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Merlin and the ERM proteins – regulators of receptor distribution and signaling at the cell cortex

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Abstract

Recent studies highlight the importance of the distribution of membrane receptors in controlling receptor output and in contributing to complex biological processes. The cortical cytoskeleton is known to affect membrane protein distribution but the molecular basis of this is largely unknown. Here, we discuss the functions of Merlin and the ERM proteins both in linking membrane proteins to the underlying cortical cytoskeleton and in controlling the distribution of and signaling from membrane receptors. We also propose a model that could account for the intricacies of Merlin function across model organisms.

Introduction

Increasing evidence indicates that the distribution and aggregation of receptors across the plasma membrane is exquisitely choreographed, particularly in the highly organized tissues of multicellular organisms. External physical cues such as contact with an adjacent cell or basement membrane can clearly affect the positioning of various adhesion receptors within the membrane; however, it is now appreciated that signaling from many types of receptors can also be regulated intrinsically at the level of the distribution of receptors across the membrane. This distribution is primarily governed by protein- and/or lipid-mediated complex assembly, which, in turn, can affect receptor trafficking and signaling. The interface between the membrane and the underlying cortical cytoskeleton has an active and dynamic role in this choreography.

Local changes in membrane–cytoskeleton interaction can affect membrane protein complexes and cortical cytoskeleton organization, contributing to the establishment and maintenance of architecturally and functionally distinct membrane compartments. Proteins such as ankyrin, spectrin, filamin and myristoylated alanine-rich C kinase substrate (MARCKS) have a key role in this process [1–3]. In addition, multiple lines of evidence indicate that proteins containing Four point one, Ezrin, Radixin, Moesin (FERM) domains are important mediators of dynamic membrane–cytoskeleton adhesion (Box 1). Here, we consider recent evidence that the FERM-domain-containing neurofibromatosis type 2 (NF2) tumor suppressor, known as Merlin, and the closely related Ezrin, Radixin and Moesin (ERM) proteins, function both to stabilize the

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membrane–cytoskeleton interface and to organize the distribution of, and signaling by, membrane receptors. First, we consider how the distribution of membrane receptors is controlled at the membrane–cytoskeleton interface and then describe the role of FERM-domain proteins, and Merlin and ERM (Merlin/ERM) proteins specifically, in regulating receptor distribution and function in different model organisms. We ultimately propose a unified model to explain the available data and complex biological consequences attributed to Merlin/ERM function across species.

Plasma membrane organization

The cortical cytoskeleton provides both tensile architectural support for cellular appendages such as microvilli and a scaffold for membrane protein complexes that partition the membrane–cytoskeleton interface into physically and functionally distinct domains. Several factors affect the assembly of specialized membrane protein complexes which, in turn, contribute to the formation of larger scale membrane appendages. For example, extracellular cues effect local changes in the delivery and retention of membrane receptors including those involved in cell–extracellular matrix or cell–cell attachment. In addition, the lipid composition of the plasma membrane is heterogeneous and also locally regulated; the existence of distinct lipid environments affects membrane protein aggregation, thereby cooperating to establish distinct membrane compartments. Finally, the controlled localization and activation of specialized scaffold proteins can assemble and stabilize multiprotein complexes at the membrane.

A key feature of membrane–cytoskeleton interactions is their ability to be regulated in a highly dynamic fashion. Adhesion between the cortical cytoskeleton and overlying plasma membrane is mediated by multiple weak, reversible interactions between cytoskeletal proteins and membrane lipids and by interaction of the cortical cytoskeleton with transmembrane receptors and associated protein complexes [3,4]. Membrane-associated cytoskeletal proteins are often conformationally regulated by small molecules, such as phospholipids, that are associated with the plasma membrane. Changes in membrane–cytoskeleton adhesiveness alter both the biophysical properties of the membrane and the distribution of membrane receptor complexes and associated plasma membrane domains.

