ABSTRACT

Kindlins are 4.1-ezrin-ridixin-moesin (FERM) domain containing proteins. There are three kindlins in mammals, which share high sequence identity. Kindlin-1 is expressed primarily in epithelial cells, kindlin-2 is widely distributed and is particularly abundant in adherent cells, and kindlin-3 is expressed primarily in hematopoietic cells. These distributions are not exclusive; some cells express multiple kindlins, and transformed cells often exhibit aberrant expression, both in the isoforms and the levels of kindlins. Great interest in the kindlins has emerged from the recognition that they play major roles in controlling integrin function. In vitro studies, in vivo studies of mice deficient in kindlins, and studies of patients with genetic deficiencies of kindlins have clearly established that they regulate the capacity of integrins to mediate their functions. Kindlins are adaptor proteins; their function emanate from their interaction with binding partners, including the cytoplasmic tails of integrins and components of the actin cytoskeleton. The purpose of this review is to provide a brief overview of kindlin structure and function, a consideration of their binding partners, and then to focus on the relationship of each kindlin family member with cancer. In view of many correlations of kindlin expression levels and neoplasia and the known association of integrins with tumor progression and metastasis, we consider whether regulation of kindlins or their function would be attractive targets for treatment of cancer.

Keywords:
Kindlins, integrins, cancer, FERMT genes, cancer therapy.

Abbreviations:
4.1-ezrin-ridixin-moesin (FERM); leukocyte adhesion deficiency type III (LAD III); Epithelial to mesenchymal transition (EMT); Transforming growth factor-beta (TGF-β); Nuclear factor kappa B (NFκB); Epidermal growth factor receptor (EGFR);

1. Introduction

Since the term “integrins” was coined more than 3 decades ago to designate a broadly distributed family of cell-surface adhesion receptors, the contributions of each of the 24 integrin family members in numerous physiological and pathological processes has remained a dominant theme in cell biology research. Indeed, it has now been broadly established that integrins have functions extending well beyond their primary roles in cell adhesion and migration; their contributions to bidirectional signaling, proliferation, gene regulation and cellular entry of pathogens have all been extensively documented. Research on
integrins has extended from very basic investigations of their ligand binding repertoires and their three-dimensional structures to the clinical relevance of their antagonism as potential therapies. Indeed, clinical trials that led to approvals of several integrin directed drugs that have been used to treat patients with a variety of disorders, including thrombosis, cancer, ulcerative colitis and multiple sclerosis. Despite the breadth and depth of these studies, unanticipated findings regarding integrins and their functions have continued to emerge. Such a finding was the implication of kindlins into the integrin field starting about 10 years ago, but these cytosolic proteins are now accepted as pivotal regulators of integrin function. A burgeoning subcontext of the relationship between kindlins and integrins is how their intercalation impacts cancer. Within the last 5 years, more than 70 publications have linked kindlins, integrins and cancer. In this review, we provide a brief synopsis of kindlin structure-function relationship, consider the latest findings on the role of kindlins in cancer, and then speculate as to the potential to target kindlins to inhibit cancer initiation, progression, metastasis and chemoresistance.

2. The kindlins

The prototypical structure of a kindlin is shown in Figure 1. Kindlins belong to the 4.1- ezrin-ridixin-moesin (FERM) domain containing protein family. Kindlins contain F1, F2 and F3 subdomains that typify FERM family members, and these subdomains are preceded by an N-terminal F0 subdomain in kindlins. A distinctive feature of kindlins is the insertion of a pleckstrin homology (PH) subdomain into the F2 subdomain (reviewed in ). There are three kindlin family members in mammals, KINDLIN-1 (FERMT1; chromosome 20p12.3), KINDLIN-2 (FERMT2; chromosome 14q22.1) and KINDLIN-3 (FERMT3; chromosome 11q13.1). The three kindlins are highly
homologous, sharing ~60% amino acid sequence identity\(^7\). Of the genomes analyzed, all metazoans, but no premetazoans, have at least one kindlin gene. Kindlin-2 is likely to have preserved the ancestral features of the kindlin family, and kindlin-1 and kindlin-3 arose from duplications of the kindlin-2 gene. The ancestral kindlin itself appears to have evolved from duplication of the FERM domain in the N-terminal region of talin, and the two proteins share an overlapping function in integrin activation.\(^1\)\(^8\)\(^9\).

In humans, mutations leading to deficiencies of kindlin-1 cause Kindler Syndrome, which manifests with symptoms of skin fragility, blister formation, cutaneous atrophy, poikiloderma, and photosensitivity. Intestinal defects also occur frequently.\(^10\)-\(^12\) Mice deficient in kindlin-1 show similar phenotypes but the intestinal defects result in death shortly after birth.\(^13\) Mutations in the kindlin-3 gene cause leukocyte adhesion deficiency type III (LAD III), which is characterized by high susceptibility to infections, spontaneous and episodic bleedings, and osteopetrosis.\(^14\)-\(^17\) These symptoms also occur in mice lacking kindlin-3 and result in mice that are only viable for a short time postnatally.\(^18\) No deficiencies of kindlin-2 in humans have been reported to date, but disruption of kindlin-2 in mice results in embryonic lethality.\(^19\) Mice with partial deficiency of kindlin-2, Kindlin-2\(^{+/+}\) mice, exhibit no overt phenotype but display abnormal response in angiogenesis, hemostasis and intracellular actin organization.\(^22\) The three kindlins exhibit differences in their expression profiles: kindlin-1 is expressed mainly in epithelial cells; kindlin-2 is broadly expressed and is plentiful in endothelial cells, smooth muscle cells and fibroblasts; and expression of kindlin-3 is restricted primarily to hematopoietic cells although it is also expressed in endothelial cells.\(^23\) Several recent studies have, however, showed that aberrant expression of the kindlins occurs in several human cancers.

