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The diversity of molecular motors: an overview

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Abstract. Rapid progress has recently been made in the identification and characterization of a large number of kinesin and myosin motor proteins. Recent work has uncovered roles for these motors in processes such as vesicle trafficking, cytoskeletal organization, and chromosome movements, to name a few. A series of reviews describing some of the significant advances in our understanding of the structure and function of myosins and kinesins is presented.

Key words. Myosin; kinesin; actin; microtubules.

One of the most striking advances in modern cell biology over the past decade has been the discovery of an astonishingly diverse array of motor proteins. A motor protein is now generically described as a protein that uses energy in the form of adenosine triphosphate (ATP) to generate directed movement along a filamentous track. The track, either an actin or microtubule filament, is a helical polymer that has intrinsic polarity. Historically, the motor domains are referred to as heads (based on the initial biochemical analysis of rabbit skeletal muscle myosin II), and the heads are joined to a wide variety of either C-terminal or N-terminal 'tails' via a 'neck' region. The tails dictate whether a given motor protein is a dimer or monomer and are presumed to play an essential role in directing localization within the cell [1, 2].

There are three different general classes of motor proteins that move along either actin or microtubule tracks—the myosins that move along actin filaments [2] and the kinesins and dyneins that move along microtubules [1]. The dyneins are relatively more conserved than the kinesins or myosins, there being only two different types: axonemal and cytoplasmic [3, 4]. In contrast, phylogenetic analyses of the known kinesins and myosins, using their respective conserved motor domains, have revealed that there are at least 15 different classes of myosin and at least 13 distinct kinesin classes [1, 2]. The generally accepted convention is to assign each class a roman numeral based on its order of discovery (e.g. myosin I, kinesin I etc.). New kinesins and myosins continue to be discovered, and it is likely that there will be at least 20 different classes of each motor once the cataloging is finished. The reader is referred to the kinesin (http://www.blocks.fhcrc.org) and myosin (http://www.mrc-lmb.cam.ac.uk/myosin/myosin.html) home pages for detailed information on each of these growing superfamilies. In light of the wealth of knowledge available for the kinesins and myosins, the rest of this discussion will focus on these two types of motors.

There are many fundamentally conserved aspects of both the kinesins and myosins, but there are several motor-specific characteristics that firmly differentiate them from each other apart from the type of track they travel along. The first is that the kinesins can be grossly separated into those that move towards the plus (fast-growing) or minus (slow-growing) end of microtubules. All of the known myosins only move towards the plus end of actin filaments (although one should not discount the possible existence of a 'retromyosin' lurking among one of the myosins that has yet to be biochemically characterized). This difference between these two types of motor proteins may be dictated by the simple differences in the way the two filament systems are arranged within the cell. The microtubules are generally arrayed with their minus ends all embedded in an

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MTOC (microtubule organizing center) or centrosome resulting in their plus ends all being pointed towards the periphery of the cell (although there are some exceptions to this rule) or in towards the center of the spindle. Actin filaments, in contrast, are arranged in a relatively random fashion throughout the cortex, with the exception of those that are in contact with the plasma membrane (the barbed end is apposed to the plasma membrane) [5, 6]. Another difference is in the body plan of each of the motor proteins. With one exception, the myosins all have the motor domain at the N-terminal region of the molecule [2]. The kinesins are equally likely to have their motor domain either at the N-terminus or C-terminus, and some even have the motor domain in the center of the molecule [1]. The third difference is with the character of the tail region of these two types of motor proteins. The myosin tail regions can be comprised of a wide range of domains found in other proteins, such as *src*-homology 3 (SH3), GTPase activating domain for the small G protein rho, plekstrin homology (PH) domains, talin homology domain and so on. The kinesins appear to have incorporated fewer of these external domains, possibly because of distinct requirements for their functions.

