Review

The microfilament system and malignancy

Uno Lindberg [a],[*], Roger Karlsson [b], Ingrid Lassing [a],
Clarence E. Schutt [c], Anna-Stina Höglund [d]

[a] *Department of Microbiology, Tumor Biology, and Cell Biology, The Karolinska Institute, Stockholm, Sweden*
[b] *Department of Cell Biology, The Wenner-Gren Institute, Stockholm University, Stockholm, Sweden*
[c] *Department of Chemistry, Princeton University, Princeton, NJ, USA*
[d] *Department of Neuroscience, Clinical Neurophysiology, Uppsala University, Uppsala, Sweden*

Abstract

Increased motile activity, increased rate of cell proliferation and removal of growth inhibiting cell–cell contacts are hallmarks of tumorigenesis. Activation of cell motility and migration is caused by activation of receptors, turning on the growth cycle. Increased expression of metalloproteinases, breaking cell:cell contacts and organ confines, allows the spread of malignant cancer cells to other sites in the organism. It has become increasingly clear that most transmembrane proteins (growth factor receptors, adhesion proteins and ion channels) are either permanently or transiently associated with the sub-membraneous system of actin microfilaments (MF), whose force generating capacity they control. Although there has been great progress in our understanding of the physiological importance of the MF-system, as will be exemplified in this issue of SCB, many aspects of actin microfilament formation and its regulation are still unclear. Redox control of the actin (MF)-system in cell motility and migration and its perturbations in pathophysiology, including cancer, is an emerging field of research.
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Keywords: Actin microfilament system; Phosphoinositide cycle; Cell motility cycle; Reactive oxygen species; Cancerogenesis

Contents

1. The microfilament system

1.1. Organization of the actin cortex

Actins are highly conserved eukaryotic proteins, which occur both in monomeric and polymerized (filamentous) form. Actin filaments with associated proteins are central elements in the microfilament (MF)-system, which drives cellular communication processes, including cell motility and migration, phagocytosis, vesicular movement, cytokinesis, and molecular
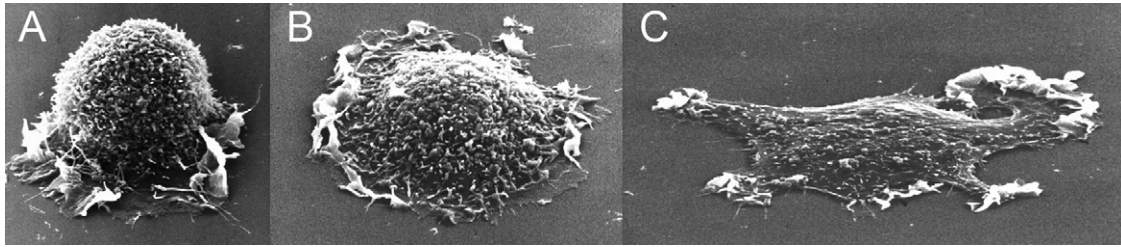
Fig. 1. Glial cells in different stages of spreading. The scanning micrographs show their surface morphology, which depends on the organization of the sub-membranous actin microfilaments. Motile activity depends heavily on force-generation in the actin microfilament system.
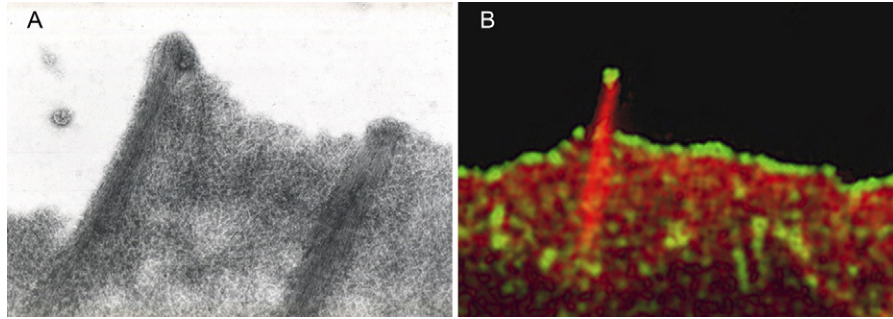

Fig. 2. The sub-membraneous layer of actin microfilaments in a lamellipodium visualized after removal of the lipid bilayer. Panel A: The actin organization is characterized by a high concentration of ordered filaments in a continuous force-generating arrangement, whose dynamics is under control by transmembrane signaling [2]. Panel B: VASP (green) is concentrated along the outer edge of the actin arrangements (red) in the lamellipodium, and at tips of filopodia (by courtesy of Staffan Grenklo).

transports between the plasma membrane and the nucleus. A highly dynamic, concentrated, and well organized cortical weave of actin microfilaments capable of extensive force-generation is juxtaposed to the inside of the plasma membrane, shaping cells and governing their integrity (Figs. 1–3) [1–3].