3. Kindlins as adaptor proteins

Kindlins are adaptor proteins. They lack intrinsic enzymatic activity but rather bind multiple effectors and thereby can build large multimolecular and multifunctional complexes. The binding sites for several kindlin binding partners have been positioned within the organization of the prototypic kindlin in Figure 1. Phospholipid binding sites exist in the F0, F1, F2, and PH subdomains of both kindlin-2 and kindlin-3, but ADAP is restricted to kindlin-2 and kindlin-3, but ADAP is restricted to kindlin-3. kindlin and may extrapolate to the other kindlin family members based on homology. Interactions of kindlins with ADAP, RACK1, \(\beta\)-catenin also have been demonstrated. Some interactions may influence the function of an individual kindlin selectively as described in chapter 4. For example, ADAP can bind to both kindlin-2 and kindlin-3, but ADAP is restricted to hematopoietic cells, where kindlin-3 exerts its major functions. Post-translational modifications of kindlins also occur, may be selective to specific kindlins and may influence the function of the modified kindlin.

4. Functions of kindlins

Integrin-dependent functions: The most studied function of kindlins revolves around their role in integrin activation. Integrins can alter their affinity/avidity for their cognate ligands, a transition that is usually induced by stimulation of the integrin-bearing cell with agonists. Agonists may include G protein–coupled receptor ligands, growth factors, cytokines and shear stress (e.g. \(41\)-\(44\)). Activation is particularly important for integrin-mediated responses of circulating blood cells, such as the adhesion of leukocytes to vascular cells, of leukocytes to other blood cells, or platelets to one another.\(^49\) These responses do not occur in patients lacking kindlin-3; the integrin \(\beta1\) or \(\beta2\) subclasses on hematopoietic cells do not undergo activation. Integrins on adherent cells can also undergo activation although the changes are not as dramatic. Such integrin activation depends on inside-out signaling, which is a consequence of the binding of talin and kindlin to the cytoplasmic domain of integrins.\(^7\)\(^50\) The detailed mechanisms of integrin activation have been the subject of
reviews and are very dependent on the definition of “activation”. Is activation defined on a structural basis as straightening of the integrin legs from a bent to an extended conformation and/or opening of the headpiece, or is it the acquisition of functionally productive ligand binding. Ligand binding and integrin clustering induce inside-out signaling. Frequently elicited consequences of outside-in signaling include cell spreading, changes in cell shape and gene expression. Kindlins are integrally involved in generating outside-in signals, which depends upon direct or indirect interactions with elements of actin cytoskeleton and the reorganization of focal adhesions, multimolecular signaling hubs within the cell.

Integrin-independent functions of kindlins: In a limited number of studies, functions have been assigned to kindlins that appear to be independent of their integrin binding activity. The integrin binding site of kindlins resides in their F3 (PTB-like) subdomain. Central to this binding function is a particular QW motif, Q614W615 in kindlin-2, and mutation of these residues to alanines markedly diminishes integrin binding activity. Using such mutant kindlins, the interaction of kindlin-2 with β-catenin to regulate Wnt signaling and kindlin-2 with clathrin to regulate cell surface expression of catabolic enzymes in endothelial cells have been identified as integrin-independent functions of kindlins. These mutations also demonstrated an integrin-independent role for kindlin-1 in Wnt signaling. This strategy presumes that integrin binding to kindlins is completely disabled by the QW mutation. Clearly these mutations markedly reduce but may not completely disable integrin binding.

5. Association of kindlins with cancer

The intimate interrelationship between integrins and cancer pathology has inevitably led to consideration of the role of kindlins in cancer. These efforts have identified associations of all three kindlin isoforms with cancers of many different tissues. In some cases, affected tissues is consistent with the distribution of the kindlin isoforms but expression levels are altered relative to the kindlin levels in the corresponding normal tissue (e.g., kindlin-1 and skin cancer); whereas, in other cases, the particular kindlin is expressed at an unusual cell type (e.g. kindlin-3 in breast cancer).

5.1. Kindlin-1 and Cancer

One of the earliest evidences implicating kindlin-1 in cancer came from measurements of its mRNA expression levels. These levels were elevated in 60% of lung and 70% of colon cancers. Kindlin-1 was also found to be associated with the pathology of glioma. Kindlin-1 mRNA also was highly expressed in the pancreatic cancer cell lines and pancreatic cancer tissue. Kindlin-1 protein was detected in the cytoplasm and membrane of the pancreatic cancer cells while normal ductal epithelial cells and stromal cells showed no expression. Sin and colleagues reported a role of kindlin-1 in the metastasis of tumors from various organs to the lungs and found that kindlin-1 expression correlated with a poor prognosis in both breast and lung adenocarcinoma.

Despite these associations of kindlin-1 with cancer from many different organs, most studies documented aberrant kindlin-1 expression levels in cancers of epithelial origin, consistent with its primary epithelial localization. In patients lacking kindlin-1 “Kindler Syndrome patients”, there is a suggestion of an increased risk of squamous cell carcinomas; however, the rarity of the Kindler Syndrome precludes broad generalizations. Since kindlin-1 deficiency is lethal in mice due to intestinal manifestations. Rognoni and colleagues generated mice deficient in kindlin-1 in keratinocytes. These mice do exhibit an increased incidence of skin tumors that formed primarily as trichofofolliculoma-like lesions and basal cell carcinomas, distinct from the tumors that were noted in patients with Kindler Syndrome.

