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Regulation of actin dynamics by PI(4,5)P_2 in cell migration and endocytosis

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The actin cytoskeleton is indispensable for several cellular processes, including migration, morphogenesis, polarized growth, endocytosis, and phagocytosis. The organization and dynamics of the actin cytoskeleton in these processes are regulated by Rho family small GTPases and kinase-phosphatase pathways. Moreover, membrane phospholipids, especially the phosphatidylinositol phosphates have emerged as important regulators of actin dynamics. From these, PI(4,5)P_2 is the most abundant at the plasma membrane, and directly regulates the activities and subcellular localizations of numerous actin-binding proteins. Here, we discuss recent studies demonstrating that actin-binding proteins interact with PI(4,5)P_2-rich membranes through drastically different affinities and dynamics correlating with their roles in cytoskeletal dynamics. Moreover, by using mesenchymal cell migration and clathrin-mediated endocytosis as examples, we present a model for how interplay between PI(4,5)P_2 and actin-binding proteins control the actin cytoskeleton in cells.

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Introduction

Coordinated polymerization of actin filaments against the plasma membrane produces forces for the generation of membrane protrusions for cell migration and morphogenesis, as well as plasma membrane invaginations for endocytotic processes. Actin filaments, together with myosin II filaments, also assemble into diverse contractile arrays such as stress fibers, muscle myofibrils, and the actomyosin cortex, where force is produced by sliding of actin filaments along bipolar myosin II filaments [1,2]. Actin filaments do not work in isolation in these processes, but their dynamics and three-dimensional organization are controlled by a large array of actin-binding proteins. These proteins can for example control actin filament nucleation (e.g. formins, Arp2/3 complex), filament elongation (e.g. VASP and heterodimeric capping protein), filament disassembly (e.g. ADF/cofilin and gelsolin), actin monomer pool (e.g. profilin, twinfilin and cyclase-associated protein), as well as cross-link actin filaments to each other (e.g. α-actinin) or to the plasma membrane (ezrin–radixin–moesin family proteins) [3].

Biochemistry of PI(4,5)P_2 — actin-binding protein interplay

The activities of actin-binding proteins in cells are precisely regulated through kinase-phosphatase networks, small GTPases, and membrane phospholipids. From the phospholipids, especially phosphatidylinositol phosphates, PI(4,5)P_2, PI(3,4)P_2 and PI(3,4,5)P_3, have been established as central regulators of the actin cytoskeleton. PI(3,4,5)P_3 is a signaling lipid that is typically present in the plasma membrane at very low concentrations. It controls the actin cytoskeleton mainly through activating the guanine exchange factors of Rho-family small GTPases. PI(3,4)P_2 is also typically present in the plasma membrane at relatively low concentrations and contributes especially to late stages of endocytosis. PI(4,5)P_2, however, is present in the plasma membrane at high concentrations (and may constitute up to 1–3% of the plasma membrane lipids), and regulates the actin cytoskeleton by interacting directly with several central actin-binding proteins [4]. Moreover, PI(4,5)P_2 binds many signaling proteins as well as Bin/Amphiphysin/Rvs (BAR) domain scaffolding proteins, which interact with actin-binding proteins to control their activities of subcellular localization [4,5].

Several central actin-binding proteins including profilin, cofilin, twinfilin, formins, N-WASP, and ezrin/radixin/moesin (ERM) interact with PI(4,5)P_2. Typically, those proteins that drive actin filament disassembly or prevent actin filament assembly are inhibited by interactions with PI(4,5)P_2, whereas those proteins that promote actin filament nucleation/polymerization are up-regulated through interactions with PI(4,5)P_2 [4]. Recent work revealed that actin-binding proteins interact with membranes via similar multivalent electrostatic interactions without specific binding pockets or penetration into the lipid bilayer [6••,7]. However, the membrane binding affinities and dynamics of the actin-binding proteins are drastically different. Moreover, actin-binding proteins sense different ranges of PI(4,5)P_2 densities, which may

define their subcellular localization. Profilin and cofilin exhibit transient, low-affinity interactions with phosphoinositide-rich membranes at physiological salt concentrations. Thus, they cannot reside in the plasma membrane for longer periods of time, but are expected to mainly function at a distance from the plasma membrane to regulate actin filament disassembly and monomer recycling. By contrast, formin Dia2 and N-WASP, which promote actin filament nucleation and assembly, display relatively high affinity, stable interactions with phosphoinositide-rich membranes. Importantly, profilin, cofilin, Dia2, and N-WASP require for membrane-binding high (>5%) 'stimulus-responsive' $PI(4,5)P_2$ density, which can be achieved via increased $PI(4,5)P_2$ synthesis or clustering [6••,8]. This $PI(4,5)P_2$ density may correspond to the one present in extending lamellipodia, where Dia2 and N-WASP localize and promote actin filament assembly. However, ezrin and moesin, which function as cross-linkers between the plasma membrane and the actin cytoskeleton, bind membranes containing much lower (1%) $PI(4,5)P_2$ density. Moreover, ezrin and moesin bind membranes with very high affinity and low dissociation dynamics, making them suitable for stably cross-linking actin filaments to the cell cortex [6••]. Thus, the $PI(4,5)P_2$ binding affinities of actin-binding proteins, as well as the phosphoinositide-densities required for their interactions with membranes, correlate precisely with their functions in cytoskeletal dynamics (Figure 1).

