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REVIEW

A biophysical perspective of the regulatory mechanisms of ezrin/radixin/moesin proteins

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Abstract

Many signal transductions resulting from ligand–receptor interactions occur at the cell surface. These signaling pathways play essential roles in cell polarization, membrane morphogenesis, and the modulation of membrane tension at the cell surface. However, due to the large number of membrane-binding proteins, including actin-membrane linkers, and transmembrane proteins present at the cell surface, the molecular mechanisms underlying the regulation at the cell surface are yet unclear. Here, we describe the molecular functions of one of the key players at the cell surface, ezrin/radixin/moesin (ERM) proteins from a biophysical point of view. We focus our discussion on biophysical properties of ERM proteins revealed by using biophysical tools in live cells and in vitro reconstitution systems. We first describe the structural properties of ERM proteins and then discuss the interactions of ERM proteins with $PI(4,5)P_2$ and the actin cytoskeleton. These properties of ERM proteins revealed by using biophysical approaches have led to a better understanding of their physiological functions in cells and tissues.

Keywords Ezrin/radixin/moesin proteins · Phosphatidylinositol 4,5-bisphosphate · Actin cytoskeleton · Membrane tension · GUVs · Supported lipid bilayers

Introduction

The cell surface is composed of the plasma membrane, membrane proteins, and a thin layer of crosslinked actin networks underlying the membrane (Chalut and Paluch 2016; Chugh et al. 2017; Chugh and Paluch 2018; Svitkina 2020; Sitarska and Diz-Muñoz 2020). The cell surface acts as an interface between cells and the extracellular environment. Many outside-in/inside-out signals are transduced through the cell surface. Thus, biochemical reactions occurring at the cell surface need to be precisely regulated. Fine-tuned biochemical signals at the cell surface result in the formation of distinct compartments in the plasma membrane, which in turn define cell morphology and polarization (Wakayama et al. 2011; Valderrama et al. 2012; Hebert et al. 2012; Fröse et al. 2018). For example, microvilli at the apical surface of epithelial cells have distinct proteins and lipid compositions compared to the rest of the plasma membrane (Ikenouchi 2018). One of the key players for this compartmentalization in the plasma membrane are ezrin/radixin/moesin (ERM) proteins (Neisch and Fehon 2011; McClatchey 2014; Chugh and Paluch 2018; Senju and Lappalainen 2019). ERM proteins are evolutionarily conserved protein families (Fig. S1a) (Mu et al. 2018). ERM proteins have high sequence homology (75.9% amino acid sequence identity between ezrin and radixin, and 72.2% amino acid sequence identity between ezrin and moesin). At the N-terminus of ERM proteins, there is a FERM domain which has a high sequence identity (85.9% amino acid sequence identity between ezrin and radixin and 85.4% amino acid sequence identity between ezrin and moesin) among human ERM proteins (Fig. 1a) (Tsukita and Yonemura 1999). The FERM domain is composed of a cloverleaf-like-shaped structure with three subdomains (F1, F2, and F3). Recent in vivo experiments showed that the binding of the FERM domain to phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$) is critical for the