Mechanistically, several interesting linkages have been uncovered between kindlin-1 and TGFβ activation, which exerts many opposing effects on the multiple steps associated with cancer progression and metastasis. Gene expression microarray studies comparing the RNA profiles of TGFβ1-treated mammary epithelial cells with non-treated cells show that kindlin-1 is a TGFβ1 inducible gene. Increase in kindlin-1 expression resulting from TGFβ1 treatment enhanced cell spreading and induced actin rearrangement, events correlated with the epithelial to mesenchymal transition (EMT), an important step in carcinogenesis. TGF-β activation can be mediated by integrin αVβ6 and kindlin-1 can activate this integrin. Thus, an amplification loop may exist in which TGF-β enhances kindlin-1 synthesis and
Kindlin-1 enhances activation of TGF-β via αVβ6. High kindlin-1 levels have also been associated with high TGFβ-1 signaling in metastatic breast cancers\textsuperscript{60}, and suppression of kindlin-1 in breast cancer cells significantly inhibited tumor growth and lung metastasis in an orthotopic mouse model. However, suppression of kindlin-1 in Kindler Syndrome patients may enhance cancer risk and, therefore, precludes broad generalizations.

5.2 Kindlin-2 and Cancer.

Kindlin-2 expression has been found to be dysregulated in several cancer types: prostate\textsuperscript{74-77}, breast\textsuperscript{64, 78-80}, lung\textsuperscript{65, 81}, colorectal cancer\textsuperscript{82}, pancreas\textsuperscript{83, 84}, ovarian\textsuperscript{85, 86}, esophageal squamous cell carcinoma\textsuperscript{87-89}, liver\textsuperscript{90}, brain\textsuperscript{91}, gastric cancer\textsuperscript{92, 93}, bladder\textsuperscript{94} and acute myeloid leukemia\textsuperscript{95}. Given the association of kindlin-2 with several cancers of different origins, one can predict an important role that kindlin-2 may play in cancer pathogenesis. Kindlin-2 regulates tumor progression and metastasis by modulating several signaling pathways that are known to be critical for the regulation of cancer cell survival, proliferation, migration, invasion and metastasis. In fact, kindlin-2 has been associated with almost every hallmark of cancer\textsuperscript{79}. In prostate cancer, kindlin-2 was found to promote the survival of prostate cancer cells by activating the nuclear factor kappa B (NFκB) survival pathway\textsuperscript{74}. The invasive potential of prostate cancer cells was also activated as a result of the NFκB-mediated upregulation of matrix metalloproteinases expression and activity\textsuperscript{84}. A positive feedback loop between kindlin-2 and TGF-β was identified to play a key role in promoting the progression and metastasis of pancreatic cancer\textsuperscript{84}, which is characterized by its aggressiveness and the lack of effective therapies. While kindlin-2 expression levels were markedly elevated by Transforming Growth Factor 1 (TGF-β1) treatment, kindlin-2, in turn, activated the expression of TGF-β receptor I, a major component of TGF-β signaling\textsuperscript{84}. Epithelial to mesenchymal transition, another significant hallmark of cancer, was found to be affected in esophageal squamous cell carcinoma as a result of dysregulation of kindlin-2\textsuperscript{87}. Zhang and colleagues\textsuperscript{87} described how the loss of miR-200b, a well-established regulator of EMT, enhances invasion of esophageal squamous cell carcinoma cells by activating the Kindlin-2/integrin β1/AKT signaling pathway. Conversely, overexpression of miR-200b in these cells inhibited the integrin β1-AKT signaling by specific targeting of kindlin-2, which in turn suppressed invasion of ESCC cells\textsuperscript{87}. Epidermal growth factor receptor (EGFR) is a known activator of cell proliferation, migration and tumor invasion in several cancers, including the one originating from the breast. A recent study by Guo et al.\textsuperscript{80} established a critical link between kindlin-2 and EGFR, where a physical interaction between the two was found to be necessary for the stabilization of EGFR and subsequent activation of the migration and invasion of breast cancer cells. Finally, several studies, including ours\textsuperscript{75}, established a critical function of kindlin-2 to the modulation of chemoresistance, yet another major hallmark of cancer\textsuperscript{72}. The Zhan lab\textsuperscript{91} described how kindlin-2 modulates the cisplatin-induced apoptosis and cell death of human glioma cells by regulating the AKT/JNK and AKT/p38 signaling pathways while the Zhang lab\textsuperscript{77} found kindlin-2 to activate the cisplatin-mediated cell death of prostate cancer cells through the regulation of the Bcl-xL cell death pathway. Our study has also established a major role for kindlin-2 in the regulation of the chemotherapy-induced cell death and apoptosis of metastatic castration-resistant prostate cancer, for which effective treatments have yet to be developed\textsuperscript{75}. Loss of expression of kindlin-2 in prostate cancer cell lines significantly enhanced the sensitivity of these cells to docetaxel-induced apoptosis and cell death. Mechanistically, we found miR-138 to specifically target and inhibit kindlin-2 in prostate cancer cell lines, which resulted in dysregulation of the kindlin-2/β1-integrin pathway, thereby identifying a novel miR-138/kindlin-2/β1-integrin signaling axis that is critical for the modulation of sensitivity to chemotherapeutics. Therefore, targeted inhibition of kindlin-2 could be combined with chemotherapy to develop an effective treatment for prostate cancer\textsuperscript{75}.

