The kindlins at a glance

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Introduction

The kindlin family of focal adhesion (FA) proteins consists of three evolutionarily conserved proteins, kindlin-1, -2 and -3 [also known as fermitin family homolog 1, 2 and 3 (FERM1, FERM2 and URP2), respectively], and was named after a rare congenital skin disease – the Kindler syndrome – which is caused by mutations in the gene encoding kindlin-1 (Jobard et al., 2003; Siegel et al., 2003). Kindlin-1 and kindlin-2 diverged from kindlin-3 during evolution and, therefore, share higher sequence identity (Siegel et al., 2003). The profound differences in tissue expression (see poster) suggest that the individual kindlin proteins acquired specific tasks during evolution.

Kindlin-1 is mainly expressed in epithelial cells, such as keratinocytes or intestinal epithelial cells, whereas kindlin-2 is almost ubiquitously expressed. Kindlin-3 expression is restricted to the hematopoietic system (Meves et al., 2009; Ussar et al., 2006).

A series of recent publications has highlighted the fundamental importance of the three kindlins for integrin function (Harburger et al., 2009; Ma et al., 2008; Montanez et al., 2008; Moser et al., 2009a; Moser et al., 2008; Ussar et al., 2008). Integrins are heterodimeric transmembrane receptors that mediate cell-extracellular matrix (ECM) and cell-cell adhesions (Hynes, 2002). Integrin-mediated adhesion triggers integrin clustering and the assembly of signaling and adaptor proteins at their cytoplasmic domains, which convey biochemical signals into different cellular compartments and link the adhesion site to the actin cytoskeleton. This mode of integrin signaling is called 'outside-in signaling' (Legate et al., 2009). A hallmark of integrins is their ability to fine-tune their affinity for their ligands by switching their extracellular domain between several different conformations. The conformational change that increases the affinity of integrins for their ligands is believed to be controlled by proteins that bind to the short cytoplasmic tails of integrins. The recruitment of these 'integrin activators' can be triggered by a wide range of cell-surface receptors and the activation of associated signaling pathways. As this process, termed inside-out signaling or integrin activation, was thought to be exclusively mediated by talin (Tadokoro et al.,

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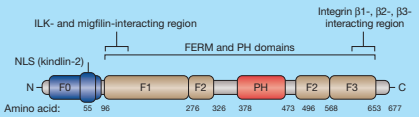
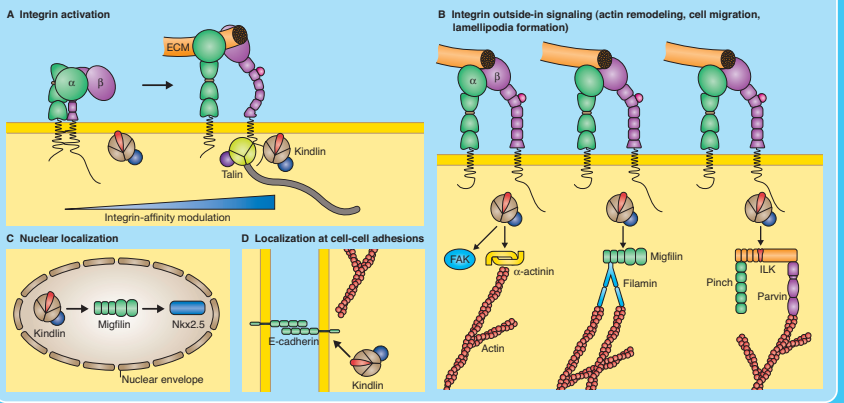
Kindlin-domain structure



Proteins	Sequence similarity
Kindlin-1 and kindlin-2	62%
Kindlin-1 and kindlin-3	49%
Kindlin-2 and kindlin-3	53%
Kindlin-1 and talin-1	28%

Domains	Sequence similarity
F0: Kindlin and talin	36%
F1: Kindlin and talin	55%
F2: Kindlin and talin	50%
F3: Kindlin and talin	54%