Transmembrane proteins, linked to the sub-membranous actin force generator, are responsible for the first level of control of the cell motility (CM)-cycle, whose four basic steps are: (1) polymerization of actin into filaments, (2) organization of filaments into ensembles by cross-linking proteins and by adhesions to extracellular structures, (3) force-generation for large scale movements through interaction between actin filaments and different myosins, and (4) depolymerization of filaments to reform unpolymerized actin for new rounds of polymerization. A multitude of factors are involved in the control of the different steps of the cycle, through which reorganization of the
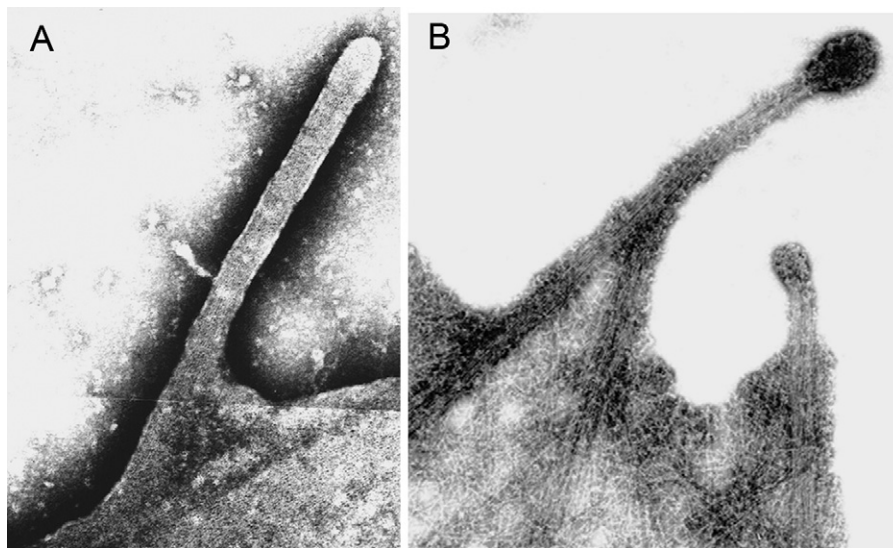
Fig. 3. The juxtapositioning of the lipid bilayer and the cortical weave of actin filaments. Panel A: The white zone along the cell edge represents the lipid bilayer in close apposition to the sub-membraneous actin organization. Panel B illustrates a similar edge protrusion after removal of the lipid bilayer [111]. The tip complex of the filopodium contains a large number of proteins, among which is the VASP protein as illustrated in Fig. 2B. Along the edge, detergent-resistant material has been captured, likely representing membrane-associated proteins, connecting the actin microfilament weave.

MF-system is executed in response to interactions between the cell and the surrounding world, i.e. growth factors, cytokines, other cells, or extracellular matrices; for reviews see [4,5].

Cell surface protrusions, lamellipodia and filopodia, are built of actin microfilaments, whose assembly takes place primarily at advancing edges of cells, and it is the polymerization of actin that provides the force for their protrusion [4,5]. Myosin-dependent processes translocate molecules and particles along lamellipodial and filopodial MF-arrangements. For instance, *VASP* and *integrins* are transported towards the tip of filopodia by *myosin X*, where they become involved in filament growth and establishment of adhesion sites, specialized multiprotein structures, connecting filopodial actin filament bundles to extracellular matrices (see Figs. 2B and 3) [6,7]. Force generating ensembles of microfilaments and myosin II, in so called stress fibers are used to move the whole cell [8], and the details of the formation and functionality of these contractile fibers are now being explored [9]. In tissues, cell:cell adhesions engage different transmembrane proteins, e.g. cadherins [10,11], which dynamically link actin microfilament arrangements in neighboring cells by mechanisms currently under special scrutiny [12,13]. Many of the proteins involved in the control of the MF-system are products derived from proto-oncogens. This issue of SCB reviews aspects of the MF-system, which are of special interest in relation to the development of malignant cancer cells.

