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Potential roles of myosin VI in cell motility

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Abstract

There is now increasing evidence that myosin motor proteins together with the dynamic actin filament machinery and associated adhesion proteins play crucial roles in the events leading to motility at the leading edge of migrating cells. Myosins exist as a large superfamily of diverse ATP-dependent motors and in this review we will focus on the unique minus-end directed myosin VI, briefly discussing its potential functions in cell motility

Keywords

myosin VI; cell motility; actin; membrane protrusion; cancer dissemination

Introduction

Cell migration is a fundamental cellular process crucial for embryonic development, tissue repair, immune response and many other cellular functions. In addition changes in the motile behaviour of cells are associated with many pathological processes such as tumour metastasis, arteriosclerosis and arthritis. Cellular locomotion involves a complex sequence of events coordinating cell polarisation, the formation of extended protrusions in the direction of migration, the assembly of stable adhesions and actin-myosin structures at the leading edge, as well as the disassembly of focal adhesions and retraction at the rear end of the cell [1]. The direction of movement is determined by the leading edge of the cell containing actin-based membrane protrusions such as broad lamellipodia and finger-like filopodia [2]. The formation of these plasma membrane extensions is closely regulated by two different subclasses of Rho-GTPases, Rac and cdc42 [3]. The downstream targets of Rac and cdc42 are the Wiskott-Aldrich syndrome protein (WASP) and WASP-family verprolin-homologous (WAVE) protein, which activate the actin-related proteins 2 and 3 (Arp2/3 complex) and thereby trigger actin polymerisation and the formation of branched actin networks found in lamellipodia [4]. The spatial and temporal coordination of actin polymerisation and the formation of stable contacts with the underlying substrate are believed to generate force to push the plasma membrane forward. In addition, a number of actin-based motor proteins called myosins are also present in the plasma membrane protrusions and there is now increasing evidence that they play essential roles in cell migration [5]. These myosins comprise a diverse superfamily of motors that use the energy derived from ATP hydrolysis to generate force by moving actin filaments. Therefore, to understand how cells move it is important to establish the contributions that myosins make

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at the leading edge of motile cells. In this review, we will focus on the potential roles in cell migration of one of these myosins, namely myosin VI.

Intracellular functions of myosin VI

In the super family of actin based motor proteins myosin VI appears to have unique cellular properties and functions, because it moves towards the minus end of actin filaments, in the opposite direction to all other myosins so far characterized [6]. Myosin VI has the basic myosin domain organization with an N-terminal motor domain, a short neck 'lever arm' region with a single IQ motif that binds calmodulin, a central tail region and a C-terminal cargo-binding domain. In addition myosin VI has a unique insert (the reverse gear) between the motor domain and lever arm that is responsible for its retrograde movement along actin filaments.

Myosin VI was first identified in *Drosophila* in 1992 and has now been shown to be ubiquitously expressed in multicellular organisms [7]. In *Drosophila*, myosin VI has a wide variety of functions; for example, it is involved in membrane remodelling during embryogenesis [8] [9], in border cell migration in the ovary [10], in asymmetric protein localisation in neuroblasts during cell division [11] and in epithelial cell morphogenesis [12] as well as spermatid individualisation [13, 14]. In mammalian cells myosin VI is intimately involved in membrane trafficking pathways and has been localised to endocytic and exocytic membrane compartments such as the trans Golgi network, the recycling compartment as well as clathrin coated pits and vesicles and internalised uncoated endocytic structures [15]. Functional studies have demonstrated that myosin VI is required for steady state organisation of the Golgi complex [16], for post-Golgi membrane traffic [17] and for sorting of transmembrane proteins to the basolateral domain in polarised epithelial cells [18]. Myosin VI also functions in clathrin-mediated endocytosis [19] and mediates delivery of endocytosed cargoes to the recycling compartment [20, 21]. In cells undergoing cytokinesis myosin VI is required for membrane delivery into the cleavage furrow in the final stages of cell-cell abscission [22]. These diverse roles of myosin VI are mediated by interaction with a range of distinct binding partners that have been identified by yeast two-hybrid screens and mass spectrometric analysis of immunoprecipitated myosin VI complexes and confirmed by direct binding assays. For example, targeting of myosin VI to clathrin-coated structures at the plasma membrane requires binding to disabled-2 (Dab2) [23] and the phosphoinositide PIP₂ [24] whereas myosin VI function in the later endocytic and recycling pathway involves binding partners such as glucose transporter binding protein GIPC (for GAIP interacting protein, C terminus) [25] and the Ser/Thr transmembrane protein kinase LMTK2 (for lemur tyrosine kinase 2) [20]. Recruitment of myosin VI to the Golgi complex is mediated by optineurin [17], whereas the interacting proteins Traf6 binding protein (T6BP) and Nuclear Dot protein 52 (NDP52), link myosin VI to vesicles in the perinuclear region of the cell [26].

