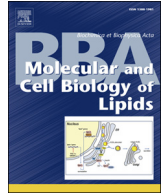




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Review

Phosphoinositides in the regulation of actin cortex and cell migration[☆]Kazuya Tsujita^{*}, Toshiki Itoh^{*}

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ABSTRACT

In order for the cell to function well within a multicellular system, the mechanical properties of the plasma membrane need to meet two different requirements: cell shape maintenance and rearrangement. To achieve these goals, phosphoinositides play key roles in the regulation of the cortical actin cytoskeleton. PI(4,5)P₂ is the most abundant phosphoinositide species in the plasma membrane. It maintains cell shape by linking the actin cortex to the membrane via interactions with Ezrin/Radixin/Moesin (ERM) proteins and class I myosins. Although the role of D3-phosphoinositides, such as PI(3,4,5)P₃, in actin-driven cell migration has been a subject of controversy, it becomes evident that the dynamic turnover of the phosphoinositide by the action of metabolizing enzymes, such as 5-phosphatases, is necessary. Recent studies have revealed an important role of PI(3,4)P₂ in podosome/invadopodia formation, shedding new light on the actin-based organization of membrane structures regulated by phosphoinositide signaling. This article is part of a Special Issue entitled Phosphoinositides.

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1. Introduction

In most eukaryotic cells, the plasma membrane (PM) closely adheres to the actin cortex, a thin network of actin filaments. It has become evident that this PM–actin cortex interaction is central to the regulation of the mechanical properties of the cell membrane. The membrane mechanics are important for the generation and maintenance of the overall cell architecture, as well as local membrane domains such as the apical microvilli [1]. On the other hand, the actin cortex needs to rapidly rearrange or locally dissociate from the membrane during cell shape changes such as membrane protrusions for cell motility or membrane invagination during endocytosis, because these phenomena are accompanied by dynamic deformations of the PM that are resisted by the force produced by PM–actin cortex adhesions [2]. Phosphoinositides, in particular phosphatidylinositol 4,5-bisphosphate (PI[4,5]P₂), have been recognized as crucial interfaces between the PM and the cytosolic proteins that link the cytoskeleton to the membrane. Over the last three decades, considerable progress has been made for the identification of actin-binding proteins whose activities are fine-tuned by direct interactions with PI(4,5)P₂ as well as other phosphoinositides [3–5]. Importantly, recent studies have revealed that PI(4,5)P₂ and its binding proteins are key regulators of the PM mechanical characteristics [6–10]. Given that the cellular levels of phosphoinositides are modified by phosphoinositide-metabolizing enzymes, the phospholipid turnover enables cells to change and maintain their shape according to the

extracellular environment, through the regulation of reversible associations between the PM and actin cortex. In this review, we focus on recent progress in the understanding of how phosphoinositides regulate actin-based cellular dynamics. First, we provide an overview of the proposed mechanisms on how phosphoinositide-binding “linker” proteins create PM–actin cortex adhesions that play important roles in cell migration driven by actin polymerization. We also discuss the roles of D3-phosphoinositides in directed cell migration during chemotaxis. Finally, the specific involvement of PI(3,4)P₂ in actin-based membrane structures such as circular dorsal ruffles and podosomes/invadopodia is introduced.

2. Regulation of PM–actin cortex adhesion by PI(4,5)P₂

The close interaction between the PM and actin cortex produces adhesion energy between the membrane and cytoskeleton, which is a critical determinant of cell morphology. Defining the force required for membrane deformation, the adhesion energy regulates several mechanical cellular functions, including cell motility, endocytosis/exocytosis, and cytokinesis. For example, a local area of the PM needs to be bent toward the cytosolic space during endocytosis in order to form membrane vesicles with diameters of several nanometers. To do this, physical forces applied to the PM, such as membrane tension, needs to be overcome by binding energy provided by cytosolic proteins with high affinity to the membrane. PM tension (also referred to as apparent membrane tension) is determined by the sum of in-plane tension, which is mostly dependent on hydrostatic pressure, and membrane–actin cytoskeleton adhesion energy (Fig. 1). Under resting states, it is thought that PM tension is largely determined by the adhesion energy [2]. Therefore, PM tension

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can be experimentally measured by the force needed to maintain a membrane tether pulled from the PM [6,11].

