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REVIEW

Kindlin protein family: physiology, pathology, and implications for development and disease

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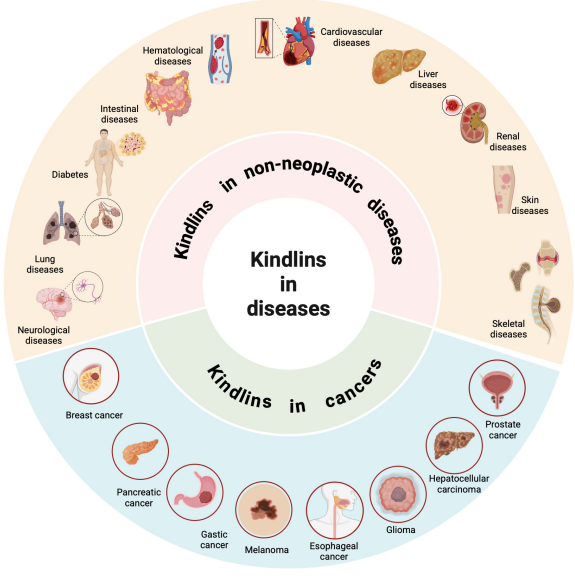
ABSTRACT: The Kindlin protein family, consisting of Kindlin-1, Kindlin-2, and Kindlin-3, is crucial in cellular physiology and pathology. Traditionally recognized as essential co-activators of integrins, Kindlins regulate integrin-dependent adhesion, migration, and signal transduction across diverse cell types. Recent advances, however, have revealed that Kindlins extend beyond integrin activation, participating in non-integrin-dependent signaling pathways and transcriptional regulation. This review provides a comprehensive summary of structural, physiological, and pathological roles of Kindlins, integrating their classical integrin-dependent and emerging integrin-independent functions. In this review, we a) offer a comprehensive overview of the structural and functional roles of Kindlin proteins across various organ systems; b) highlight their integrin-independent signaling functions and exact regulatory mechanisms; c) discuss their contributions to pathologies and explore the potential of Kindlins as biomarkers and therapeutic targets.



KEYWORDS: Kindlin protein family, integrin, pathology, signaling pathway, therapeutic target

1 Introduction

The Kindlin protein family comprises three evolutionarily conserved members: Kindlin-1, Kindlin-2 (also called Mig-2), and Kindlin-3-encoded by the KIND1 (FERMT1; chromosome 20p12.3), KIND2 (FERMT2; chromosome 14q22.1), and the KIND3 (FERMT3; chromosome 11q13.1) genes, respectively[1,2]. Kindlins share significant sequence and structural homology, each possessing a pleckstrin homology (PH) domain and a bipartite four-point-one, ezrin, radixin, moesin (FERM) domain located in the C-terminal region, as predicted by computational models[3]. Loss-of-function mutations in KIND1 and KIND3 lead to Kindler syndrome (KS) and leukocyte adhesion deficiency type III (LAD-III), respectively. However, no human disease has yet been associated with mutations in the KIND2 gene[4].

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Kindlin-1-mediated integrin regulation was initially highlighted by studies of keratinocytes from patients with KS, where mutations in KIND1 result in a deficiency of Kindlin-1[5]. These keratinocytes exhibit significant defects in migration, adhesion, and spreading, suggesting a disruption in integrin signaling. This was further corroborated by similar observations in Kindlin-1-deficient murine intestinal epithelial cells and keratinocytes, which demonstrated impaired integrin β1 activation[6]. Kindlin-2 is the human counterpart of the nematode UNC-112 protein[7,8]. As the most extensively studied Kindlin member, Kindlin-2 shows broad expression in central and peripheral tissues[7]. Knockout mice deficient in Kindlin-2 exhibit peri-implantation lethality for severe epiblast and endoderm detachment by day 7.5 of embryonic development, a finding that explains the absence of human diseases linked to KIND2 mutations[9]. Kindlin-3 is predominantly expressed in hematopoietic cells, particularly in red blood cells, platelets and megakaryocytes[1,10]. Kindlin-3 displays a crucial role in thrombosis and hemostasis and has been the focus of extensive research. Mice deficient in Kindlin-3 suffer from severe hemorrhages in multiple organs, including the gastrointestinal tract, bladder, skin and brain, which eventually lead to death shortly after birth[11]. Pathogenic

mutations in the Kindlin-3 gene lead to LAD-III, which manifests as defective integrin β activation in platelets, lymphocytes, and neutrophils[12,13].