Myosin VI in cancer cell migration

A number of recent studies have demonstrated that myosin VI is dramatically over-expressed in prostate and ovarian cancer cells and it has been suggested that it causes an increase in the motility of these tumour cells [27] [28]. Changes in cell motility are a prerequisite for cancer cells to migrate from the primary site into surrounding tissues to disseminate and to metastasize. Up to now the best studied example of the role of myosin VI in cell motility is in the migration of border cells in *Drosophila* ovaries [10], which has also served as a paradigm for cancer cell invasion [29]. Initially border cells are a subgroup of polarised follicle epithelial cells with apical and basolateral domains divided by cell-cell junctions. However, when they separate from the epithelium and start migrating, their cell polarity changes from apical/basolateral to planar with a leading and trailing edge and the

cell-cell junction proteins reorganise at the leading edge to facilitate cell movement. At the start of border cell migration myosin VI is recruited into and is required for the formation of extensions at the leading edge of the cell and if myosin VI is missing these protrusions are lost and border cell movement ceases. In these cells myosin VI was isolated in a complex with the adhesion proteins E-cadherin and β -catenin. So one possible model could be that myosin VI by binding to these stationary adhesion complexes in the plasma membrane could develop a protrusive force by pushing actin filaments outwards, while moving itself towards the minus end of actin filaments away from the plasma membrane.

A number of high-grade ovarian cancer cell-lines express an excess of myosin VI compared to normal ovarian tissues[28]. Myosin VI over-expression is clearly linked to an increase in migration in aggressive ovarian tumours, since loss of myosin VI from ovarian carcinoma cells reduces cell spreading and migration *in vitro* and ovarian tumour dissemination *in vivo*. A connection between myosin VI and cancer cell migration has also been established for prostate cancer tissues [27]. Gene expression micro-array analysis of cancerous prostate tissues from 240 patients have identified myosin VI as one of the genes most highly and consistently overexpressed. Also in prostate cancer the overexpressed myosin VI may stimulate the motility and invasive capability of these cells, since loss of myosin VI from prostate cancer cell lines decreases their migration *in vitro*.

Molecular function of myosin VI in cell migration?

Although myosin VI is clearly required for cell migration in cancer cells, further work is needed to understand the molecular mechanism and regulation of myosin VI function in cell motility in mammalian cells. So in the following sections we will briefly discuss what is known about the molecular role of myosin VI and how it might function in cell migration.

1. Is myosin VI required for maintenance of cell polarity and cell-cell contact sites?

In both mammalian and *Drosophila* cells it has been shown that myosin VI has a role in cadherin-based cell-cell adhesion and migration. The cadherin family of proteins regulate cell-cell adhesion during embryonic development and in adult tissues and defects in cadherin expression and function are characteristic of many cancers [30]. In the early stages of cancer development, an increase in cell migration is accompanied by a change in polarity from apical/basolateral to planar and a reorganisation of cell-cell contact sites [31]. As described earlier in migrating *Drosophila* border cells myosin VI binds and stabilises E-cadherin and β -catenin complexes and promotes E-cadherin dependent cell-cell-based migration [10]. During early *Drosophila* embryogenesis myosin VI is crucial for maintenance of cell-cell contacts during dorsal closure [12]. During this process when the epithelia cell layer moves across the amnioserosa, myosin VI is recruited into filopodia and lamellipodia at the leading edge of the moving epithelial sheets. The absence of myosin VI leads to detachment of the cells from the epithelial cell layer and results in defects in movement of this epithelial cell layer.

In mammalian epithelial cells myosin VI has been shown to regulate the maturation of cadherin-dependent cell-cell contacts during polarisation [32]. Myosin VI can be isolated from these cells in a complex together with E-cadherin and vinculin, an actin binding protein that connects adhesion receptors to the actin cytoskeleton. Depletion of myosin VI from these epithelial cells leads to a loss of vinculin from adhesion sites and a weakening of the cadherin adhesion complex and its attachment to the underlying actin belt and this results in a loss of cohesive forces in the epithelial layers, a prerequisite for invasive cancer cell migration.