Cellular roles of $PI(4,5)P_2$ in regulating the actin cytoskeleton

Several studies demonstrated that an increase in plasma membrane $PI(4,5)P_2$ results in elevated actin filament assembly, whereas depletion of $PI(4,5)P_2$ leads to diminished actin filament assembly and defects in actin-dependent cellular and developmental processes [4]. In the following chapters, we focus on the cellular roles of $PI(4,5)P_2$ in actin dynamics by using cell migration and clathrin-mediated endocytosis as examples. In addition to $PI(4,5)P_2$, other phosphoinositides, especially $PI(3,4)P_2$ and $PI(3,4,5)P_3$, were linked to actin dynamics in several studies [4,9–11,12•], but are not extensively discussed below.

Cell migration

Cell migration is critical for development and physiology of multicellular animals. The two most thoroughly characterized cell migration types are *mesenchymal*, adhesion-dependent migration, and *amoeboid* migration mode that is driven by contractile actomyosin cortex of the cell [13]. From these, the role of phosphoinositides in regulating the actin cytoskeleton is better established in the mesenchymal migration mode, and therefore this will be discussed in more detail.

Mesenchymal cell migration is driven by Arp2/3-nucleated, branched actin filament networks of thin sheet-like lamellipodial protrusions at the leading edge of the cell. The coordinated polymerization of actin filaments against the membrane promotes advancement of the leading edge. Actin filament assembly at the membrane is balanced by ADF/cofilin-mediated filament disassembly at the proximal regions of the lamellipodial actin filament network [3]. In addition to the branched lamellipodial actin network, thin finger-like actin filament protrusions, called filopodia, extend from the leading edge. These structures are filled by a tightly-packed bundle of actin filaments, and they are important for the cell to sense its environment. Finally, mesenchymal cell migration depends on focal adhesions, which are complex, multi-protein structures that link the actin cytoskeleton to the extracellular matrix through integrins and actin-associated proteins such as talin, vinculin, and α-actinin [13].

$PI(4,5)P_2$ is central for cell adhesion during motility. Local synthesis of $PI(4,5)P_2$ by PIP kinase Type I γ (PIPKIγ) in focal adhesions is critical for actin-integrin force coupling and thus for integrin-mediated cell adhesion [14]. $PI(4,5)P_2$ also binds several focal adhesion proteins such as vinculin, talin, kindlin, and α-actinin [4,15]. For example, talin interacts with $PI(4,5)P_2$-rich membranes through its FERM domain and this interaction is important for releasing the auto-inhibited conformation of the protein [16,17]. Moreover, $PI(4,5)P_2$ interacts with and activates vinculin, an actin-binding protein that links the adhesion complex to actin filaments at focal adhesions [18]. These data provide an explanation why $PI(4,5)P_2$ is required for the formation of focal adhesions in migrating cells.

Studies using specific PH domains as probes revealed that $PI(4,5)P_2$ also accumulates to the actin-rich leading edge lamellipodium [19]. Acute depletion of $PI(4,5)P_2$ results in retraction of the actin-rich leading edge, demonstrating the importance of this phosphoinositide in the generation and maintenance of lamellipodial protrusions [20]. However, $PI(4,5)P_2$ may have more complex and cell-type specific roles in cell migration. This is because in rapidly moving cells, such as neutrophils, $PI(4,5)P_2$ regulates the myosin II-driven retraction of the cell rear, and in amoeboids altering $PI(4,5)P_2$ levels results in changes in their migratory mode [21•,22].

At lamellipodium, $PI(4,5)P_2$ regulates the functions of several actin-binding proteins such as Dia1 and Dia2 formins and N-WASP. These proteins shuttle between closed auto-inhibited and open active conformations. In the case of N-WASP, which is an activator of actin-nucleating Arp2/3 complex, interactions with $PI(4,5)P_2$ contribute to conversion of the protein to an active form at the plasma membrane [23,24]. In the case of Dia1 and Dia2 formins, which promote actin filament nucleation and polymerization, interactions with $PI(4,5)P_2$ appear to be important for their targeting to the $PI(4,5)P_2$-rich

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