPA, semaphorin 3A, and ephrin A2 activate the Rho–Rho kinase pathway, which results in increased Myo2 light chain phosphorylation and Myo2-dependent axonal retractions (Amano et al. 1998, Gallo et al. 2002, Wylie and Chantler 2003, Gallo 2006), which are likely involved in refining neuronal connections. A recent study provided evidence that semaphorin 3A causes Myo2a redistribution from the

growth cone into the neurite, thereby facilitating collapse, while Myo2b mediates semaphorin 3A-induced neurite retraction (Brown et al. 2009). On the other hand, Myo2b has also been implicated in neurite outgrowth and turning (Wylie et al. 1998, Tullio et al. 2001, Wylie and Chantler 2001, Turney and Bridgman 2005), traction force production, and growth cone motility (Bridgman et al. 2001), as well as retrograde flow (Brown and Bridgman 2003b). The mechanism of Myo2-regulated axonal growth is dependent on the substrate: on laminin, Myo2 mediates adhesion, while on poly-lysine, Myo2 prevents microtubule advance into the growth cone periphery (Ketschek et al. 2007). Furthermore, Myo2 negatively regulates the development of neuronal polarity (Kollins et al. 2009). In summary, a large body of evidence indicates that Myo2 regulates various aspects of neuronal growth cone motility and axonal growth.

4.2.2.3 Myosin II in Synapse Function

Myo2b has been detected in different neurons both pre- and postsynaptically (Miller et al. 1992, Mochida et al. 1994, Takagishi et al. 2005, Ryu et al. 2006). In cultured rat SCG neurons, neurotransmitter release was reduced when a recombinant Myo2b heavy chain tail fragment was injected, but not when a corresponding Myo2a fragment was used (Takagishi et al. 2005), confirming earlier studies that implicated Myo2 in transmitter release (Mochida et al. 1994). In the CNS, dynamic dendritic spine morphology, motility, and synaptic function of hippocampal neurons depend on Myo2b activity (Ryu et al. 2006); however, the details of how Myo2b is involved in dendritic spine morphology as well as in synaptic vesicle release are not known. A recent ultra-structural localization study by the Svitkina lab identified Myo2 in the neck of dendritic spines of hippocampal neurons, suggesting a role of actomyosin contractility in spine development (Korobova and Svitkina 2010).

4.2.3 Class V Myosins

The polarized morphology of neurons and the extremely long axons require an efficient organelle and protein transport system for both neuronal development and function. While axonal long-range transport is mainly mediated by the microtubule-based motors kinesins and dyneins, short-range transport at specific locations such as growth cones, presynaptic terminals, and dendritic spines is achieved by actin-based myosin motors. Myo5 is a barbed end-directed, two-headed motor whose heavy chains contain six IQ motifs followed by a coiled-coil domain and a globular tail (Fig. 4.1; Cheney et al. 1993). Myo5 has several properties that make it an effective organelle motor (Fig. 4.1): (1) the globular tail binds cargo via adaptor proteins; (2) the coiled-coil domain allows the formation of a double-headed motor; (3) the high affinity for F-actin results in attachment of at least one head at all times; (4) the long neck allows Myo5 to take large (36 nm) steps, making it a highly processive motor (reviewed in Sellers and Veigel 2006). A variety of biochemical, structural, genetic, and cellular studies largely performed in neurons, melanocytes, and yeast

have made Myo5 the best characterized organelle motor within the myosin superfamily (Reck-Peterson et al. 2000, Langford 2002, Bridgman 2004). Many studies addressing the organelle motor function of Myo5a have used the *dilute-lethal* mice, which carry a null mutation in the *Myo5a* gene, exhibit a lightened coat color, seizures and other neurological defects, and die around 3 weeks of age (Mercer et al. 1991).

Three different members of class V myosins have been identified in vertebrates: Myo5a, Myo5b, and Myo5c, all exhibiting wide but distinct expression patterns (Rodriguez and Cheney 2002). Myo5a is strongly expressed in the brain and in other parts of the nervous system (Espindola et al. 1992, Espreafico et al. 1992, Rodriguez and Cheney 2002). Both Myo5b and Myo5c are less abundant than Myo5a in the brain but exhibit higher expression in kidney, liver, colon, and placenta (Myo5b), and in colon, pancreas, salivary gland, and stomach (Myo5c) (Zhao et al. 1996, Rodriguez and Cheney 2002, Lise et al. 2006).