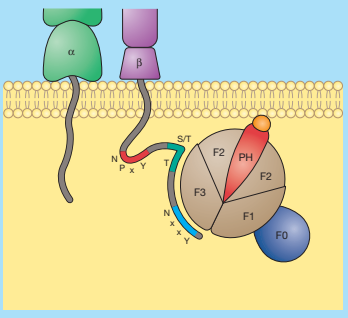
Kindlin-interaction partners and their subcellular localization



Alternative gene and protein names

Canonical gene name	Gene name: synonyms	Protein names
FERMT1	*KIND1, UNC112A, URP1, C20orf42*	FERM1, kindlin-1, kindlerin
FERMT2	*KIND2, UNC112B, MIG2, PLEKHC1*	FERM2, kindlin-2
FERMT3	*KIND3, UNC112C, MIG2B*	URP2, kindlin-3

Kindlin-binding sites in integrin β1, β2 and β3 tails



Kindlin-associated diseases and phenotypes of null mice*

Family member	Associated disease	Phenotypes in null mice
Kindlin-1	Kindler syndrome (Has et al., 2009; Ussar et al., 2008)	Skin atrophy, ulcerative colitis (Jobard et al., 2003; Siegel et al., 2003)
Kindlin-2	None reported so far	Peri-implantation lethality, endoderm and epiblast detachment from basement membrane (Montanez et al., 2008)
Kindlin-3	LAD type III (also known as LAD-1 variant) (McDowall et al. 2010; Moser et al., 2009b; Svensson et al., 2009)	Generalized hemorrhages, LAD, abnormal erythrocyte membrane organization, fulminant osteopetrosis (Moser et al., 2009a; Moser et al., 2008)

Kindlin expression in different tissues and cell types*

Organ, tissue or cell type	Kindlin-1	Kindlin-2	Kindlin-3
Bladder	+	+	–
Brain	–	+	–
Colon	+	+	–
Embryonic stem cell	–	+	–
Endothelial cell	–	+	+
Epithelial cell	+	+	–
Fibroblast	–	+	–
Heart	–	+	–
Kidney	+	+	–
Leukocyte	–	–	+
Liver	–	+	–
Lung	–	+	+
Lymph node	–	+	+
Skeletal muscle	–	+	–
Skin	+	+	–
Small intestine	+	+	–
Spleen	–	+	+
Stomach	+	+	–
Thymus	+	+	+

Sources: Bialkowska et al., 2010; Hruz et al., 2008; Ussar et al., 2006.

Abbreviations: ECM, extracellular matrix; FAK, focal adhesion kinase; FERM, 4.1 protein, ezrin, radixin, moesin; ILK, integrin-linked kinase; LAD, leukocyte adhesion deficiency; PH, pleckstrin homology; NLS, nuclear localization signal.

*Please see accompanying article for full citations.

(See poster insert)

2003; Wegener et al., 2007), the finding that kindlins were also required for integrin activation was surprising (Moser et al., 2009b).

Similar to the two talin isoforms (talin-1 and talin-2), the three kindlins contain a 4.1 protein, ezrin, radixin, moesin (FERM) domain, which typically consists of three subdomains called F1, F2 and F3. In addition, it has recently been shown that both talins and kindlins posses a C-terminal F0 domain that is required for efficient integrin activation (Bouaouina et al., 2008; Goult et al., 2009a) (see the domain structure of kindlins depicted in the poster). The F3 subdomains of kindlins and talins form phosphotyrosine binding (PTB) folds that directly interact with β-integrin cytoplasmic domains (Bottcher et al., 2009; Goult et al., 2009b; Meves et al., 2009). Kindlins possess a pleckstrin homology (PH) domain, which is inserted into the F2 subdomain (a unique feature among FERM domain-containing proteins).

