Interior decoration
Tropomyosin in actin dynamics and cell migration

Justin G. Lees,1 Cuc T.T. Bach1,2 and Geraldine M. O’Neill1,2,*

1Children’s Cancer Research Unit; Kids Research Institute; The Children’s Hospital at Westmead; Westmead, Australia; 2Discipline of Paediatrics and Child Health; University of Sydney; Sydney, Australia

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Cell migration and invasion requires the precise temporal and spatial orchestration of a variety of biological processes. Filaments of polymerized actin are critical players in these diverse processes, including the regulation of cell anchorage points (both cell-cell and cell-extracellular matrix), the uptake and delivery of molecules via endocytic pathways and the generation of force for both membrane protrusion and retraction. How the actin filaments are specialized for each of these discrete functions is yet to be comprehensively elucidated. The cytoskeletal tropomyosins are a family of actin associating proteins that form head-to-tail polymers which lay in the major groove of polymerized actin filaments. In the present review we summarize the emerging isoform-specific functions of tropomyosins in cell migration and invasion and discuss their potential roles in the specialization of actin filaments for the diverse cellular processes that together regulate cell migration and invasion.

Actin is the most abundant protein in eukaryotic cells and is critical for maintaining structural integrity. The polymerization of globular (G)-actin monomers forms actin filaments (F-actin),1 which play a role in diverse and complex cellular functions including intercellular transport of organelles and vesicles,2,3 cytokinesis,4 apoptosis5 and cell motility.6 Intricate details describing the molecular scale interactions between regulatory proteins and actin have been extensively investigated but the mechanistic control of diverse actin filament functions remain largely unclear. Recent improvements in analysis techniques7 and the use of physiologically relevant models of 3D cell culturing8 have now begun to reveal mechanisms of actin cytoskeleton regulation. Accruing evidence suggests that the actin decorating protein tropomyosin is a key regulator of actin filament specialization. Of particular interest is the impact that tropomyosin regulation has on actin filament activity during cell migration and invasion that underpins immunological cell homing, development, wound healing and metastasis.

A Diverse Palette of Tropomyosins

Tropomyosins are highly abundant proteins found in virtually all life-forms except plants and bacteria.9 Two essential and non-redundant tropomyosin isoforms encoded by separate genes are present in the yeast Saccharomyces cerevisiae.10 The pattern is considerably more complex in vertebrates, with the human genome containing four separate tropomyosin genes: TPM1 (or α-tropomyosin), TPM2 (or β-tropomyosin), TPM3 (or γ-tropomyosin) and TPM4 (or δ-tropomyosin).11 The presence of the same four tropomyosin genes in other vertebrate species, including chickens, indicates that divergence of this gene family took place more than 300 million years ago prior to the separation of birds and mammals.11 Multiple promoters and alternative splicing of up to 15 exons enables the production of at least 40 different tropomyosin isoforms,12 recently comprehensively reviewed in reference 9. Based on their molecular mass, tropomyosins are conventionally referred to as either high (HMW: ~284 amino acids) or low (LMW: ~248 amino acids) molecular weight; however both LMW and HMW isoforms can be expressed from the same gene.13 The failure to produce viable embryos following homozygous deletion of specific exons from the TPM3 gene,14 suggests that these proteins have non-redundant functions.