The molecular basis of how the cortical cytoskeleton impacts membrane receptor distribution is not well understood. A role for the cortical cytoskeleton in the internalization and movement of endocytic vesicles is well established [5]. However, increasing evidence indicates that the cortical cytoskeleton is also an active participant in establishing and reorganizing plasma membrane domains, which in turn could affect the endocytic routes chosen by certain receptors. Single particle tracking of individual receptors at the cell surface indicates that the cortical cytoskeleton and associated membrane proteins can form 'fences' or 'corrals' that restrain receptors within plasma membrane compartments, impeding their lateral movement and increasing the likelihood that they will aggregate [6]. Alternatively, the cortical cytoskeleton could actively tether receptors at the plasma membrane surface, potentially in close proximity to downstream, cytoplasmic components of a signal transduction pathway. Either way, specialized membrane–cytoskeleton linking proteins are poised to have active roles in membrane–protein distribution and signal transduction.

FERM-domain-containing proteins integrate multiple signals at the cell cortex

Studies of the mature erythrocyte cytoskeleton provide both a historical foundation and a useful model for considering the interface between membrane receptors and the cortical cytoskeleton [2]. The red blood cell membrane adheres tightly to the underlying spectrin–actin cytoskeleton through direct association of spectrin with membrane lipids and through the membrane–

cytoskeleton linking proteins ankyrin and Protein 4.1, which interact with membrane receptors. This tight linkage is associated with the rigid and static elliptical shape of the erythrocyte relative to other cells, and with restricted mobility of membrane proteins [3]. Protein 4.1, the prototype of the FERM-domain protein superfamily (Box 1), facilitates the spectrin–actin interaction through a carboxyl-(C)-terminal domain, and promotes a stable association between Glycophorin C and the membrane-associated guanylate kinase (MAGUK) p55 through its amino-(N)-terminal FERM domain, immobilizing Glycophorin C in the membrane [2]. Thus, Protein 4.1 can apparently simultaneously stabilize the cortical cytoskeleton, promote the association between membrane proteins and the cortical cytoskeleton, and assemble protein complexes at the membrane. It is not yet clear if these activities are regulated or if Protein 4.1 controls the activity of the membrane complexes that it assembles.

The NF2 tumor suppressor, Merlin, and the closely related ERM proteins form a subgroup of the Protein 4.1 superfamily [7]. Mounting evidence indicates that Merlin/ERM proteins can simultaneously provide regulated linkage between membrane proteins and the cortical cytoskeleton, and control the surface availability of certain membrane receptors (Figure 1). Furthermore, Merlin/ERM proteins can control signaling from members of the Rho family of small GTPases, probably by associating with Rho regulators or effectors such as Rho GDI or Pak [8–14].

Structural studies have provided important insight into how the architecture of Merlin/ERM proteins contributes to their function [15–19]. Merlin/ERM proteins are composed of an N-terminal FERM domain, an ensuing α -helical domain and a C-terminal domain that includes an actin-binding module in the ERM proteins but not in Merlin. The FERM domain adopts a cloverleaf structure composed of three interdependent lobes and seems designed to bring multiple proteins together at the membrane [15]. This is well supported by the long list of proteins that have been reported to interact with the Merlin/ERM FERM domain, including transmembrane receptors such as CD43 and CD44, and the tandem PDZ-domain-containing adapters Na⁺/H⁺ exchanger regulatory factor (NHERF)-1 and -2, which in turn associate with a variety of membrane receptors [20] (Table 1). The FERM domain can also associate with regulators of Rho GTPase signaling [11, 14, 21–23].

The α -helical and C-terminal portions of Merlin/ERMs can fold back and envelop the FERM domain, masking all known sites of protein interaction in both the FERM and the C-terminal domains, including the ERM actin-binding domain [15, 16]. For the ERM proteins, this self-associated 'closed' conformation is inactive [7]. For Merlin, by contrast, evidence from studies of mammalian cells indicates that this is the active growth-suppressing conformation [24]. However, genetic studies in *Drosophila* indicate that the C-terminal interaction domain of Merlin (dMerlin) is dispensable, suggesting that the open form might be 'active' or at least that the regulation of Merlin activity might be more complex than a simple interconversion between 'open' and 'closed' states [23].