2. Does myosin VI's involvement in the endocytic and recycling pathways play a role in regulating the polarised distribution of cell adhesion molecules at the leading edge?

During cell migration extracellular matrix receptors such as the integrins are selectively inserted into the leading edge of the cell to form adhesion complexes with the underlying substrate. Substrate adhesion coupled to a protrusive force at the leading edge is then believed to move the cell forward [33]. The temporal and spatial organisation of adhesion receptors at the leading edge are tightly controlled by cycles of polarised receptor endocytosis and recycling and inhibition of endosomal trafficking or recycling disrupts cell polarity and directed migration [34]. We have previously demonstrated that myosin VI has important roles in the endocytic and recycling pathways [21] and recent work has shown that myosin VI and its interacting protein GIPC are involved in the endocytosis of activated $\alpha 5 \beta 1$ integrin, thereby clearly linking myosin VI directly to focal adhesion turnover [35].

3. Is myosin VI required for delivery of transmembrane receptors and extracellular matrix proteases from the Golgi complex to the plasma membrane?

Selective delivery of transmembrane proteins to the leading edge of the cell can also be accomplished by transport of newly synthesised adhesion or signalling receptors in the anterograde secretion pathway from the trans-Golgi network into the lamellipodium [36]. They would replace receptors that have been degraded or left behind still attached to the substrate. This localised delivery of signalling and adhesion receptors would support Rac activation and reorganisation of the actin cytoskeleton network at the leading edge of the cell. In addition in cancer tissues the secretion of proteases, which modify the extracellular matrix, or the secretion of growth factors and their receptors could facilitate the migration of cancer cells so as to invade and metastasize [31]. We have shown that myosin VI plays an important role in constitutive secretion for delivery of cargo from the Golgi complex to the plasma membrane and identified optineurin as the adaptor protein linking myosin VI to the Golgi complex and its function in this secretory pathway [17]. Further work however is needed to establish whether myosin VI's and optineurin's involvement in this secretory pathway are linked to myosin VI's role in cell migration.

4. Does myosin VI regulate actin filament dynamics at the leading edge of motile cells in analogy to its reported function in the *Drosophila* sperm individualisation process?

Directed migration of a cell depends initially on Rac activation at the leading edge, which then activates the WASP and WAVE family of proteins and thereby triggers Arp2/3-mediated polymerisation of actin filaments that drive plasma membrane protrusions [4]. During spermatogenesis in the *Drosophila* testes myosin VI has been linked to Arp2/3 dependent regulation of actin filament branching [37]. In the testes, cellular reorganisation during sperm individualisation separates a cyst of 64 syncytial spermatids into individual cells each surrounded by a single membrane. This membrane remodelling process is driven by an actin growth cone, which moves from the spermatid heads down to their tails. The front of the actin cone is composed of an Arp2/3 dependent meshwork of actin filaments, whereas the rear end of the cone contains the actin-bundling proteins villin and fascin, which generate a parallel array of actin filaments. The actin network of the individualisation cone shares certain features with a lamellipodia at the leading edge of a migrating cell, however, the direction of actin polymerisation and filament orientation are reversed. In the lamellipodia the fast polymerising barbed ends of actin filaments face outward towards the plasma membrane whereas in the *Drosophila* growth cone the opposite pointed ends of the actin filaments face outwards. As expected for a reverse motor, myosin VI accumulates at the front of the growth cone containing the pointed ends of the actin filaments. The loss of myosin VI in *Drosophila* testis leads to a loss of actin filaments as well as actin regulatory proteins such as cortactin and Arp2/3 from the growth cone and consequently leads to

defects in sperm individualisation. These observations suggest that myosin VI may regulate actin dynamics in *Drosophila* testes by either tethering cortactin and Arp2/3 directly in the actin cone or by recruiting into the front part of the actin cone signalling molecules that activate the Arp2/3 complex, such as a Rac-activating factor or Rac itself [38] [37].