Tropomyosin Decoration of Actin Filaments

Tropomyosin molecules form dimers containing partially repeated actin binding sequences.15 When associated with actin, tropomyosin forms a coiled polymer in which dimers of tropomyosin associate head to tail and lie in the major groove of the actin filament16 (Fig. 1). The coil is characterized by a heptapeptide amino acid repeat sequence common to all α-helices with the consensus motif -B-N-X-X-N-A-X-, where N indicates non-polar residues, B indicates basic residues and A signifies acidic residues.16,17 Hydrophobic interactions within the coil core and interaction between side chains of amino acids situated in close proximity maintain the stability of the coiled coil. Variability in the positioning of particular amino acid residues at key binding sites is thought to impact the flexibility of the tropomyosin polymer, thereby affecting its ability to interact with F-actin.17,18 Heterodimerization can occur between tropomyosin isoforms from separate genes;19 for example, heterodimerization between α-skeletal muscle isoforms from the TPM1 gene and β-skeletal muscle isoforms from the TPM2 gene are required to maintain...
absolute amounts of many amino acids. At the time the protein was described in 1948 these analysis techniques were the best available and tropomyosin was initially incorrectly thought to be either a precursor of myosin or a unit of the myosin polymer.22 Tropomyosin’s role in skeletal muscle contraction, where it interacts with actin, myosin II and the troponin complex (Fig. 1), has been the subject of extensive investigation.16,23 The thin muscle fibers comprise skeletal tropomyosin in a coiled-coil around actin filament and bound to the troponin complex. The thick muscle fiber is made of multiple myosin II chains that are activated upon binding to actin, creating mechanical activity via an ATP driven power stroke and muscle contraction. Electrical stimulation of Ca²⁺-channels promotes the binding of troponin C to Ca²⁺, shifting the troponin C binding position relative to tropomyosin, in turn altering tropomyosin-binding to the actin filament. The movement of the tropomyosin coiled coil unmasks the myosin II binding site allowing actomyosin contraction to take place.24 Repositioning of the tropomyosin coiled coil in the major groove of the actin filament and consequent regulation of myosin association is thought to be a primary mechanism for tropomyosin determination of actin dynamics.25

In contrast to the stable actin structures controlling muscle contraction, the actin filament system in migrating non-muscle cells is highly dynamic, allowing for rapid and responsive reorganization. Tropomyosins are proposed to contribute to the dynamic state of the actin cytoskeleton by imparting isoform-specific inhibitions of critical actin filament regulators. Current knowledge regarding the effects of individual cytoskeletal tropomyosin isoforms is summarized in Table 1. Certain tropomyosin isoforms compete with or recruit ADF/cofilin binding to F-actin,26-30 while others anneal actin filaments that are severed and capped by gelosin 31,32 and can inhibit the branching and actin polymerization activity of Arp2/3 in vitro.33,34 Different tropomyosin isoforms compete with actin bundling proteins,35 and can also coordinate with caldesmon to inhibit the activity of fascin.36 In contrast, in fission yeast the actin bundling protein fimbrin dissociates tropomyosin from actin filaments, promoting access for ADF/cofilin and potentially other actin regulating proteins.37 Recent data suggest that the association of discrete isoforms with actin filaments can determine the sensitivity to actin depolymerizing drugs such as latrunculin.38 Thus, contrary to the previously held view that tropomyosins universally stabilize...
the actin filament, it is now becoming appreciated these proteins can either increase or decrease the filament stability depending on the associated tropomyosin isoform.

Tropomyosins also bind to members of the tropomodulin protein family at the pointed end of actin filaments and affect cytoskeletal dynamics within both muscle and non-muscle cells. Coordinated activity between tropomyosin and tropomodulin thus decreases the rate of depolymerization at the pointed end, which leads to stabilization of the actin filament.39 The effectiveness of this pointed end capping process is determined by the specific tropomyosin isoform decorating the actin filament.40-41

A Framework for Cell Migration

Specialized actin-based structures create a framework for migrating cells that generates contractile force required for pushing and pulling through complex extracellular environments and regulates cell-cell and cell-extracellular matrix adhesion. Early studies of migrating cells suggested that tropomyosins may be restricted to decorating stable actin filaments located behind the lamellipodia in the lamella region (~2–15 μm behind the cells leading edge).44 Microinjection of skeletal muscle αTm into non-muscle cells inhibited lamellipod formation due to increased stabilization of the actin filaments and exclusion of Arp2/3 and ADF/cofilin from the leading edge. Myosin II activity was significantly increased in the injected cells and both the rate of migration and persistence were increased. Based on these studies, it has been supposed that lack of tropomyosin localization to the leading edge of migrating cells may be important to the characteristic organization of actin at the leading edge (i.e., highly dynamic and branched). However, other studies have suggested that LMW tropomyosin isoforms are detectable in the ruffles of chicken embryo fibroblasts and human bladder carcinoma cells45 and, furthermore, immunohistochemical analysis suggested that both LMW and HMW tropomyosin are present at the leading edge, with LMW isoforms being more concentrated in this region.46 Possibly these discrepant findings may reflect cell-type specific patterns. However, the fact that tropomyosins have been detected at the leading edge of at least some cell types means that we must be cautious in applying a model where a tropomyosin-free compartment at the leading edge of a migrating cell promotes actin dynamics and membrane protrusion. Rather, based on the currently available data, we might envisage a model where restricted targeting of certain isoforms to the leading edge is permissive for the actin dynamics that are involved in membrane ruffling at the leading edge of migrating cells.

