How myosin organisation of the actin cytoskeleton contributes to the cancer phenotype

Michelle Peckham

School of Molecular and Cellular Biology, Faculty of Biological Sciences, University of Leeds, Leeds, LS2 9JT
Corresponding author:
E-mail: m.peckham@leeds.ac.uk

School of Molecular and Cellular Biology
Faculty of Biological Sciences
University of Leeds
Leeds
UK
LS2 9JT
Phone: 44 (0)1133434348
Fax: 44 (0)1133434228

Key words: myosin, actin, cytoskeleton

Abstract

The human genome contains 39 genes that encode myosin heavy chains, classified on the basis of their sequence similarity into 12 classes. Most cells express at least 12 different genes, from at least 8 different classes, which are typically composed of several class 1 genes, at least one class 2 gene, and classes 5, 6, 9, 10, 18 and 19. While the different myosin isoforms all have specific and non-overlapping roles in the cell, in combination they all contribute to the organisation of the actin cytoskeleton, and the shape and phenotype of the cell. Over (or under) expression of these different myosin isoforms can have strong effects on actin organisation, cell shape, and contribute to the cancer phenotype as discussed in this review.

Introduction

Myosins are molecular motors that generate force and movement when they interact with filamentous actin, powered by ATP. They consist of a combination of heavy chains (1 or 2) and light chains (usually calmodulin, regulatory or essential light chains, from 1 to 6 in total depending on the myosin isoform). In total, there are 39 genes encoding myosin heavy chains in the human genome, which are organised into 12 classes based on their sequence similarity (Fig. 1). The largest class of myosins is class 2, which contains 13 genes including 9 genes that encode skeletal and cardiac myosin heavy chains, 1 that encodes the smooth muscle myosin heavy chain and 3 that encode non-muscle myosin heavy chains [1, 2]. Class 1 is the next largest class, containing 8 separate genes (1A-H). The remaining genes are subdivided into a further 10 classes (3, 5, 6, 7, 9, 10, 15, 16, 18 and 19) that contain between 1 and 3 genes.

Each myosin is composed of several distinct domains. The N-terminal motor domain contains the actin binding and nucleotide binding regions, and is responsible for the ATP-driven movement along actin filaments. The motor domain is followed by the lever, which binds light chains and amplifies the size of the step that myosin takes as it interacts with actin. The size of this lever varies between myosin isoforms. Following the motor and lever, subsequent domains are more variable, distinctive for each class of myosin [1, 2], and linked to their cellular functions (Fig. 1).

A single mammalian non-muscle cell is well known to express multiple myosin isoforms [3, 4]. Each of these myosin isoforms are specialised for specific cellular roles, with little in the way of overlapping functions. Together with our recent screening of myosin expression by different prostate cancer cell lines [5], it is likely that any particular cell type is likely to express at least 12 different types of myosin isoforms from 8 different classes. These include at least one class 2 myosin (a non-muscle myosin isoform), several class 1 myosins, and myosins from classes 5, 6, 9, 10, 18 and 19. Of the remaining myosin classes, those in class 3, 7 and 15 (Fig. 1) have a much more restricted expression pattern, and are mainly found in the ear and the eye [6-8]. MYO16 (Myr8; Fig. 1) is expressed in most but not all cultured cells [5, 9]. While each myosin isoform has specific roles in cells, they can work together in concert to generate a cellular phenotype. It is therefore important to know which myosin isoforms are expressed in any particular cell and how each of them influences the organisation of the actin cytoskeleton.

The actin cytoskeleton is well known to be important in cancer as discussed in recent reviews on this topic [10-14]. In particular, filopodia, filopodium-like protrusions, and related structures known as invadopodia, are important in driving metastasis. Overexpression of the protein fascin, which bundles actin filaments and is required to form filopodia and related structures, was one of the first filopodial markers associated with aggressive metastatic cancer (reviewed in [11]). Likewise MYO10 is important in both filopodia and invadopodia, and its overexpression has already been linked to several aggressive cancers (reviewed in [11]). In addition to MYO10, there are many examples of individual links between cancers and myosin (recently reviewed in [13]). This review will first provide an brief overview of the different myosin isoforms, and then specifically highlight findings in prostate cancer cells and tissue ([5], Fig 1) in which a comprehensive approach was taken to look at the entire myosin family.

Class 1 myosin isoforms

All myosin 1 isoforms are monomeric, with a single motor domain, lever and a tail domain (Fig. 1) that binds to lipids, linking the plasma membrane and/or vesicles to the F-actin cytoskeleton. 4 of the 8 genes that encode class 1 myosins (MYO1B, MYO1C, MYO1D and MYO1E) are widely expressed, and the remainder (MYO1A, MYO1F, MYO1G, MYO1H) have a more restricted expression pattern. Of the widely expressed myosins, MYO1B is known to regulate actin organisation on post-Golgi carriers [15] and endocytic organelles [16, 17] and it maintains cortical tension at the plasma membrane, where it specifically associates with dynamic, non-tropomyosin containing actin filaments [18, 19]. Its localisation to plasma/vesicular membranes depends on its ability to bind PtdIns(3,4,5)P_3 and PtdIns(4,5)P_2 [20] (Fig. 2A). MYO1C regulates the endocytosis of cadherin [21] and promotes fusion of exocytic vesicles to the plasma membrane [22]. MYO1D is important in the organisation of basal bodies of cilia in epithelial cells of the trachea and the ependyma [23], and is found in the terminal web, and tips of apical microvilli (brush border) of epithelial cells lining the intestine [24]. MYO1E has been implicated in endocytosis, is associated

with the slits formed by podocytes in the kidney, and has been associated with invadopodia [25-27].

Of the class 1 myosins, MYO1B is of particular interest as it is most strongly implicated in metastasis. MYO1B (Myr1/MM1α) [28] is expressed at high levels in metastatic prostate cancer tissue [5] and the metastatic prostate cancer cell line (PC-3), head and neck cancers [29] and melanomas [30]. High levels of MYO1B expression are likely to affect the organization of the actin cytoskeleton. In MYO1B overexpressing cells, MYO1B's ability to bind to lipids in the plasma membrane and to the F-actin cytoskeleton is likely to increase the levels of cortical actin. This may increase the cortical stiffness of these cells enabling them them to migrate more effectively through the extracellular matrix in vivo. We found that knockdown of MYO1B expression in PC-3 cells, increases their spread area, and induces the formation of long, sparse stress fibres (Fig. 2A) [5]. We speculated that this could be consistent with partial re-organisation of cortical actin into stress fibres.

Two further class 1 myosins have also been implicated in metastasis. MYO1F is highly expressed by cells in the immune system [31, 32] and in some cases of infant acute leukaemia, exon 7 or exon 9 of the mixed lineage leukaemia (MLL/KMTA) gene is fused to the second exon of MYO1F [33, 34]. This places approximately the first half of the MLL protein at the N-terminus of MYO1F, disrupting MLL function, and potentially contributing to the increased expression levels of MYO1F found in leukaemic cells [34]. The loss of MYO1F in neutrophils reduces cortical actin, and increases exocytosis of integrin-containing granules and cell adhesion. Thus overexpressing MYO1F may have the opposite effects, thus contributing to the metastatic phenotype in a similar way to MYO1B. In contrast, MYO1A expression levels commonly decrease, rather than increase in colorectal tumours [35]. MYO1A is highly enriched in the microvilli of epithelial cells of the intestine where it links actin bundles to the plasma membrane, and it is important for polarization and differentiation of these cells. Its loss contributes to a re-organisation of the actin cytoskeleton, and dedifferentiation of intestinal epithelial cells, leading to tumour progression (reviewed in [13]).