In mammalian cells myosin VI is linked to regions of the cells characterised by highly dynamic actin remodelling. Myosin VI is recruited into membrane ruffles at the leading edge of human epidermoid carcinoma cells (A431) that have been induced to ruffle by epidermal growth factor (EGF). EGF stimulation leads to a fourfold increase in the level of myosin VI phosphorylation in the motor domain [39]. *In vitro* results suggest that p21-activated kinase (PAK), which is a down stream effector of Rac and has been shown to be important for cell motility in mammalian cells [40], may be responsible for phosphorylation of myosin VI *in vivo* at a threonine residue (T405) within the actin binding region in the motor domain [39]. Phosphorylation at the threonine residue in the corresponding position in *Acanthamoeba* myosins IA and IB regulates their actin-activated ATPase activities [41], however whether phosphorylation at this site regulates myosin VI activity *in vivo* still needs to be established.

In conclusion the dual roles of myosin VI in the maintenance of cadherin-containing cell-cell contacts and in integrin receptor recycling might coordinate the epithelial-mesenchymal transition (loss of cell-cell contact) with the initiation of integrin-dependent cell migration. In addition the reported association of myosin VI with membrane ruffles and with the machinery involved in regulating actin polymerisation suggests that myosin VI may play a central role in coordinating various aspects of the complex process of cell migration. Obviously further work is needed to establish whether a single or a series of overlapping myosin VI functions are required for cell migration. In addition although ample evidence supports a role for myosin VI in cell migration, detailed studies are needed to elucidate the exact molecular mechanisms and interacting proteins involved in myosin VI-dependent protrusion and ruffle formation.

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Abbreviations

WASP	Wiskott-Aldrich syndrome protein
WAVE	WASP-family verprolinhomologous protein
Arp2/3 complex	actin-related proteins 2 and 3
Dab2	disabled-2
GIPC	GAIP interacting protein, C terminus
LMTK2	lemur tyrosine kinase 2
T6BP	Traf6 binding protein
NDP52	Nuclear Dot protein 52
EGF	epidermal growth factor
PAK	p21-activated inase

References

1. Ridley AJ, Schwartz MA, Burridge K, Firtel RA, Ginsberg MH, Borisy G, Parsons JT, Horwitz AR. Cell migration: integrating signals from front to back. *Science*. 2003; 302:1704–1709. [PubMed: 14657486]
2. Chhabra ES, Higgs HN. The many faces of actin: matching assembly factors with cellular structures. *Nat Cell Biol*. 2007; 9:1110–1121. [PubMed: 17909522]
3. Heasman SJ, Ridley AJ. Mammalian Rho GTPases: new insights into their functions from in vivo studies. *Nat Rev Mol Cell Biol*. 2008; 9:690–701. [PubMed: 18719708]
4. Pollard TD, Borisy GG. Cellular motility driven by assembly and disassembly of actin filaments. *Cell*. 2003; 112:453–465. [PubMed: 12600310]
5. Conti MA, Adelstein RS. Nonmuscle myosin II moves in new directions. *J Cell Sci*. 2008; 121:11–18. [PubMed: 18096687]
