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Myosin Motor Proteins are Involved in the Final Stages of the Secretory Pathways

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Abstract

In eukaryotes, the final steps in both the regulated and constitutive secretory pathways can be divided into four distinct stages: 1) the ‘approach’ of secretory vesicles/granules to the plasma membrane; 2) the ‘docking’ of these vesicles/granules at the membrane itself; 3) the ‘priming’ of the secretory vesicles/granules for the fusion process; and finally 4) the ‘fusion’ of vesicular/granular membranes with the plasma membrane to permit content release from the cell. Recent work indicates that nonmuscle myosin II and the unconventional myosin motor proteins in classes 1c/1e, Va, and VI are specifically involved in these final stages of secretion. In this review, we examine the roles of these myosins in these stages of the secretory pathway and the implications of their roles for an enhanced understanding of secretion in general.

Keywords

Myosin; Exocytosis; Secretion; Actin; Fusion; Vesicle

Introduction

Secretion/exocytosis is a fundamental mechanism for the extracellular release of proteins synthesized within the cell. It can be broadly divided into the two main categories: a) regulated secretion and b) constitutive secretion, which can be distinguished by differences in their temporal progression through a series of similar stages [1]. During constitutive secretion, proteins synthesized on the ribosomes of the endoplasmic reticulum (ER) are transported in tubular/vesicular carriers from the ER to the Golgi complex, where they are processed and sorted for delivery to the plasma membrane (PM) for immediate release from the cell [2–4]. Proteins on the regulated secretory pathway pass through the same ER to Golgi to PM pathway route, but are then stored in either secretory granules or neuronal synaptic vesicles [5]. Rather than immediately releasing their cargo upon arrival at the plasma membrane, these carriers remain arrested near the PM until triggered to release their contents by a specific intracellular signal or ligand, such as a change in calcium ion concentration [6]. Thus by targeting certain proteins to the constantly active constitutive

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pathway versus the temporally regulated pathway, the eukaryotic cell can carefully control the rates and levels of secretion into the extracellular environment.

The final stages of the secretory pathway are a critical control point for regulating the release of secretory cargo at the plasma membrane. The vesicular or granular secretory carriers proximal to the plasma membrane in both the regulated and constitutive secretion pathways undergo four main phases: 1) approach, 2) docking, 3) priming, and 4) fusion [7, 8] (Figure 1). Remodeling of the cortical actin network plays a key role during these stages; for example, during regulated secretion in chromaffin cells the crosslinked actin filament network underneath the plasma membrane is reorganized and partially disassembled to allow secretory vesicles to be transported through this dense physical barrier. However, complete depolymerization of actin filaments inhibits secretion in many cell types, indicating that actin filaments also provide the tracks for transport of secretory carriers through the actin network to specific regions near the membrane ('Approach') [9]. The actin cytoskeleton may also provide the framework for the tethering or exact positioning of these carriers at the membrane before they dock to a specific complex of SNARE docking proteins ('Docking') [10]. The subsequent 'priming' of these carriers is a broad term encompassing the gathering of fusion machinery and the execution of any protein and lipid modifications necessary to prepare the carriers for the upcoming fusion event ('Priming') [11]. In the fourth and final stage, carrier membranes fuse with the plasma membrane to create aqueous channels called fusion pores that can open and close reversibly to permit release of the secretory cargo ('Fusion') [12].

The precise mechanisms involved in secretory carrier transport and regulation during these four final stages of secretion are presently unclear. A plethora of studies, however, highlight the important roles of the cortical actin filament network and the myosin superfamily of molecular motor proteins, particularly the unconventional myosin proteins 1c, 1e, Va, and VI and the nonmuscle myosin II [13] (Figure 1). In this review we will examine what is known about the roles that each of these myosins play in the final stages of exocytosis and speculate how these roles may improve our understanding of these phases in the secretory pathway.

Myosin 1

Myosin 1e, a single-headed, long-tailed myosin motor protein, has been shown to play an important role in the final stages of regulated secretion during *Xenopus laevis* oocyte maturation [14]. In response to stimuli that trigger secretion, myosin 1e rapidly relocalizes from a cytosolic pool to the surface of cortical granules to facilitate their subsequent secretion. The localization and function of myosin 1e during cortical granule secretion is believed to be due to its interaction with cysteine string proteins (molecular chaperones), which are well-characterized constituents of granule membranes that play a crucial role in exocytic events. Since myosin 1e is recruited to these granules prior to the onset of secretion, it has been suggested that it functions in a pivotal step in the preexocytic 'approach' stage of granule transport. For example, myosin 1e could mediate the translocation of secretory granules through the dense actin filament network in the cell cortex to position these granules in close proximity to the plasma membrane, enabling the final phases of secretion to occur.