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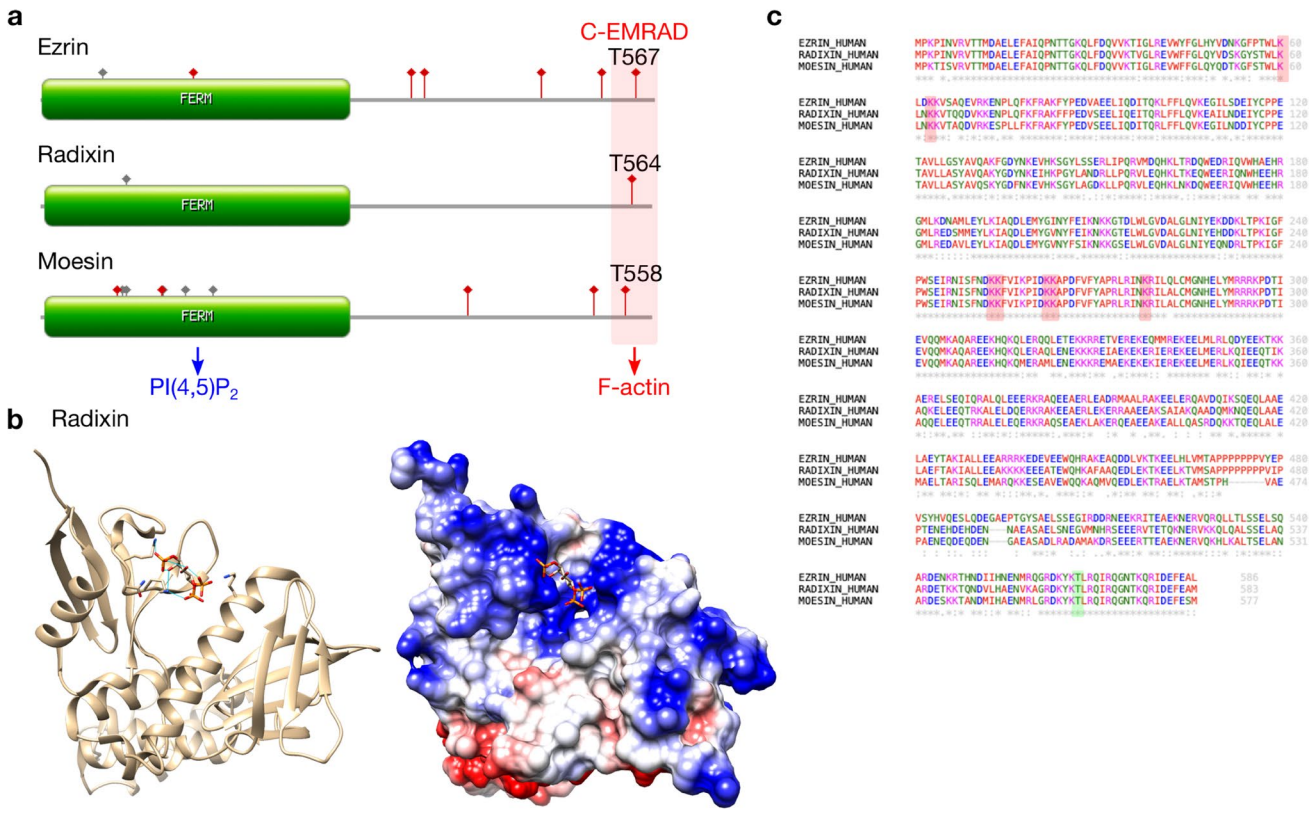

Fig. 1 (**a**) Domain structure and post-translational modification of *Homo sapiens* ERM proteins are generated using PROSITE. Red (depicted with square) indicates the phosphorylation site, and gray indicates other post-translational modifications. The FERM domain interacts with PI(4,5)P_2, and C-EMRAD interacts with the actin cytoskeleton. (**b**) Multiple sequence alignment of *Homo sapiens* ERM proteins is generated using Clustal Omega. Note that the phosphorylation sites of ROCK and other kinases (T567 for ezrin, T564 for radixin, and T558 for moesin, depicted with green box) and PI(4,5)P_2-binding sites (depicted with red box) responsible for the activation of ERM proteins are well-conserved. (**c**) Ribbon and coulombic surface of radixin FERM domain-inositol-(1,4,5)-triphosphate (IP3) complex structure (PDB: 1GC6). IP3 (the head group of PI(4,5)P_2) binds the negatively-charged surface (blue) of the radixin FERM domain. Hydrogen bonds between radixin FERM domain and three lysines (Lys60 and Lys63 from subdomain F1, and Lys278 from subdomain F3) and one asparagine (Asn62 from subdomain A) interacting with the three phosphate groups of IP3 are depicted by blue lines

function of ERM proteins (Ramalho et al. 2020). PI(4,5)P_2 is one of the phosphoinositides that is negatively charged and acts as a second messenger to play vital roles in signal transduction and protein localization at the membrane compartments in cells. At the C-terminus, ERM proteins have an actin-binding domain (C-ERMAD). Thus, ERM proteins play key roles in cell signaling, morphogenesis, motility, and metastasis partly by modulating the linkage between the actin cytoskeleton and the plasma membrane (Muriel et al. 2016; Schön et al. 2019).