Self-association of Merlin/ERM proteins seems to be highly regulated through multiple mechanisms. Phosphorylation and lipid-binding are thought to weaken self-association by disrupting individual binding interfaces; multiple signals are probably required to completely disrupt this self-associated architecture and alter the state of Merlin/ERM activation [15, 16]. Thus, Merlin/ERMs, although held in check by self-association, seem poised to locally integrate multiple signals at the membrane and to transmit that information, in turn, to multiple intracellular effectors. Release of self-association also enables the membrane–cytoskeleton linking activity of the ERM proteins and, perhaps, Merlin.

Merlin/ERM-mediated membrane–cytoskeleton attachment

In an 'open', active conformation, the ERM C-terminal domain can directly bind to actin filaments. Local activation of the membrane–cytoskeleton linking activity of the ERM proteins is important during bleb retraction and drives crucial changes in cortical stiffness and spindle positioning that are necessary for successful progression through spindle assembly checkpoints during mitosis [25–27]. Defects in ERM-mediated membrane–cytoskeleton attachment and cortical tension have been proposed to contribute to the abnormal morphology of the apical membrane and associated apical junctions of ERM-deficient epithelia in the worm, fly and mouse *in vivo* [28–30]. In addition, studies in the fly indicate that ERM proteins also contribute to cortical actin function indirectly through their effects on the activity of the RhoA pathway [8].

Merlin lacks the C-terminal actin-binding domain present in the ERM proteins, but evidence indicates that Merlin associates with cortical actin and that the actin cytoskeleton is altered in the absence of Merlin [31–36]. Recent studies in mammalian cells suggest that the N-terminal 18 amino acids of Merlin, which are not present in the ERM proteins, are necessary for stable decoration of the cortical cytoskeleton and for Merlin-mediated membrane-receptor distribution and proliferation control [36]. Phosphorylation of this N-terminal extension on any or all of several serine residues might regulate the association of Merlin with the cortical cytoskeleton and influence actin cytoskeleton organization [35,36]. In addition, Merlin has been shown to negatively regulate Rac GTPase signaling, which itself has a major role in the regulation of cytoskeletal assembly and function [10,11].

Merlin might stabilize the membrane–cytoskeleton interface locally at sites of cell–cell contact (Figure 1b). Merlin localizes to cell–cell junctions in mammals and flies and is required for stable adherens junction formation in several types of mammalian cells [13,34,37,38], although adherens junction defects have not been reported in *Drosophila* Merlin mutants [23]. In primary mouse keratinocytes, the cortical actin ring is normally intimately associated with the apical junctions; this cortical actin ring collapses in the absence of Merlin, suggesting that Merlin might be important in stabilizing the junction–cortical actin interface in these cells [34]. Collectively, these studies underscore the notion that stabilization of the membrane–cytoskeleton interface is a crucial component of Merlin/ERM function.

ERM-controlled membrane-receptor complexes

In addition to stabilizing the membrane–cytoskeleton interface, an increasing number of studies now recognize that the ERM proteins also, probably simultaneously, affect the distribution and function of receptors at the plasma membrane. Here, we describe three examples that highlight the variety of ways in which the ERM proteins impact the distribution of membrane receptors. In each case, the control of individual membrane receptor complexes probably contributes to larger-scale membrane organization, perhaps through the ability of the ERM proteins to locally regulate Rho GTPase-dependent remodeling of the cytoskeleton.