4.2.3.1 Myosin V in Axonal Transport, Growth Cones, and Presynaptic Terminals

Several studies provided evidence for actin-based organelle transport in axons and growth cones (Kuznetsov et al. 1992, Evans and Bridgman 1995, Morris and Hollenbeck 1995), and implicated Myo5a as the relevant motor (Prekeris and Terrian 1997, Evans et al. 1998, Tabb et al. 1998, Bridgman 1999). Myo5a was detected predominantly in the central domain and transition zone of growth cones (Evans et al. 1997, Suter et al. 2000). Evans et al. (1997) showed that neurite outgrowth, growth cone morphology, and cytoskeletal organization of *dilute-lethal* SCG growth cones are normal. A different growth cone phenotype was reported in another study, which showed that local Myo5a inactivation by micro-CALI affects filopodia extension dynamics (Wang et al. 1996). The filopodia effects in the CALI study could be due to reduced membrane traffic to the filopodia. On the other hand, Myo5a might have a role in axonal extension, since climbing fibers of *dilute* Purkinje cells exhibit reduced innervation (Takagishi et al. 2007).

With which organelles is Myo5a associated in axons and growth cones? In vitro motility, immunolocalization, and biochemical studies revealed Myo5a association and Myo5a-mediated transport of large endoplasmic reticulum (ER) vesicles (Tabb et al. 1998), synaptic vesicle precursors (Evans et al. 1998, Miller and Sheetz 2000), and potential synaptic vesicles (Prekeris and Terrian 1997). In addition, mitochondria are good candidates for cargo organelles in axons (Hollenbeck and Saxton 2005). Finally, Myo5a associates with neurofilaments, implicating a role of this interaction for the proper distribution of neurofilaments in axons (Rao et al. 2002). This hypothesis was confirmed when green fluorescent protein (GFP)-tagged neurofilaments were observed in axons of dilute-lethal mice (Alami et al. 2009). Fluorescent live cell imaging in both normal and *dilute-lethal* axons further revealed that Myo5a-associated vesicles move along microtubules over long distances and use actin/Myo5a-based transport for local movements, such as in presynaptic terminals (Bridgman 1999). Interestingly, the presynaptic terminals in *dilute-lethal*

mice have increased cross-sectional area and greater numbers of synaptic vesicles (Bridgman 1999). These findings suggest that Myo5a may act as modulator of vesicle transport slowing down microtubule/kinesin-based anterograde transport into the presynaptic terminal. In conclusion, studies in both neurons and melanocytes have shown that multiple microtubule- and actin-based motors reside on organelles that may become engaged/activated at specific subcellular sites during the journey of an organelle (Bridgman 1999, Gross et al. 2002, Levi et al. 2006). This model is particularly intriguing in light of the fact that the cargo-binding domain of Myo5a directly binds to kinesin, thus forming a hetero-motor complex for fast switching of the cytoskeletal track system (Huang et al. 1999).

Based on the studies discussed above, one might expect a potential role for Myo5a in synaptic vesicle release. Both pre- and postsynaptic function of *dilute* hippocampal CA3-CA1 synapses appeared normal when compared to littermate controls (Schnell and Nicoll 2001). In agreement with this study, no effects of Myo5a on synaptic transmission were reported for SCG neurons from Myo5a mutant rats (Takagishi et al. 2005). On the other hand, Myo5a binds to the t-SNARE syntaxin-1A and mediates Ca^{2+}-induced exocytosis of vesicles in chromaffin cells (Watanabe et al. 2005). Thus, the presynaptic function of Myo5a is still controversial and may depend on the specific neuronal connection. In addition, other myosins present in presynaptic terminals of Myo5a mutant animals may compensate for the lack of functional Myo5a.

