Editorial Overview: Myosins in reviews

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The myosin superfamily is composed of more than 30 classes of actin-based motor proteins that play a role in a wide spectrum of complex cellular processes, such as muscle contraction, cell locomotion, membrane trafficking, cytokinesis, cytoskeletal structure and tension maintenance to name just a few (1, 2). To accomplish these cellular tasks, humans have evolved to express 39 myosins belonging to 12 classes (3). To establish the specific molecular roles of the different classes of unconventional (non-muscle) myosins in nearly all cellular pathways, it is essential to understand how these motors have adapted their kinetic motor properties, how they select specific cargoes and how their activities are regulated by cargo attachment or through their actin filament tracks. This set of reviews therefore captures and summarises important new insights into the formation of motor-cargo complexes, regulation of motor activity and variations in the kinetic cycle, all of which allow the different classes of myosins to perform distinct functions such as in the autophagy pathway.

The first review by Li and colleagues (Jianchao Li, Qing Lu and Mingjie Zhang. Structural Basis of Cargo Recognition by Unconventional Myosins in Cellular Trafficking. Traffic 2016: DOI: 10.1111/tra.12383) summarizes the most recent high-resolution structural data on the tail domains of myosins of class I, V, VI and X alone or when bound to specific cargo (4, 5). These structures illustrate the different mechanisms by which the unconventional myosins recognise their cargo. The authors present models of how cargo binding may regulate the activity of these myosins in cellular trafficking pathways. However, so far little is known about the actual mechanisms that determine how cargo binding and release is regulated by the different myosins to ensure initial uptake and then delivery at the exact time to the correct locations in the cell. Recent improvements in high-resolution cryo-EM imaging, single molecule biophysical methods and improved structural analysis techniques together with cell biological assays should provide useful clues to these important questions.

The review by Batters and Veigel (Christopher Batters and Claudia Veigel, Mechanics and activation of unconventional myosins, Traffic 2016; DOI: 10.1111/tra.12400) discusses the roles of the different structural regions (motor domain, lever arm and tail) on the

mechanics, activation and regulation of the unconventional myosins. Single molecule technology, such as optical tweezers, has enabled the identification of the different mechanical properties of the motor domains essential for performing specific cellular functions including tethering/tension maintenance, movement, or both. Furthermore, calmodulin and calcium signalling play a pivotal role by controlling the structural rigidity of the lever arm and thus regulate the precise movement and targeting of myosins of class I, V and VI (6). In addition, the authors illustrate that an additional mechanism of calcium regulatory control mediated by tail-motor domain interaction operates in several classes of myosins (II, V, VI and X). In these myosins, the tails are not only involved in cargo binding/oligomerisation but also regulate the myosin by a tail folding (inactive)/unfolding (active) mechanism.

In the review by Heissler and Sellers (Sarah M. Heissler and James R. Sellers **,** Kinetic Adaptations of Myosins for Their Diverse Cellular Functions Traffic 2016: DOI: 10.1111/tra.12388), the *in vitro* kinetic and mechanical properties of the different classes of myosin and their complexes are discussed in great detail. The review summarises recent studies that demonstrate how the kinetic parameters of the motors are precisely adapted, how their structural elements are modified and how their regulatory behaviours are altered so that they are able to carry out a particular function under a variety of cellular conditions. The remarkable feature is that all the myosins follow the same highly conserved kinetic cycle, which only differs in its maximum ATPase rates and velocity on actin. These class-specific variations in their kinetic cycles, together with their select lever arms and specialised multi-domain tails, allow the different myosins to carry out a vast array of sophisticated physiological functions. The authors suggest that the myosins may be divided into five groups based on their functional properties: 1) fast movers; 2) slow/force holders; 3) tension/strain sensors; 4) processive motors and 5) inactive kinetic motors (7). These *in vitro* studies have helped us understand the capabilities and functions of many of these myosins in their cellular environments.

The review by Manstein and Mulvihill (Dietmar J. Manstein and Daniel P. Mulvihill, Tropomyosin-mediated Regulation of Cytoplasmic Myosins. Traffic 2016: DOI: 10.1111/tra.12399) highlights new data on tropomyosin-mediated regulation of non-muscle myosins. In mammalian cells, four distinct tropomyosin (Tpm) genes encode more than 40

isoforms, the majority of them in non-muscle cells (8). The abundance of these isoforms has intrigued us over the years, but only recently have answers to their unique functional properties emerged. In non-muscle cells, each Tpm isoform exhibits a different subcellular localisation and tissue-specific interactions with a distinct actin cytoskeleton network, leading to the recruitment of a specific non-muscle myosin II or unconventional myosin. Each actin-Tpm-myosin complex appears to drive distinct contractile and/or transport processes. So the fascinating questions are: how are the different Tpm isoforms targeted to distinct actin filament networks and then how do they recognise and recruit their specific myosin? The authors propose a model whereby each actin-Tpm isoform-myosin complex forms distinct cytoskeletal superstructures that are required for the wide range of activities essential for the integrity and function of the cell ranging from structural maintenance to organelle/vesicle transport, migration and cell division to name just a few.

The final review by Kruppa, et al. (need to get this in press still) highlights the involvement of three different classes of myosins together with the actin cytoskeleton in the autophagy pathway that the cell uses to maintain cellular homeostasis and target ubiquitylated protein aggregates, cytosolic pathogens and damaged organelles such as mitochondria for selective degradation by the lysosome. Dynamic actin networks regulated by a host of nucleating, stabilising and anchoring proteins, including ARP2/3, Annexin A2 and the WASH complex, are crucial for the delivery of vesicles from various cellular compartments to form the double membrane autophagosome that engulfs the ubiquitylated target and mediates lysosomal degradation (9, 10). A surprising recent observation is that branched actin filament networks not only surround the outside but also assemble within the closing autophagosome (11). So far only the myosins in class I, II and VI have been shown to be involved in different stages of the autophagy pathway. Non-muscle MYO2A is activated by the ULK complex in the very early stages of the pathway and mediates membrane delivery during phagophore induction and formation of the autophagosome (12). In contrast, MYO1C that associates with cholesterol-rich lipid rafts and MYO6 that binds to specific autophagy adaptor proteins are involved in late stages of the pathway, mediating the delivery of endosomal membranes essential for autophagosome maturation and for the final stages of fusion with

the lysosome (13, 14). It is likely in the future that additional myosins playing vital roles in this crucial cellular degradation pathway will be discovered.

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