ERM proteins can be scaffold proteins in the regulation of many fundamental physiological processes, such as the establishment of cell polarity (Wakayama et al. 2011; Valderrama et al. 2012; Hebert et al. 2012; Abeysundara et al. 2018; Fröse et al. 2018), microvilli formation (Zwaenepoel et al. 2012; Viswanatha et al. 2012, 2014; Dehapiot and Halet 2013), blebbing (Charras and Paluch 2008; Fritzsche et al. 2014; Ikenouchi and Aoki 2017; Hinojosa et al. 2017; Ikenouchi 2018), cell migration (Arpin et al. 2011; Parameswaran et al. 2011; Liu et al. 2012; Mak et al. 2012; Valderrama et al. 2012; Hsu et al. 2012; Saito et al. 2013; DeSouza et al. 2013; Parameswaran and Gupta 2013; Baeyens et al. 2013; García-Ortiz and Serrador 2020; Rahimi et al. 2021), cell division (Roubinet et al. 2011; Kunda et al. 2012; Hebert et al. 2012; Solinet et al. 2013; Sabino et al. 2015; Vilmos et al. 2016; Abeysundara et al. 2018; Yang et al. 2021; Rahimi et al. 2021), endocytosis (Li et al. 2017), exocytosis (Carmosino et al. 2012), phagocytosis (Mu et al. 2018; Roberts et al. 2020), podosome formation (Pan et al. 2013), transendothelial cell macroaperture (Stefani et al. 2017), cell–cell adhesions (Valderrama et al. 2012; Hsu et al. 2012; Amsellem et al. 2014), and epithelial-mesenchymal transition (Haynes et al. 2011; Wang et al. 2012; Fröse et al. 2018). Additionally, ERM proteins contribute to the modulation of some mechanical properties of the cell surface, such as tension, stiffness, and dynamics by regulating the actin cortex (Liu et al. 2012; Rouven Brückner et al. 2015; Stefani et al. 2017; Chugh and Paluch 2018; Roberts et al.

2020; Sitarska and Diz-Muñoz 2020). To accomplish the above-mentioned cellular processes, cells rely on the precise spatiotemporal regulations of ERM proteins via reversible activation cycles.

Although several cell types and tissues express more than one ERM protein, the expression levels of each ERM protein vary in cells and tissues according to their distinct functions (Fig. S1b) (Wang et al. 2012). For example, ezrin is highly expressed in intestinal epithelial cells, radixin in hepatocytes, and moesin in vascular endothelial cells (Fehon et al. 2010). Thus, although ERM proteins share high homology sequences, individual ERM proteins may have specific and unique physiological functions in different tissues.

In this review, we discuss several biophysical characterizations of ERM proteins, focusing on their activation upon PI(4,5)P_2-binding and phosphorylation, and the regulation of the dynamics of the actin cytoskeleton revealed by using biophysical tools in live cells and in vitro reconstitution systems.

ERM protein regulation in cells

The regulation (activation and inactivation) of ERM proteins is reversible and fine-tuned at the cell surface to achieve their physiological functions (Tachibana et al. 2015). The inactivated ERM proteins have a closed configuration as cytosolic monomers or dimers due to a head-to-tail intra or intermolecular interaction between the FERM domain and the C-ERMAD; in this closed configuration, the actin-binding site of ERM proteins is masked. "Opening up" ERM proteins requires FERM domain-PI(4,5)P_2 binding and post-translational modifications (Bosk et al. 2011; Jayasundar et al. 2012; Maniti et al. 2012; Shabardina et al. 2016; Lubart et al. 2018). So far, the precise mechanism of ERM protein regulation remains unclear.