1.2. Actin polymerizing machineries

The actin filament is a twisted ribbon with a barbed and a pointed end [14,15]. *In vitro*, the barbed end is the fast polymerizing (+)-end. *In vivo*, this end is located at the advancing edge of lamellipodia and filopodia together with actin polymerizing multiprotein complexes operating within a 0.1–0.2 µm wide zone at the tip of the cell edge [4,5]. Actin filaments are generated either by de novo actin nucleation/elongation or by elongation of pre-existing filaments. Four basically different mechanisms are involved in formation of actin polymers: (1) the *Arp2/3*-dependent nucleation/elongation system operating together with either *WASP/N-WASP* (Wiskott Aldrich syndrome proteins) or *WAVE* (WASP-verprolin homology proteins). These proteins are components of high molecular weight, multiprotein assemblies [16,17], executing spatio-temporal actin polymerization under the control of the small GTPases, Cdc42 and Rac, reviewed by [18–21], and their activities give rise to branched filament arrangements *in vitro* [4]. Electron microscopy images of lamellipodia have been interpreted to demonstrate that filament branching is a prominent feature also *in vivo* [22], although this is an issue of debate [23]. Arp2/3-WASP/N-WASP actin polymerizations are involved primarily in endo- and exocytosis, but also in the formation of podosomes, invadosomes, and filopodia; see contributions by Vignjevic and Montagnac and Gimona in this issue, while the Arp2/3-WAVE dependent polymerization is involved in lamellipodia formation; (2) the *formins* polymerize actin in association with filament (+)-ends at advancing cell edges, and are also under the control of small GTPases [24]; (3) the *Spir* and *cordon-bleu* (cobl) proteins are newly discovered actin filament nucleating proteins [25,26]. They are widely expressed in embryonic tissues, but seem to be limited primarily to the central nervous system of adults. Their activity in filament formation *in vivo* is yet unclear; (4) *Ena/VASP* family of proteins finally are also linked to polymerization of actin [27–31]. VASP is recruited to the distal parts of lamellipodia, in amounts that are directly proportional to the rate of protrusion [32], and it is required for the proper formation of the actin filament tail of *Listeria monocytogenes* and for optimal movement of the bacterium [33].

The major part of the unpolymerized actin in the cell is complexed to profilin, and there is convincing evidence that profilin:actin is used as the precursor by all the polymerizing systems, bringing ATP-actin to the polymerization site [21] (Figs. 2B, 4 and 5). VASP has binding sites for profilin, profilin:actin, G-actin and F-actin, but the exact molecular mechanisms, by which the protein operates during actin polymerization has been difficult to assess. Recent investigations, however, have led to new insights concerning the energetics and structural basis for the interactions of profilin:actin and VASP [34,35]. The results have led to an intriguing, yet plausible model, for VASP-dependent recruitment of profilin:actin, and its processing through a series of binding sites on VASP prior to incorporation of the actin into the growing filament. Likely, VASP binds to filament (+)-ends set free by uncapping, or resulting from the action of actin filament-fragmenting (severing) proteins, or by de novo nucleation. The polarity of the actin filaments, the high degree of order in their organization, and relative synchrony of the polymerization at sites along advancing lamellipodial edges provides directionality to the motile activity driving the cell forward [21,36,37].

Recent observations indicate that *tropomyosins* (TM) may be critically involved in the regulation of actin filament formation and function, as reflected in the alterations in TM isoform expression seen as a result of the development of the malignant state of cancers [38–40]. TMs are dimeric, coiled coil structures, which can associate in a head-to-tail fashion, forming copolymers with actin filaments; one strand of TMs on each side of the actin ribbon. TM is encoded by four genes, and through multiple promoters and alternative splicing a large number of isoforms can be produced [41].