4.2.3.2 Myosin V in Dendrites and Postsynaptic Function

The roles of Myo5a and Myo5b are better defined on the postsynaptic side and in dendrites where both myosins have been localized (Espindola et al. 1992, Naisbitt et al. 2000, Walikonis et al. 2000, Lise et al. 2006). Indirect binding of Myo5a to postsynaptic density-95 (PSD-95) suggests a potential role for Myo5a in the transport of the PSD-95 complex (Naisbitt et al. 2000). Myo5a activity is required for smooth ER localization in dendritic spines, local calcium release, and postsynaptic functions such as long-term synaptic depression (Dekker-Ohno et al. 1996, Takagishi et al. 1996, Miyata et al. 2000). Furthermore, Myo5a facilitates the transport of the mRNA-binding protein TLS and its target RNA Nd1-L in a Ca^{2+}-dependent manner into dendritic spines of mouse hippocampal neurons, implicating a role for Myo5a in synaptic plasticity (Yoshimura et al. 2006). Myo5a and Myo5b have been implicated in dendritic trafficking and recycling of the AMPA-type glutamate receptor subunit GluR1, the dendritic K^+ channel Kv4.2, as well as of the muscarinic acetylcholine receptor subunit M4, although the functional involvement of these two myosin V isoforms in synaptic plasticity has remained somewhat controversial (Volpicelli et al. 2002, Lise et al. 2006, Correia et al. 2008, Lewis et al. 2009). Myo5b appears to be an important Ca sensor in synaptic plasticity. Ca influx after NMDA receptor activation causes rapid recruitment of Myo5b to recycling endosomes and thereby exocytosis of AMPA receptors (Wang et al. 2008). How is the specificity between motor proteins and cargo receptors achieved? Increasing evidence from both neuronal and melanocyte systems indicates that the

small GTPases of the Rab family and linker proteins may provide such specificity (Seabra and Coudrier 2004). In summary, class V myosin motors modulate long-range organelle transport and control short-range transport to specific neuronal compartments, thereby supporting the development and function of neuronal connections.

4.2.4 Class VI Myosins

Myo6 contains a head, a short neck region with one IQ motif, and a C-terminal tail domain that is capable of dimerization (Fig. 4.1; Kellerman and Miller 1992, Hasson and Mooseker 1994, Buss et al. 2004). Despite the presence of only one IQ motif, each heavy chain binds two calmodulins (Bahloul et al. 2004). Myo6 has some special structural features that result in mechanochemical properties that are unique from other myosins and enable Myo6 to perform special functions. The most intriguing feature of Myo6 is the fact that it moves "backward" toward the pointed end of actin filaments (Wells et al. 1999). Another special feature of Myo6 is that it appears to exist both as a monomer and a dimer, perhaps with cargo binding inducing dimerization (Park et al. 2006, Sweeney and Houdusse 2007). This mechanism would allow the formation of the processive, dimerized motor at the right subcellular location, e.g., the plasma membrane, enabling Myo6 to carry out its well-described function in endocytosis (Buss et al. 2004, Sweeney and Houdusse 2007). Myo6 was originally identified in *Drosophila melanogaster* (Kellerman and Miller 1992), where it has been implicated in several functions, including transport of cytoplasmic particles in the embryo (Mermall et al. 1994). In mammalian cells, Myo6 has been localized to membrane ruffles, endocytotic vesicles, the cytosol, and the Golgi complex, where it has both transport and anchoring roles in membrane traffic, cell adhesion, and migration (Buss et al. 2004, Sweeney and Houdusse 2007).

4.2.4.1 Myosin VI in Nervous System Development

What is known about Myo6 functions in the nervous system? It is expressed in all major parts of the mouse brain at similar levels from postnatal day 1 (P1) into adulthood (Osterweil et al. 2005). In chick brains, Myo6 was detected as early as E6, while in DRGs expression starts from E10 on (Suter et al. 2000). Within cultured neurons, Myo6 is found in all subcellular compartments (Suter et al. 2000, Osterweil et al. 2005). In chick DRG growth cones, Myo6 shows the highest concentration in the central domain similarly to Myo5a; however, Myo6a is less cytoskeleton-associated than Myo5a (Suter et al. 2000). Could Myo6 be involved in growth cone motility and axonal outgrowth? Considering that Myo6 is a pointed end-directed motor that can bind to plasma membrane (Spudich et al. 2007), one could imagine a mechanism by which membrane-bound Myo6 moves actin filaments forward in the direction of growth; however, there is as yet no experimental evidence for this model. Myo6 is also involved in early neuronal development in *Drosophila.* Myo6

is required for basal localization of Miranda, an adaptor protein which in turn localizes cell fate determinants Prospero and Staufen to the basal side of the neuroblast (Petritsch et al. 2003).