Class 2 non-muscle (NM) myosin isoforms

Myosin isoforms in class 2 all contain a long coiled-coil tail that enables them to form filaments. In non-muscle cells the non-muscle myosin (NM) isoforms 2A, 2B and 2C form short filaments of ~20-30 molecules, which are about ~200nm long [36]. Moreover, filament formation is highly dynamic [37] and organization of NM2 filaments contributes to cell shape, adhesion and cytokinesis [38, 39]. Inactive NM2 forms a globular shape ('10S' conformation), in which the long extended coiled-coil tail wraps around one of the motor domains (Fig 2B). Phosphorylation of the regulatory light chain (RLC) activates NM2 by abolishing this head-tail interaction. This allows the molecule to adopt an extended ('6S') conformation, which can assemble into filaments, and interact with actin [40].

NM myosin isoforms are important for cell shape, cell adhesion and migration, and thus mis-regulation of their expression and/or organisation can affect the cellular phenotype and contribute to metastasis. Moreover, NM2B was recently shown to be important for nuclear translocation during 3D invasion, while NM2A was required for generating traction forces during intial adhesion and spreading [41]. While no changes to NM2B have so far been reported in cancer, increased expression levels of NM2A have been linked to gastric cancer [42], non small cell lung cancer [43], oesophageal [44] and bladder cancer [45], while decreased levels are associated with squamous cell carcinomas [46], where NM2A was identified as a tumour suppressor. In contrast, expression levels of NM2A were the same for a range of LNCaP, PC3 and DU145 prostate cancer cell lines, and were unchanged in prostate cancer tissues with low and high metastatic potential [5]. However, in highly metastatic prostate cancer (PC-3) cells, the level of NM2A filaments was low, suggesting that while NM2A is expressed, filament formation is inhibited. The reduced number of NM2A filaments is likely to contribute to the low numbers of stress fibres and focal adhesions observed in PC-3 cells.

This raises the important point that the proportion of total NM2A organised into filaments is likely to be important rather than the levels of expression per se. While both increased or decreased levels of NM2A could affect the numbers of NM2A filaments, and thus affect F-actin organisation, a range of other proteins can modulate the extent to which NM2A can form filaments. For example, the

metastasis inducing protein S100A4 binds to NM2A [47] and dissociates NM2A filaments, reducing cell adhesion and increasing cell migration [48]. Intriguing, two other myosin isoforms; MYO9A and MYO18A, can also modulate NM filament organisation, and are implicated in cancer.

MYO9B and MYO18A, modulators of NM2 filament organisation

There are two class 9 genes, MYO9A and MYO9B (Fig. 1), both of which can modulate NM2 myosin filament organisation by specifically inactivating small Rho GTPases. MYO9B is highly expressed in leukocytes and at lower levels in some epithelial cells [3, 49]. MYO9A is highly expressed in ciliated cells in various organs [50]. Both isoforms contain a GTPase activating domain in their tails, which inhibits Rho [51] (Fig. 1, 2B). Inhibition of Rho reduces ROCK (Rho-kinase) activity, which in turn reduces levels of regulatory light chain (RLC) phosphorylation, thereby reducing the numbers of NM2 filaments, and thus numbers of stress fibres (Fig. 2B). In normal cells, MYO9B is mostly associated with the leading edge rather than the rear, where its downregulation of Rho reduces filament formation and allows membrane ruffles to form [52].

High expression levels of MYO9B are associated with metastatic prostate cancer (PC-3) cells, prostate cancer tumours [5], lung [53] and oesophageal cancer (resulting from a single nucleotide polymorphism in intron 28) [54]. The human protein atlas shows MYO9B to be expressed at a high level in a wide range of tumours (http://www.proteinatlas.org/ENSG00000099331-MYO9B/cancer). High levels of MYO9B expression are expected to decrease the extent of NM filament formation, and indeed, we found low numbers of NM2A filaments and a lack of stress-fibres in PC-3 cells, which express high levels of MYO9B (Fig. 2) [5]. MYO9B knockdown increased the number of NM2A filaments, levels of RLC phosphorylation, and cell spread area in PC-3 cells [5]. Thus high levels of MYO9B promote actin re-organisation, through a reduction in NM2A filaments, contributing to the cancer phenotype by promoting stress fibre disassembly and reducing cell adhesion, thereby promoting metastasis.

MYO18A also modulates NM2A filament formation [55]. Class 18 contains two genes, MYO18A and MYO18B, which show a similar domain organisation (Fig. 1). MYO18A is widely expressed, while MYO18B is highly expressed in striated muscle where it localises to Z-discs [56], but expressed at low levels in other tissues [57]. Knockout of MYO18B is embryonic lethal in mice [58], caused by major effects on myofilament formation in the heart. A mutation (S2302*) in MYO18B in humans, which truncates the protein and results in near loss of the protein through nonsense mediated decay, causes skeletal muscle myopathy [59]. Unlike most other myosin isoforms, MYO18A does not have an active motor domain, lacking key residues in regions of the molecule important for ATP hydrolysis for example [60-62]. From their sequence similarity, it is likely that MYO18B does not have an active motor domain either. MYO18A contains a long region of coiled coil, but has been shown to be unable to form filaments [63]. However, it can co-polymerise with filamentous NM2A through its coiled-coil domain, and this interaction reduces the number of NM2A molecules in, and thus the length of, the NM2A filaments [63]. The N-terminal PDZ domain of MYO18A binds to membrane proteins that can localize NM2A filaments to the plasma membrane [63] (Fig. 1, 2D).

MYO18A is overexpressed in metastatic prostate cancer (PC-3) cells, and this is likely to contribute to the reduction in NM2A stress fibres, and predominant localisation of NM2A close to the plasma membrane that we observed in these cells (Fig. 2D) [5]. Knockdown of MYO18A in PC-3 cells increased the cell-spread area, and markedly increased formation of centripetally organised NM2A filaments in the lamella consistent with its effects on NM2A filament formation (Fig. 2D). However, MYO18A was not overexpressed in prostate cancer tissues, and so far has not been associated with other cancers. In contrast, MYO18B, has been identified as a tumour suppressor gene, with loss of expression, deletions and/or mutations reported for a lung cancer cell line, and malignant pleural mesothelioma [64] as well as ovarian [65] and other lung cancers [57, 66], melanoma and pancreatic carcinoma [67]. Restoration of MYO18B expression in the lung cancer cell line H1299 inhibited anchorage independent growth and motility through an interaction with HOMER2 [58]. Of the 18 missense mutations in MYO18B associated with lung cancers [57], one (R661W) is in the P-loop, the sequence of which is GRSGAGKT for MYO18B, compared to the conserved sequence of GESGAGKT for the majority of myosin isoforms. It is unclear how this mutation would affect function, given that MYO18B is unlikely to have an active ATPase, and still

generally unclear how MYO18B acts as a tumour suppressor, unless it too is able to modulate NM2 filament formation.

Class 5, 6, 10 and 19 myosin isoforms

The remaining widely-expressed myosin isoforms all play a role in trafficking. Class 5 myosins, which are dimeric, have a range of functions. A specific splice isoform of MYO5A traffics melanosomes, pigment granules found in melanocytes [68], whereas in the brain MYO5A traffics the endoplasmic reticulum in neurones [69]. MYO5B traffics recycling endosomes (reviewed in [70]). MYO5C is highly expressed in epithelial cells, where it is found in F-actin rich apical regions, and it has also been implicated in melanosome and secretory granule trafficking [71-73]. MYO6 is unusual in that it is the only 'backwards' motor, moving towards the pointed end of actin filaments and not the barbed end [74]. It has diverse functional roles including endocytosis, in which it is recruited to clathrin coated vesicles through its globular tail domain (Fig. 1) by Dab2, and secretion, in which it is recruited to the Golgi through its globular tail domain via optineurin, and autophagy [75]. MYO6 can also bind to phosphoinositides [76]. MYO19 (Fig. 1) is less well studied, but was recently shown to traffic mitochondria [77], and it can position them towards the tips of starvation-induced filopodia [78].