5.3 Kindlin-3 and Cancer

Although Kindlin-3 is mainly expressed in the hematopoietic system, there are surprisingly only limited reports about its involvement in blood cell cancers. Kindlin-3 was found to be associated with the pathology of chronic myeloid leukemia\textsuperscript{90} and acute myeloid leukemia\textsuperscript{91}. Qu and colleagues\textsuperscript{92} showed that kindlin-3 may regulate the proliferation of human chronic myeloid leukemia K562 cells
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6. Kindlins as a cancer therapeutic target

Two independent studies have shown that reduction in kindlin-2 levels, either with siRNA that targets kindlin mRNA directly or by overexpression of miRNAs that reduce kindlin expression, sensitizes tumor cell lines to chemotherapeutic agents such as docetaxel and cisplatin. Knockdown of kindlin-2 would also blunt certain properties of tumor cells that are associated with cancer progression, such as angiogenesis, invasion, recruitment of tumor promoting macrophages and formation of invadopodia.

Rather than at the gene expression level, it may be feasible to selectively inhibit selective functions of a specific kindlin family member. For example, most of the functions of kindlin in tumor cell biology revolve around their interaction with the cytoplasmic tails of integrins. Specific short peptide sequences within integrin β tails have been located that are necessary for kindlins to exert their integrin regulatory activity. Peptides or peptidomimetics of these sequences that block kindlin binding to integrins could be delivered into cells and blunt responses. These sequences could be tailored to block interaction of kindlins with specific integrins, or individual kindlins with specific integrins. However, knocking down kindlins may not be the panacea for cancer treatment. In a recent publication, Rognoni et al. provided a comprehensive and valuable list of the reports in which kindlin levels were altered in tumors. In most of the listed studies, the levels of the kindlin under investigation were increased, but in six of the 20 reports, reduced levels of kindlin were associated with cancer or a transformed cell phenotype. As noted above, the absence of kindlin-1 in Kindler Syndrome patients appears to be associated with an increase in cancer. Thus, just as there is a TGF-β paradox, there may be a “kindlin paradox” and the value of a kindlin targeted therapy may need to be context specific. Despite this uncertainty, the relationship between kindlins and cancer remains an important interrelationship to dissect, and manipulation of kindlin functions and/or levels may provide insights into tumorogenesis and may ultimately offer a therapeutic strategy.

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Conflict of Interest
The authors have no conflicts of interest to disclose.