It is possible that the TM family of proteins play a drastically different role in the organization and activity of actin in non-muscle cells than previously recognized. Binding of tropomyosin to gelsolin-capped actin oligomers eliminates the capping activity of gelsolin, resulting in annealing of the oligomers into long filaments. This suggests that TM might be involved in controlling the accessibility of the (+)-end of actin filaments *in vivo* [42]. TM protects actin filaments from being severed by gelsolin and cofilin, a protection which is further strengthened by binding of caldesmon to the actin-TM copolymer [43]. TM is required for the formin-dependent formation of the actin filament cable essential for bud growth in *Saccharomyces cerevisiae* [44]; if missing, only a fuzzy filamentous material is seen at the expected site of actin polymerization. In mammalian cells, TMs are found at the distal parts of lamellipodia and filopodia [45], and the binding of TM to the C-terminus of formins results in their activation [46]. Furthermore, the TM-
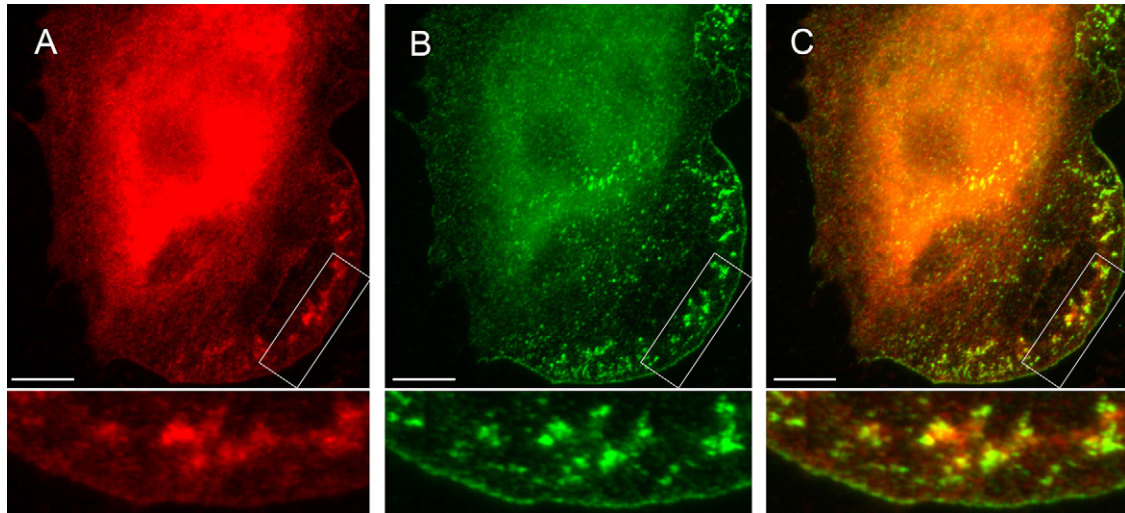
Fig. 4. Distribution of profilin:actin (red) and the p34 subunit of the Arp2/3 complex (green). Note the fine rim of both components seen along the advancing edge in the magnified areas (by courtesy of Yu Li).

1 isoform is phosphorylated in an ERK-dependent pathway, a modification shown to be required for stress fiber formation in endothelial cells [47,48]. Inhibition of the phosphorylation abrogates stress fiber formation and causes extensive, actin polymerization-dependent blebbing of the cells.

While the major part of the cellular tropomyosin recides in the cytomatrix, periodically distributed along actin filaments in stress fibers and thinner actin ensembles, the soluble part of the cytoplasm (cytosol) contains TM in isoform-specific particles of high molecular weight (MW_{app} 600,000–800,000) (Lindberg and collaborators, unpublished). More than 90% of the soluble TM appears in particle form, with small amounts of TM

dimers. The lamellpodial TM is seen as a diffuse staining and as abundant, more intensively stained dots out to the edge of the protrusions [45]. The dots are identified as the TM particles.