The X-ray crystal structure of radixin has revealed that its FERM domain binds to the IP3 (head group of PI(4,5)P_2) (Fig. 1b) (Hamada et al. 2000). The interaction is based on two major binding sites: the "pocket" and the "patch" (two pairs of lysine residues). The Lys60, Lys63 and Lys278, and clustered patches Lys253-Lys254 and Lys262-Lys263 of subdomain F3 are responsible for PI(4,5)P_2 binding. These residues are well-conserved among the FERM domains of ERM proteins, indicating a similar binding mode to PI(4,5)P_2 (Fig. 1c). FERM domains have a certain structural orientation against the membrane, as determined by their PI(4,5)P_2 interactions. The patch is proposed to be more accessible than the pocket in autoinhibited moesin (Ben-Aissa et al. 2012). Thus, PI(4,5)P_2 may bind to the more accessible patch first and then to the pocket (Ben-Aissa et al. 2012).

Several post-translational modifications have been reported for ERM proteins. Of these, the phosphorylation of T567 for ezrin (*Homo sapiens*), T564 for radixin (*Homo sapiens*), and T558 for moesin (*Homo sapiens*) are well-conserved and critical for the activation of ERM proteins (Fig. 1c) (Pelaseyed et al. 2017; Lubart et al. 2018; Ramalho et al. 2020; 2017). In the closed conformation of ERM proteins, these phosphorylation sites are buried at the interface between the FERM domain and the C-ERMAD. The binding of the FERM domain to PI(4,5)P_2 changes the conformational structure of the ERM proteins to render the actin-binding site of the C-ERMAD more accessible for threonine phosphorylation (Bosk et al. 2011; Ben-Aissa et al. 2012; Braunger et al. 2014; Shabardina et al. 2016). Phosphorylation at the C-terminus of ERM proteins then "opens up" the proteins by the repulsive interaction between the FERM domain and the C-ERMAD due to the negative charge of the additional phosphate group. Thus, binding to PI(4,5)P_2 followed by the phosphorylation of threonine in the C-ERMAD cooperatively promotes the full activation of ERM proteins (Fig. 2) (Pelaseyed et al. 2017).

Phosphorylation of ERM proteins is specifically mediated by ROCK (Belkina et al. 2009). PKC isoforms (Wald et al. 2008; Hong et al. 2011), LOK/STK10 (Belkina et al. 2009; Viswanatha et al. 2012; Pelaseyed et al. 2017), SLK (Viswanatha et al. 2012), and JNK (Pan et al. 2013) can also phosphorylate the above-mentioned sites of ERM proteins; however, their distinct mechanisms of physiological regulation remain elusive. Of note, LOK and SLK both localize at the apical membrane of epithelial cells, where PI(4,5)P_2 is present, and specifically phosphorylate ezrin at the cell surface (Viswanatha et al. 2012; Pelaseyed et al. 2017).

Phosphorylated ERMs are dephosphorylated by several phosphatases, such as MLCP (Kovacs-Kasa et al. 2016) and protein phosphatase 1 (PP1) (Yang et al. 2012; Kunda et al. 2012; Canals et al. 2012). These phosphatases inactivate ERM proteins to form a closed conformation in the cytoplasm. In the closed conformation, the FERM domain of ERM proteins interact with C-ERMAD in a head-to-tail manner by masking the membrane and actin-binding surfaces (Ben-Aissa et al. 2012; Jayasundar et al. 2012).

In addition to filamentous actin (F-actin) and microtubules (see below), ERM proteins directly or indirectly bind to several other proteins (Fig. S1c), for example, scaffold proteins (IQGAP1, NHERF-1, NHERF-2), actin-regulatory proteins (ELMO, EPS8, RhoGAP conundrum), transporter proteins (anoctamin-1, aquaporin-2, NHE-3, NKCC2), receptors (CD44, thrombomodulin), metal-binding proteins (PDZD8, S100-A4), and adhesion molecules (ICAM-2, podocalyxin, TMIGD1) Henning et al. 2011; Carmosino et al. 2012; Hsu et al. 2012; Perez-Cornejo et al. 2012; Zwaenepoel et al. 2012; Boratkó and Csortos 2013; Neisch et al. 2013; Amsellem et al. 2014; Liu et al. 2014; Singh et al. 2014; Viswanatha et al. 2014; Chen et al. 2015; Epting et al. 2015; Nammalwar et al. 2015; Biri-Kovács et al.