Loss of Ezrin, the only ERM protein expressed in the mouse gut epithelium, leads to both a loss of apical membrane (brush border) integrity and failure of the ERM-binding adapter NHERF-1 to localize to the apical brush border, suggesting that brush border receptors that are localized or regulated by NHERF-1 are probably affected [30]. Indeed, intestinal function is compromised in these mice. Among the many interactions between NHERF-1 and transmembrane receptors in different cell types, the association of NHERF-1 with the cystic fibrosis transmembrane conductance regulator (CFTR) and Na⁺/H⁺ exchanger (NHE3) in the intestinal and colonic epithelium are the best studied [39] (Table 1). The CFTR and NHE3 perform major physiological roles in anion secretion and sodium absorption, respectively, in the gastrointestinal tract, and both interact directly with NHERF-1. Several models explaining

the functional consequences of Ezrin–NHERF-1 association with CFTR and NHE3 have been proposed, including roles in receptor recycling, dimerization, lateral mobility, surface retention and recruitment of regulatory proteins [39]. All involve the orchestrated assembly of multiprotein membrane complexes that associate with the cortical cytoskeleton. Indeed, the Ezrin–NHERF-1 association could regulate the activity of a particular receptor in multiple ways within the same cell, via distinct multiprotein complexes. The assembly of Ezrin–NHERF-1-associated complexes probably contributes to the higher order organization of the microvillus itself (for example, see Ref. [40]). Although it has not been studied in detail, there seems to be a single NHERF orthologue in *Drosophila*, called Sip-1. Curiously, although well conserved, *Drosophila* Sip-1 has only one PDZ domain instead of the tandem PDZ domains present in mammalian NHERF-1 and -2. Preliminary data indicate that Sip-1 interacts functionally with *Drosophila* Moesin (S.C. Hughes and R.G.F, unpublished).

The field of immunology provides a second example. Studies of T-cell interactions with chemokines and/or antigens reveal that the ERM proteins have a key role in establishing cortical asymmetry in unattached rounded-up cells by modulating both membrane–cytoskeleton interactions and membrane receptor distribution [41]. Instead of a smooth, homogeneous surface such as that exhibited by red blood cells, circulating T cells are covered with microvilli, to which adhesion receptors are differentially segregated. Experimental elimination of ERM expression in transformed T cells induces loss of microvilli, supporting a role for the ERM proteins in establishing or maintaining microvilli in these cells [42]. Certain low-affinity surface receptors localize to microvillus tips and mediate transient adhesive interactions between the T cell and endothelium, whereas high-affinity receptors tend to be excluded from microvilli [43–45]. Chemokine stimulation leads to ERM inactivation and microvillus breakdown, promoting redistribution of high affinity adhesion receptors, tight endothelial adhesion and migration through the vessel wall into the surrounding tissue (extravasation) [46, 47]. Similarly, activation of the T-cell receptor (TCR) upon contact with an antigen-presenting cell (APC) is followed by rapid (~1 min) ERM inactivation, microvillar collapse and establishment of the immunological synapse (IS) between T cell and APC [48–50]. Notably, reduced cortical rigidity is thought to contribute to the redistribution of adhesion receptors at the IS [50]. This is followed by ERM reactivation and orchestrated movement of the ERM proteins and associated membrane receptors, such as CD43, towards the opposite pole, where they help to form the distal pole complex (DPC) [48]. Some evidence indicates that the DPC functions to sequester inhibitory signals away from the site of TCR activation, but there is evidence that the DPC might also actively signal [41].

As another example, several studies highlight the importance of ERM function in establishing or maintaining the architecture of multicellular epithelial tissues *in vivo* in mammals and flies [8, 30]. A recent study suggests that fly Moesin stabilizes actin at the adherens junction during cellularization by interacting with the membrane-associated synaptotagmin-like protein Bitesize [51]. Although Bitesize itself is not a membrane receptor, the stabilization of actin by Bitesize-associated Moesin at the apical junctional region (AJR) has a profound impact on the organization of other membrane receptors at the AJR, including E-cadherin. Notably, the apical polarity protein Par3/Bazooka is necessary for Bitesize–Moesin localization to adherens junctions, suggesting a stratified organization of membrane receptors across the AJR. In this case, it seems that the local stabilization of actin by Moesin drives the organization of membrane adhesion receptors. However, Bitesize is poorly conserved in mammalian cells and lacks the Moesin-interacting domain, indicating that other proteins can carry out this function in mammalian epithelia.