Studies of circulating erythrocytes have shown that at the cell membrane LMW tropomyosin from the TMP3 gene and Tm5a from the TPM1 gene form complexes with short actin filaments (~35 nm) which are capped by tropomodulin. These short filaments link together a hexagonal lattice of spectrin, providing a membrane that can withstand the stress and strain of migration throughout the circulatory system.47 However, due to concentrated research efforts in the area of cancer cell migration and invasion that underpins metastatic progression, much of our current knowledge of tropomyosins in migration and invasion has come from investigations of tumor and cancer cell biology. Tumor profiling reveals consistent suppression of HMW tropomyosins during malignant transformation (reviewed in ref. 48). In particular, the HMW isoforms Tm1 and Tm2, from the TPM2 and TPM1 genes respectively, are frequently downregulated or lost.49-50 Both isoforms are predominantly associated with bundles of polymerized actin filaments, known as stress fibers. Current models based on cell migration on 2D surfaces suggest that stress fibers are critical both for the generation of force that allows cells to move forward and retraction of the trailing edge. Importantly, the use of 3D culture models and in vivo imaging of tagged actin,51 have similarly revealed the presence of stress fibers in vivo. Forced re-expression of Tm1 reverts cells to a non-transformed morphology, typically restoring anchorage dependent growth, stress fibers52,53 and decreasing proliferation.54 However, the power of Tm1 to revert transformed cells is not true for all cell types.55-56

It is currently unclear how Tm1 downregulation might be mechanistically associated with malignant progression and increased invasion and metastasis. One potential mechanism can be envisaged based on the fact that Tm1 restoration precipitates
metalloproteases and a host of other signaling and structural molecules to the leading edge. While kinesin- and dynein-mediated transport along microtubules is a well-established trafficking mechanism, it is becoming increasingly clear that the actin filament system also operates as an important pathway for trafficking. For example, delivery of key regulators of cell migration such as Src kinase to integrin-based focal adhesions at the plasma membrane is an actin-dependent process. Importantly, a series of studies provide evidence to support the notion that tropomyosins are involved in vesicle trafficking along actin filaments. While the specific role for tropomyosins in regulating trafficking required for cell migration and invasion is currently not known, the association between tropomyosin expression and integrin receptor expression profiles and focal adhesion structures raises the interesting question of whether the tropomyosins may be playing a role in actin-dependent vesicle trafficking in cell migration.

**The Low Molecular Weight Tropomyosin Isoform Tm5NM1**

Of all the cytoskeletal tropomyosin isoforms, the most studied to date in terms of a role in cell migration is the LMW Tropomyosin 5 non-muscle isoform 1 (Tm5NM1). Accumulating evidence has revealed that high-level Tm5NM1 expression inhibits cell migration and invasion, while conversely, loss of Tm5NM1 increases cell migration. An elevated level of Tm5NM1 expression promotes both myosin II recruitment and inhibition of ADF/cofilin activity which together result in stabilization and altered arrangement of the actin filaments (Fig. 2 and reviewed in ref. 69). Importantly, the effect of Tm5NM1 expression on ADF/cofilin activity is a dose-dependent effect. As the levels of Tm5NM1 are increased, more filaments are anticipated to be decorated with Tm5NM1 polymers. Based on the model that Tm5NM1 association blocks subsequent ADF/cofilin interaction with the actin filament (although it is currently not known how this leads to ADF/cofilin phosphorylation) there may be a feedback mechanism that then stimulates ADF/cofilin phosphorylation. Such differences in expression levels of Tm5NM1 reflect the range of endogenous Tm5NM1 expression seen across different tissues. Notably, some reports suggest that Tm5NM1 (and other LMW TPM3 isoforms) may be increased in some invasive cancer cells, with increased expression levels of 1.5–1.8-fold. However, others report either no change or slightly reduced expression of LMW TPM3 products in other transformed cell types.