Beyond their established integrin-dependent roles, this review thoroughly analyzes the emerging integrin-independent signaling functions of Kindlins, detailing the intricate regulatory mechanisms involved and their broader implications in cell biology. Also, we highlight the diverse roles of Kindlin proteins, emphasizing both their classical integrin-dependent functions and emerging integrin-independent mechanisms that influence various biological processes and contribute to various cancers and multiple non-neoplastic disorders. Additionally, the review underscores the translational relevance of Kindlins as therapeutic targets and biomarkers, while identifying knowledge gaps and proposing future research directions to advance understanding and application in health and disease contexts.

2 Structure basis of Kindlins

Kindlins exhibit approximately 50% sequence identity at the amino acid level and are characterized by alternating segments of conserved regions and brief divergent sequences. Belonging to the FERM superfamily, these proteins maintain a conserved architecture featuring F0-F1-F2-F3 modular organization, with an additional C-terminal octapeptide tail following the canonical F3 subdomain[14]. The F0 subdomain is also called a ubiquitin-like (UBL) domain. The UBL domain is a structural motif found in many proteins, not just the Kindlin family, which serves critical regulatory functions in protein-protein interactions, protein stability, and cellular signaling[15]. A defining feature of Kindlins compared to canonical FERM proteins lies in the presence of a PH domain embedded within their F2 subdomain. The F3 subdomain harbors the principal integrin-binding interface, which has a PTB-like structure, while the PH domains conserved across all three Kindlin isoforms serve as lipid-binding sites. The FERM regions in Kindlin family proteins share significant homology with that of talin, as both utilize their F3 modules to interact with integrin β subunit cytoplasmic tails (CT)[16] (Fig. 1a).

However, Kindlins and talins interact with distinct, non-overlapping regions on the integrin β CT, bringing the molecules in close proximity without direct overlap[17]. The crystal structure analyses of Kindlin proteins, both in isolation and when bound to integrin β CT, confirm that Kindlins are capable of multimerization. For Kindlin-2, dimerization promotes integrin activation, while trimerization of Kindlin-3 inhibits integrin activation. These structural studies underscore the essential function of the conserved QW sequence motif within the F3 modules of Kindlin proteins, which mediates their interaction with integrin β CT, highlighting its centrality in the regulation of integrin activation[17-20]. Overall, the structural insights into Kindlins reveal key features of their interaction with integrins, including the importance of their FERM domain, PH domain, and multimerization tendencies in controlling integrin activation (Fig. 1b).