Merlin regulates receptor surface abundance and signaling

Despite extensive analyses of Merlin function over the past 15 years, its role in tumor suppression remains obscure. However, recent studies in flies and in mice indicate that Merlin controls proliferation by regulating growth-factor-receptor abundance and/or availability at the cell surface (Figure 2a). In *Drosophila*, this function is redundant with another FERM-domain-containing tumor suppressor, Expanded [12,⁵²]. In cells lacking both Merlin and Expanded, growth-factor receptors including the epidermal growth factor receptor (EGFR), Notch and Patched are upregulated at the cell surface [12]. Pulse-chase studies show that Notch receptor is cleared abnormally slowly from the surface of these cells, suggesting a defect in endocytosis and degradation of surface receptors. Consistent with the model that increased surface accumulation of receptor can lead to increased signaling output and overproliferation, a downstream reporter for EGFR signaling is upregulated in mutant cells [12].

Recent studies in mammalian cells concur that Merlin can control the surface availability of certain membrane receptors such as EGFR [13]. Studies have revealed that Merlin can block the internalization of ligand-bound EGFR specifically in contacting (confluent) cells in culture. Notably, in mammalian cells, internalization is required for a full EGFR signaling response [53]. In fact, whereas wild-type, Merlin-expressing cells normally downregulate EGFR signaling at high cell density, Merlin-deficient cells fail to do so and also fail to undergo contact-dependent inhibition of proliferation – a phenotype reversed by pharmacologic inhibition of EGFR. A contact-dependent complex between E-cadherin, Merlin and EGFR was observed, supporting a model wherein, upon cell contact, Merlin is recruited to nascent adherens junctions and can then sequester EGFR into a non-internalizing, non-signaling membrane compartment (Figure 2b). NHERF-1 is required for Merlin–EGFR association but it is not clear how Merlin associates with the adherens junction [13,⁵⁴]. Notably, a mutant version of Merlin that fails to stably decorate the cortical cytoskeleton cannot prevent EGFR internalization or restore contact-dependent inhibition of proliferation to Merlin-deficient cells [36].

Despite these insights, it remains unclear how Merlin controls the distribution of membrane receptors. In particular, although studies in mammals and in the fly both suggest altered receptor function at the cell surface, they differ in interpretation of the proximal effect of Merlin on plasma membrane receptor levels [12,¹³]. Studies in the fly suggest that Merlin normally facilitates the removal of receptors from the cell surface, whereas studies in confluent cultured mammalian cells indicate that Merlin sequesters EGFR on the surface, thereby preventing internalization and signaling. Closer inspection reveals several key differences in the ways in which the fly and mammalian studies were carried out. For example, the fly studies examined total receptor levels, whereas the mammalian studies largely examined ligand-bound (activated) EGFR. In addition, the fly studies were carried out *in vivo*, where all cells are contacting other cells and contact-dependent inhibition of proliferation must be established and overridden without loss of cell:cell adhesion. By contrast, cell contact is manipulated in an all-or-none fashion in cultured mammalian cells. Moreover, the fly studies examined concomitant loss of both Merlin and Expanded, but the mammalian studies examined loss of Merlin alone. Both studies conclude that the primary effect of Merlin on EGFR takes place at the plasma membrane. One model that could explain both sets of observations is presented in Figure 2c. In this model, Merlin directs EGFR to a particular membrane compartment from which it is poised to follow a particular endocytic route. Species-specific differences in the subsequent trafficking of EGFR, perhaps owing to differences in EGFR-associated adapters could yield apparent differences in surface abundance.