Pull-down assays with purified integrin tails have shown that the core binding sites for talin and kindlins are the membrane-proximal NPxY motif and the membrane-distal NxxY motif, respectively. (These motifs are depicted in the poster as red and blue sections in the β-integrin tail, respectively.) The ability of talin to activate integrins depends on additional interactions with other residues of the integrin tail (Wegener et al., 2007). Similarly, the kindlins also require threonine (T788 and T789 in mouse β1-integrin tails) or serine/threonine (S778 and T779 in mouse β3-integrin tails) residues (represented by the green region of the β-integrin tail) in addition to the membrane-distal NxxY motif to interact with integrin tails. In line with these binding properties, deletion of the genes that encode kindlins, or mutations in crucial binding residues within β-integrin tails, abrogate integrin activation (Harburger et al., 2009; Ma et al., 2008; Montanez et al., 2008; Moser et al., 2009a; Moser et al., 2008; Ussar et al., 2008).

Upon integrin activation, kindlins remain at adhesion sites where they link ligated integrins to the cytoskeleton (Bottcher et al., 2009) and probably trigger biochemical signaling. It is not fully understood how kindlins mediate the linkage between integrins and the actin cytoskeleton. It might occur through the ability of kindlins to bind to important actin-regulatory and actin-binding proteins, including integrin-linked kinase (ILK) (Mackinnon et al., 2002), migfilin (Tu et al., 2003), focal adhesion kinase (FAK) and α-actinin (Has et al., 2009) (see 'Integrin outside-in signaling' in poster).

In addition to their functions at integrin-mediated adhesion sites, kindlins can also exert integrin-independent functions: kindlin-3 can stabilize the membrane cytoskeleton in erythrocytes (Kruger et al., 2008); kindlin-1 and -2 can localize to cell-cell junctions in epithelial cells; and kindlin-2 is found in the nucleus of smooth-muscle cells and possibly also in other cell types (Kato et al., 2004; Meves et al., 2009). The role of kindlins at cell-cell adhesion sites and in the nucleus has not been explored thus far.

In this article and the accompanying poster, we provide an overview of the current knowledge of the three kindlins with respect to their expression patterns in cells and tissues, their functions in physiology and pathology, and their interactions with other proteins.

Kindlin-1

The discovery that mutations in *FERMT1*, which encodes kindlin-1, cause a rare congenital skin disease called Kindler syndrome led to the identification of a novel family of proteins that reside and function in FAs. Kindler syndrome is characterized by skin abnormalities, including blistering, skin atrophy, photosensitivity, pigmentation defects, enhanced risk of acquiring squamous cell carcinomas and gastrointestinal abnormalities resembling ulcerative colitis (Lai-Cheong et al., 2009; Meves et al., 2009). Genetic ablation of the kindlin-1 gene in mice also leads to skin atrophy and a fulminant colitis characterized by massive epithelial detachment and inflammation (Ussar et al., 2008). The intestinal inflammation is a consequence of the loss of epithelial cells, which is caused by a combination of impaired integrin-mediated adhesion to the underlying basement membrane and mechanical sheer stress applied by the stool (Ussar et al., 2008). In intestinal epithelial cells and keratinocytes, kindlin-1 predominantly localizes to the basolateral plasma membranes, where it is crucially involved in integrin-mediated adhesion (Ussar et al., 2008; Ussar et al., 2006). The fact that Kindler syndrome develops despite normal levels of kindlin-2 expression suggests that kindlin-1 fulfils non-redundant functions. Indeed, cultured keratinocytes from patients with Kindler syndrome and from kindlin-1-deficient mice have defects in cell adhesion and spreading, despite the fact that kindlin-2 redistributes from cell-cell adhesion sites to FAs in cultured keratinocytes (Lai-Cheong et al., 2009; Lai-Cheong et al., 2008; Meves et al., 2009). In addition to its ability to bind to and activate integrins, kindlin-1 can also interact with FA proteins, such as migfilin, α-actinin and FAK (Has et al., 2009; Lai-Cheong et al., 2009). These molecular interactions might be involved in the mechanisms by which kindlin-1 relays outside-in signals and links integrins to the actin cytoskeleton. In line with this hypothesis, kindlin-1 depletion in human keratinocytes leads to reduced formation of lamellipodia and reduced cell migration owing to the defective signaling of Rho GTPases (Has et al., 2009), which are known to be involved in remodeling of the actin cytoskeleton.