4.2.4.2 Myosin VI in Synaptic Function

Because of its transport and anchoring properties, Myo6 could mediate complex membrane-trafficking events at the synapse. A number of binding partners have been identified for Myo6, including Dab2, GIPC, and SAP97 (Buss et al. 2004). GIPC is an adapter protein between the BDNF receptor TrkB and Myo6 in hippocampal neurons (Yano et al. 2006). This interaction is important for specific presynaptic functions, including BDNF–TrkB-mediated long-term potentiation and enhancement of glutamate release (Yano et al. 2006). A recent study implicated Myo6 in postsynaptic structure and AMPA-type glutamate receptor endocytosis (Osterweil et al. 2005). Homozygous *Snell's waltzer* mice that lack Myo6 exhibit fewer synapses and shorter dendritic spines in the hippocampal CA1 region when compared with heterozygous mice. Furthermore, hippocampal neurons from *Snell's waltzer* mice show reduced AMPA-type receptor GluR1 subunit internalization because of disrupted clathrin-mediated endocytosis (Osterweil et al. 2005). The interaction between Myo6 and the GluR1–AMPA receptor is mediated by the adapter protein SAP97 and important for AMPA receptor trafficking (Wu et al. 2002, Nash et al. 2010). In summary, Myo6 forms specific complexes with membrane proteins at the pre- and postsynaptic sites and thereby regulates both synaptic vesicle release and neurotransmitter receptor trafficking. Considering the well-established role of Myo6 in membrane trafficking in other cellular systems, more discoveries on Myo6's actions in the nervous system are expected in the future.

4.2.5 Classes IX, X, and XVI Myosins

I discuss myosins of these three classes briefly, since they have been detected in neuronal tissues, but are not well characterized with respect to functions in the nervous system.

4.2.5.1 Class IX Myosins

The hallmark structural feature of class IX myosins is the GTPase-activating protein (GAP) domain in the tail, which activates Rho but not Rac or Cdc42 (Fig. 4.1; Muller et al. 1997, Post et al. 1998). Additional structural features are an N-terminal extension of the head domain, a highly basic insertion at the presumed actin-binding site, a neck region with 4–6 IQ motifs, and a zinc-binding motif in front of the GAP domain. The best-characterized class IX myosins include Myo9b (rat myr 5) and Myo9a (rat myr 7) (Reinhard et al. 1995, Wirth et al. 1996, Chieregatti et al. 1998). Biophysical and biochemical studies suggest that Myo9b is a single-headed, processive motor that binds actin with high affinity (Post et al. 1998, 2002, Kambara

and Ikebe 2006). In the developing and adult brain, Myo9a is expressed at higher levels than Myo9b (Chieregatti et al. 1998). While no data on potential class IX myosin functions in the nervous system are currently available, the developmental expression pattern and the Rho GAP activity indicate that at least Myo9a may be involved in actin-dependent developmental processes, e.g., neuronal migration, axonal growth, or synaptogenesis.

4.2.5.2 Class X Myosins

Only one member of class X myosins (Myo10) has been identified in vertebrates so far (Berg et al. 2001). Following the head domain, the neck with three IQ motifs, and a short coiled-coil region, the Myo10 tail contains three pleckstrin homology (PH) domains implicated in phosphoinositide signaling, a myosin tail homology 4 (MyTH4) domain, and a band 4.1/ezrin/radixin/moesin (FERM) domain for binding to transmembrane proteins (Fig. 4.1; Berg et al. 2000). Expression of both full-length and headless isoforms of Myo10 in the brain is developmentally regulated (Sousa et al. 2006). Myo10 is enriched at the leading edge of lamellipodia, tips of filopodia, and membrane ruffles in several cell lines, including the neuronal CAD cells (Berg et al. 2000, Sousa et al. 2006). Furthermore, Myo10 undergoes intrafilopodial motility and functions in filopodia formation (Berg and Cheney 2002, Bohil et al. 2006). Interestingly, it can act as a linker between actin filaments and β-integrin receptors (Zhang et al. 2004). This linker function may likely play role in axonal outgrowth; thus, the actin/Myo10/integrin complex may be involved in the redistribution of adhesion receptors or in substrate–cytoskeletal coupling (Fig. 4.3). In support of a role for Myo10 in axonal guidance, it has been shown that the FERM domain of Myo10 interacts with the DCC, a receptor for the guidance molecule netrin-1 (Zhu et al. 2007). Importantly, both expression of a headless Myo10 and suppression of Myo10 expression by siRNA reduced DCC localization at the tips of neurites and affected netrin-induced neurite outgrowth and axonal guidance. Because of its linker function, Myo10 is likely to mediate additional interactions between receptors and the cytoskeleton that are important for axonal growth and guidance.