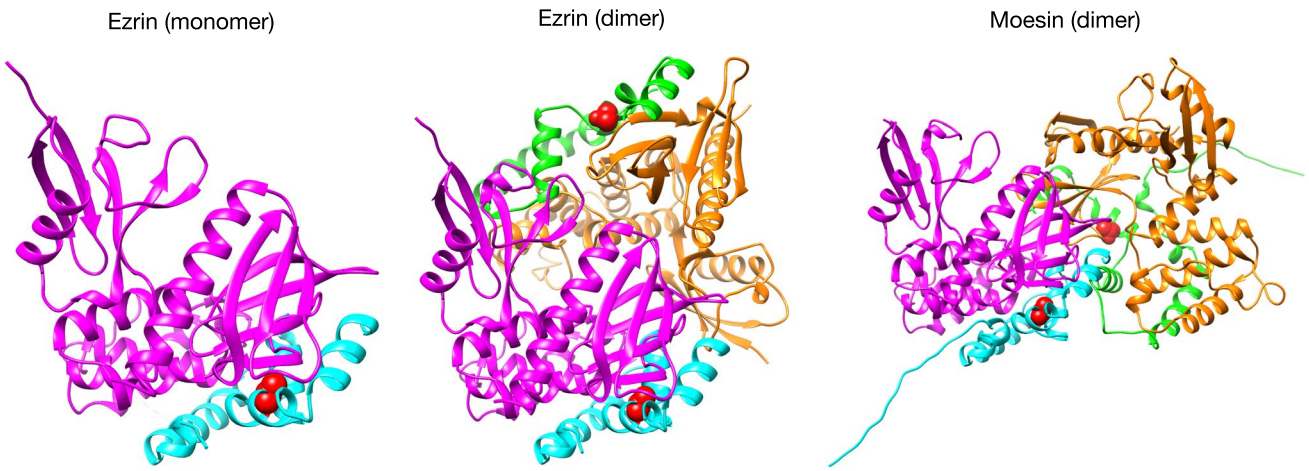

Fig. 2 Crystal structures of auto-inhibition with head-to-tail interaction of ERM proteins (PDB: 4RM9 for ezrin monomer, PDB: 4RM8 for ezrin dimer, PDB: 1EF1 for moesin dimer). The phosphorylation sites buried at the interface between the FERM domain and the C-ERMAD are depicted with red sphere

2017; Li et al. 2017; Fröse et al. 2018; Rahimi et al. 2021). Upon PI(4,5)P_2 binding, some of the interaction partners of ERM proteins bind selectively with either phosphorylated or non-phosphorylated forms of ERM proteins (Viswanatha et al. 2013; Biri-Kovács et al. 2017). Although validations of this interactome are ongoing, the activation of ERM proteins involves several selective protein–protein interactions which are spatiotemporally regulated at specific subcellular compartments.

ERM proteins link the cytoskeleton to the plasma membrane

Activated ERM proteins can link the actin cytoskeleton to the plasma membrane or integral membrane proteins (CD43/44, CFTR, ICAM-1/2, and NHE3) (Tsukita and Yonemura 1999; Bretscher et al. 2002; Fehon et al. 2010; Neisch and Fehon 2011; Braunger et al. 2014). This interaction is achieved directly, or indirectly with scaffold proteins, for example, NHERF (Terawaki et al. 2006; Kawaguchi et al. 2017). The interaction between ERM proteins and F-actin with or without their interaction partners is essential for regulating cortical actin assembly for instance in microvilli of epithelial cells and filopodia of migrating cells (Sauvanet et al. 2015). Thus, ERM proteins regulate spatiotemporal turnover of actin assembly and disassembly in specific subcellular structures (Muriel et al. 2016). It was shown that moesin promotes F-actin network formation on early endosomes. Besides actin, moesin has also been demonstrated to interact with microtubules (Solinet et al. 2013; Lubart et al. 2018). It was shown that moesin directly binds to microtubules upon phosphorylation in vitro and stabilizes microtubules at the cell cortex in vivo. This ERM–microtubule interaction is required for regulating spindle organization during metaphase and cell shape transformation after anaphase onset; however, the detailed molecular mechanisms of ERM–microtubule interaction and the corresponding physiological roles remain elusive.