A role for Merlin in controlling membrane receptor distribution before internalization and endocytosis would be consistent with data from both mammalian and fly cells and could, in principle, affect receptor dimerization, adapter association and internalization. However, such

a mechanism does not preclude the possibility of additional post-internalization functions for Merlin, for example in receptor recycling. In fact, Merlin has been reported to localize to endocytic vesicles in both flies and mammals [55,⁵⁶]. In addition, Merlin seems to associate with sterol-rich membrane (SRM) fractions in a variety of cells [57]. Recent work on the EGF and transforming growth factor- β (TGF- β) receptors indicates that SRMs have a crucial role in clearing the receptor from the plasma membrane, and thereby in controlling signal output [58,⁵⁹]. A higher resolution view of the membrane distribution of EGFR and Merlin in both systems should provide key insight into the validity of this model.

Signaling and biological output

A key unmet challenge is to delineate the complexity of Merlin/ERM-containing membrane complexes in a given cell or tissue. Does the FERM domain simultaneously associate with multiple membrane proteins? Do Merlin/ERM proteins assemble multiple different complexes within the same cell? Competition between membrane targets could provide the basis for how Merlin/ERM proteins nucleate distinct complexes within the same cell. Indeed, structural studies suggest that the interaction of the radixin FERM domain with NHERF-1 causes a structural shift that precludes the association of the same FERM domain with transmembrane receptors such as CD43, which bind to a nearby cleft [17]. Additional complexity and specificity is probably achieved by the ability of NHERF-1 (and the closely related NHERF-2) and Merlin/ERM proteins to oligomerize [7,²⁰]. The ability of Merlin/ERM proteins to nucleate protein complexes that sense and respond to multiple extracellular cues could explain the complex biological outputs associated with Merlin/ERM activity or loss.

An example of how Merlin/ERM proteins could coordinate information from multiple receptors is reflected by the ability of Merlin to complex with both E-cadherin and EGFR [13]. In this case, Merlin might be involved in sensing cell contact and responding by associating with and negatively regulating EGFR. Given that fly Merlin controls the surface abundance of other receptors in addition to EGFR, this paradigm could extend to other combinations of receptors [12]. For example, coordination of signaling from EGFR and Notch receptors could provide a way to integrate developmental cell fate and proliferation decisions.

In addition to assembling membrane receptor complexes, Merlin/ERM proteins can associate with regulators and/or effectors of Rho GTPases, probably contributing to their ability to stabilize the cortical cytoskeleton locally [9] (Table 1). The ability to locally coordinate membrane receptor signaling with Rho GTPase signaling and cortical cytoskeletal stabilization or destabilization could facilitate the assembly of larger scale membrane compartments and enable complex biological activities such as cell migration, metastasis and epithelial morphogenesis. For example, recent studies suggest that the internalization of certain growth-factor receptors yields local, spatially restricted activation of Rac and that this is important for directed cell motility [60]. Alternatively, local control of Rho-mediated contractility could be crucial for junctional remodeling during epithelial morphogenesis [9]. In this regard, it is interesting that the FERM-domain-containing protein Talin is thought to function as a molecular 'clutch', linking the contractile cortical actin network to matrix-bound receptors such as β 1-integrin. Talin is necessary for assembling mature focal adhesions and for their associated traction forces during cell spreading and migration [61]. Dynamic regulation could enable Talin to function as a rheostat, sensing and responding to changes in traction during cell movement. Similarly, another FERM-domain-containing protein, focal adhesion kinase (FAK), coordinates signaling by growth-factor receptors and integrins to regulate Rho-mediated tension at focal adhesions [62,⁶³].