MYO10 is required for filopodia formation [79, 80], thin actin-rich protrusions that are important for cell migration [81], often termed the 'pathfinders' of the cell. Overexpression of MYO10 is well known to result in high numbers of filopodia which are important for cell migration. Filopodia are stabilised by integrins present at the tips of filopodia, and these integrins are trafficked and held at the filopodial tips by MYO10 [82]. MYO10 has also been implicated in phagocytosis [83] and in epithelial junction assembly [84]. It localises to the plasma membrane through its pleckstrin homology (PH) domains (Fig. 2). Myo10 contains three PH domains (Fig. 1), of which the first one is split, with the second domain emerging from a loop in the first. These domains bind to PtdIns(3,4,5)P_3 [83, 85] and can also bind to PtdIns(3,5)P_2 and to PtdIns(4,5)P_2 (the latter with lower affinity) [86]). The PH domains are followed by a myosin tail homology (MyTH) 4 domain, and a Four point one Ezrin Radixin Moesin (FERM) domain (Fig. 1). The MyTH4 domain has been shown to interact with microtubules [87], and the FERM domain with integrins [82].

Myosin 5 isoforms have been associated with various cancers. MYO5A expression levels are increased in colorectal cancer in response to the transcription factor Snail [88], and it was suggested that its interaction with the pro-apoptotic protein Bmf, helps to prevent apoptosis as cells become less adhesive and invade the surrounding tissue. Decreased levels of MYO5B are associated with gastric cancer [89, 90] and microvillus inclusion disease, a rare homozygous recessive disease [91]. Loss of MYO5B affects apical cargo protein transport in intestinal cells, which in turn causes intestinal brush border atrophy. A similar mechanism could lead to dedifferentiation and tumour progression in patients with colorectal and gastric cancer. MYO5C was expressed by all three prostate cancer cell lines we tested (LNCaP, PC-3, and DU145), and its levels were similar in each of these [5]. MYO5A was additionally expressed in DU145 cells, and a GEO analysis appeared to show an increase in MYO5A expression (at the RNA level) in tumours, but not in metastatic cells (unpublished). It would be interesting to determine if a loss of MYO5A might contribute to metastasis in prostate (or other) cancers.

MYO6 is overexpressed in lung [92] and breast cancer [93], hepatocellular carcinoma [94], high grade ovarian carcinomas [95] and in prostate cancers (specifically medium-grade cancers, rather than more aggressive types [96], [5]). The 3' UTR of MYO6 has been reported to be a target for miR-143 and miR-145 in prostate cancer, both of which are downregulated in cancerous tissue [97], providing a mechanism by which MYO6 levels can increase. However, levels of MYO6 are only high in one of the three commonly used prostate cancer cell lines (LNCaP) [5]. In LNCaP cells, MYO6 is mostly associated with recycling endosomes and not endocytic vesicles or the Golgi, likely due to the reduced levels of Dab2 and optineurin in these cells, and it increases secretion of PSA and VEGF, which may increase cell motility [98] and thus enhance metastasis. Decreasing MYO6 expression in hepatocellular carcinoma, lung and breast cancer cell lines, decreases proliferation and blocks cell cycle progression and activates stress response signalling pathways in hepatocellular carcinoma cell lines [94].

It is becoming clear that MYO10 is likely to play a key role in several cancers. MYO10 expression levels are increased in breast cancer [99, 100], lung adenocarcinoma [101], non-small lung cell cancers [102], and prostate cancer tissues and metastatic prostate cancer cell lines (e.g. PC-3) [5]. Knockdown of MYO10 in the prostate cancer cell line (PC-3) ablated filopodia, reduced cell motility, increased cell spread area and initiated the formation of F-actin bundles in the centre of the cell (Fig. 1C) [5]. As the actin bundling protein fascin is also overexpressed in prostate cancer [103], we speculated that when MYO10 is knocked down in PC-3 cells, fascin mislocalises and bundles actin filaments in the cell body. Overexpression levels of MYO10 have been linked to a reduction in levels of miR-340 [104] and to an interaction with mutant p53 [99] in breast cancer. However, we did not find a link between mutant p53 and MYO10 in prostate cancer cells [5].

Much less is known about any association between MYO19 and cancer. In our experiments, we did not find any changes in expression of MYO19 in prostate cancer cell lines [5]. However, a recent report of a linkage analysis for part of chromosome 17 identified MYO19 as a possible candidate for Glioma, with 2 missense mutations identified [105]. However, the chromosome positions reported currently appear to map to an upstream lincRNA and not to the MYO19 gene. In a breast cancer cell line BT-474, the first 30 basepairs encoding SKA2 are fused to the 382nd basepair in the coding sequence of MYO19B [106]. The resulting fusion is out of frame for MYO19, and this is likely to lead to a loss of functional MYO19B [106], which would be expected to disrupt mitochondrial trafficking.

Conclusion

Overall, many different myosins have now been implicated in cancer, as tumour suppressors, through overexpression, or through mutant isoforms/gene fusions. While many of these studies have identified these myosins as candidate genes, very little work has been performed to understand how these proteins contribute to the metastatic process, and in particular to effects on the organisation of the actin cytoskeleton, which is important in both maintaining the differentiated state in normal cells, and in promoting the metastatic phenotype in cancerous cells. Moreover, more than one myosin could contribute to any cancer phenotype, as we showed for prostate cancer. Overexpression, loss of expression, or mutations in these proteins would all be expected to affect actin organisation, promoting de-differentiation, tumour progression and/or metastasis. A clear example of this, is the link between MYO10 and filopodia formation. In addition, modulating non-muscle myosin 2 organisation, through MYO18A (or B) and MYO9B is also likely to contribute to cell adhesion and migration. Overexpression of class 1 myosins, and in particular MYO1B, affects cortical actin organisation, possibly resulting in a stiffer acto-myosin cortex. Working in concert, disruption to normal myosin expression levels can contribute to a reduced cell-substrate adhesion (through a reduction in stress fibres), an increased ability to navigate a path via an increased number of filopodia, and a stiffer acto-myosin cortex, to increase the ability of these cells to migrate through a 3D matrix. Thus, the mechanism by which different myosin isoforms contribute to organising the actin cytoskeleton shapes the cells, and can contribute to the cancer phenotype.

Acknowledgements
MP would like to acknowledge funding for her work on myosin including a Yorkshire Cancer Research pilot grant MS/JF/LPP044, a CRUK studentship (C37059/A11941), the MRC DTP for a studentship, the Wellcome Trust for funding a confocal (WT104918MA), and the BBSRC (BB/I007423/1) for funding research into myosin. She would like to express her thanks to Steve Baldwin, for his support and help with MP's research during her time at Leeds. He is much missed.