Growth factor-stimulated cells rapidly change their levels of TM isoforms in the cytosol, changes, which coincide with actin polymerization, leading to formation of lamellipodia and filopodia. Thus, the particles might constitute a storage form of TM, from which TM can be recruited to sites of actin polymerization, possibly by activated actin polymerizing machineries. The activity of the TM in particles must be under tight control. They coexist in the cytosol with high concentrations of non-polymerized β- and γ-actin, which in turn are controlled by the
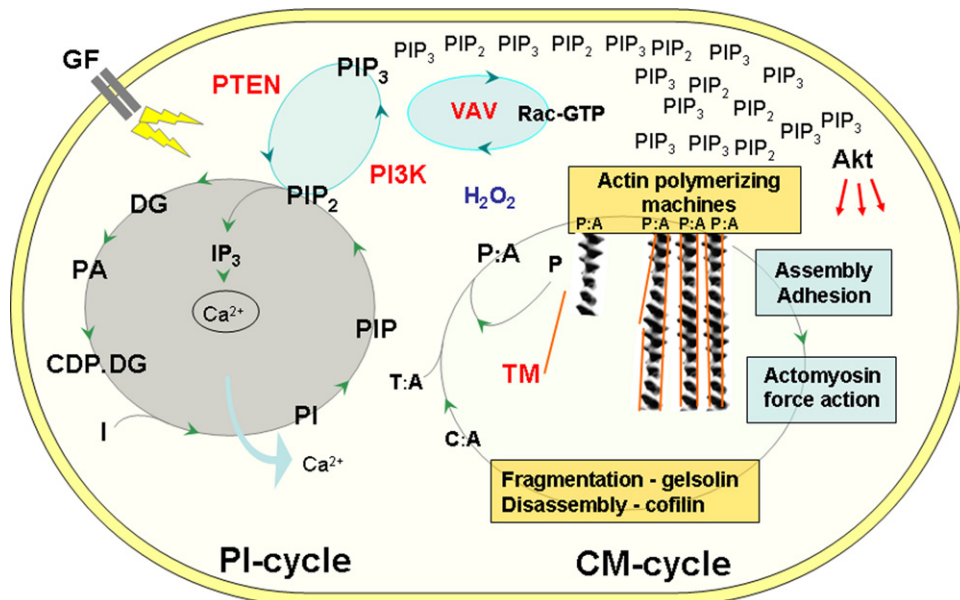
Fig. 5. The PI-/CM-cycle relationship. This simplified scheme illustrates the close integration of the turnovers in the phosphoinositides (PI)-cycle and actin dynamics (CM)-cycle at the plasma membrane. Activation of cells with growth factors stimulates the PI-cycle and the activity of PI3 kinase, resulting in lipoprotein membrane rafts enriched in PI4,5P$_2$/PI3,4,5P$_3$, which in turn organizes actin polymerizing machineries and Akt/PKB. Arrows from Akt in the scheme denote subsequent activation of the kinase and its release to the cytosol for stimulation of proliferation, metabolism, and inhibition of apoptosis. The involvement of hydrogen peroxide is also denoted in the scheme. The rendition of the actin filaments is from Lepault et al. [15].

actin monomer-binding proteins profilin, cofilin and thymosin. If unleashed in an uncontrolled fashion, the actin and TM in the cytosol would give rise to an immediate formation of a caotic meshwork of actin filaments incompatible with further life of the cell.

Malignant cells have drastically altered levels of TMs in the cytosol and cytomatrix. The so called high molecular weight and low molecular weight isoforms, appear to influence different aspects of the functioning of the MF-system; one class primarily being involved in controlling the motile activity of lamellipodia and filopodia, and the other controlling the formation of cell adhesions and stress fibers. The occurrence of differential and specific changes in the expression of TM isoforms during development of malignant tumor cells makes them interesting targets for chemotherapy [49]. For a review of TM physiology, see Gunning and collaborators in this issue of SCB.

1.3. Depolymerization of actin filaments

Relatively little is known about depolymerization of actin filaments, an important process closing the CM-cycle. The prime actors in this process are the actin depolymerising factors, belonging to the *ADF/cofilin* family of proteins (here referred to as cofilin) [50]. *In vitro*, the dephosphorylated form of cofilin has the capacity both to fragment (sever) actin polymers and to accelerate depolymerization from their pointed (−)-end, and there is evidence that depolymerization takes place in the proximal parts of lamellipodia and filopodia, away from the advancing cell edge. Likely, depolymerization occurs also at other sites in the microfilament organizations, and severing, not only by cofilin, but also by other actin filament severing proteins like gelsolin, contributes to accelerated reorganization of actin microfilaments. Depolymerization of filaments yields ADP-carrying monomers, which can be recycled, with the ultimate reformation of profilin:actin, which again can provide ATP-actin to polymerizing machines [21].

Cofilin, is also thought to exist in a PI4,5P_2 bound state in the membrane [51], from which it could be released in an active, non-phosphorylated state by receptor-activated lipases, e.g. PLCγ. Released cofilin might sever unprotected filaments and thereby produce increased numbers of filament (+)-ends, which could be used as starting points for new filament growth [52]. Polymerization would be further supported by concomitant depolymerization at the (−)-ends of formed actin oligomers, producing actin monomers to be recycled to polymerization machineries via profilin:actin [21].