Although most work on merlin and the ERM proteins has concentrated on their role in regulating signaling at the level of receptors or membrane associated proteins, some data

indicate a function in signaling events further downstream. Recent studies in the fly suggest that Merlin and the FERM-domain-containing tumor suppressor Expanded function in a linear pathway upstream of the Hippo-Warts-Yorkie (HWY) proliferation control pathway by regulating the activity of the Hippo kinase [64]. It has been suggested that this pathway also operates in mammalian cells and can regulate contact-dependent inhibition of proliferation [65]; however, the mechanism of how the HWY pathway is regulated by extracellular cues has not been elucidated. The relationship between the role of Merlin in controlling receptor abundance and/or distribution has also not been reconciled with this putative role in Hippo activation. Studies of this pathway could potentially provide an excellent example of how Merlin/Expanded transmit extracellular signals, yielding context-dependent regulation of this important growth control pathway, although presently the details remain obscure.

Concluding remarks and future perspectives

Future studies that probe the molecular basis of how Merlin/ERM proteins regulate receptor abundance and localization are likely to advance our understanding of Merlin/ERM-dependent changes in membrane-receptor distribution and more broadly of the mechanisms cells use to control receptor localization and activity in flies and mammals. This has important implications not only for understanding how cells normally orchestrate receptor distribution and function during development and in adult tissues, but also for how altered receptor distribution contributes to various disease states including, but not limited to, cancer. Indeed, these studies suggest new ways in which tumor cells, for example, might evade the normal control of receptors such as EGFR. Therefore, in addition to advancing our understanding of the molecular causes of NF2 and prompting the development of badly needed therapeutic advances for that disease, these studies could have a broader impact in cancer biology. Indeed, several studies have linked Ezrin function positively to the complex process of tumor metastasis [24]. A key future challenge will be to delineate the complexity of functional Merlin/ERM-containing complexes within any given cell and to begin to coordinate that information with the complex and context-dependent biological consequences of their activities *in vivo*.

Box 1. FERM-domain-containing proteins

The FERM domain superfamily of proteins includes > 50 and > 20 members in mammals and flies, respectively [7]. The FERM domain is usually N-terminal and mediates association with membrane proteins; most FERM-domain-containing proteins are involved in signaling at the membrane–cytoskeleton interface. A variety of other functional modules are linked to the FERM domain, including actin-binding, protein tyrosine phosphatase (PTP), Ptd95-DlgA-ZO-1 (PDZ) and Dbl-homology, Rho-activating (DH) domains, suggesting an expansive repertoire of functions attributable to this interesting group of proteins. Mutations in the genes encoding FERM domain superfamily members have been linked causally to several human diseases, including hereditary elliptocytosis (*band 4.1R*), the familial cancer syndrome neurofibromatosis type 2 (*NF2*), Kindler syndrome (*KIND1*) and cerebral cavernous malformations (*KRIT-1/CCM*) [24,^{66–70}].

Evolutionarily, the FERM domain is not found in yeast and seems to be a metazoan 'invention' that arose during the transition to multicellularity – a transition that demanded that cells develop ways to organize their membranes into distinct functional compartments that underlie the assembly of cells into functioning tissues. Interestingly, however, the recently sequenced genome of the actin-containing choanoflagellate *Monosiga brevicollis*, one of the closest eukaryotic unicellular relatives of metazoans, reveals several FERM-domain-containing proteins, including putative ERM and Merlin orthologues [71]. Notably, the choanoflagellate genome also includes the earliest examples of both cadherin and tyrosine kinase receptors [72,⁷³]. Thus, it is possible that the FERM domain coevolved with both intercellular junctions and intercellular signaling mechanisms that control tissue

growth and differentiation. In this view, the FERM domain might have had a very early and essential role in establishing increased membrane complexity required for the transition to multicellularity.

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Figure 1.