6. Wells AL, Lin AW, Chen LQ, Safer D, Cain SM, Hasson T, Carragher BO, Milligan RA, Sweeney HL. Myosin VI is an actin-based motor that moves backwards. *Nature*. 1999; 401:505–508. [PubMed: 10519557]
7. Kellerman KA, Miller KG. An unconventional myosin heavy chain gene from *Drosophila melanogaster*. *J Cell Biol*. 1992; 119:823–834. [PubMed: 1429838]
8. Deng W, Leaper K, Bownes M. A targeted gene silencing technique shows that *Drosophila* myosin VI is required for egg chamber and imaginal disc morphogenesis. *J Cell Sci*. 1999; 112(Pt 21): 3677–3690. [PubMed: 10523504]
9. Mermall V, Miller KG. The 95F unconventional myosin is required for proper organization of the *Drosophila* syncytial blastoderm. *J Cell Biol*. 1995; 129:1575–1588. [PubMed: 7790355]
10. Geisbrecht ER, Montell DJ. Myosin VI is required for E-cadherin-mediated border cell migration. *Nat Cell Biol*. 2002; 4:616–620. [PubMed: 12134162]
11. Petritsch C, Tavasani G, Turck CW, Jan LY, Jan YN. The *Drosophila* myosin VI Jaguar is required for basal protein targeting and correct spindle orientation in mitotic neuroblasts. *Dev Cell*. 2003; 4:273–281. [PubMed: 12586070]
12. Millo H, Leaper K, Lazou V, Bownes M. Myosin VI plays a role in cell-cell adhesion during epithelial morphogenesis. *Mech Dev*. 2004; 121:1335–1351. [PubMed: 15454264]
13. Hicks JL, Deng WM, Rogat AD, Miller KG, Bownes M. Class VI unconventional myosin is required for spermatogenesis in *Drosophila*. *Mol Biol Cell*. 1999; 10:4341–4353. [PubMed: 10588662]
14. Rogat AD, Miller KG. A role for myosin VI in actin dynamics at sites of membrane remodeling during *Drosophila* spermatogenesis. *J Cell Sci*. 2002; 115:4855–4865. [PubMed: 12432073]
15. Buss F, Kendrick-Jones J. How are the cellular functions of myosin VI regulated within the cell? *Biochem Biophys Res Commun*. 2008; 369:165–175. [PubMed: 18068125]
16. Warner CL, Stewart A, Luzio JP, Steel KP, Libby RT, Kendrick-Jones J, Buss F. Loss of myosin VI reduces secretion and the size of the Golgi in fibroblasts from Snell's waltzer mice. *Embo J*. 2003; 22:569–579. [PubMed: 12554657]
17. Sahlender DA, Roberts RC, Arden SD, Spudich G, Taylor MJ, Luzio JP, Kendrick-Jones J, Buss F. Optineurin links myosin VI to the Golgi complex and is involved in Golgi organization and exocytosis. *J Cell Biol*. 2005; 169:285–295. [PubMed: 15837803]
18. Au JS, Puri C, Ihrke G, Kendrick-Jones J, Buss F. Myosin VI is required for sorting of AP-1B-dependent cargo to the basolateral domain in polarized MDCK cells. *J Cell Biol*. 2007; 177:103–114. [PubMed: 17403927]
19. Buss F, Luzio JP, Kendrick-Jones J. Myosin VI, a new force in clathrin mediated endocytosis. *FEBS Lett*. 2001; 508:295–299. [PubMed: 11728438]
20. Aschenbrenner L, Lee T, Hasson T. Myo6 facilitates the translocation of endocytic vesicles from cell peripheries. *Mol Biol Cell*. 2003; 14:2728–2743. [PubMed: 12857860]
21. Chibalina MV, Seaman MN, Miller CC, Kendrick-Jones J, Buss F. Myosin VI and its interacting protein LMTK2 regulate tubule formation and transport to the endocytic recycling compartment. *J Cell Sci*. 2007; 120:4278–4288. [PubMed: 18029400]