Accelerated turnover in the CM-cycle is a signature of malignancy, and cofilin controls crucial aspects of motility and migration of cells. The expression of the activity of different components of the proposed "cofilin pathway" [53] are significantly altered in connection to cancerogenesis, again illustrating the importance of cell motility in the development of cancer malignancy. The binding of cofilin to actin is controlled by the Lim kinase/slingshot phosphatase pair [54,55]. Lim kinase is activated by phosphorylation by PAK under the control of small GTPases, and phosphorylation of cofilin inhibits its interaction with actin. Thus, phosphorylation of cofilin, subsequent to cell

stimulation, must occur after its severing action not to violate the proposed model. Recently, it has been demonstrated that cofilin directly interacts with PLD1 and upon phosphorylation stimulates its lipase activity, pointing to additional functions of cofilin [56].

Cell variations and redundancies of individual components make it difficult to assess how the complexity of the PI-/CM-cycle relationship is used by different cells in time and space (see below). Notably, altered expression of proteins belonging to the MF-system, e.g. *profilin*, *cofilin*, *tropomyosin*, *gelsolin*, α-*actinin*, and *vinculin*, is frequently associated with malignant transformation [53,57–61].

2. The PI-cycle drives the CM-cycle

Transmembrane signaling caused by binding of growth factors to their cognate receptors results in immediate increases in the turn-over of the phosphatidylinositol (PI)-cycle [62,63], activation of the RhoGTPases (e.g. Cdc42, Rac, and Rho) [18,64], and stimulation of actin polymerization and motile activity [2,65–67]. The discovery of the profilin:actin complex [68] and the specific effect of PI4,5P_2 on the stability of the complex 5 [69] led to the proposition that the PI-cycle is coupled to the CM-cycle [70]. It is now known that virtually all cells respond to a variety of extracellular agonists with an increased turnover in the PI-cycle [71], and that the PI- and the CM-cycles, are interlinked through many factors and feed back loops (see Fig. 5). Stimulation of cells with growth factors and other agonists leads to rapid phosphorylation of phosphatidyl inositol (PI) by activated kinases giving rise to increased levels of PI4,5P_2 in the membrane [72], and PI3 kinase in turn converts PI4,5P_2 to PI3,4,5P_3, which is a key molecule turning on the CM-cycle [73].

The PI3 kinase is the pivot in the control of the PI- and CM-cycle relationship. Its activation by tyrosine-phosphorylated growth factor receptors initiates the formation of complex multiprotein assemblies at the membrane, producing the polyphospho-inositides, whose importance can be ascribed to their capacity to *recruit* and *activate* proteins at the plasma membrane, among which are Arp2/3-dependent actin polymerizing machineries including the WASP/WAVE family of proteins [16,17,74–77]. The PI3,4,5P_3 product of PI3 kinase also recruits Akt/PKB to the membrane for activation with subsequent phosphorylation of a large number of target proteins involved in the regulation of metabolism, cell growth and proliferation, and survival as the result. Significantly, alterations of the activity of the PI3 kinase and Akt/PKB are often coupled to tumorigenesis [78–80].

The polyphospho-inositide-response depends on GEF-activated small GTPases, operating on the phosphatidyl inositol kinases. The Vav family of proteins constitute one such group of GEFs, controlling the relationship between the PI- and the CM-cycles. The nucleotide exchange activity of the Vav proteins is stimulated by phosphorylation as well as by binding of the product of the PI3 kinase, PI3,4,5P_3, leading to accelerated production of PI4,5P_2 and ultimately to PI3,4,5P_3 [81]. Through this positive feed-back loop, the activity in the CM-cycle can be accelerated. The function of the Vav feed-back loop is even more

sophisticated, since PI4,5P$_2$ by direct interaction with Vav interferes with its GEF activity and thereby indirectly dampens the PI3,4,5P$_3$ production by reducing the formation of the substrate for the PI3 kinase. The importance of mechanisms balancing the concentration of PI3,4,5P$_3$ is emphasized by the existence of PTEN (phosphatase homologous to tensin), which can remove the phosphate in the 3-position of the polyphospho-inositide, and the fact that perturbations of the PI3 kinase Akt/PKB signaling pathways are frequent in human cancers [80].