The tether force measurements using optical tweezers revealed that membrane–actin cytoskeleton adhesion energy is primarily regulated by PI(4,5)P₂, as both sequestration and depletion of PI(4,5)P₂ led to decreases in the adhesion energy [6]. Consistently, megakaryocytes from mice deficient in PIPKI γ , an enzyme that produces PI(4,5)P₂, exhibited a decrease in PM–cytoskeletal adhesion energy [12]. Because cells employ a subset of phosphoinositide kinases/phosphatases to control the amount of PI(4,5)P₂, phosphoinositide metabolism seems to be important for the regulation of PM–actin cortex adhesion. In addition, phospholipase C (PLC), which irreversibly hydrolyzes PI(4,5)P₂ into diacylglycerol (DG) and inositol 1,4,5-trisphosphate (Ins[1,4,5]P₃), plays an active role in the regulation of membrane–cytoskeleton adhesion. In fact, a decrease in the adhesion energy following platelet-derived growth factor (PDGF) stimulation is inhibited by the PLC inhibitor U73122 [6], suggesting that dissociations of the “linker” proteins such as those of the Ezrin/Radixin/Moesin (ERM) family (see following section) from the PM by PLC-mediated PI(4,5)P₂ hydrolysis contribute to rearrangement of the membrane–cytoskeleton interactions.

2.1. ERM-mediated PM–actin cortex adhesions

ERM proteins are major linkers between the PM and actin cytoskeleton, involved in cell shape changes such as directed cell migration and cell polarity formation [13] (Fig. 1). ERM proteins contain the band 4.1, Ezrin, Radixin and Moesin (FERM) domains that directly bind to PI(4,5)P₂ with high affinity [14], as well as C-terminal ERM-association domains (C-ERMAD) containing an F-actin-binding site, that collectively enable them to connect between the PM and the actin cortex [13]. It is believed that the ERM proteins are regulated by an intramolecular interaction between FERM domain and C-ERMAD that is relieved by PI(4,5)P₂-binding and phosphorylations at the C-terminal region [13,15]. Importantly, direct interaction with PI(4,5)P₂ is a requisite for the PM localization of ERM proteins, as mutants with FERM domains defective in PI(4,5)P₂-binding could not be recruited to the PM [16]. Hao et al. [17] demonstrated in lymphocytes that the PLC inhibitor blocks chemokine-induced dissociation of ERM proteins from the PM. The study also showed that acute depletion of PI(4,5)P₂ is sufficient for the dissociation of ERM proteins from the PM, indicating that PI(4,5)P₂

metabolism regulates the PM–actin cortex adhesion via ERM [17]. Such a mechanism is important for cell shape changes in lymphocytes during chemotaxis, because the dissociation of ERM proteins from the PM is correlated with the transition of cell morphology from a quiescent spherical state to a moving one with membrane protrusions [18]. It was also observed that cell spreading is enhanced by the reduction in membrane–cytoskeleton adhesion [19]. Indeed, atomic force microscopy (AFM) revealed that membrane–cytoskeleton adhesion energy is significantly reduced in ERM-deficient cells when compared to the control cells [7]. This observation was confirmed by a subsequent study that demonstrated a marked PM tension increase in lymphocytes expressing constitutively active ezrin [20]. Interestingly, ERM-deficient cells, as well as PI(4,5)P₂-depleted cells, exhibited the formation of more membrane blebs than wild type cells did [6,7]. Membrane blebs are formed by the local detachment of cortical actin cytoskeleton from the PM [2, 21]. Therefore, PLC-mediated decrease of PI(4,5)P₂ results in a release of ERM proteins, and thus the actin cortex from the PM, which leads to a cell shape change in response to extracellular stimuli.