ERM protein dynamics on the membrane and with the actin cytoskeleton

The complexity of studying ERM–membrane interactions in cells can be circumvented by using purified ERM proteins and model membranes (Maniti et al. 2013; Sarkis and Vié 2020). The methodological advances have enabled the generation of model membranes containing PI(4,5)P_2 (Carvalho et al. 2008; Maniti et al. 2013; Drücker et al. 2014; Beber et al. 2019; Schäfer et al. 2020). In the past decades, rich and insightful information on how ERM proteins are activated and how they bind to PI(4,5)P_2 and F-actin have been provided by in vitro reconstitution systems composed of purified ERM proteins and model membranes. Typical model membranes are supported lipid bilayers (SLBs), multilamellar vesicles (MLVs, typical diameters larger than 500 nm), small unilamellar vesicles (SUVs, typical diameters smaller than 100 nm), large unilamellar vesicles (LUVs, typical diameters of 100–1000 nm), and giant unilamellar vesicles (GUVs, typical diameters larger than 1 µm) (Lin et al. 2010; Sezgin and Schwille 2012; Dimova and Marques 2019).

MLVs, LUVs, and SUVs have been intensively used to study protein–membrane interactions quantitatively, for example, by using EM microscopy, co-sedimentation assays, and spectroscopic techniques (Blin et al. 2008; Maniti et al. 2012; Senju and Zhao 2021; Senju et al. 2021). These vesicles have a relatively smaller size compared to

cells. It is noteworthy that when using SUVs, their membrane curvature could contribute to how proteins interact with the membranes. This is because the diameter of SUVs, which is usually on the order of 100 nm, is only a few times larger than protein sizes; for instance, Bin/amphiphysin/Rvs (BAR) domains have a length of around 20 nm (Carman and Dominguez 2018). Therefore, when binding on SUVs, proteins may be bent or may have a certain configuration that would allow binding to the curved SUV surfaces. Besides, the curvature of SUVs could be quite different from that of the membranes of cellular organelles, and hence this should be considered when comparing lipid–protein interactions on SUVs with those in cell membranes. Furthermore, as the membrane tension of these three vesicle types is generally high compared with that of GUVs, protein-driven membrane deformation, if any, is not readily assessable.

Using PI(4,5)P_2-containing MLVs, LUVs, or SUVs combined with co-sedimentation assays or fluorescence correlation spectroscopy (FCS), the binding affinities and modes of ERM proteins with PI(4,5)P_2 have been obtained (Blin et al. 2008; Maniti et al. 2013; Senju et al. 2017). The apparent dissociation constant (Kd) is around 5 μM for ezrin and moesin to PI(4,5)P_2-containing liposomes whose lipid compositions are similar to that of the plasma membrane. Cooperative binding of PI(4,5)P_2 with ERM proteins has also been observed (Jayasundar et al. 2012; Lubart et al. 2018). Thus, the initial binding of one PI(4,5)P_2 molecule to ERM proteins may promote additional PI(4,5)P_2 binding, thereby inducing PI(4,5)P_2 clustering.

GUVs have been well-recognized as an important model system to study protein–membrane interactions given that GUV membranes resemble many, if not all, properties of cellular membranes (Litschel et al. 2021). Some key advantages of using GUVs are (1) micron-size allowing readily observation by conventional microscopy; (2) deformable, free-standing membranes; and (3) readiness for optical, mechanical and chemical manipulations, for instance to change membrane tension or GUV shapes.