References

1 Berg, J. S., Powell, B. C. and Cheney, R. E. (2001) A millennial myosin census. Mol Biol Cell. **12**, 780-794

2 Peckham, M. (2011) Coiled coils and SAH domains in cytoskeletal molecular motors. Biochem Soc Trans. **39**, 1142-1148

3 Bement, W. M., Hasson, T., Wirth, J. A., Cheney, R. E. and Mooseker, M. S. (1994) Identification and overlapping expression of multiple unconventional myosin genes in vertebrate cell types. Proc Natl Acad Sci U S A. **91**, 6549-6553

4 Wells, C., Coles, D., Entwistle, A. and Peckham, M. (1997) Myogenic cells express multiple myosin isoforms. J Muscle Res Cell Motil. **18**, 501-515

5 Makowska, K. A., Hughes, R. E., White, K. J., Wells, C. M. and Peckham, M. (2015) Specific Myosins Control Actin Organization, Cell Morphology, and Migration in Prostate Cancer Cells. Cell Rep. **13**, 2118-2125

6 Dose, A. C. and Burnside, B. (2000) Cloning and chromosomal localization of a human class III myosin. Genomics. **67**, 333-342

7 Hasson, T., Heintzelman, M. B., Santos-Sacchi, J., Corey, D. P. and Mooseker, M. S. (1995) Expression in cochlea and retina of myosin VIIa, the gene product defective in Usher syndrome type 1B. Proc Natl Acad Sci U S A. **92**, 9815-9819

8 Wang, A., Liang, Y., Fridell, R. A., Probst, F. J., Wilcox, E. R., Touchman, J. W., Morton, C. C., Morell, R. J., Noben-Trauth, K., Camper, S. A. and Friedman, T. B. (1998) Association of unconventional myosin MYO15 mutations with human nonsyndromic deafness DFNB3. Science. **280**, 1447-1451

9 Patel, K. G., Liu, C., Cameron, P. L. and Cameron, R. S. (2001) Myr 8, a novel unconventional myosin expressed during brain development associates with the protein phosphatase catalytic subunits 1alpha and 1gamma1. J Neurosci. **21**, 7954-7968

10 Arjonen, A., Kaukonen, R. and Ivaska, J. (2011) Filopodia and adhesion in cancer cell motility. Cell Adh Migr. **5**, 421-430

11 Courson, D. S. and Cheney, R. E. (2015) Myosin-X and disease. Exp Cell Res. **334**, 10-15

12 Gross, S. R. (2013) Actin binding proteins: their ups and downs in metastatic life. Cell Adh Migr. **7**, 199-213

13 Ouderkirk, J. L. and Krendel, M. (2014) Non-muscle myosins in tumor progression, cancer cell invasion, and metastasis. Cytoskeleton (Hoboken). **71**, 447-463

14 Paz, H., Pathak, N. and Yang, J. (2014) Invading one step at a time: the role of invadopodia in tumor metastasis. Oncogene. **33**, 4193-4202

15 Almeida, C. G., Yamada, A., Tenza, D., Louvard, D., Raposo, G. and Coudrier, E. (2011) Myosin 1b promotes the formation of post-Golgi carriers by regulating actin assembly and membrane remodelling at the trans-Golgi network. Nat Cell Biol. **13**, 779-789

16 Cordonnier, M. N., Dauzonne, D., Louvard, D. and Coudrier, E. (2001) Actin filaments and myosin I alpha cooperate with microtubules for the movement of lysosomes. Mol Biol Cell. **12**, 4013-4029

17 Raposo, G., Cordonnier, M. N., Tenza, D., Menichi, B., Durrbach, A., Louvard, D. and Coudrier, E. (1999) Association of myosin I alpha with endosomes and lysosomes in mammalian cells. Mol Biol Cell. **10**, 1477-1494

18 Coluccio, L. M. and Geeves, M. A. (1999) Transient kinetic analysis of the 130-kDa myosin I (MYR-1 gene product) from rat liver. A myosin I designed for maintenance of tension? J Biol Chem. **274**, 21575-21580

19 Tang, N. and Ostap, E. M. (2001) Motor domain-dependent localization of myo1b (myr-1). Curr Biol. **11**, 1131-1135

20 Komaba, S. and Coluccio, L. M. (2010) Localization of myosin 1b to actin protrusions requires phosphoinositide binding. J Biol Chem. **285**, 27686-27693

21 Tokuo, H. and Coluccio, L. M. (2013) Myosin-1c regulates the dynamic stability of E-cadherin-based cell-cell contacts in polarized Madin-Darby canine kidney cells. Mol Biol Cell. **24**, 2820-2833

22 Bose, A., Robida, S., Furcinitti, P. S., Chawla, A., Fogarty, K., Corvera, S. and Czech, M. P. (2004) Unconventional myosin Myo1c promotes membrane fusion in a regulated exocytic pathway. Mol Cell Biol. **24**, 5447-5458

23 Hegan, P. S., Ostertag, E., Geurts, A. M. and Mooseker, M. S. (2015) Myosin Id is required for planar cell polarity in ciliated tracheal and ependymal epithelial cells. Cytoskeleton (Hoboken). **72**, 503-516
24 Benesh, A. E., Nambiar, R., McConnell, R. E., Mao, S., Tabb, D. L. and Tyska, M. J. (2010) Differential localization and dynamics of class I myosins in the enterocyte microvillus. Mol Biol Cell. **21**, 970-978
25 Krendel, M., Osterweil, E. K. and Mooseker, M. S. (2007) Myosin 1E interacts with synaptojanin-1 and dynamin and is involved in endocytosis. FEBS Lett. **581**, 644-650
26 Mele, C., Iatropoulos, P., Donadelli, R., Calabria, A., Maranta, R., Cassis, P., Buelli, S., Tomasoni, S., Piras, R., Krendel, M., Bettoni, S., Morigi, M., Delledonne, M., Pecoraro, C., Abbate, I., Capobianchi, M. R., Hildebrandt, F., Otto, E., Schaefer, F., Macciardi, F., Ozaltin, F., Emre, S., Ibsirlioglu, T., Benigni, A., Remuzzi, G., Noris, M. and PodoNet, C. (2011) MYO1E mutations and childhood familial focal segmental glomerulosclerosis. N Engl J Med. **365**, 295-306
27 Ouderkirk, J. L. and Krendel, M. (2014) Myosin 1e is a component of the invadosome core that contributes to regulation of invadosome dynamics. Exp Cell Res. **322**, 265-276
28 Gillespie, P. G., Albanesi, J. P., Bahler, M., Bement, W. M., Berg, J. S., Burgess, D. R., Burnside, B., Cheney, R. E., Corey, D. P., Coudrier, E., de Lanerolle, P., Hammer, J. A., Hasson, T., Holt, J. R., Hudspeth, A. J., Ikebe, M., Kendrick-Jones, J., Korn, E. D., Li, R., Mercer, J. A., Milligan, R. A., Mooseker, M. S., Ostap, E. M., Petit, C., Pollard, T. D., Sellers, J. R., Soldati, T. and Titus, M. A. (2001) Myosin-I nomenclature. J Cell Biol. **155**, 703-704
29 Ohmura, G., Tsujikawa, T., Yaguchi, T., Kawamura, N., Mikami, S., Sugiyama, J., Nakamura, K., Kobayashi, A., Iwata, T., Nakano, H., Shimada, T., Hisa, Y. and Kawakami, Y. (2015) Aberrant Myosin 1b Expression Promotes Cell Migration and Lymph Node Metastasis of HNSCC. Mol Cancer Res. **13**, 721-731
30 Singh, C. K., George, J., Nihal, M., Sabat, G., Kumar, R. and Ahmad, N. (2014) Novel downstream molecular targets of SIRT1 in melanoma: a quantitative proteomics approach. Oncotarget. **5**, 1987-1999
31 Kim, S. V., Mehal, W. Z., Dong, X., Heinrich, V., Pypaert, M., Mellman, I., Dembo, M., Mooseker, M. S., Wu, D. and Flavell, R. A. (2006) Modulation of cell adhesion and motility in the immune system by Myo1f. Science. **314**, 136-139
32 Patino-Lopez, G., Aravind, L., Dong, X., Kruhlak, M. J., Ostap, E. M. and Shaw, S. (2010) Myosin 1G is an abundant class I myosin in lymphocytes whose localization at the plasma membrane depends on its ancient divergent pleckstrin homology (PH) domain (Myo1PH). J Biol Chem. **285**, 8675-8686
33 Duhoux, F. P., Ameye, G., Libouton, J. M., Bahloula, K., Iossifidis, S., Chantrain, C. F., Demoulin, J. B. and Poirel, H. A. (2011) The t(11;19)(q23;p13) fusing MLL with MYO1F is recurrent in infant acute myeloid leukemias. Leuk Res. **35**, e171-172
34 Taki, T., Akiyama, M., Saito, S., Ono, R., Taniwaki, M., Kato, Y., Yuza, Y., Eto, Y. and Hayashi, Y. (2005) The MYO1F, unconventional myosin type 1F, gene is fused to MLL in infant acute monocytic leukemia with a complex translocation involving chromosomes 7, 11, 19 and 22. Oncogene. **24**, 5191-5197
35 Mazzolini, R., Dopeso, H., Mateo-Lozano, S., Chang, W., Rodrigues, P., Bazzocco, S., Alazzouzi, H., Landolfi, S., Hernandez-Losa, J., Andretta, E., Alhopuro, P., Espin, E., Armengol, M., Tabernero, J., Ramon y Cajal, S., Kloor, M., Gebert, J., Mariadason, J. M., Schwartz, S., Jr., Aaltonen, L. A., Mooseker, M. S. and Arango, D. (2012) Brush border myosin Ia has tumor suppressor activity in the intestine. Proc Natl Acad Sci U S A. **109**, 1530-1535
36 Billington, N., Wang, A., Mao, J., Adelstein, R. S. and Sellers, J. R. (2013) Characterization of three full-length human nonmuscle myosin II paralogs. J Biol Chem. **288**, 33398-33410
37 Shutova, M. S., Spessott, W. A., Giraudo, C. G. and Svitkina, T. (2014) Endogenous Species of Mammalian Nonmuscle Myosin IIA and IIB Include Activated Monomers and Heteropolymers. Curr Biol. **24**, 1958-1968
38 Mogilner, A. and Keren, K. (2009) The shape of motile cells. Curr Biol. **19**, R762-771
39 Vicente-Manzanares, M., Ma, X., Adelstein, R. S. and Horwitz, A. R. (2009) Non-muscle myosin II takes centre stage in cell adhesion and migration. Nat Rev Mol Cell Biol. **10**, 778-790
40 Cross, R. A. (1988) What is 10S myosin for? J Muscle Res Cell Motil. **9**, 108-110