The intimate relationship between the PI- and CM-cycles is further illustrated by the fact that many other actin-binding proteins interact with polyphospho-inositides [82]. For instance, PI4,5P$_2$ binds to proteins like *capping protein* (CP) and gelsolin, which control growth of actin filaments at their (+)-end, leading to uncapping of the (+)-end, allowing filament elongation [83]. As mentioned above, *profilin* as well as profilin:actin both bind PI4,5P$_2$ and PI3,4,5P$_3$ [69,84,85], suggesting that profilin and profilin:actin also might accumulate in polyphospho-inositide-rich regions in the membrane, proximal to actin polymerizing protein complexes. A series of observations show that profilin:actin is not only required for maximal rate of actin incorporation in *in vitro* systems, but also *in vivo* mutations in either profilin or VASP, or the introduction of cross-linked profilin:actin into live cells, strongly interferes with filament formation, indicating profilin:actin as the provider of actin to the actin polymerizing machineries [29,31,33,86,87]. Cells treated with siRNA to reduce the level of profilin leads to loss of persistent directionality of migration of endothelial cells [88], and melanoma cells when similarly treated, also show a reduced growth rate (Li and Karlsson, unpublished). Over-expression of profilin in breast cancer cells reduces their tumorigenic potential, and elimination of the actin-binding capacity of profilin abrogates this effect [60,61]. The reason for this is unclear. *In vitro*, the binding to polyphospho-inositides labilizes the profilin:actin complex, causing its dissociation, but if this occurs *in vivo* is unclear. It is noteworthy that binding of actin and PI4,5P$_2$ to profilin does not necessarily have to be mutually exclusive [69,89].

3. H$_2$O$_2$ in the control of the MF-system

In addition to polyphospho-inositides and small GTPases, transient generation of H$_2$O$_2$ seems to play important roles in regulating formation and activity of cell edge protrusions, integrin-mediated adhesion, and migration [90,91]. Apparently, H$_2$O$_2$ acts as a rapidly produced and effective second messenger, whose spatio-temporal appearance in cells correlates with changes in the microfilament system [91,92]. Its involvement in the activation of the MF-system is demonstrated by the fact that quenching ROS production eliminates the effects of growth factors on the motile activity of cells [92]. Furthermore, there is evidence that β-actin, and the actin-regulating proteins profilin and tropomyosin are oxidized and glutathionylated *in vivo* [93]. Non-muscle β-actin has six cysteines, two of which are particularly sensitive to oxidation. Oxidation of the penultimate C374 affects the stability of the actin filament, while the role played by the most sensitive, cysteine 272 is unknown ([94] and Lass-

ing, unpublished). The tumor suppressor PTEN is of decisive importance in the control of cell motility. Its oxidation by H$_2$O$_2$ [95] upsets the control of cell motility. Altered PTEN activity is a frequent characteristic of malignant cancer cells.

The major sources of ROS in both phagocytotic and non-phagocytotic cells appears to be NAD(P)H oxidase-like protein complexes (NOX) and lipoxygenases (LOX). Both function downstream cytokine receptors [96,97], in direct interaction with actin [98,99]. These enzyme complexes are membrane associated and activated by association with the GTPase Rac [100], the overexpression of which leads to increased ROS levels in endothelial cells [101]. Consistently, overexpression of a dominant negative form of Rac1 inhibits ROS generation [102]. As described in connection to the PI-cycle above, association with GEFs targets Rac1 and causes its concomitant, spatially restricted activation at the membrane [103], where, in migrating cells, actin reorganization is maximal. Thus, amplification of a H$_2$O$_2$ signal *in vivo* would seem to occur through the integration of the CM- and PI-cycles [104], where activation of Rac1 [105] is central. Increased lipid phosphorylation through the activity of PI3 kinase, resulting from oxidative inhibition of phosphatases is a signature of H$_2$O$_2$ signalling [106,107]. The conclusion would be that the activation of LOX and NOX is integrated with actin via Rac. It is noteworthy that 5′OH-lipoxygenase, which metabolizes lipase-released arachidonic acid to yield H$_2$O$_2$ as one of the products, can bind to actin filaments in competition with the actin filament-binding protein coactosin [108]. This gives further credence to the view that lipoxygenases operate in association with the MF-system, and points to the possibility that also lipohydroxyperoxides produced by 5′OH-lipoxyenase are involved in the control of the MF-system. As pointed out above, cofilin stimulates phopholipase D activity and may therefore be involved in release of arachidonic acid for further metabolism generating reactive oxygen species [109]. Interestingly, attention was recently drawn to the fact that alterations in the activity of both cyclooxygenases and lipoxygenases appear to be linked to carcinogenesis [110].