Merlin/ERM proteins organize membrane receptor complexes and membrane domains. **(a)** Merlin/ERM proteins can assemble multiprotein complexes containing membrane receptors, adapters and Rho GTPase regulators or effectors and link them to the cortical cytoskeleton. Merlin/ERM proteins can interact directly with the positively charged juxtamembrane region of certain membrane receptors; alternatively, Merlin/ERM proteins can associate with the tandem PDZ-domain-containing adapter NHERF-1, which, in turn, can directly associate with several receptors including multipass receptors such as NHE3 or CFTR and single-pass receptors such as EGFR or PDGFR. Larger multiprotein membrane complexes could be assembled via homo-, hetero- or oligo-merization of Merlin/ERMs and/or NHERF proteins.

The presence of unique lipid environments, to which specific proteins localize, might cooperate to establish unique membrane receptor complexes containing Merlin/ERM proteins. **(b)** The ERM proteins (green) are particularly important for strengthening the membrane–cortical–cytoskeleton interface and controlling the surface availability of certain membrane receptors at the apical membrane. In addition, fly Moesin stabilizes cortical actin at the apical junctional region through association with Bitesize. By contrast, Merlin (red) function is important for establishing stable adherens junctions, perhaps by stabilizing the interface between the junction and cortical cytoskeleton. Merlin can also control the surface availability of certain receptors, particularly in the apical junctional region.

Figure 2.

Models of Merlin-dependent membrane receptor distribution in flies and mammalian cells. Studies in flies and mammals both conclude that Merlin can control the surface abundance or distribution of EGFR (and other receptors in flies), but they seem to reach differing conclusions as to the proximal effect of Merlin on EGFR. **(a)** In flies, loss of Merlin and the related tumor suppressor Expanded yield increased surface abundance of and signaling from EGFR, suggesting that Merlin might normally promote receptor clearance (endocytosis and degradation) or inhibit receptor recycling. **(b)** In mammalian cells, loss of Merlin yields persistent EGFR internalization and signaling at high cell density, which does not occur in confluent wild-type cells, indicating that Merlin normally prevents EGFR endocytosis and

signaling upon cell:cell contact. NHERF-1 is required for Merlin–EGFR interaction in mammalian cells. Merlin also complexes with both EGFR and E-cadherin upon cell:cell contact, which could facilitate the establishment of stable adherens junctions. We believe that the apparently contradictory conclusions of the fly and mammalian studies can be reconciled through the model shown in Figure 2c. This model posits that the primary function of Merlin is to direct EGFR to a specific membrane compartment from which it is poised to use a particular endocytic pathway.

Table 1Merlin/ERM-associated membrane receptors and adapters^{a,b}

Membrane protein	Associates with	Organism	Refs
NHERF-1 and -2 ^c	Merlin/ERMs	Mammals	[74,75]
α 1 b-adrenergic receptor	ERMs	Mammals	[76]
β 2-integrin	ERMs	Mammals	[77]
β -dystroglycan	ERMs	Mammals	[78]
Bitesize	Moesin	Flies	[51]
CD44	Merlin/ERMs	Mammals	[79,80]
CD43	Merlin/ERMs	Mammals	[81]
DCC	ERMs	Mammals	[82]
ICAM1/2/3/VCAM-1	ERMs	Mammals	[81,83,84]
Layilin	Merlin/ERMs	Mammals	[85]
Na ⁺ /K ⁺ -ATPase	ERMs	Mammals	[86]
Neutral endopeptidase	ERMs	Mammals	[87]
Paranodin	Merlin	Mammals	[88]
PSGL-1	ERMs	Mammals	[89]
Syndecan-2	ERMs	Mammals	[90]
Telencephalin	ERMs	Mammals	[91]
TRP channels	Moesin	Flies	[92]

^a Only membrane receptors and adapters that have been reported to associate directly with Merlin/ERMs are listed. Many other Merlin/ERM-associated signaling molecules are not shown.

^b Abbreviations: DCC, deleted in colorectal cancer; ICAM, intercellular adhesion molecule; PSGL-1, P-selectin glycoprotein ligand-1; TRP, transient receptor potential.

^c NHERF-1 and -2 can link Merlin/ERMs to many different membrane receptors.