41 Thomas, D. G., Yenepalli, A., Denais, C. M., Rape, A., Beach, J. R., Wang, Y. L., Schiemann, W. P., Baskaran, H., Lammerding, J. and Egelhoff, T. T. (2015) Non-muscle myosin IIB is critical for nuclear translocation during 3D invasion. J Cell Biol. **210**, 583-594
42 Liu, T., Ye, Y., Zhang, X., Zhu, A., Yang, Z., Fu, Y., Wei, C., Liu, Q., Zhao, C. and Wang, G. (2015) Downregulation of nonmuscle myosin IIA expression inhibits migration and invasion of gastric cancer cells via the cJun Nterminal kinase signaling pathway. Mol Med Rep
43 Katono, K., Sato, Y., Jiang, S. X., Kobayashi, M., Nagashio, R., Ryuge, S., Fukuda, E., Goshima, N., Satoh, Y., Saegusa, M. and Masuda, N. (2015) Prognostic significance of MYH9 expression in resected non-small cell lung cancer. PLoS One. **10**, e0121460
44 Xia, Z. K., Yuan, Y. C., Yin, N., Yin, B. L., Tan, Z. P. and Hu, Y. R. (2012) Nonmuscle myosin IIA is associated with poor prognosis of esophageal squamous cancer. Dis Esophagus. **25**, 427-436
45 Xiong, D., Ye, Y. L., Chen, M. K., Qin, Z. K., Li, M. Z., Zhang, H., Xu, L. H., Xu, Z. Z. and Zeng, M. S. (2012) Non-muscle myosin II is an independent predictor of overall survival for cystectomy candidates with early-stage bladder cancer. Oncol Rep. **28**, 1625-1632
46 Schramek, D., Sendoel, A., Segal, J. P., Beronja, S., Heller, E., Oristian, D., Reva, B. and Fuchs, E. (2014) Direct in vivo RNAi screen unveils myosin IIa as a tumor suppressor of squamous cell carcinomas. Science. **343**, 309-313
47 Chen, H., Fernig, D. G., Rudland, P. S., Sparks, A., Wilkinson, M. C. and Barraclough, R. (2001) Binding to intracellular targets of the metastasis-inducing protein, S100A4 (p9Ka). Biochem Biophys Res Commun. **286**, 1212-1217
48 Du, M., Wang, G., Ismail, T. M., Gross, S., Fernig, D. G., Barraclough, R. and Rudland, P. S. (2012) S100P dissociates myosin IIA filaments and focal adhesion sites to reduce cell adhesion and enhance cell migration. J Biol Chem. **287**, 15330-15344
49 Wirth, J. A., Jensen, K. A., Post, P. L., Bement, W. M. and Mooseker, M. S. (1996) Human myosin-IXb, an unconventional myosin with a chimerin-like rho/rac GTPase-activating protein domain in its tail. J Cell Sci. **109 (Pt 3)**, 653-661
50 Thelen, S., Abouhamed, M., Ciarimboli, G., Edemir, B. and Bahler, M. (2015) Rho GAP myosin IXa is a regulator of kidney tubule function. Am J Physiol Renal Physiol. **309**, F501-513
51 Reinhard, J., Scheel, A. A., Diekmann, D., Hall, A., Ruppert, C. and Bahler, M. (1995) A novel type of myosin implicated in signalling by rho family GTPases. EMBO J. **14**, 697-704
52 Hanley, P. J., Xu, Y., Kronlage, M., Grobe, K., Schon, P., Song, J., Sorokin, L., Schwab, A. and Bahler, M. (2010) Motorized RhoGAP myosin IXb (Myo9b) controls cell shape and motility. Proc Natl Acad Sci U S A. **107**, 12145-12150
53 Kong, R., Yi, F., Wen, P., Liu, J., Chen, X., Ren, J., Li, X., Shang, Y., Nie, Y., Wu, K., Fan, D., Zhu, L., Feng, W. and Wu, J. Y. (2015) Myo9b is a key player in SLIT/ROBO-mediated lung tumor suppression. J Clin Invest. **2015**
54 Menke, V., Van Zoest, K. P., Moons, L. M., Pot, R. G., Siersema, P. D., Kuipers, E. J. and Kusters, J. G. (2012) Myo9B is associated with an increased risk of Barrett's esophagus and esophageal adenocarcinoma. Scand J Gastroenterol. **47**, 1422-1428
55 Billington, N., Heissler, S. M., Guzik-Lendrum, S. and Sellers, J. R. (2013) Interaction of myosin 18A with nonmuscle myosin 2. Mol Biol Cell. **24**, 373
56 Salamon, M., Millino, C., Raffaello, A., Mongillo, M., Sandri, C., Bean, C., Negrisolo, E., Pallavicini, A., Valle, G., Zaccolo, M., Schiaffino, S. and Lanfranchi, G. (2003) Human MYO18B, a novel unconventional myosin heavy chain expressed in striated muscles moves into the myonuclei upon differentiation. J Mol Biol. **326**, 137-149
57 Nishioka, M., Kohno, T., Tani, M., Yanaihara, N., Tomizawa, Y., Otsuka, A., Sasaki, S., Kobayashi, K., Niki, T., Maeshima, A., Sekido, Y., Minna, J. D., Sone, S. and Yokota, J. (2002) MYO18B, a candidate tumor suppressor gene at chromosome 22q12.1, deleted, mutated, and methylated in human lung cancer. Proc Natl Acad Sci U S A. **99**, 12269-12274
58 Ajima, R., Kajiya, K., Inoue, T., Tani, M., Shiraishi-Yamaguchi, Y., Maeda, M., Segawa, T., Furuichi, T., Sutoh, K. and Yokota, J. (2007) HOMER2 binds MYO18B and enhances its activity to suppress anchorage independent growth. Biochem Biophys Res Commun. **356**, 851-856
59 Alazami, A. M., Kentab, A. Y., Faqeih, E., Mohamed, J. Y., Alkhalidi, H., Hijazi, H. and Alkuraya, F. S. (2015) A novel syndrome of Klippel-Feil anomaly, myopathy, and characteristic facies is linked to a null mutation in MYO18B. J Med Genet. **52**, 400-404