4. From lamellipodia to focal complexes and focal adhesions

Cell migration is executed by repeated cycles of protrusion (actin polymerization), matrix adhesions (formation of focal complexes/focal adhesions in association with actin filaments) and retraction (actomyosin force-generation). Cell surface protrusions explore the immediate surroundings for possible adhesion sites. The electron micrograph in Fig. 6 visualizes discrete structures (tip complexes) at the outer edge of lamellipodia [1,2,111–113], which might harbor actin polymerizing machines, together with accessory proteins. Actin microfilaments, emanating from foci in the cell edge, diverge towards the interior part of lamellipodia. Such foci can be seen also alongside the base of filopodia, whereas large tip complexes are present at their distal end (Fig. 3).

Integrins appear at the outer edge of cell protrusions, and presumably as a result of integrins interacting with the extra-cellular matrix, focal complexes (FX) appear at a distance of
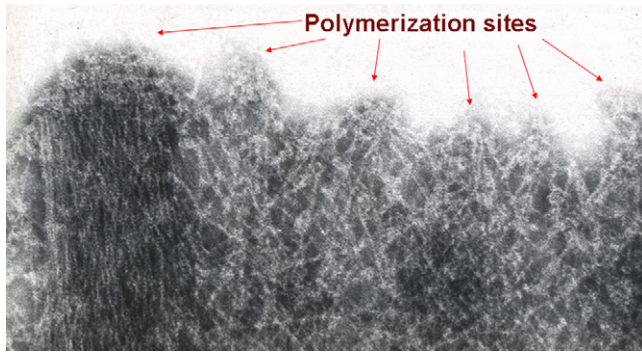
Fig. 6. Visualization of the detailed organization of actin filaments in the outer part of the lamellipodium. The foci with filaments diverging into the lamellipodium might represent actin polymerizing machines in the initial stages of focal complex formation [1,3].

about 1 μm from the advancing edge [114,115], a subject also treated by Strömblad and collaborators in this issue. Detailed light microscopic analysis revealed a sequential addition of specific proteins, transforming focal complexes to focal adhesions (FA). The initial FXs are enriched in tyrosine-phosphorylated components, and integrin, talin, paxillin, low levels of vinculin and FAK, but appear to lack zyxin and tensin [116–118] The latter proteins are added to the structure during maturation of FX to FA – now referred to as the adhesome [119,120]. Recently, it has been discovered that stress forces from outside or actomyosin-dependent forces positively influence actin polymerization at the focal adhesions, which also increase in size under these conditions [121]. This signaling involves the RhoGTPase Rac [122], suggesting a linkage to the generation of ROS [123], and phosphorylated TM-1 [47,48]. In this issue, the contributions by Gimona and Tilghman and Parsons, respectively, deal with mechanosensing and focal adhesions.

Integrins execute cell–matrix as well as cell–cell interactions, whereas adhesion via the cadherin family of adhesion proteins is preferentially intercellular. Cadherin–cadherin interactions link the MF-systems of adjacent cells. For example, E-cadherin, the prototypic member of the cadherin family, regulates cell adhesion in epithelial cells [10,11]. During embryonic development, down-regulation of E-cadherin function initiates a complex program wherein epithelial cells adopt a fibroblast-like phenotype and display tissue invasive activity, a process called epithelial-mesenchymal transition (EMT). Repression of E-cadherin appears to play a major role in EMT of epithelial-derived cancer types. E-cadherin repression frequently occurs in tandem with activation of the Wnt signaling cascade [124]. For a detailed account of cadherins in cell–cell interactions see the article by Nelson this issue.

5. Cell motility and malignancy—a concluding remark

Hanahan and Weinberg [125] defined six major characteristics of malignant cancer cells: self-sufficiency in growth signals, insensitivity to anti-growth signals, tissue invasion and metastasis, limitless replicative potential, sustained angiogenesis, evading apoptosis. The contributions in this issue of SCB

draw attention to the fact that cancerogenesis and transformation to the malignant state are highly correlated with changes in the organization and activity of the MF-system, and that the molecular alterations in signaling behind the acquired capabilities of cancer cells in most, if not all, cases change the regulation of the PI/CM-cycle relationship. Growth factors, their receptors, and signaling intermediates are products of protooncogenes, which when expressed pathologically, activate both the MF-system and gene expression, resulting in increased motile activity and cell proliferation. Alterations in the expression or activity of PI3 kinase and Akt/PKB are frequent in malignancy [79]. The same is true for the tumor suppressor PTEN, linked to actin filaments in lamellipodia and focal adhesions [126–128]. Mutations inactivating PTEN lead to accumulation of $PI3,4,5P_3$ [129], making cells run amuck.

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