4.2.5.3 Class XVI Myosins

Myo16 was identified as rat myr 8 during a search for myosins involved in cerebellar granule neuron migration (Patel et al. 2001). The motor domain is preceded by eight ankyrin repeats and followed by a single IQ domain and either a short or a longer C-terminal tail in the Myo16a or Myo16b isoform, respectively (Fig. 4.1; Patel et al. 2001). Myo16b is expressed in various brain regions, particularly between P0 and P10, and has been detected in cerebellar granule neurons both in vitro and in vivo (Patel et al. 2001). Heterologous expression of Myo16b in COS-7 cells revealed that the C-terminal tail can target this motor to the nucleus during the interphase and that it may have a role in cell cycle control (Cameron et al. 2007); however, it remains to be determined if Myo16b indeed plays a role in neuronal migration.

4.3 Myosins in Sensory Cells

Sensory cells have developed a high degree of functional specialization to convert various stimuli into electrical signals that are transmitted to the nervous system. In the case of hair cells of the inner ear and photoreceptors of the retina, special cytoskeletal and membranous compartments support these signal transduction functions. The following section summarizes the key functions of several myosins that have been extensively characterized in these two sensory cells. I refer to a number of reviews for a more detailed discussion of the experimental evidence for myosin functions in hair cells and photoreceptors (Brown and Bridgman 2004, Gillespie and Cyr 2004, El-Amraoui and Petit 2005, Lin et al. 2005).

Inner ear hair cells are probably the best-characterized cell type with respect to the number of different myosins. At least six myosins are essential for hearing and balance based on mutants characterized in both mice and humans, including Myo1a, Myo2a, Myo3a, Myo6, Myo7a, and Myo15a (Friedman et al. 1999, Gillespie and Cyr 2004, El-Amraoui and Petit 2005). To transduce mechanical forces into electrical signals, hair cells develop highly organized F-actin-rich protrusions called stereocilia that are interconnected with cadherin molecules. Classes I, II, III, VI, VII, and XV myosins have been localized to specific subcellular regions in the hair cell where they have distinct roles for the development, maintenance, and sensory function of this cell (Fig. 4.4). In the photoreceptor cell, classes II, III, V, VI, and VII myosins have been detected, of which classes III and VII have been characterized the best with respect to a role in vision.

4.3.1 Class I Myosins

Three of the eight class I myosins in higher vertebrates, Myo1b, Myo1c, and Myo1e, are strongly expressed in cochlea and vestibular organs of rodents at birth (Dumont et al. 2002). While mutations in the *Myo1a* gene have been linked to deafness in humans but not in mice, there is no information available about the localization of Myo1a in the inner ear (Donaudy et al. 2003, Tyska et al. 2005). Myo1b is mainly expressed in the supporting cells that surround the hair cells and in an apical ring of the hair cell (Dumont et al. 2002). Myo1c is enriched at tips of stereocilia and in the pericuticular necklace of vestibular hair cells, and uniformly distributed along the stereocilia of auditory hair cells (Fig. 4.4; Gillespie et al. 1993, Hasson et al. 1997, Dumont et al. 2002, Schneider et al. 2006). Myo1c is an important component of the hair cell's adaptation complex that allows closing of the transduction channel in both the slow and fast adaptation mechanisms by releasing tension (Holt et al. 2002, Gillespie and Cyr 2004, Stauffer et al. 2005). Myo1c is reported to interact via its neck domain with PIP_2 and cadherin 23, the presumptive tip link, at the tips of stereocilia (Siemens et al. 2004, Hokanson and Ostap 2006, Phillips et al. 2006). This interaction enables Myo1c to reposition the tip complex during adaptation. Myo1e was detected in the cuticular plate of cochlear and vestibular hair cells (Dumont et al. 2002); however, there are no experimental data on the role of Myo1b or Myo1e in hair cells.