Kindlin-2

Kindlin-2 was the first kindlin family member that was linked to integrin-mediated adhesion. Early studies in *Caenorhabditis elegans* identified *unc-112*, the worm ortholog of kindlin-2, as an intracellular protein that colocalizes with integrins at cell-matrix adhesion sites. Mutations in *unc-112* resulted in aberrant assembly of dense bodies and M-lines, which are the equivalents of muscle costameres and intercalated disks in worms (Rogalski et al., 2000). The deletion of *Fit2,* the kindlin-2 ortholog in *Drosophila melanogaster*, also leads to a muscle-rounding phenotype, suggesting that kindlin-2 has an essential role in development and/or maintenance of skeletal muscle (Bai et al., 2008). Morpholino-mediated knockdown of kindlin-2 expression in zebrafish leads to severe myocardial defects, which occur because the formation of intercalated discs is disrupted and myofibrils fail to attach to integrin-mediated adhesion complexes (Dowling et al., 2008a). Because coupling of mechanical forces to integrins seems to be essential for normal muscle function, the muscle defects observed in the absence of kindlin-2 underline an important function of kindlin-2 in linking integrin-mediated adhesions to the actin cytoskeleton.

Loss of kindlin-2 expression in mice leads to peri-implantation lethality caused by extensive detachment of the primitive endoderm and the epiblast (Dowling et al., 2008a; Dowling et al., 2008b; Montanez et al., 2008). Embryonic stem cells (ESCs) express only kindlin-2 and are, therefore, an excellent system in which to analyze the function of this protein (Montanez et al., 2008). Studies using embryoid bodies (EBs) generated from kindlin-2-deficient ESCs revealed that defective adhesion to the primitive endoderm and epiblast is caused by impaired activation of integrins (Montanez et al., 2008). Although manganese treatment of kindlin-2-deficient EBs forced integrins into a high-affinity and ligand-binding competent conformation, it failed to rescue the spreading defects of kindlin-2-deficient endoderm cells. These data indicate that kindlin-2 is a bi-directional signaling protein: it initially activates integrins and subsequently links them to a dynamic actin cytoskeleton.

How does kindlin-2 mediate the actin linkage? The FA-associated proteins migfilin and ILK were identified as kindlin-2-interacting proteins in genetic experiments and in yeast two-hybrid screens (Mackinnon et al., 2002; Tu et al., 2003). It is conceivable that these two interaction partners relay integrin signals to

actin through their interaction with adaptors such as filamin, vasodilator-stimulated phosphoprotein (VASP) and parvins (Lange et al., 2009; Tu et al., 2003; Zhang et al., 2006). Kindlin-2 colocalizes with ILK and migfilin at FAs, and depletion of kindlin-2 disrupts the recruitment of ILK to FAs (Mackinnon et al., 2002; Montanez et al., 2008; Tu et al., 2003). The finding that ILK- and kindlin-2-null cells display similar spreading defects (Legate et al., 2009; Sakai et al., 2003) indicates that kindlin-2 functions depend on ILK recruitment, at least in part. Kindlin-2 is also found in cell-cell junctions of keratinocytes and in adherens junctions in heart and colon (Dowling et al., 2008b; Lai-Cheong et al., 2008; Ussar et al., 2008; Ussar et al., 2006) (see 'Localization at cell-cell adhesions' in the poster). The function of kindlin-2 at these sites is not clear, nor is the mechanism underlying its recruitment. In skin, kindlin-2 is almost exclusively localized at cell-cell junctions and is absent from the dermoepidermal junction (DEJ) where kindlin-1 localizes (Lai-Cheong et al., 2008; Meves et al., 2009). This differential subcellular localization might explain why kindlin-2 cannot compensate for the loss of kindlin-1 in Kindler syndrome.