References
1. Larjava H, Plow EF, Wu C. Kindlins: essential regulators of integrin signalling and cell-matrix adhesion. EMBR Rep. 2008 Nov 7;9:1203-8.
2. Plow EF, Qin J, Byzova T. Kindling the flame of integrin activation and function with kindlins. Curr.Opin.Hematol. 2009 Sep;16(5):323-8.
3. Meves A, Stremmle C, Gottschalk K, Fassler R. The Kindlin protein family: new members to the club of focal adhesion proteins. Trends Cell Biol. 2009 Aug 19;19(10).
4. Malinin NL, Plow E.F., Byzova TV. Kindlins in FERM adhesion. Blood 2010;115:4011-7.
5. Ye F, Petrich BG. Kindlin: helper, co-activator, or booster of talin in integrin activation? Curr. Opin. Hematol. 2011 Sep;18(5):356-60.
6. Shattil SJ, Kim C, Ginsberg MH. The final steps of integrin activation: the end game. Nat.Rev.Mol.Cell Biol. 2010 Apr;11(4):288-300.
7. Ye F, Lagarrigue F, Ginsberg MH. Snapshot: talin and the modular nature of the integrin adhesome. Cell 2014 Mar 13;156(6):1340.
8. Khan AA, Janke A, Shimokawa T, Zhang H. Phylogenetic analysis of kindlins suggests subfunctionalization of an ancestral unduplicated kindlin into three paralogs in vertebrates. Evol.Bioinform.Online. 2011;7:7-19.
9. Meller J, Rogozin IB, Poliakov E, Meller N, Bedanov-Pack M, Plow EF, et al.. Emergence and subsequent functional specialization of kindlins during evolution of cell adhesiveness. Mol.Biol.Cell 2015 Feb 15;26(4):786-96.
10. Siegel DH, Ashton GH, Penagos HG, Lee JV, Feiler HS, Wilhelmsen KC, et al. Loss of kindlin-1, a human homolog of the Caenorhabditis elegans actin-extracellular-matrix linker protein UNC-112, causes Kindler syndrome. Am...J..Hum..Genet. 2003 Jul.;73(1):174-87.
11. White SJ, McLean WH. Kindler surprise: mutations in a novel actin-associated protein cause Kindler syndrome. J.Dermatol.Sci. 2005 Jun;38(3):169-75.
12. Duperrêt ET, Ridyk TW. Kindler syndrome in mice and men. Cancer Biol.Ther. 2014 Sep;15(9):1113-6.
13. Ussar S, Moser M, Widmaier M, Rognoni E, Harrer C, Genzel-Boroviczeny O, et al. Loss of Kindlin-1 causes skin atrophy and lethal neonatal intestinal epithelial dysfunction. PLoS. Genet. 2008 Dec;4(12):e1000289.
14. Mory A, Feigelson SW, Yarali N, Kilic SS, Bayhan GI, Gershoni-Baruch R, et al. Kindlin-3: a new gene involved in the pathogenesis of LAD-III. Blood 2008 Sep 15;112(6):2591.
15. Kuijpers TW, van d, V, Weterman MA, de BM, Tool AT, van den Berg TK, et al. LAD-1/variant syndrome is caused by mutations in FERMT3. Blood 2009 Dec 8;113:4740-6.
16. Malinin NL, Zhang L, Choi J, Ciocca A, Razorenova O, Ma Y-Q, et al. A point mutation in kindlin-3 ablates activation of three integrin subfamilies in humans. Nature Med. 2009;15:313-8.
17. Svensson L, Howarth K, McDowall A, Patzkai I, Evans R, Ussar S, et al. Leukocyte adhesion deficiency-III is caused by mutations in KINDLIN3 affecting integrin activation. Nat. Med. 2009 Mar;15(3):306-12.
18. Moser M, Niewandt B, Ussar S, Pozgajova M, Fassler R. Kindlin-3 is essential for integrin activation and platelet aggregation. Nat. Med. 2008 Mar;14(3):325-30.
19. Dowling JJ, Gibbs E, Russell M, Goldman D, Minarcik J, Golden JA, et al. Kindlin-2 is an essential component of intercalated discs and is required for vertebrate cardiac structure and function. Circ.Res. 2008;102:423-31.
20. Pluskota E, Dowling JJ, Gordon N, Golden JA, Szpak D, West XZ, et al. The integrin coactivator kindlin-2 plays a critical role in angiogenesis in mice and zebrafish. Blood 2011 May 5;117(18):4978-87.
21. Pluskota E, Ma Y, Bledzka K, Bialkowska K, Soloviev DA, Szpak D, et al. Kindlin-2 Regulates Hemostasis By Controlling Endothelial Cell Surface Expression of ADP/AMP Catabolic Enzymes via a Clathrin-Dependent Mechanism. Blood 2013 Oct 3;122:2491-9.
22. Bledzka K, Bialkowska K, Sossey-Alaoui K, Vaynberg J, Pluskota E, Qin J, et al. Kindlin-2 directly binds actin and regulates integrin outside-in signaling. J.Cell Biol. 2016 Apr 11;213(1):97-108.
23. Ussar S, Wang HV, Linder S, Fassler R, Moser M. The Kindlins: subcellular localization and expression during murine development. Exp.Cell Res. 2006 Oct 1;312(16):3142-51.
24. Bialkowska K, Ma Y-Q, Bledzka K, Sossey-Alaoui K, Izem L, Zhang X, et al. The integrin coactivator kindlin-3 is expressed and functional in a non-hematopoietic cell, the endothelial cell. J Biol. Chem. 2010;285:18640-9.
25. Goult BT, Bouauina M, Harburger MS, Bate N, Patel B, Anthis NJ, et al. The structure of the N-terminus of kindlin-1: a domain important for alphaibbeta3 integrin activation. J. Mol. Biol. 2009 Dec 18;394(5):944-56.
26. Perera D, Ma Y.Q., Yang J, Hirbawi J, Plow E.F., Qin J. Membrane Binding of the N-Terminal Ubiquitin-Like Domain of Kindlin-2 Is Crucial for Its Regulation of Integrin Activation. Structure 2011;19:1664-71.
27. Bouauina M, Goult BT, Huet-Calderwood C, Bate N, Brahme NN, Barsukov IL, et al. A conserved lipid-binding loop in the kindlin FERM F1 domain is required for kindlin-mediated alphalIbeta3 integrin coactivation. J. Biol. Chem. 2012 Mar 2;287(10):6979-90.

28. Yan M, Zhang L, Wu Y, Gao L, Yang W, Li J, et al. Increased expression of kindlin-2 is correlated with hematogenous metastasis and poor prognosis in patients with clear cell renal cell carcinoma. FEBS Open Bio. 2016; 1-15.

29. Qu H, Tu Y, Shi X, Larjava H, Saleem MA, Shattil SJ, et al. Kindlin-2 regulates podocyte adhesion and fibronectin matrix deposition through interactions with phosphoinositides and integrins. J. Cell Sci. 2011 Mar 15;124(Pt 6):879-91.

30. Liu J, Fukuda K, Xu Z, Ma Y.Q., Hirbawi J, Mao X, et al. Structural Basis of Phosphoinositide Binding to Kindlin-2 Pleckstrin Homology Domain in Regulating Integrin Activation. J Biol Chem. 2011;286:3334-42.

31. Fukuda K, Bledzka K, Yang J, Perera HD, Plow EF, Qin J. Molecular basis of kindlin-2 binding to integrin-linked kinase pseudokinase for regulating cell adhesion. J Biol Chem. 2014 Oct 10;289(41):28363-75.

32. Huet-Calderwood C, Brahme NN, Kumar N, Stiegler AL, Raghavan S, Boggon TJ, et al. Differences in binding to the ILK complex determines kindlin isoform adhesion localization and integrin activation. J Cell Sci. 2014 Oct 1;127(Pt 19):4308-21.

33. Theodosiou M, Widmaier M, Bottcher RT, Rognoni E, Veelders M, Bharadwaj M, et al. Kindlin-2 cooperates with talin to activate integrins and induces cell spreading by directly binding paxillin. Elife. 2016;5:e10130.