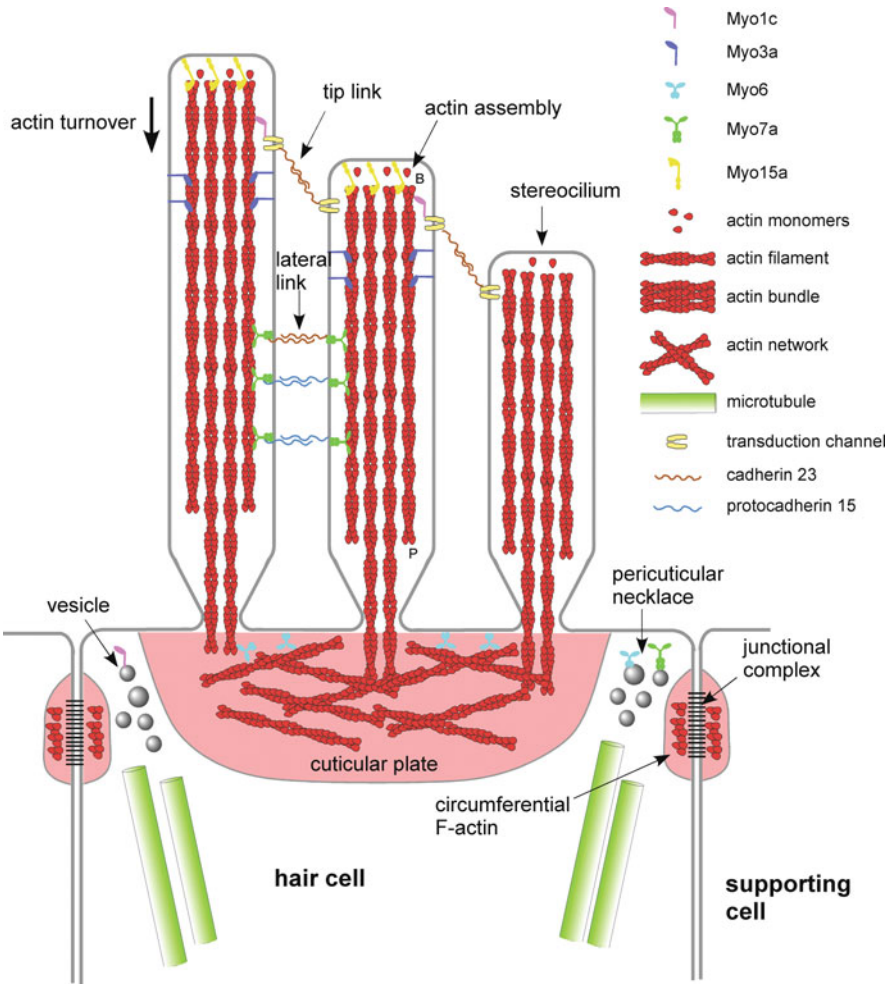

Fig. 4.4 Myosin functions in hair cells. Schematic cross section through the apical side of an inner ear hair cell depicting the location of different myosins with important functions in hair cell development and function. Myo15a forms a cap on top of the F-actin bundles where it controls the length of stereocilia. Actin filaments are oriented with barbed (B) end toward the tip of stereocilia and the pointed (P) end toward the base. Myo1c is found at the tip of stereocilia where it adjusts the position of the transduction channel during adaptation. Myo3a is located in a ring around the tip of stereocilia and controls their shape. Myo6 may connect the apical plasma membrane to the F-actin network in the cuticular plate and connect the stereocilia to the plate. Myo7a is located along the side of the stereocilia and stabilizes them via lateral links. Myo1c, Myo6, and Myo7 are also found in the pericuticular necklace, a vesicle-rich area around the cuticular plate where they could mediate organelle traffic

4.3.2 Class II Myosins

A mutation in Myo2a results in the human nonsyndromic deafness DFNA17 (Mhatre et al. 2006). Myo2a has been localized along the stereocilia of mouse cochlear hair cells and may stabilize the stereocilia (Mhatre et al. 2006). A similar function for class II myosins has been found in the retina. In *Drosophila* photoreceptors, nonmuscle myosin II *zipper* forms two stripes of actomyosin extending along the sides of each of the R1–6 rhabdomeres, suggesting that this cytoskeletal system may be important for the alignment of the rhabdomeres with the optical axis (Baumann 2004). This hypothesis was supported by the distorted rhabdomeres in *zipper* flies carrying a mutation in the motor domain (Baumann 2004).