60 Guzik-Lendrum, S., Heissler, S. M., Billington, N., Takagi, Y., Yang, Y., Knight, P. J., Homsher, E. and Sellers, J. R. (2013) Mammalian myosin-18A, a highly divergent myosin. J Biol Chem. **288**, 9532-9548
61 Guzik-Lendrum, S., Nagy, A., Takagi, Y., Houdusse, A. and Sellers, J. R. (2011) Drosophila melanogaster myosin-18 represents a highly divergent motor with actin tethering properties. J Biol Chem. **286**, 21755-21766
62 Taft, M. H., Behrmann, E., Munske-Weidemann, L. C., Thiel, C., Raunser, S. and Manstein, D. J. (2013) Functional characterization of human myosin-18A and its interaction with F-actin and GOLPH3. J Biol Chem. **288**, 30029-30041
63 Billington, N., Beach, J. R., Heissler, S. M., Remmert, K., Guzik-Lendrum, S., Nagy, A., Takagi, Y., Shao, L., Li, D., Yang, Y., Zhang, Y., Barzik, M., Betzig, E., Hammer, J. A., 3rd and Sellers, J. R. (2015) Myosin 18A coassembles with nonmuscle myosin 2 to form mixed bipolar filaments. Curr Biol. **25**, 942-948
64 Edakuni, N., Ikuta, K., Yano, S., Nakataki, E., Muguruma, H., Uehara, H., Tani, M., Yokota, J., Aizawa, H. and Sone, S. (2006) Restored expression of the MYO18B gene suppresses orthotopic growth and the production of bloody pleural effusion by human malignant pleural mesothelioma cells in SCID mice. Oncol Res. **16**, 235-243
65 Yanaihara, N., Nishioka, M., Kohno, T., Otsuka, A., Okamoto, A., Ochiai, K., Tanaka, T. and Yokota, J. (2004) Reduced expression of MYO18B, a candidate tumor-suppressor gene on chromosome arm 22q, in ovarian cancer. Int J Cancer. **112**, 150-154
66 Tani, M., Ito, J., Nishioka, M., Kohno, T., Tachibana, K., Shiraishi, M., Takenoshita, S. and Yokota, J. (2004) Correlation between histone acetylation and expression of the MYO18B gene in human lung cancer cells. Genes Chromosomes Cancer. **40**, 146-151
67 Bleeker, F. E., Lamba, S., Rodolfo, M., Scarpa, A., Leenstra, S., Vandertop, W. P. and Bardelli, A. (2009) Mutational profiling of cancer candidate genes in glioblastoma, melanoma and pancreatic carcinoma reveals a snapshot of their genomic landscapes. Hum Mutat. **30**, E451-459
68 Wu, X. S., Rao, K., Zhang, H., Wang, F., Sellers, J. R., Matesic, L. E., Copeland, N. G., Jenkins, N. A. and Hammer, J. A., 3rd. (2002) Identification of an organelle receptor for myosin-Va. Nat Cell Biol. **4**, 271-278
69 Wagner, W., Brenowitz, S. D. and Hammer, J. A., 3rd. (2011) Myosin-Va transports the endoplasmic reticulum into the dendritic spines of Purkinje neurons. Nat Cell Biol. **13**, 40-48
70 Trybus, K. M. (2008) Myosin V from head to tail. Cell Mol Life Sci. **65**, 1378-1389
71 Bultema, J. J., Boyle, J. A., Malenke, P. B., Martin, F. E., Dell'Angelica, E. C., Cheney, R. E. and Di Pietro, S. M. (2014) Myosin vc interacts with Rab32 and Rab38 proteins and works in the biogenesis and secretion of melanosomes. J Biol Chem. **289**, 33513-33528
72 Jacobs, D. T., Weigert, R., Grode, K. D., Donaldson, J. G. and Cheney, R. E. (2009) Myosin Vc is a molecular motor that functions in secretory granule trafficking. Mol Biol Cell. **20**, 4471-4488
73 Rodriguez, O. C. and Cheney, R. E. (2002) Human myosin-Vc is a novel class V myosin expressed in epithelial cells. J Cell Sci. **115**, 991-1004
74 Wells, A. L., Lin, A. W., Chen, L. Q., Safer, D., Cain, S. M., Hasson, T., Carragher, B. O., Milligan, R. A. and Sweeney, H. L. (1999) Myosin VI is an actin-based motor that moves backwards. Nature. **401**, 505-508
75 Tumbarello, D. A., Kendrick-Jones, J. and Buss, F. (2013) Myosin VI and its cargo adaptors - linking endocytosis and autophagy. J Cell Sci. **126**, 2561-2570
76 Spudich, G., Chibalina, M. V., Au, J. S., Arden, S. D., Buss, F. and Kendrick-Jones, J. (2007) Myosin VI targeting to clathrin-coated structures and dimerization is mediated by binding to Disabled-2 and PtdIns(4,5)P2. Nat Cell Biol. **9**, 176-183
77 Quintero, O. A., DiVito, M. M., Adikes, R. C., Kortan, M. B., Case, L. B., Lier, A. J., Panaretos, N. S., Slater, S. Q., Rengarajan, M., Feliu, M. and Cheney, R. E. (2009) Human Myo19 is a novel myosin that associates with mitochondria. Curr Biol. **19**, 2008-2013
78 Shneyer, B. I., Usaj, M. and Henn, A. (2015) Myo19 is an Outer Mitochondrial Membrane Motor and Effector of Starvation Induced Filopodia. J Cell Sci
79 Berg, J. S., Derfler, B. H., Pennisi, C. M., Corey, D. P. and Cheney, R. E. (2000) Myosin-X, a novel myosin with pleckstrin homology domains, associates with regions of dynamic actin. J Cell Sci. **113 Pt 19**, 3439-3451