22. Arden SD, Puri C, Au JS, Kendrick-Jones J, Buss F. Myosin VI is required for targeted membrane transport during cytokinesis. *Mol Biol Cell*. 2007; 18:4750–4761. [PubMed: 17881731]
23. Morris SM, Arden SD, Roberts RC, Kendrick-Jones J, Cooper JA, Luzio JP, Buss F. Myosin VI binds to and localises with Dab2, potentially linking receptor-mediated endocytosis and the actin cytoskeleton. *Traffic*. 2002; 3:331–341. [PubMed: 11967127]
24. Spudich G, Chibalina MV, Au JS, Arden SD, Buss F, Kendrick-Jones J. Myosin VI targeting to clathrin-coated structures and dimerization is mediated by binding to Disabled-2 and PtdIns(4,5)P(2). *Nat Cell Biol*. 2007; 9:176–183. [PubMed: 17187061]
25. Bunn RC, Jensen MA, Reed BC. Protein interactions with the glucose transporter binding protein GLUT1CBP that provide a link between GLUT1 and the cytoskeleton. *Mol Biol Cell*. 1999; 10:819–832. [PubMed: 10198040]
26. Morriswood B, Ryzhakov G, Puri C, Arden SD, Roberts R, Dendrou C, Kendrick-Jones J, Buss F. T6BP and NDP52 are myosin VI binding partners with potential roles in cytokine signalling and cell adhesion. *J Cell Sci*. 2007; 120:2574–2585. [PubMed: 17635994]
27. Dunn TA, Chen S, Faith DA, Hicks JL, Platz EA, Chen Y, Ewing CM, Sauvageot J, Isaacs WB, De Marzo AM, Luo J. A novel role of myosin VI in human prostate cancer. *Am J Pathol*. 2006; 169:1843–1854. [PubMed: 17071605]
28. Yoshida H, Cheng W, Hung J, Montell D, Geisbrecht E, Rosen D, Liu J, Naora H. Lessons from border cell migration in the Drosophila ovary: A role for myosin VI in dissemination of human ovarian cancer. *Proc Natl Acad Sci U S A*. 2004; 101:8144–8149. [PubMed: 15146066]
29. Naora H, Montell DJ. Ovarian cancer metastasis: integrating insights from disparate model organisms. *Nat Rev Cancer*. 2005; 5:355–366. [PubMed: 15864277]
30. Wheelock MJ, Shintani Y, Maeda M, Fukumoto Y, Johnson KR. Cadherin switching. *J Cell Sci*. 2008; 121:727–735. [PubMed: 18322269]
31. Friedl P, Wolf K. Tumour-cell invasion and migration: diversity and escape mechanisms. *Nat Rev Cancer*. 2003; 3:362–374. [PubMed: 12724734]
32. Maddugoda MP, Crampton MS, Shewan AM, Yap AS. Myosin VI and vinculin cooperate during the morphogenesis of cadherin cell cell contacts in mammalian epithelial cells. *J Cell Biol*. 2007; 178:529–540. [PubMed: 17664339]
33. Gupton SL, Waterman-Storer CM. Spatiotemporal feedback between actomyosin and focal-adhesion systems optimizes rapid cell migration. *Cell*. 2006; 125:1361–1374. [PubMed: 16814721]
34. Caswell P, Norman J. Endocytic transport of integrins during cell migration and invasion. *Trends Cell Biol*. 2008; 18:257–263. [PubMed: 18456497]
35. Valdembri D, Caswell PT, Anderson KI, Schwarz JP, Konig I, Astanina E, Caccavari F, Norman JC, Humphries MJ, Bussolino F, Serini G. Neuropilin-1/GIPC1 signaling regulates alpha5beta1 integrin traffic and function in endothelial cells. *PLoS Biol*. 2009; 7:e25. [PubMed: 19175293]
36. Prigozhina NL, Waterman-Storer CM. Protein Kinase D-mediated anterograde membrane trafficking is required for fibroblast motility. *Curr. Biol*. 2004; 14:88–98. [PubMed: 14738729]
37. Noguchi T, Lenartowska M, Rogat AD, Frank DJ, Miller KG. Proper cellular reorganization during Drosophila spermatid individualization depends on actin structures composed of two domains, bundles and meshwork, that are differentially regulated and have different functions. *Mol Biol Cell*. 2008; 19:2363–2372. [PubMed: 18353976]
38. Noguchi T, Lenartowska M, Miller KG. Myosin VI stabilizes an actin network during Drosophila spermatid individualization. *Mol Biol Cell*. 2006; 17:2559–2571. [PubMed: 16571671]
39. Buss F, Kendrick-Jones J, Lionne C, Knight AE, Cote GP, Paul Luzio J. The localization of myosin VI at the golgi complex and leading edge of fibroblasts and its phosphorylation and recruitment into membrane ruffles of A431 cells after growth factor stimulation. *J Cell Biol*. 1998; 143:1535–1545. [PubMed: 9852149]
40. Sells MA, Boyd JT, Chernoff J. p21-activated kinase 1 (Pak1) regulates cell motility in mammalian fibroblasts. *J Cell Biol*. 1999; 145:837–849. [PubMed: 10330410]
41. Brzeska H, Knaus UG, Wang ZY, Bokoch GM, Korn ED. p21-activated kinase has substrate specificity similar to Acanthamoeba myosin I heavy chain kinase and activates Acanthamoeba myosin I. *Proc Natl Acad Sci U S A*. 1997; 94:1092–1095. [PubMed: 9037011]

Figure.

Possible roles of myosin VI during cell migration. 1. The localisation of myosin VI in the perinuclear region at/around the Golgi complex and its function in the secretory pathway suggests that it might regulate the delivery of newly synthesised adhesion or signalling receptors from the trans-Golgi network into the leading edge. 2. At the plasma membrane and in endosomes myosin VI might participate in cell adhesion receptor endocytosis and recycling. 3. At the leading edge myosin VI could provide a protrusion force by moving towards the minus end of actin filaments and while binding to stationary cell adhesion receptors, it could move the polymerising actin filaments towards the membrane and thus enhance a protrusion. 4. Also at the front of the moving cell myosin VI may recruit Arp2/3 or upstream signalling molecules such as a Rac-activating factor or Rac itself into the leading edge.