The field has grown considerably since the discovery of the first motor protein, skeletal muscle myosin. Motor proteins were originally thought to be highly specialized proteins that power the contraction of muscle and the beat of flagella, or that carry out directed axonal transport. Studies to define the molecular roles of motor proteins of all types now impinge on many important fields in modern biology—cell biology, developmental biology and neuroscience, to name a few. A host of motor proteins are now known to have dynamic roles in processes such as vesicle transport, chromosome movement, nuclear movement, constriction of the cell, to name a few. These proteins may also play structural roles such as contributing to the organization of microvilli. Additionally, several human diseases are now known to be the result of altered motor protein function. Mutations in three distinct myosins (myosin VI, VII, XV) result in deafness [7–11], loss of another results in pigmentation and immunological defects (myosin V) [12], and mutations in kinesin (a kinesin II) lead to situs inversus (inappropriate placement of internal organs) [13, 14].

Despite the fact that motor proteins have been the focus of intense study for nearly half a century, one of the major questions that remains to be answered is how chemical energy in the form of ATP is converted into movement. Rapid progress in solving this fundamental question has been made in the past decade. The ability to express motor proteins in heterologous systems (such as *Escherichia coli* and baculovirus) allows the purification of biochemical quantities of the motor domain of kinesins. This approach has enabled the crystallization and kinetic analysis of several different kinesins [15, 16]. Having detailed structural and biochemical information for kinesin superfamily members with widely varying functions has provided new clues about the fundamental domains of a given kinesin and those regions, when modified, alter the properties of the motor significantly. For example, important information about structural transitions and nucleotide-binding states has been obtained from such studies as well as the role of the neck helix for motor function [17]. Similar advances have been made possible for myosin by the ability to express large quantities of the *Dictyostelium* myosin II motor domain in *Dictyostelium* cells. The effect of mutations on the structure and function of a given motor domain can now be carried out to test existing models of motor protein function [18, 19].

The other exciting advance that has occurred during this decade is the recognition that there are likely to be extensive interactions between microtubule- and actin-based cellular transport systems. The initial realization of possible motor system cross-talk came from the elegant observation by Kusnetsov et al. [20] that vesicles that move on microtubule tracks can switch and move on actin tracks. More recent experiments have shown that myosin VI can bind to a microtubule-interacting protein, CLIP-170 [21], and that myosin V can directly bind to kinesin I [22]. Additionally, *Xenopus* melanophores have been shown to be capable of moving along both microtubules and actin filaments in vitro, and kinesin II, cytoplasmic dynein and myosin V have all been implicated as the motor responsible for these movements [23, 24]. Given these interesting initial observations, it is likely that there will soon be more examples of interactions between these two transport systems.

The reviews presented here provide readers with an overview of recent progress in the field. Rapid advances are being made in determining the atomic structure of both myosin and several kinesins. The availability of crystal structures for a myosin II (the myosin responsible for muscle contraction and cytokinesis in nonmuscle cells) and kinesins of both types, plus- and minus-end-directed, has allowed one to see the elements that are fundamentally conserved between these two classes of motors. Equally important, it is now possible to define the molecular determinants of the directionality of kinesins (as reviewed by Hirose and Amos). The identification of mutants that lack kinesin function has uncovered new roles for these proteins in the functioning of the nervous system (reviewed by Martin et al.) and, more surprisingly, in the building of cilia and flagella (reviewed by Cole). One of the original areas of motility research was in the rapid movement of organelles in plants (referred to as cytoplasmic streaming).

Molecular biology and persistent biochemical studies have begun to pry open the secrets to cytoplasmic streaming and have led to the identification of novel plant myosins with unusual properties (reviewed by Yamamoto et al.). One of the most studied of the 'new' myosins is myosin V, as it is one of the three classes of myosins (those being I, II and V) that appear to be most widely distributed throughout phylogeny (reviewed by Provance and Mercer). This myosin is also of great interest because of its potential role in organelle movement and neuronal function. Finally, the amazing diversity in myosin tail structures suggests many different roles for each class of myosin (reviewed by Oliver et al.). Understanding the functional domains of the various myosins is expected to provide clues about what each myosin might be doing in the cell. It is not possible to cover all aspects of the field, but this collection of papers should provide the reader with a glimpse into the state of the art and provide some insight into the new directions in which the field is heading.

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