There is a striking stabilization of focal adhesions concomitant with Tm5NM1-mediated stabilization of actin filaments. The precise mechanism by which Tm5NM1 decoration of actin filaments determines the dynamics of focal adhesions is still unknown. However, interesting recent data suggests that actin filaments are bundled and polymerized at the cytoplasmic face of the focal adhesion there is isoform-specific recruitment of tropomyosins (Lappalainen P, personal communication). This new data suggests that rather than indirectly affecting the focal adhesion dynamics, the tropomyosins may play a direct

**Figure 2. Tm5NM1-mediated changes to the actin cytoskeleton.** (A) B35 neuroblastoma control cells and expressing exogenous Tm5NM1, grown on fibronectin/laminin coated glass coverslips and stained with fluorescently-tagged phalloidin to detect filamentous actin. Arrows point to prominent dendritic actin network at the leading edge of control cells and the strong stress fibers visible in the Tm5NM1 cells. Scale bars 20 μm. (B) The same cells as in (A), but instead grown embedded in collagen gels to provide a 3-D environment. Cells were transfected with GFP-tagged Lifeact (a probe that detects filamentous actin). Arrows point to membrane protrusions in control cells and short spikes of filamentous actin in the Tm5NM1 cells. Shown are maximum projections of a confocal z-series, scale bars 10 μm.
role in determining the stability and lifetime of adhesions to the extracellular matrix; presumably this may extend to cell-cell adhesions.

Confirming the idea that tropomyosins may play a role in determining cell adhesion, we have recently shown that Tm5NM1 inhibits mesenchymal cell invasion,61 an invasion mode employed by cells as they negotiate a 3-D environment that is critically dependent on integrin-mediated adhesion to the extra-cellular matrix. This invasion mode is characterized by elongated cells that display branching polarized membrane protrusions in the direction of migration (Fig. 2 and reviewed in ref. 75). Critically, inhibition of mesenchymal invasion can cause some cells to switch to amoeboid invasion, characterized by amorphic morphology, non-apoptotic plasma membrane blebbing and abundant cortical actin.73 Rapid expansion and contraction of cortical actin allows amoeboid cells to squeeze through obstructing matrix and this is highly dependent on actomyosin contractility.76,77 Notably, Tm5NM1 inhibition of mesenchymal cell migration does not cause amoeboid transition.61 Given that Tm5NM1 induces non-muscle myosin II activation,28 it is intriguing that Tm5NM1 does not cause amoeboid transition and understanding this is likely to shed light on our understanding of amoeboid invasion. Although the signaling mechanisms regulating mesenchymal to amoeboid transition are now being revealed,77 the contribution of actin dynamics in this process has been less clear. The lack of amoeboid invasion induced by Tm5NM1 may suggest the role of Tm5NM1 in migration and invasion is separate to its effects on acto-myosin contractility. However, while acto-myosin contractility is required for focal adhesion maturation and stabilization, conversely, acto-myosin-dependent amoeboid invasion is characterized by reduced requirement for integrin-mediated interaction with the extra-cellular matrix. Thus, the key may lie in the stable focal adhesions induced by Tm5NM1, preventing amoeboid transition. The Tm5NM1 data highlight a critical role for a dynamic actin cytoskeleton in the switch between invasion modes and elucidation of this dynamic state may help identify new targets for treating metastatic cancer.

Conclusion

Studies of tropomyosins, in particular the investigation of their isoform-specific effects, are beginning to reveal new insights into how actin filament populations may be specified to perform discrete functions during cell migration. To date studies have focused on the role of one specific cytoskeletal isoform, Tm5NM1, in cell migration. Given the abundance of other tropomyosin isoforms available to decorate the actin filaments we anticipate that more members of this protein family will emerge as important coordinators of actin filament specialization during migration.

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