4.3.3 Class III Myosins

Class III myosins, Myo3a and Myo3b, are single-headed motors that have an N-terminal kinase domain, a neck with variable IQ motifs, and a short tail (Fig. 4.1; Dose and Burnside 2000, Berg et al. 2001). The kinase domain has serine–threonine kinase activity (Ng et al. 1996) and is essential in *Drosophila* phototransduction (Porter and Montell 1993). Class III myosins were originally identified in *Drosophila* as two proteins encoded by the *ninaC* gene (Montell and Rubin 1988). NinaC mutant flies exhibit reduced amounts of rhodopsin in the photoreceptors and abnormal electroretinograms. The exact role of Myo3 in the photoreceptor rhabdomeres is still unclear; it may have structural role (Hicks et al. 1996), a signaling (Porter and Montell 1993, Wes et al. 1999), or transport function for components of the phototransduction machinery (Cronin et al. 2004, Lee and Montell 2004, Liu et al. 2008). An essential role for Myo3a in inner ear function is indicated by the fact that point mutations in the motor domain lead to the human nonsyndromic hearing loss DFNB30 (Walsh et al. 2002). Myo3a has recently been localized in a thimble-like pattern around the tips of the hair cell stereocilia (Fig. 4.4; Schneider et al. 2006). Deletion of the kinase domain caused lengthening of stereocilia and bulging of the tips, suggesting that Myo3a might regulate actin bundle maintenance, transport of the transduction complex to the stereocilia tip, or be part of the tip complex itself (Schneider et al. 2006). A recent study provided new insights into the role of Myo3a in hair cells showing that this motor regulates the length of stereocilia by transporting the actin-bundling protein espin 1 to the plus end of actin filaments (Salles et al. 2009).

4.3.4 Class V Myosins

Elegant genetic studies in *Drosophila* by the Ready lab have recently revealed that the organelle motor Myo5 with the help of the small GTPase Rab11 and the linker protein dRip11 transports rhodopsin-containing secretory vesicles to the photoreceptor rhabdomeres, which are critical for photoreceptor morphogenesis

(Li et al. 2007). Furthermore, the same laboratory also reported that calcium-activated Myo5 transports pigment granules to the rhabdomeres in response to bright light in order to close the fly pupil (Satoh et al. 2008). Thus, Myo5 is important for both photoreceptor development and physiology.

4.3.5 Class VI Myosins

Myo6 has been localized to the actin-rich cuticular plate of hair cells, indicating that it could be important for the anchoring of the stereocilia or membrane–actin interactions (Fig. 4.4; Hasson et al. 1997). A role for Myo6 in hair cell function was originally established when a recessive mutation in Myo6 was identified as the cause of deafness observed in the *Snell's Waltzer* mouse in which hair cells degenerate (Avraham et al. 1995). Myo6 mutations have also been linked to deafness in humans (Melchionda et al. 2001, Ahmed et al. 2003). During hair cell development in both *Snell's Waltzer* mice and zebrafish Myo6b mutants, the apical surface protrudes and stereocilia fuse together, suggesting that Myo6 is critical for anchoring the apical plasma membrane to the underlying actin-rich cuticular plate (Self et al. 1999, Kappler et al. 2004, Seiler et al. 2004). In photoreceptor cells, Myo6 has been localized to the inner segments, and *Snell's Waltzer* photoreceptors show a decreased responsiveness (Kitamoto et al. 2005). In summary, evidence from several systems implicates Myo6 in the development and function of inner ear hair and photoreceptor cells.

4.3.6 Class VII Myosins

Class VII myosins have a head, five IQ motifs, a short coiled-coil domain, and two sets of MyTH4 and FERM domains in the C-terminal tail that are separated by an SH3 domain (Fig. 4.1; Berg et al. 2001). Like Myo6, the short coiled-coil domain could dimerize upon cargo or actin binding and thereby generate a processive motor (Yang et al. 2006). Class VII myosins are expressed in a wide range of organisms from dictyostelium to humans and are involved in adhesion, phagocytosis, and organelle transport (Berg et al. 2001, Krendel and Mooseker 2005). Myo7a is expressed in retina, cochlea, kidney, and testis (Hasson et al. 1995). Mutations in Myo7a result in the most frequent and severe form of deafness and blindness in humans, called Usher 1 syndrome (Weil et al. 1995, El-Amraoui and Petit 2005), nonsyndromic deafness in humans (Liu et al. 1997, Weil et al. 1997), as well as deafness in mice (*shaker-1*) (Gibson et al. 1995). Stereocilia of *shaker-1* mice hair cells do not develop normally, implicating Myo7a in the assembly of the actin bundles (Self et al. 1998). Myo7a is localized to the pericuticular necklace and along the stereocilia in close association with the lateral connections mediated by cadherin 23 and protocadherin 15; thus, Myo7a may be an intracellular anchor for these linkages in order to maintain the integrity of the hair bundle (Fig. 4.4; Hasson et al. 1997, El-Amraoui and Petit 2005). Recent mosaic complementation experiments provided

evidence that Myo7a regulates the length of stereocilia by affecting actin dynamics (Prosser et al. 2008). Finally, hair cell currents are affected in certain *shaker-1* mutants, suggesting that Myo7a could also participate in hair cell adaptation (Kros et al. 2002).