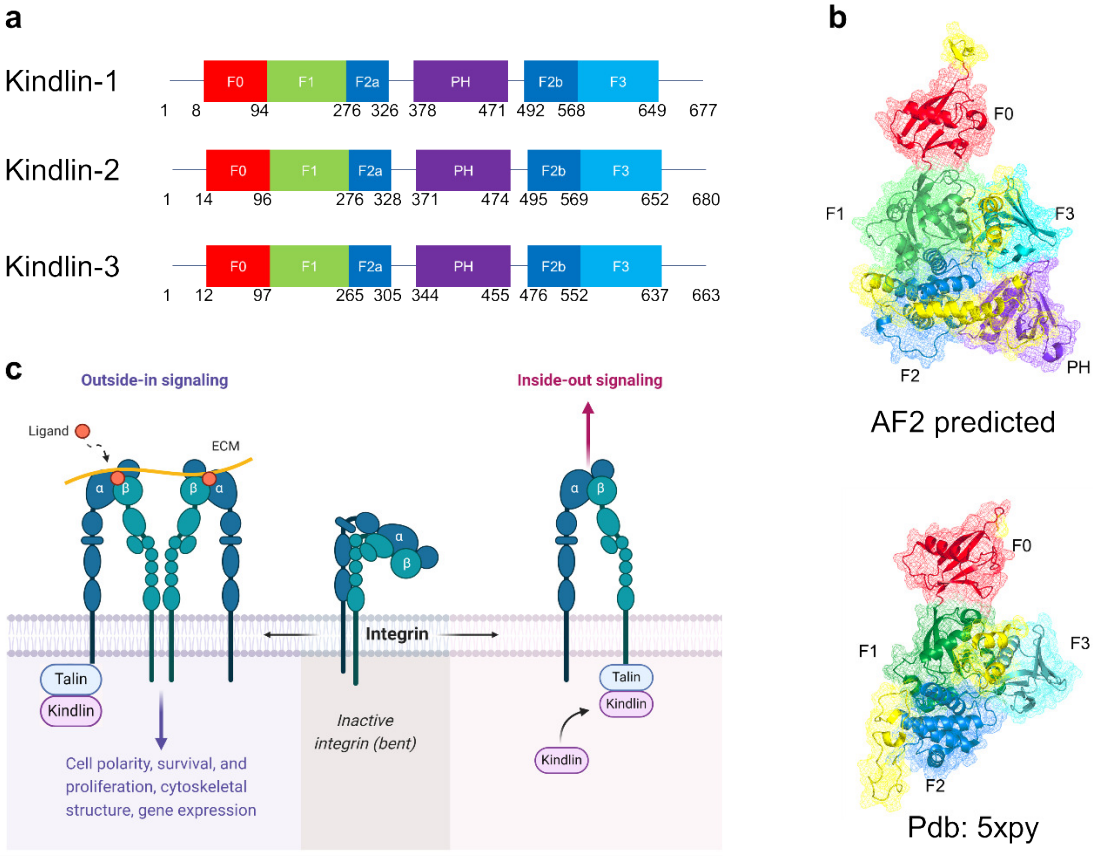

Figure 1 Overview of the Kindlins gene and protein structure and functions. (a) Domain architecture of the Kindlins. (b) The structure of Kindlin-2 is shown as a representative model due to the high conservation across the Kindlin family. Top, Alphafold2 predicted structure. Bottom, Crystallographic structure of the Kindlin-2 structure (PDB: 5xpy). (c) Overview of the Kindlins involved in the integrin pathway (Created with BioRender.com).

3 Biology functions of Kindlins

3.1 Kindlins in integrin activation

Integrin receptors, consisting of non-covalently associated α and β polypeptide chains, function as crucial mediators of cellular attachment to ECM components and cellular counter-receptors, such as vascular cell adhesion protein (VCAM) and intercellular adhesion molecule (ICAM)[21]. The activation of integrins is essential for their functional roles, depending on the simultaneous engagement of Kindlin and talin with specific sites on the β CT. Previous research by Ye et al. proposed that the contribution of Kindlins in integrin activation is primarily linked to their ability to cluster integrins, while talin's role centers around inducing affinity modulation[22]. Specifically, talin extends the integrin stalk, whereas Kindlins open the integrin headpiece, leading to functional integrin β2, with the PH domain of Kindlin-3 being identified as crucial for this activation pathway[23]. Additionally, correlation microscopy demonstrated that Kindlin-2 localizes to nascent adhesions prior to talin recruitment, further supporting the distinct functions of Kindlin and talin in integrin activation[24]. Emerging experimental evidence demonstrates that the interaction of integrin-linked kinase (ILK) with Kindlin promotes the translocation of Kindlin to focal adhesion sites, contributing to Kindlin-mediated integrin activation[25].

In contrast to talins, Kindlins exhibit selective binding affinity for the membrane-distal NxxY motif in the CT of integrins, serving as crucial molecular hubs for protein-protein interactions. This hub recruits various complexes, including the parvin complex, the integrin-linked pseudo-kinase PINCH (LIMS1), the paxillin and Arp2/3 complex, to integrins[26]. Despite the clear evidence of their roles in integrin activation, it remains uncertain whether Kindlin and talin bind to the integrin β tail consecutively or jointly, and whether they are responsible for different steps in the activation process[3]. Although the functional contributions of both Kindlin and talin in integrin activation have been extensively characterized, their distinct contributions, particularly Kindlin's function in integrin clustering and its interaction with various protein complexes, remain subjects of ongoing exploration. Further research is needed to clarify the sequential or concurrent binding of Kindlins and talins and to elucidate their precise roles in integrin activation.

3.2 Kindlins in mitochondria function

Mitochondria, crucial organelles for energy production, cell signaling, and cellular homeostasis maintenance, are regulated by various proteins to ensure proper cellular function. Their dynamics, such as fusion, fission, and trafficking, play a vital role in this process[27]. Recent studies have revealed the involvement of Kindlin proteins, particularly Kindlin-2, in the regulation of mitochondrial physiology and function. Kindlin-2 has been shown to interact with mitochondrial components and influence mitochondrial dynamics. For instance, in C. elegans, acute RNAi treatment against UNC-112/Kindlin-2 results in muscle protein degradation, mitochondrial fragmentation, and impaired energy production, indicating a role for Kindlin-2 in mitochondrial stability and function[28].