34. Xu Z, Chen X, Zhi H, Gao J, Bialkowska K, Byzova TV, et al. Direct Interaction of Kindlin-3 With Integrin alphalIbeta3 in Platelets Is Required for Supporting Arterial Thrombosis in Mice. Arterioscler. Thromb. Vasc. Biol. 2014 Jun 26;9:1961-7.

35. Xu Z, Gao J, Hong J, Ma YQ. Integrity of kindlin-2 FERM subdomains is required for supporting integrin activation. Biochem.Biophys.Res.Commun. 2013 May 3;434(2):382-7.

36. Kasirer-Friede A, Kang J, Kahner B, Ye F, Ginsberg MH, Shattil SJ. ADAP interactions with talin and kindlin promote platelet integrin alphalIbeta3 activation and stable fibrinogen binding. Blood 2014 Feb 12;120:3156-65.

37. Feng C, Li YF, Yau YH, Lee HS, Tang XY, Xue ZH, et al. Kindlin-3 mediates integrin alphaLbeta2 outside-in signaling, and it interacts with scaffold protein receptor for activated-C kinase 1 (RACK1). J. Biol. Chem. 2012 Mar 30;287(14):10714-26.

38. Liu Z, Lu D, Wang X, Wan J, Liu C, Zhang H. Kindlin-2 phosphorylation by Src at Y193 enhances Src activity and is involved in Migfilin recruitment to the focal adhesions. FEBS Lett. 2015 Jul 8;589(15):2001-10.

39. Yu Y, Wu J, Wang Y, Zhao T, Ma B, Liu Y, et al. Kindlin 2 forms a transcriptional complex with betacatenin and TCF4 to enhance Wnt signalling. EMBO Rep. 2012 Aug;13(8):750-8.

40. Bialkowska K, Byzova TV, Plow EF. Site-specific phosphorylation of kindlin-3 protein regulates its capacity to control cellular responses mediated by integrin alphalIbeta3. J. Biol. Chem. 2015 Mar 6;290(10):6226-42.

41. Coughlin SR. Thrombin signalling and protease-activated receptors. Nature 2000;407:258-64

42. Remijn JA, Wu YP, Jeninga EH, IJsseldijk MJ, van WG, de Groot PG, et al. Role of ADP receptor P2Y(12) in platelet adhesion and thrombus formation in flowing blood. Arterioscler. Thromb. Vasc. Biol. 2002 Apr 1;22(4):686-91.

43. Byzova TV, Goldman CK, Panpuri N, Thomas KA, Bett A, Shattil SJ, et al. A mechanism for modulation of cellular responses to VEGF: activation of the integrins. Mol Cell 2000;6:851-60

44. Katsumi A, Orr AW, Tzima E, Schwartz MA. Integrins in mechanotransduction. J. Biol. Chem. 2004 Mar 26;279(13):12001-4.

45. Carlos TM, Harlan JM. Leukocyte-endothelial adhesion molecules. Blood 1994;84:2068-101.

46. Diamond MS, Springer TA. The dynamic regulation of integrin adhesiveness. Curr. Biol. 1994;4:506-17.

47. Diacovo TG, Roth SJ, Buccola JM, Bainton DF, Springer TA. Neutrophil rolling, arrest, and transmigration across activated, surface-adherent platelets via sequential action of P-selectin and the b2 integrin CD11b/CD18. Blood 1996;88:146-57.

48. Ehlers R, Ustinov V, Chen Z, Zhang X, Rao R, Luscinskas FW, Lopez J, et al. Targeting platelet-leukocyte interactions: identification of the integrin Mac-1 binding site for the platelet counter receptor glycoprotein Iba. J. Exp. Med. 2003;198:1077-88.

49. Marguerie GA, Plow EF. The fibrinogen dependent pathway of platelet aggregation. Ann.N.Y.Acad.Sci. 1983;408:556-67.

50. Bledzka K, Liu J, Xu Z, Perera HD, Yadav SP, Bialkowska K, et al. Spatial coordination of kindlin-2 with talin head domain in interaction with integrin beta cytoplasmic tails. J. Biol. Chem. 2012 Jul 13;287(29):24585-94.