Another member of the class I family of myosins, myosin 1c, has been identified as a crucial motor in the insulin-stimulated secretion of GLUT4-glucose transporter-containing vesicles, enabling glucose to be taken up in adipose [15] and muscle tissue [16]. Myosin 1c is recruited to GLUT4-positive vesicles by its binding partner, the small GTPase RalA [15, 17]. In response to insulin, it actively drives these vesicles through the cortical actin network and anchors them to the actin cytoskeleton beneath the plasma membrane ('approach') [18].

Fusion of the GLUT4-vesicles with the plasma membrane requires phosphatidylinositol(PI)-3-kinase activity. Interestingly, a block in this fusion event caused by a PI-3-kinase inhibitor, can be overridden by overexpression of myosin 1c suggesting that myosin 1c may also have a role during fusion at the plasma membrane in this final step in the secretory pathway [18]. Since myosin 1c is known to drive localized remodeling of the actin cytoskeleton at the cell surface, it is possible that this motor creates fusion hot-spots that speed up GLUT4-vesicle secretion.

Myosin II

There is now extensive evidence that nonmuscle myosin II is implicated in the ‘approach’ and ‘fusion’ steps of the final stages in the secretory pathways. Interestingly it is the myosin IIA isoform that is involved in these events in the apical domain below the plasma membrane [27]. Numerous studies have shown that myosin II modulates the approach of secretory vesicles to the plasma membrane via regulation of the cortical actin filament network; for example, myosin II has been implicated in the regulation of actin filament distribution and reorganization during secretion in adrenal chromaffin cells [19, 20], in the assembly, stabilization, and remodeling of actin filaments in anterior pituitary lactotrophs [21], and in the regulation of cortical actin filaments in parietal cells [22]. In addition, myosin II plays a well-studied role in the ‘fusion’ stage of exocytosis; for example, myosin II has been shown to maintain an open fusion pore in secretory epithelial cells [23], to promote fusion pore expansion in chromaffin cells [24], and to regulate the duration of fusion pore opening in neuroendocrine PC12 cells [25]. It has been suggested that myosin II interacts with the cortical F-actin network to provide the tension necessary to expand the fusion pore for full secretory protein release [26] however so far there is no information on the ‘assembly state/organization’ of the myosin II that could generate this effect. There is a vast array of data on how force generation and filament assembly is regulated by nonmuscle myosin IIs *in vitro*, and thus it will be interesting in the future to determine how these regulatory properties of myosin II control specific steps in the secretory pathways in cells [27]. The combined roles of myosin II in both the ‘approach’ of secretory carriers to the plasma membrane and the actual ‘fusion’ of these carriers with the plasma membrane render this myosin a potentially critical contributor to the dynamics of the late secretory pathway.

Myosin Va

Myosin Va has been strongly linked to three of the four final stages of exocytosis: approach, docking, and priming. A protein well-known for its role in the ‘cooperative capture’ of pigment granules in the actin filament network in melanocytes [28], it has been suggested that myosin Va may play a similar role in the capture, tethering, and transport of secretory vesicles approaching the plasma membrane through the actin cytoskeleton [29]. In particular, myosin Va has been shown to transport secretory granules through the F-actin cortex in pancreatic β -cells [30, 31] and upon stimulation to transport insulin granules toward exocytic sites for the final stages of regulated secretion in INS-1E cells [32]. Furthermore, expression of a dominant negative form of myosin Va (missing the motor domain) causes a reduction or loss of secretory vesicle mobility in the cortical F-actin of PC12 cells [33, 34]. When a vesicle arrives at the plasma membrane, myosin Va plays a further role in mediating the docking of secretory carriers to the membrane itself [35]. As myosin Va has been shown to bind directly to the SNARE proteins syntaxin 1A [36] and VAMP2 [37, 38], this docking function may be based on myosin Va’s roles in the actual formation of SNARE docking complexes or in the binding of secretory carriers to preformed SNARE complexes. In addition to its roles in ‘approach’ and ‘docking,’ myosin Va has been suggested to play a role in the ‘priming’ of docked vesicles for later fusion [28, 32, 38]. The widespread functions of myosin Va throughout the ‘approach,’ ‘docking,’ and ‘priming’

stages of secretion render this protein an important focal point for examining the final stages of the secretory pathway.