80 Bohil, A. B., Robertson, B. W. and Cheney, R. E. (2006) Myosin-X is a molecular motor that functions in filopodia formation. Proc Natl Acad Sci U S A. **103**, 12411-12416
81 Faix, J. and Rottner, K. (2006) The making of filopodia. Curr Opin Cell Biol. **18**, 18-25
82 Zhang, H., Berg, J. S., Li, Z., Wang, Y., Lang, P., Sousa, A. D., Bhaskar, A., Cheney, R. E. and Stromblad, S. (2004) Myosin-X provides a motor-based link between integrins and the cytoskeleton. Nat Cell Biol. **6**, 523-531
83 Cox, D., Berg, J. S., Cammer, M., Chinegwundoh, J. O., Dale, B. M., Cheney, R. E. and Greenberg, S. (2002) Myosin X is a downstream effector of PI(3)K during phagocytosis. Nat Cell Biol. **4**, 469-477
84 Liu, K. C., Jacobs, D. T., Dunn, B. D., Fanning, A. S. and Cheney, R. E. (2012) Myosin-X functions in polarized epithelial cells. Mol Biol Cell. **23**, 1675-1687
85 Isakoff, S. J., Cardozo, T., Andreev, J., Li, Z., Ferguson, K. M., Abagyan, R., Lemmon, M. A., Aronheim, A. and Skolnik, E. Y. (1998) Identification and analysis of PH domain-containing targets of phosphatidylinositol 3-kinase using a novel in vivo assay in yeast. EMBO J. **17**, 5374-5387
86 Tacon, D., Knight, P. J. and Peckham, M. (2004) Imaging myosin 10 in cells. Biochem Soc Trans. **32**, 689-693
87 Weber, K. L., Sokac, A. M., Berg, J. S., Cheney, R. E. and Bement, W. M. (2004) A microtubule-binding myosin required for nuclear anchoring and spindle assembly. Nature. **431**, 325-329
88 Lan, L., Han, H., Zuo, H., Chen, Z., Du, Y., Zhao, W., Gu, J. and Zhang, Z. (2010) Upregulation of myosin Va by Snail is involved in cancer cell migration and metastasis. Int J Cancer. **126**, 53-64
89 Dong, W., Chen, X., Chen, P., Yue, D., Zhu, L. and Fan, Q. (2012) Inactivation of MYO5B promotes invasion and motility in gastric cancer cells. Dig Dis Sci. **57**, 1247-1252
90 Dong, W., Wang, L. and Shen, R. (2013) MYO5B is epigenetically silenced and associated with MET signaling in human gastric cancer. Dig Dis Sci. **58**, 2038-2045
91 Schneeberger, K., Vogel, G. F., Teunissen, H., van Ommen, D. D., Begthel, H., El Bouazzaoui, L., van Vugt, A. H., Beekman, J. M., Klumperman, J., Muller, T., Janecke, A., Gerner, P., Huber, L. A., Hess, M. W., Clevers, H., van Es, J. H., Nieuwenhuis, E. E. and Middendorp, S. (2015) An inducible mouse model for microvillus inclusion disease reveals a role for myosin Vb in apical and basolateral trafficking. Proc Natl Acad Sci U S A. **112**, 12408-12413
92 Yu, H., Zhu, Z., Chang, J., Wang, J. and Shen, X. (2015) Lentivirus-Mediated Silencing of Myosin VI Inhibits Proliferation and Cell Cycle Progression in Human Lung Cancer Cells. Chem Biol Drug Des. **86**, 606-613
93 Wang, H., Wang, B., Zhu, W. and Yang, Z. (2015) Lentivirus-Mediated Knockdown of Myosin VI Inhibits Cell Proliferation of Breast Cancer Cell. Cancer Biother Radiopharm. **30**, 330-335
94 Ma, X., Yan, J., Chen, W., Du, P., Xie, J., Yu, H. and Wu, H. (2015) Knockdown of Myosin VI Inhibits Proliferation of Hepatocellular Carcinoma Cells In Vitro. Chem Biol Drug Des. **86**, 723-730
95 Yoshida, H., Cheng, W., Hung, J., Montell, D., Geisbrecht, E., Rosen, D., Liu, J. and Naora, H. (2004) 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. **101**, 8144-8149
96 Dunn, T. A., Chen, S., Faith, D. A., Hicks, J. L., Platz, E. A., Chen, Y., Ewing, C. M., Sauvageot, J., Isaacs, W. B., De Marzo, A. M. and Luo, J. (2006) A novel role of myosin VI in human prostate cancer. Am J Pathol. **169**, 1843-1854
97 Szczyrba, J., Loprich, E., Wach, S., Jung, V., Unteregger, G., Barth, S., Grobholz, R., Wieland, W., Stohr, R., Hartmann, A., Wullich, B. and Grasser, F. (2010) The microRNA profile of prostate carcinoma obtained by deep sequencing. Mol Cancer Res. **8**, 529-538
98 Puri, C., Chibalina, M. V., Arden, S. D., Kruppa, A. J., Kendrick-Jones, J. and Buss, F. (2010) Overexpression of myosin VI in prostate cancer cells enhances PSA and VEGF secretion, but has no effect on endocytosis. Oncogene. **29**, 188-200
99 Arjonen, A., Kaukonen, R., Mattila, E., Rouhi, P., Hognas, G., Sihto, H., Miller, B. W., Morton, J. P., Bucher, E., Taimen, P., Virtakoivu, R., Cao, Y., Sansom, O. J., Joensuu, H. and Ivaska, J. (2014) Mutant p53-associated myosin-X upregulation promotes breast cancer invasion and metastasis. J Clin Invest. **124**, 1069-1082

100 Cao, R., Chen, J., Zhang, X., Zhai, Y., Qing, X., Xing, W., Zhang, L., Malik, Y. S., Yu, H. and Zhu, X. (2014) Elevated expression of myosin X in tumours contributes to breast cancer aggressiveness and metastasis. Br J Cancer. **111**, 539-550
101 Bidkhori, G., Narimani, Z., Hosseini Ashtiani, S., Moeini, A., Nowzari-Dalini, A. and Masoudi-Nejad, A. (2013) Reconstruction of an integrated genome-scale co-expression network reveals key modules involved in lung adenocarcinoma. PLoS One. **8**, e67552
102 Sun, Y., Ai, X., Shen, S. and Lu, S. (2015) NF-kappaB-mediated miR-124 suppresses metastasis of non-small-cell lung cancer by targeting MYO10. Oncotarget. **6**, 8244-8254
103 Darnel, A. D., Behmoaram, E., Vollmer, R. T., Corcos, J., Bijian, K., Sircar, K., Su, J., Jiao, J., Alaoui-Jamali, M. A. and Bismar, T. A. (2009) Fascin regulates prostate cancer cell invasion and is associated with metastasis and biochemical failure in prostate cancer. Clin Cancer Res. **15**, 1376-1383
104 Chen, C. P., Sun, Z. L., Lu, X., Wu, W. X., Guo, W. L., Lu, J. J., Han, C., Huang, J. Q. and Fang, Y. (2016) miR-340 suppresses cell migration and invasion by targeting MYO10 in breast cancer. Oncol Rep. **35**, 709-716
105 Jalali, A., Amirian, E. S., Bainbridge, M. N., Armstrong, G. N., Liu, Y., Tsavachidis, S., Jhangiani, S. N., Plon, S. E., Lau, C. C., Claus, E. B., Barnholtz-Sloan, J. S., Il'yasova, D., Schildkraut, J., Ali-Osman, F., Sadetzki, S., Johansen, C., Houlston, R. S., Jenkins, R. B., Lachance, D., Olson, S. H., Bernstein, J. L., Merrell, R. T., Wrensch, M. R., Davis, F. G., Lai, R., Shete, S., Aldape, K., Amos, C. I., Muzny, D. M., Gibbs, R. A., Melin, B. S. and Bondy, M. L. (2015) Targeted sequencing in chromosome 17q linkage region identifies familial glioma candidates in the Gliogene Consortium. Sci Rep. **5**, 8278
106 Edgren, H., Murumagi, A., Kangaspeska, S., Nicorici, D., Hongisto, V., Kleivi, K., Rye, I. H., Nyberg, S., Wolf, M., Borresen-Dale, A. L. and Kallioniemi, O. (2011) Identification of fusion genes in breast cancer by paired-end RNA-sequencing. Genome Biol. **12**, R6
107 Allsop, G. and Peckham, M. (2011) Cytoskeleton and Cell Motility. Comprehensive Biotechnology. **1**, 191-204