2.2. Role of class I myosins

Another class of linker proteins between the PM and actin cortex is class I myosin family proteins (Fig. 1). Class I myosin is a member of the single-head myosin superfamily that acts as a membrane–cytoskeleton linker [8]. Similar to the ERM proteins, class I myosins have an acidic phospholipid-binding motif, called the C-terminal tail homology 1 (TH1) domain [8]. Originally, the TH1 domain was reported to bind to phosphatidylserine (PS) through electrostatic interactions [22]. Subsequent studies revealed that the TH1 domain shows higher affinity for PI(4,5)P₂ than PS [23], due to its putative PH domain structure [24]. PM-localization of class I myosins appears to be mediated by PI(4,5)P₂, as a mutant defective in PI(4,5)P₂-binding cannot be localized in the PM [24]. Importantly, class I myosins are thought to be critical regulators of PM tension by linking the actin cytoskeleton to the PM. PM tension in the brush border membrane of the small intestine isolated from myosin-1c knockout mice was significantly lower than that in wild type samples, whereas overexpression of myosin-1c resulted in an increase in membrane tension [11]. An independent study confirmed that membrane–cytoskeleton adhesion energy is reduced in myosin 1b-deficient mesoderm cells [7]. Interestingly, the TH1 domain alone exhibits a

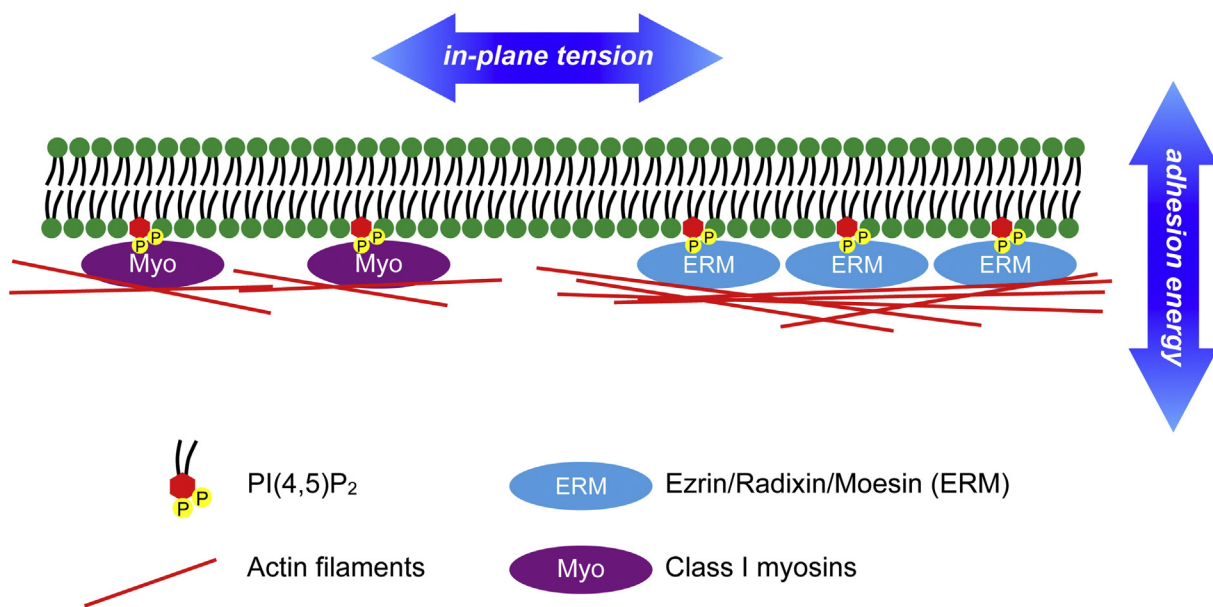


Fig. 1. Generation of the PM–actin cortex adhesion by PI(4,5)P₂. Phosphatidylinositol 4,5-bisphosphate (PI[4,5]P₂) connects “linker proteins” such as ERMs and class I myosins with membrane, generating adhesion energy between the PM and actin cytoskeleton. The apparent PM tension can be considered as the sum of the adhesion energy and in-plane tension applied to the PM (blue arrows).

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