Myosin VI

Although the retrograde motor myosin VI has been broadly implicated in the overall process of secretion [39–42], a role for this protein in the final stages of the exocytic pathway is only now emerging. Recent work highlights the interaction between myosin VI and its binding partner optineurin as a control point for regulating the dynamics of the fusion pore formed between the vesicular and plasma membranes in the fourth and final ‘fusion’ stage of the secretory pathway [43]. It has been suggested that the movement of secretory vesicle-bound myosin VI toward the minus ends of actin filaments might provide the tension/force necessary to stabilize or open the fusion pore during constitutive exocytosis [43]. A similar role for myosin VI in the final stages of regulated secretion is intimated by the recent discovery that myosin VI binds to the transmembrane protein otoferlin [44, 45], an exocytic calcium sensor that has been shown to directly regulate SNARE-mediated membrane fusion in auditory hair cells [44, 45]. Although the precise interaction between myosin VI and otoferlin needs to be established, it is possible that the functional interaction between these proteins occurs during the fusion stage of regulated synaptic vesicle exocytosis. Overall, these recent demonstrations that myosin VI is involved in the later stages of the secretory pathway highlights this protein as an interesting target for future studies.

Discussion

Studying the dynamic events that occur in the final stages of the secretory pathway (approach, docking, priming, and fusion) reveals a critical involvement of the myosin motor proteins in these later stages of both regulated and constitutive secretion (Figure 1). Secretory vesicles or granules approaching the plasma membrane are transported by myosin Va, myosin 1e and myosin 1c along an F-actin filament path, probably as a multi-motor complex organized and regulated by myosin II. When the secretory vesicles/granules arrive at their precise location underneath the plasma membrane, they are tethered to the actin cytoskeleton and held in position by myosin 1c. They are then docked to the membrane by the direct interaction between myosin Va and the SNARE docking complex. Priming of these docked vesicles or granules for fusion relies on the membrane remodeling capabilities of myosin Va. Finally, fusion of primed secretory vesicles/granules is modulated by tension-based interactions of myosin VI, myosin II, and perhaps even myosin 1c with the F-actin cytoskeleton, which also regulate the dynamics (opening/closing) of the exocytic fusion pore.

The precise details of the involvement of each of these myosins in secretion at the molecular level however, still need to be elucidated. Which of the myosins act primarily as transporters, moving the secretory vesicles/granules to their correct locations in the cell, and which are mainly anchors, flexibly linking them to the dynamic actin (depolymerizing/repolymerizing) cytoskeleton? Could they work in both capacities depending on the identity of their adaptor/binding proteins? Which of their specific adaptor/binding proteins are involved in each precise step? Extensive further work will be required to identify and characterize the precise adaptor/binding protein for each of the myosins in different secretory cells. In addition, since it is likely that the myosins act cooperatively with overlapping functions, it will be necessary to conduct future studies on the joint cellular functions of multiple motors, rather than examining each motor in isolation.

Further detailed studies on the roles of these myosins in secretion are particularly important due to the potential biomedical implications of their involvement in this process. It is possible that diseases linked to malfunctions in the final stages of secretion, such as

Huntington's disease [46] and Alzheimer's disease [47], occur due to functional defects in the role of the myosins in these phases of the secretory pathways. Similarly, diseases arising from the improper function of myosins Ic/Ie/II/Va/VI, such as inclusion body myopathy [48], Griscelli syndrome [49], or hypertrophic cardiomyopathy [50], could arise from an inability of these myosins to function properly in the secretory pathways. Future studies exploring the precise role of these myosins in secretion may therefore help us understand the pathogenesis of many modern diseases.

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Figure 1. Roles played by myosin motor proteins in the final stages of secretion

Secretory vesicles or granules ('carriers') in the final stages of constitutive or regulated exocytosis undergo four discrete stages: 1) approach; 2) docking; 3) priming and 4) fusion. Transfer of carriers through these four stages relies on the actions of many different myosin motor proteins, particularly nonmuscle myosin II and unconventional myosins in classes 1c, 1e, V, and VI. The approach of secretory carriers to the plasma membrane through the F-actin cytoskeleton relies on transport by myosins 1c, 1e, and Va, as well as F-actin reorganization by myosin II. The docking of these carriers to SNARE proteins at the plasma membrane relies on the actions of myosin Va, which binds directly to the SNARE proteins syntaxin 1A and VAMP2. Priming of carriers at the membrane for subsequent fusion relies on carrier membrane remodeling by myosin Va. Finally, the fusion of individual carriers with the membrane is modulated by interactions between myosin II, myosin VI, and possibly myosin 1c with the actin cytoskeleton that produce the force necessary to open or close the fusion pore formed between each carrier and the plasma membrane.