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Minireview

Cell responses regulated by early reorganization of actin cytoskeleton

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Abstract Microfilaments exist in a dynamic equilibrium between monomeric and polymerized actin and the ratio of monomers to polymeric forms is influenced by a variety of extracellular stimuli. The polymerization, depolymerization and redistribution of actin filaments are modulated by several actin-binding proteins, which are regulated by upstream signalling molecules. Actin cytoskeleton is involved in diverse cellular functions including migration, ion channels activity, secretion, apoptosis and cell survival. In this review we have outlined the role of actin dynamics in representative cell functions induced by the early response to extracellular stimuli.

Keywords: Actin cytoskeleton; Cell response; TNFα; GPCRs; Ion channel; Membrane-androgen receptor

1. Introduction

Actin is an evolutionary conserved 42-kDa protein and one of the major cytoskeletal components in eukaryotic cells. Actin occurs in two forms, the globular or G-actin which polymerizes into the other form which is called filamentous or F-actin. Filamentous actin can be found as bundles called stress fibers or as fine network underneath the plasma membrane called microfilaments. There is also a third filamentous structure called contractile ring, which is critical for the separation of a cell during cytokinesis. Each microfilament has two different ends, at which polymerization takes place at different rates: a fast growing or 'plus' end and a slow-growing or 'minus' end. In cells the plus end of the filaments is oriented towards the cell membrane while the minus end towards the cytoplasm [1,2]. The association of microfilaments with cell membrane plays a fundamental role in anchoring membrane proteins whereas stress fibers maintain the connections between the cell and the surface on which it grows.

The relative proportion of F- and G-actin is determined by the concentration of monomeric actin protein. At a critical concentration of G-actin, the plus end of the microfilament will constantly grow while the minus end simultaneously decays thus the length of microfilament remains constant (treadmill) [3,4]. The polymerization state of actin, the length of microfilaments and their properties in the cells are regulated by the 'actin-binding' or 'actin-associated' proteins. There are numerous functionally important actin – associated proteins[5]. Their binding to G- or F-actin has various functions: they serve to control the length of filaments or to keep the filaments at a certain length (e.g. villin, cofilin, gelsolin, fragmin, and severin), to produce bundles of actin filaments (e.g. villin, filamin, and fimbrin), to cross-link actin filaments forming a meshwork such as that found in association with the cell membrane (e.g. fibrin, vinculin, a-actinin, and talin) or to control G-actin pool by preventing the polymerization of actin (e.g. profilin). A key regulator of a number of actin binding proteins is the PI(4,5)P2, the concentration of which is altered by the enzymes phospholipase C-gamma (PLC-γ) and PI3-kinase: PLC-γ hydrolyzes PI(4,5)P2 into diagylglycerol and inositol-3-phosphate whereas PI3-kinase phosphorylates PI(4,5)P2 producing PI(3,4,5)P3. The binding of profilin, gelsolin, villin and cofilin with PI(4,5)P2 is competitive with that of actin whereas WASP, a-actinin, and vinculin require PI(4,5)P2 to bind actin[6,7]. Additionally, an important type of actin-associated protein is the family of myosins which convert chemical energy to produce movement of actin filaments. The best characterized myosin, myosin II, slides actin filaments past each other either to power contraction of the contractile ring during cytokinesis or to produce cell migration [8–10].

The cell can control the physical properties of the cytoplasm and to respond to extracellular stimuli by modulating the state of microfilament network. The polymerization/depolymerization of actin filaments is a dynamic process which is involved and/or mediates various cell responses. In the present chapter we summarize representative data showing the role of early actin cytoskeleton reorganization in the modulation of various cell responses (Fig. 1).

2. Actin cytoskeleton in the regulation of cell migration-invasion

The role of actin filaments in cell migration and invasion has been extensively studied. Since the discovery of the Rho-family of small GTPases [11,12] a lot of data has been accumulated showing how these proteins regulate the actin cytoskeleton during cell movement. Actin polymerization or depolymerization is induced by an extracellular or intracellular signal that activates members of the Rho-family. The mechanisms by which Rho-family proteins affect the dynamics of actin filaments and migration are complex [13–18] however, a simplified model is that Rac proteins are involved in lamellipodia formation: Cdc42 in filopodia formation and Rho in stress fibers

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Abbreviations: TNFα, tumor necrosis factor-α; GPCRs, G-protein coupled receptors.

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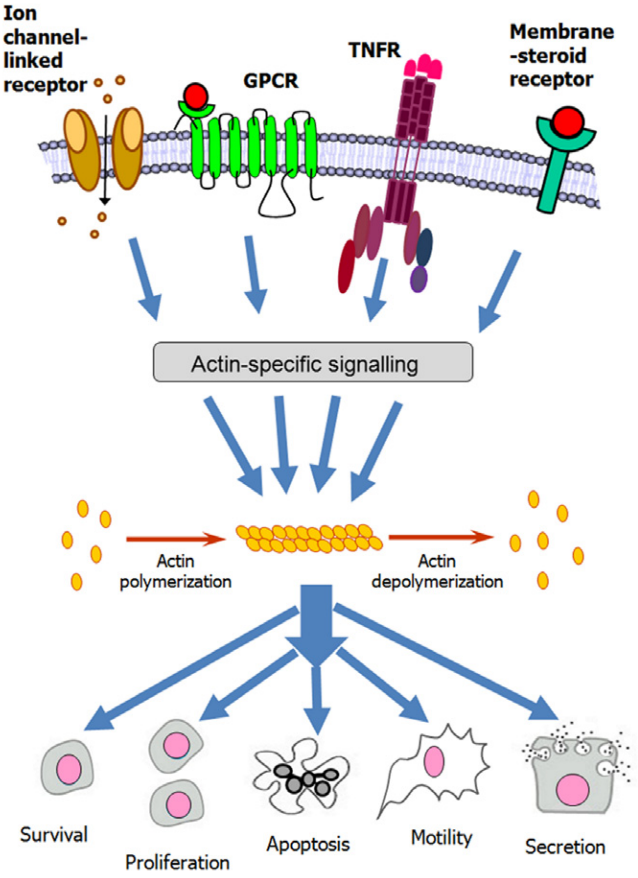