51. Schurpf T, Springer TA. Regulation of integrin affinity on cell surfaces. EMBO J. 2011 Nov 30;30(23):4712-27.
52. Karakose E, Schiller HB, Fassler R. The kindlins at a glance. J.Cell Sci. 2010 Jul 15;123(Pt 14):2353-6.
53. Plow EF, Meller J, Byzova TV. Integrin function in vascular biology: a view from 2013. Curr .Opin. Hematol. 2014 May; 21(3):241-7.
54. Pluskota E, Ma Y, Bledzka KM, Bialkowska K, Soloviev DA, Szpak D, et al. Kindlin-2 regulates hemostasis by controlling endothelial cell-surface expression of ADP/AMP catabolic enzymes via a clathrin-dependent mechanism. Blood 2013 Oct 3;122(14):2491-9.
55. Rognoni E, Widmaier M, Jakobson M, Ruppert R, Ussar S, Katsougri K, et al. Kindlin-1 controls Wnt and TGF-beta availability to regulate cutaneous stem cell proliferation. Nat. Med. 2014 Apr;20(4):350-9.
56. Sossey-Alaoui K, Pluskota E, Davuluri G, Bialkowska K, Das M, Szpak D, et al. Kindlin-3 enhances breast cancer progression and metastasis by activating Twist-mediated angiogenesis. FASEB J. 2014 May;28(5):2260-71.
57. Weinstein EJ, Bourner M, Head R, Zakeri H, Bauer C, Mazzarella R, URPI: a member of a novel family of PH and FERM domain-containing membrane-associated proteins is significantly over-expressed in lung and colon carcinomas. Biochim.Biophys.Acta 2003 Apr 17;1637(3):207-16.
58. Bauer R, Ratzinger S, Wales L, Bosserhoff A, Senner V, Grifka J, et al. Inhibition of collagen XVI expression reduces glioma cell invasiveness. Cell Physiol Biochem. 2011;27(3-4):217-26.
59. Mahawithitwong P, Ohuchida K, Ikenaga N, Fujita H, Zhao M, Kozono S, et al. Kindlin-1 expression is involved in migration and invasion of pancreatic cancer. Int.J.Oncol. 2013 Apr;42(4):1360-6.
60. Sin S, Bonif T, Petit V, Meseure D, Lallemant F, Bieche I, et al. Role of the focal adhesion protein kindlin-1 in breast cancer growth and lung metastasis. J. Natl. Cancer Inst. 2011 Sep 7;103(17):1323-37.
61. Ma HX, Shu QH, Pan JI, Liu D, Xu GL, Li JS, et al. Expression of Kindlin-1 in human hepatocellular carcinoma and its prognostic significance. Tumour Biol. 2015 Jun;36(4):4235-41.
62. Bedal KB, Grassel S, Oefner PJ, Reinders J, Reichert TE, Bauer R. Collagen XVI induces expression of MMP9 via modulation of AP-1 transcription factors and facilitates invasion of oral squamous cell carcinoma. PLoS ONE. 2014;9(1):e86777.
63. Mizutani H, Masuda K, Nakamura N, Takenaka H, Tsuruta D, Katoh N. Cutaneous and laryngeal squamous cell carcinoma in mixed epidermolysis bullosa, kindler syndrome. Case. Rep. Dermatol. 2012 May;4(2):133-8.
64. Zhan J, Zhu X, Guo Y, Wang Y, Wang Y, Qiang G, et al. Opposite role of Kindlin-1 and Kindlin-2 in lung cancers. PLoS One. 2012;7(11):e50313.
65. An Z, Dobra K, Lock JG, Stromblad S, Hjerpe A, Zhang H. Kindlin-2 is expressed in malignant mesothelioma and is required for tumor cell adhesion and migration. Int. J. Cancer 2010 Nov 1;127(9):1999-2008.
66. Ashton GH. Kindler syndrome. Clin. Exp. Dermatol. 2004 Mar;29(2):116-21.
67. Arita K, Wessagowit V, Inamadar AC, Palit A, Fasshi H, Lai- Cheong JE, et al. Unusual molecular findings in Kindler syndrome. Br. J. Dermatol. 2007 Dec;157(6):1252-6.
68. Lai- Cheong JE, Tanaka A, Hawche G, Emanuel P, Maari C, Taskesen M, et al. Kindler syndrome: a focal adhesion genodermatosis. Br. J. Dermatol. 2009 Feb;160(2):233-42.
69. Emanuel PO, Rudikoff D, Phelps RG. Aggressive squamous cell carcinoma in Kindler syndrome. Skinned. 2006 Nov;5(6):305-7.
70. Has C, Herz C, Zimina E, Qu HY, He Y, Zhang ZG, et al. Kindlin-1 Is required for RhoGTPase-mediated lamellipodia formation in keratinocytes. Am. J. Pathol. 2009 Oct;175(4):1442-52.
71. Lotem M, Raben R, Zeltsar R, Landau M, Sela M, Wygodz A, et al. Kindler syndrome complicated by squamous cell carcinoma of the hard palate: successful treatment with high-dose radiation therapy and granulocyte-macrophage colony-stimulating factor. Br. J. Dermatol. 2001 Jun;144(6):1284-6.
72. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011 Mar 4;144(5):646-74.
73. Kloecker S, Major MB, Calderwood DA, Ginsberg MH, Jones DA, Beckerle MC. The Kindler syndrome protein is regulated by transforming growth factor-beta and involved in integrin-mediated adhesion. J. Biol. Chem. 2004 Feb 20;279(8):6824-33.
74. Yang JR, Pan TJ, Yang H, Wang T, Liu W, Liu B, et al. Kindlin-2 promotes invasiveness of prostate cancer cells via NF-kappaB-dependent upregulation of matrix metalloproteinases. Gene. 2016 Jan 15;576(1 Pt 3):571-6.
75. Sossey-Alaoui K, Plow EF. miR-138-Mediated Regulation of KINDLIN-2 Expression Modulates Sensitivity to Chemotherapeutics. Mol. Cancer Res. 2016 Feb;14(2):228-38.
76. Gao J, Khan AA, Shimokawa T, Zhan J, Stromblad S, Fang W, et al. A feedback regulation between Kindlin-2 and GLI1 in prostate cancer cells. FEBS Lett. 2013 Mar 18;587(6):631-8.
77. Gong X, An Z, Wang Y, Guan L, Fang W, Stromblad S, et al. Kindlin-2 controls sensitivity of
prostate cancer cells to cisplatin-induced cell death. Cancer Lett. 2010 Dec 18;299(1):54-62.

78. Yu Y, Wu J, Guan L, Qi L, Tang Y, Ma B, et al. Kindlin-2 promotes breast cancer invasion via epigenetic silencing of the microRNA200 gene family. Int. J. Cancer 2013 Sep 15;133(6):1368-79.