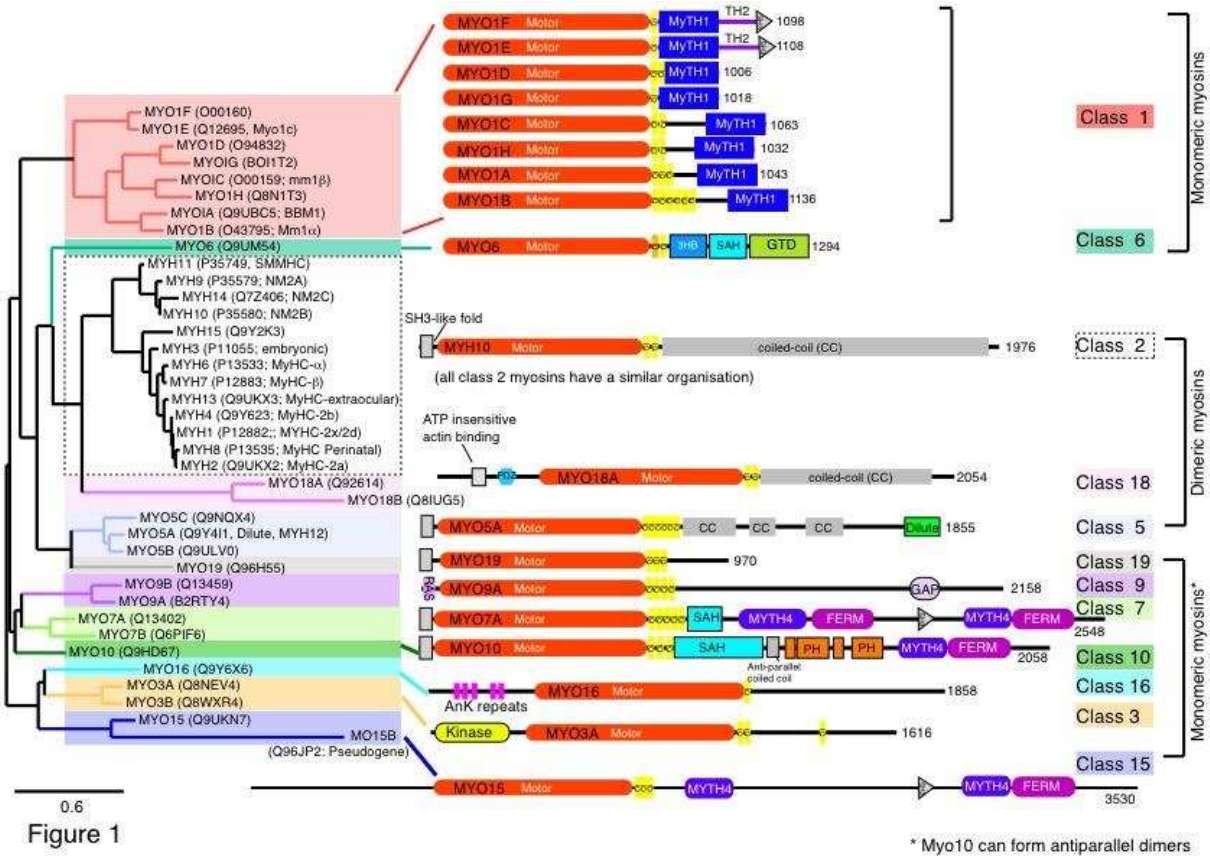

Figure 1

Figure 1. The myosin family tree. An overview of the myosin superfamily, showing the domain organisation for each class, and members within a class where appropriate. The Uniprot reference number is shown in brackets, next to the name of each myosin (adapted from [107]. MyTH: Myosin tail homology. SAH: single alpha helix. FERM: 4.1, Ezrin, Radixin, Moesin. GAP: GTPase activating domain. 3HB: 3 helix bundle. Ank: Ankyrin. SH3: Src Homology 3 (grey triangles). IQ: IQ motifs, to which light chains bind. CC: coiled coil. GTD: globular tail domain.

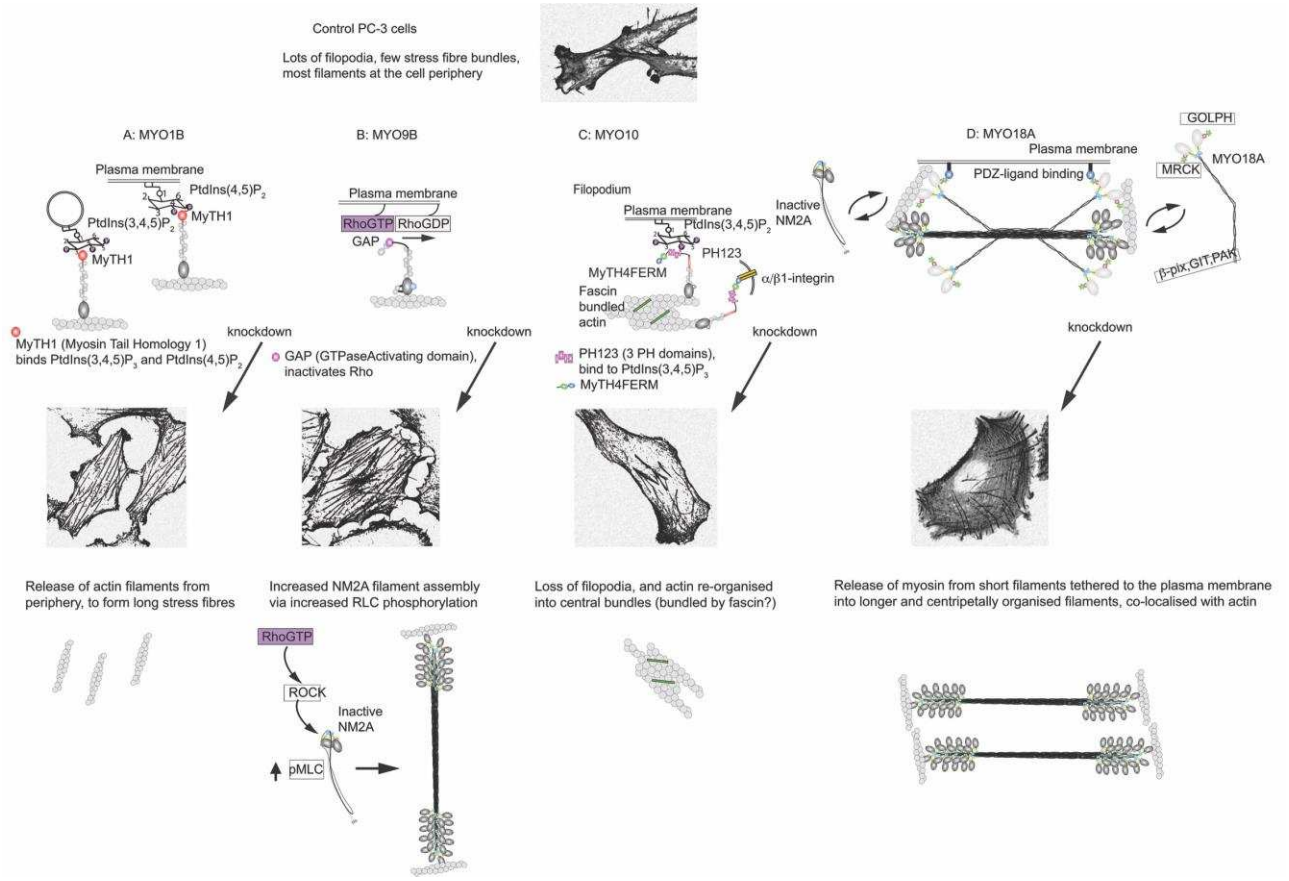

Figure 2. Effects of depleting overexpressed myosin isoforms on actin organization in the prostate cancer cell line PC-3. MYO1B, MYO9B, MYO10 and MYO18A, are all overexpressed in PC3 cells, which have many filopodia, and few stress fibre bundles (as shown at the top of the figure). Knockdown of MYO1B causes formation of long sparse actin stress fibres (A), knockdown of MYO9B (B) increases Rho activity, resulting in increased phosphorylation of the myosin light chain, and increased actin and NM2A filament formation in stress fibres. Knockdown of MYO10 (C) ablates filopodia, and increases F-actin bundles in the cell centre. Knockdown of MYO18A (D) causes an increase in centripetally organized actin and NM2A filaments. The potential mechanism by which this occurs is diagrammed.