Fig. 1. Transmission of signals to actin cytoskeleton triggers a variety of cell responses. A signal is created by activation of membrane receptors such as ion channel-linked receptors, GPCRs, TNF receptor, and membrane-androgen receptors. Signal transduction molecules relay the signal to the actin cytoskeleton. Alterations of actin polymerization/depolymerization state have been implicated in various cell responses including cell survival, proliferation, apoptosis, motility, and secretion.

formation, actomyosin assembly and adhesion [14,19–21]. The regulation of Rho activity has to be well defined since elevated Rho activity induces high levels of stress fibers and substrate adhesions preventing migration [14,16,22–25]. High cellular levels of active Rac most often correlated with low levels of active Rho, and vice versa [16,26,27] whereas p110δ isoform of PI3-kinase also keeps RhoA activity in the correct balance for proper migration [28]. Lamellipodia are veil-like sheets which contain branched and cross-linked actin filaments whereas fillopodia are finger-like structures that project beyond the lamellipodium and contain bundles of actin filaments [5]. Membrane protrusions are formed because of rapid actin filament elongation at the tip of the leading edge [29]. The ADF/cofilin family of proteins, the N-WASP/Arp2/3 complex and gelsolin play pivotal role in nucleation of actin and the Arp2/3 complex and cortactin are important for the formation of actin branches found in lamellipodia [30–33]. Proteins such as villin, fimbrin and fascin are involved in stabilizing the bundles of actin filaments in fillopodia [33–38]. Branched actin filaments also determine the formation of the characteristic structures of invasive cells called invadopodia and podosomes [39].

Motility is an important cell function under normal or pathological conditions including formation of tissues, embryonic development, immune response and cancer. Defects or mutations in actin-binding proteins or in actin gene or in proteins involved in the regulation of actin polymerization/depolymerization dynamics have been considered to cause human disorders [40]. The Wiskott Aldrich Syndrome, neural tube closure defects and neutrophil dysfunction are some among other diseases characterized by impaired cell motility related to defected actin polymerization [41–44]. Although, malignancy-related mutations in β-actin have been found in a limited number of tumors [45,46], the defects in actin dynamics that have been correlated with enhanced motility of tumor cells are caused by misregulation of upstream signalling molecules such as the Rho-GTPases, LIMK, and PAK, or altered expression of certain actin-binding proteins including gelsolin, cofilin, profilin, and Arp2/3 [40,47–56].

3. Actin cytoskeleton and ion channel activity

Epithelial cells show a well established polarized morphology and its maintenance is highly dependant on actin cytoskeleton architecture [57,58]. Cell–cell and cell-extracellular matrix interactions, and specialized adhesion complexes such as tight junctions, adherens junctions and desmosomes establish the polarized morphology of epithelial cells [59]. The plasma membrane of epithelial cells consists of distinct domains as a result of their polarization: the apical and basolateral membrane domains which are essential for the absorptive and secretory functions of those cells [60]. The activities of various transport proteins, channels for ions or water have been shown to depend on the extent of actin polymerization [61–65]. Epithelial ion channels interact directly or indirectly with actin and this serves to maintain the polarized transport of ion channels to specific membrane domains and to regulate their activity [66].

Renal proximal tubule cells represent a characteristic type of epithelial cells with complex structure that mirrors the variety of physiological processes they perform. The cells forming the proximal tubule possess a dense brush border on the luminal surface which is formed by the microvilli of the cells [67]. The main cytoskeletal component of the brush border membrane of renal proximal tubular epithelial cells is actin microfilaments. Renal microvilli contain bundles of microfilaments as well as actin-binding proteins such as villin and fibrin, which are involved in stabilizing the actin filaments bundles, calmodulin and its associated 110-kDa protein, that are involved in the association of microfilaments with cell membrane [68].

Renal inorganic phosphate (Pi) reabsorption is performed by proximal tubule cells and determines the Pi homeostasis which is critical for normal cellular metabolism. Eighty percent of the Pi in the glomerular infiltrate is reabsorbed by proximal tubule cells upon physiological hormone levels and dietary conditions [69–71]. Transepithelial transport of Pi is performed by a Na/Pi cotransport system located in the apical membrane of renal proximal tubule cells [69]. In an attempt to examine factors that control Pi reabsorption induced by low extracellular Pi concentration we have previously found that the polymerization state of actin plays a key role in this process. Up-regulation of Na/Pi cotransport induced a significant depolymerization of actin filaments that was necessary for the Pi