Fluorescence recovery after photobleaching (FRAP) experiments have revealed that ezrin and moesin are stably associated to PI(4,5)P_2-containing GUV membranes, whose lipid composition is similar to that of the plasma membrane (Fig. 3) (Senju et al. 2017). Previous FRAP studies in epithelial cell microvilli and melanoma cell blebs have indicated the presence of more than two pools of ezrin fluorescence recovery with different timescales (Coscoy et al. 2002; Fritzsche et al. 2014). The fast turnover pool of ezrin in cell blebs reflects its binding and unbinding to F-actin (Fritzsche et al. 2014). Interestingly, in microvilli, ezrin was found to be "immobile" when binding to F-actin. These different observations indicate the plausible contribution of membrane shape (the rather flat membrane in blebs and the highly curved membrane in microvilli) in the physiological function of ERM proteins. In addition to the change in the binding/unbinding constant owing to the differences in membrane curvatures, it could also be difficult for proteins to diffuse in or out of the microvilli because of their small diameter. In cellular

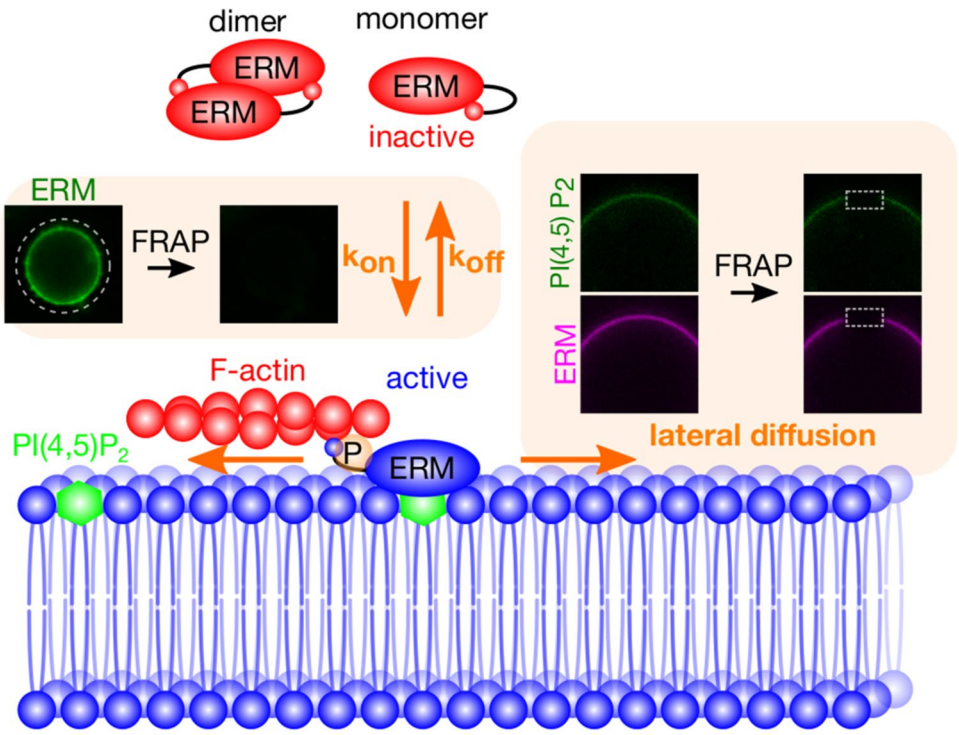

Fig. 3 A working model for the dynamics of ERM proteins on PI(4,5)P_2-containing membranes. The association/dissociation of ERM proteins with membranes, and the lateral diffusion of ERM proteins and PI(4,5)P_2 can be analyzed by using giant unilamellar vesicles (GUVs) and fluorescent recovery after photo bleaching (FRAP)

structures and on GUVs, the slow ezrin turnover indicates that ezrin binds to PI(4,5)P_2-containing membranes with high affinity and slow dissociation dynamics. Furthermore, the FERM domain of ezrin was found to regulate PI(4,5)P_2 lateral diffusion by slowing it down (Senju et al. 2017). This slow diffusion is postulated to be the result of protein crowding or the oligomerization of the ezrin on the membrane. PI(4,5)P_2 is known to be clustered in specific microdomains in cells (Wen et al. 2021). Thus, ERM proteins would compensate for the negative charge of the PI(4,5)P_2 head group by binding with their positively charged residues on the membrane. Recently, using a newly developed tool, bioluminescence resonance energy transfer (BRET)-based conformational biosensors, a pool of closed inactive but membrane-associated ezrin was found in cells. This pool of ezrin was rapidly activated before the further recruitment of other closed inactive ezrin from the cytosol to the plasma membrane. This recent work provides new insights into the long-standing question of the mechanism of ERM protein regulation.