79. Zhao T, Guan L, Yu Y, Pei X, Zhan J, Han L, et al. Kindlin-2 promotes genome instability in breast cancer cells. Cancer Lett. 2013 Apr 28;330(2):208-16.

80. Guo B, Gao J, Zhan J, Zhang H. Kindlin-2 interacts with and stabilizes EGFR and is required for EGFR-induced breast cancer cell migration. Cancer Lett. 2015 Jun 1;361(2):271-81.

81. Shen Z, Ye Y, Kauttu T, Seppanen H, Vainionpaa S, Wang S, et al. The novel focal adhesion gene kindlin-2 promotes the invasion of gastric cancer cells mediated by tumor-associated macrophages. Oncol. Rep. 2013 Feb;29(2):791-7.

82. Ren Y, Jin H, Xue Z, Xu Q, Wang S, Zhao G, et al. Kindlin-2 inhibited the growth and migration of colorectal cancer cells. Tumour Biol. 2015 Jun;36(6):4107-14.

83. Mahawithitwong P, Ohuchida K, Ikenaga N, Fujita H, Zhao M, Kozono S, et al. Kindlin-2 expression in peritumoral stroma is associated with poor prognosis in pancreatic ductal adenocarcinoma. Pancreas 2013 May;42(4):663-9.

84. Zhan J, Song J, Wang P, Chi X, Wang Y, Guo Y, et al. Kindlin-2 induced by TGF-beta signaling promotes pancreatic ductal adenocarcinoma progression through downregulation of transcriptional factor HOXB9. Cancer Lett. 2015 May 28;361(1):75-85.

85. Ren C, Du J, Xi C, Yu Y, Hu A, Zhan J, et al. Kindlin-2 inhibits serous epithelial ovarian cancer peritoneal dissemination and predicts patient outcomes. Biochem. Biophys. Res. Commun. 2014 Mar 28;446(1):187-94.

86. Yang M, Du J, Lu D, Ren C, Shen H, Qiao J, et al. Increased expression of kindlin 2 in luteinized granulosa cells correlates with androgen receptor level in patients with polycystic ovary syndrome having hyperandrogenemia. Reprod. Sci. 2014 Jun;21(6):696-703.

87. Zhang HF, Alshareef A, Wu C, Li S, Jiao JW, Cao HH, et al. Loss of miR-200b promotes invasion via activating the Kindlin-2/integrin beta1/AKT pathway in esophageal squamous cell carcinoma: An E-cadherin-independent mechanism. Oncotarget. 2015 Oct 6;6(30):28949-60.

88. Cao HH, Zhang SY, Shen JH, Wu ZY, Wu JY, Wang SH, et al. A three-protein signature and clinical outcome in esophageal squamous cell carcinoma. Oncotarget. 2015 Mar 10;6(7):5435-48.

89. Zhang HF, Zhang K, Liao LD, Li LY, Du ZP, Wu BL, et al. miR-200b suppresses invasiveness and modulates the cytoskeletal and adhesive machinery in esophageal squamous cell carcinoma cells via targeting Kindlin-2. Carcinogenesis 2014 Feb;35(2):292-301.

90. Ge YS, Liu D, Jia WD, Li JS, Ma JL, Yu JH, et al. Kindlin-2: a novel prognostic biomarker for patients with hepatocellular carcinoma. Pathol. Res. Pract. 2015 Mar;211(3):198-202.

91. Ou YW, Zhao ZT, Wu CY, Xu BN, Song YM, Zhan QM. Mig-2 attenuates cisplatin-induced apoptosis of human glioma cells in vitro through AKT/JNK and AKT/p38 signaling pathways. Acta Pharmacol. Sin. 2014 Sep;35(9):1199-206.

92. Shen Z, Ye Y, Kauttu T, Seppanen H, Vainionpaa S, Wang S, et al. Novel focal adhesion protein kindlin-2 promotes the invasion of gastric cancer cells through phosphorylation of integrin beta1 and beta3. J. Surg. Oncol. 2013 Aug;108(2):106-12.

93. Shen Z, Ye Y, Dong L, Vainionpaa S, Mustonen H, Puolakkainen P, et al. Kindlin-2: a novel adhesion protein related to tumor invasion, lymph node metastasis, and patient outcome in gastric cancer. Am. J. Surg. 2012 Feb;203(2):222-9.

94. Talaat S, Somji S, Toni C, Garrett SH, Zhou XD, Sens MA, et al. Kindlin-2 expression in arsenite- and cadmium-transformed bladder cancer cell lines and in archival specimens of human bladder cancer. Urology 2011 Jun;77(6):1507.

95. Wu WB, Zhang Q, Li Y, Shan SL, Li XY, Tian Z, Tet al. [Expression of Kindlins and angiopoietins in acute myeloid leukemia]. Zhongguo Shi Yan.Xue.Ye.Xue.Za Zhi. 2012 Feb;20(1):7-11.

96. Qu J, Ero R, Feng C, Ong LT, Tan HF, Lee HS, et al. Kindlin-3 interacts with the ribosome and regulates c-Myc expression required for proliferation of chronic myeloid leukemia cells. Sci.Rep. 2015;5:18491.

97. Djaafri I, Khayati F, Menashi S, Tost J, Podgornak MP, Sadoux A, et al. A novel tumor suppressor function of Kindlin-3 in solid cancer. Oncotarge. 2014 Oct 15;5(19):8970-85.

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