Kindlin-2 is the only kindlin family member that contains a nuclear localization signal (Ussar et al., 2008). The protein has so far only been observed in the nuclei of smooth muscle cells (Kato et al., 2004), although the nuclear function of kindlin-2 is unknown. The kindlin-2-interacting protein migfilin can also localize to the nucleus, where it was shown to bind to the transcription factor Csx (also known as Nkx2.5), which is crucial for cardiac development (Akazawa et al., 2004). It is therefore possible that the interaction between kindlin-2 and migfilin also have a functional relevance in the nucleus (see 'Nuclear localization' in the poster).

Kindlin-3

Kindlin-3 is mainly expressed in hematopoietic cells, including platelets and erythrocytes (Lai-Cheong et al., 2009; Pasini et al., 2006; Siegel et al., 2003; Ussar et al., 2006). The only exception reported thus far is expression of kindlin-3 in endothelial cells (Bialkowska et al., 2010). Ablation of *Fermt3*, the gene encoding kindlin-3 in mice, provided the first evidence that kindlins are involved in integrin activation. Kindlin-3 deficiency in mice leads to lethality a few days after birth and is associated with severe hemorrhages in multiple organs, fulminant osteopetrosis, leukocyte adhesion deficiency and impaired separation of the developing lymphatic vessel sprouts from the vascular system (Moser et al., 2009a; Moser et al., 2008; Uhrin et al., 2010). The entire spectrum of defects in kindlin-3-deficient mice is due to a complete inability to activate integrins on hematopoietic cells (Moser et al., 2008). A similar spectrum of abnormalities, also associated with integrin-activation defects, is also found in a rare hereditary human disease called leukocyte-adhesion deficiency (LAD) type III (also named LAD-1 variant). The genetic cause of the disease was unknown until recently, when it was found by several groups that LAD type III is caused by mutations in *FERMT3* (Kuijpers et al., 2009; Malinin et al., 2009; Manevich-Mendelson et al., 2009; Svensson et al., 2009). In addition to defects in immune cells and platelets, patients with LAD type III also suffer from osteopetrosis, but milder than that found in kindlin-3-deficient mice (Etzioni, 2009; Kilic and Etzioni, 2009; Moser et al., 2008).

Kindlin-3 is also expressed in erythrocytes (Pasini et al., 2006). Although mature erythrocytes lack integrin expression, kindlin-3-deficient erythrocytes are abnormally shaped and sequestered by the reticuloendothelial system of the spleen. A quantitative SILAC-based proteomics study revealed that membrane-skeleton proteins such as ankyrin-1, band 4.1, adducin-2, and dematin were absent from the membrane fraction of kindlin-3-deficient erythrocytes, suggesting that kindlin-3 has an important role in stabilizing the plasma membrane of erythrocytes (Kruger et al., 2008; Lai-Cheong et al., 2009).

Outlook and perspectives

The kindlin field is rapidly evolving. To further unravel the molecular mode of action of the kindlins it will be important to characterize the kindlin family members in different tissues using the Cre/loxP system, elucidate their structure and identify their binding partners. Although kindlins have been shown to be required for integrin activation, further studies are needed to address how kindlins and talin cooperate to modulate integrin affinity. Recent reports suggest that kindlins have differential effects on specific integrin heterodimers (Harburger et al., 2009; Manevich-Mendelson et al., 2009), a finding that needs to be addressed further. It is also necessary to investigate how kindlins orchestrate integrin outside-in signaling and how they link integrins to the actin cytoskeleton. Finally, kindlins are expressed in the nucleus and at cell-cell junctions, where they have integrin-independent functions that are almost totally unexplored. Therefore, elucidating the complete kindlin interactome would be a major step forward in understanding the role of kindlins in these different cellular compartments.

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