SLBs are lipid bilayers formed on solid substrates such as glass and mica. Thanks to the solid support, one can change buffers, and protein type and concentration readily, for instance by using microfluidic devices. Additionally, since the membrane is sitting on top of the substrate, one can easily implement total internal reflection fluorescence (TIRF) microscopy to achieve an outstanding signal-to-noise ratio, as well as several microscopy techniques such as FCS (Haustein and Schwille 2007) and fluorescence resonance energy transfer (FRET), and super-resolution microscopies such as direct stochastic optical reconstruction microscopy (dSTORM) and stimulated emission depletion (STED) microscopy to reveal protein clustering and assembly at a nanometer resolution (Mashaghi et al. 2014; Sezgin 2017; Migliorini et al. 2018; Barbotin et al. 2020). A series of studies using SLBs and purified ezrin, for instance the mutant ezrin T567D that mimics the phosphorylation of the threonine residue, has been carried out (Bosk et al. 2011; Shabardina et al. 2016). They showed that the phosphorylation of ezrin T567 enhances its conformational change to the active state upon PI(4,5)P_2-binding, which is capable of binding to F-actin. Recently, the roles of actin crosslinkers, fascin and α-actinin, in the architecture of the ezrin-mediated actin cortex assembled on PI(4,5)P_2-SLBs were investigated (Schön et al. 2019). The addition of these crosslinkers was found to influence the architecture of the ezrin-mediated actin network. Moreover, ezrin can be recruited to negatively curved membrane tubes via a direct interaction with the I-BAR domain of IRSp53, which is reminiscent of cellular filopodia (Tsai et al. 2018). The molecular details provided in the above-mentioned studies contribute to our understanding of the vital roles of PI(4,5)P_2 and the actin cytoskeleton in ERM protein association and signaling in cells.

Conclusions and future perspectives

ERM proteins have many vital physiological functions in cell polarity, morphogenesis, and the modulation of membrane tension, partly via their actin–membrane linking ability. To carry out this wide range of functions, ERM proteins orchestrate the assembly of protein complexes at the cell surface.

This review highlights the need for further investigation of the interactions of PI(4,5)P_2 molecules with the FERM domain of ERM proteins, for example, their cooperative or non-cooperative binding. The physiological role of moesin and microtubule interaction, and moesin-mediated interplay between the actin cytoskeleton and microtubule need to be investigated. Additionally, it remains unclear how PI(4,5)P_2 hydrolysis may contribute to the inactivation of ERM proteins and induce their subsequent dissociation from the plasma membrane in vivo. A better understanding of the physiological roles of post-translational modifications, other than the well-characterized threonine phosphorylation at the C-ERMAD of ERM proteins, is also needed. To gain further insights into the regulation of ERM proteins, the clarification of whether ERM proteins function as monomers, dimers with a head-to-tail orientation (Phang et al. 2016; Lubart et al. 2018), or oligomers at the cell surface (Lubart et al. 2018) is needed. The generally accepted knowledge in cells is that the monomeric form of ERM proteins is active and localized at the plasma membrane, whereas the dimeric form is inactive and mostly found in the cytoplasm. The recently found pool of inactive ERM proteins that are stably associated with the plasma membrane calls for future studies to answer this question in cell biology. Little is known regarding how ERM proteins are spatiotemporally regulated in vivo. Biophysical approaches using the well-defined systems that we have introduced here will certainly provide new insights into these fundamental questions.

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Code availability Not applicable.

Declarations

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Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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