In photoreceptors, Myo7a has been localized to the cilium that connects the inner and outer segments, where it transports opsin into the outer segment (Liu et al. 1999, Wolfrum and Schmitt 2000). Myo7a is highly expressed in the pigment epithelial cells, which constantly absorb the shed-off membrane discs of the outer photoreceptor segments. In *shaker-1* mice, these cells exhibit both delayed phagocytosis of outer segment membranes (Gibbs et al. 2003). Thus, Myo7a has important functions in the maintenance of the outer segments, which are severely affected in Usher 1 syndrome patients (El-Amraoui and Petit 2005). The lack of retinitis pigmentosa in the *shaker-1* mouse could be explained by the shorter life span of mice or by the differences in the photoreceptor anatomy and physiology between mice and humans.

4.3.7 Class XV Myosins

Vertebrate Myo15a is a 395-kDa motor with a large N-terminal extension of unknown function and a C-terminal tail similar to Myo7a, which allows interactions with membrane and scaffolding proteins (Liang et al. 1999). This motor is expressed in the cochlea and vestibular systems in the developing mouse inner ear, and mutations result in severe hearing loss both in mice (*shaker 2*) and humans (DFNB3) (Probst et al. 1998, Wang et al. 1998). In wild-type hair cells, Myo15a localizes as a cap on the top of stereocilia, and the amount of Myo15a correlates with the length of the bundles (Fig. 4.4; Belyantseva et al. 2003, Rzadzinska et al. 2004, Delprat et al. 2005). *Shaker 2* stereocilia are considerably shorter than wild type and do not exhibit the staircase pattern (Belyantseva et al. 2003, Rzadzinska et al. 2004). Thus, Myo15a controls the length of stereocilia, for example, by regulating the rate of F-actin assembly at the top of the bundles that slowly turn over by retrograde flow (Rzadzinska et al. 2004, Belyantseva et al. 2005, Delprat et al. 2005). On the other hand, the formation and function of the hair cell transduction complex does not require Myo15a (Stepanyan et al. 2006). Future biophysical and biochemical studies will provide important insights regarding if and how this large motor protein regulates actin dynamics and/or membrane/actin interactions.

4.4 Summary and Perspectives

Neurons and sensory cells of the nervous system have harnessed the wide spectrum of functionality of all the major myosin classes for morphogenesis, cell movement, cell maintenance, and signaling. Probably the best-characterized motor with respect to function is Myo2 in actomyosin contraction and neurite outgrowth. However, it

Table 4.1 Summary of proposed myosin functions in neurons and sensory cells

	Myo1 b c e	Myo2 a b	Myo3 a	Myo5 a b	Myo6	Myo7 a	Myo10	Myo15 a
Neuroblast diff.					x			
Neuronal migration		x						
Growth cone motility, axonal growth	x x	x x		x			x	
Axonal transport	x			x	x			
Presynaptic function	x	x		x	x			
Postsynaptic function		x		x x	x			
Hair cell development		x	x		x	x		x
Hair cell function	x		x		x	x		
Photoreceptor development		x	x	x	x	x		
Photoreceptor function			x	x	x	x		

has become evident that myosins have many additional roles in the nervous system, most of them involving one type of membrane–cytoskeletal interactions, such as endocytosis, organelle transport, membrane protrusion and stability, cell adhesion, and signaling (Table 4.1). The functional diversity of myosins within a single cell is particularly intriguing in the inner ear hair cell, where at least six different myosins have specific roles in cellular morphogenesis and mechanotransduction. While most of the earlier reports implicated myosins in various steps of nervous system development, recent studies have also provided accumulating evidence for both pre- and postsynaptic functions, as well as for morphogenesis and signal transduction in sensory cells.

Despite the recent progress there are still open questions and challenges. What are the functions of classes IX and XVI myosins in the nervous system? Do class I myosins play a role in organelle transport and growth cone motility? Because of the presence of multiple myosin proteins within one cell, it will be essential to use more specific chemical inhibitors, as well as temporally and spatially restricted knockdown approaches to further dissect functions. In addition, while several motors have been well characterized biochemically and genetically, future cellular studies involving live cell imaging techniques will advance our understanding of the various myosin functions. It will be important to simultaneously visualize membrane, F-actin, and myosin movements in processes where myosins have been implicated as coupling agents. Furthermore, the polarity of several subcellular actin structures in the nervous system needs to be determined. Finally, identification of additional cargo and linker proteins will benefit our understanding of the multiple roles of myosins in the nervous system.

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