In cancer cells, Kindlin-2 interacts with Parkin, an E3 ubiquitin ligase, at the mitochondria, undergoing ubiquitination and proteasomal degradation. This process regulates focal adhesion turnover and integrin β1 activation, which in turn affects cell migration and invasion. However, Parkin-mediated degradation of Kindlin-2 does not impact tumor cell proliferation or apoptosis, suggesting that Kindlin-2's role in mitochondrial dynamics is more closely linked to migration and metastasis[29]. Furthermore, in response to extracellular matrix (ECM) stiffening, Kindlin-2 translocates to mitochondria, where it interacts with pyrroline-5-carboxylate reductase 1 (PYCR1), a key enzyme in proline synthesis. This interaction promotes increased proline biosynthesis and cell proliferation, a pathway commonly activated in fibrosis and cancer, contributing to ECM remodeling and disease progression[30]. These findings highlight Kindlin-2's emerging role as a regulator of mitochondrial dynamics and its involvement in pathological processes like cancer and fibrosis, offering potential therapeutic targets for disease intervention.

3.3 Kindlins in post-translational modification

Post-translational modifications (PTMs) refer to the chemical modifications of proteins after their synthesis, which are crucial for regulating protein function, localization, stability, and interactions[31]. PTMs, including phosphorylation, acetylation, ubiquitination, glycosylation, and more, are essential for numerous physiological processes such as intracellular communication, protein turnover, and adaptation to environmental stressors[32]. Kindlins, a family of integrin co-activators, are subject to various PTMs, which are critical for cell adhesion, migration, and signal transduction. Bialkowska et al. reviewed the phosphorylation modifications in Kindlin proteins, identifying 65 phosphorylation sites across Kindlin-1, -2, and -3, with a predominance of serine residues[33]. For instance, phosphorylation of Kindlin-1 at centrosomes, mediated by Polo-like kinase 1, is essential for mitotic spindle assembly and cellular survival[34]. Similarly, phosphorylation of Tyr residues in the integrin β3 cytoplasmic tail modulates Kindlin-2 binding, influencing integrin activation and cell migration[35]. Additionally, Kindlin-2 tyrosine phosphorylation is crucial for integrin outside-in signaling, with Src kinase playing a key role in this process, affecting cell migration and proliferation[36]. In Kindlin-3, phosphorylation of Thr482 and Ser484 regulates integrin αIIbβ3 activation, with a disruption in phosphorylation leading to impaired cell adhesion and spreading[37].

Research also highlights the significant role of E3 ubiquitin ligases such as Parkin and Smurf1 in modulating the stability of Kindlins, thereby influencing integrin activation. Parkin, altered in Parkinson's disease, ubiquitinates Kindlin-2 at Lys581 and Lys582, leading to its proteasomal degradation and a shortened half-life, which impairs integrin activation and suppresses tumor cell migration, invasion, and interactions with the ECM. This ubiquitin-mediated regulation is critical for maintaining cellular dynamics, including focal adhesion turnover, lamellipodia size, and mitochondrial function, particularly in tumor cells[29]. In contrast, Smurf1 controls the degradation of Kindlin-2 but not Talin, restricting integrin activation and cell adhesion. The knockout of Smurf1 in fibroblasts results in enhanced integrin activation, correlating with increased Kindlin-2 levels, suggesting a feedback loop between Smurf1 and Kindlin-2. Moreover, the interplay between Kindlin-2 and these ubiquitin ligases is essential for precisely modulating integrin-mediated cellular functions, including migration, invasion, and adhesion[14]. These studies underscore the central role of PTMs in regulating Kindlin function, highlighting their importance in cellular processes like integrin activation, cell adhesion, and migration, with implications in diseases such as

cancer and genetic disorders like KS.

4 Kindlins in cellular signaling pathway

4.1 Kindlins in integrin signaling pathway

Integrins transition between three states-inactive, inside-out signaling, and outside-in signaling- to precisely control cellular processes[38]. In the inactive state, they adopt a bent structure that is maintained through a cytoplasmic salt bridge, preventing ligand binding. Inside-out signaling disrupts this salt bridge via activators like talin and Kindlins, shifting integrins to an extended, high-affinity state that binds extracellular ligands, enabling adhesion and motility. Outside-in signaling occurs upon ligand binding, triggering cytoplasmic changes that recruit signaling proteins to regulate survival, proliferation, and migration[39]. Kindlins are key in these processes, synergizing with talin to promote activation, clustering, and downstream signaling (Fig. 1c).

4.1.1 Kindlins in inside-out integrin signaling pathway

The Kindlin family, comprising Kindlin-1, Kindlin-2, and Kindlin-3, is crucial in regulating inside-out integrin signaling by activating integrins and facilitating integrin-dependent cellular processes[3]. Structurally, Kindlins share a conserved FERM domain at their C-terminus, comprising F1, F2, F3 subdomains. Integrin activation occurs through the specific recognition of the membrane-distal NxxY sequence on the β-subunit cytoplasmic tail by Kindlin's F3 subdomain, particularly through its PTB site. This interaction initiates structural modifications within the integrin complex, converting it to a high-affinity state necessary for establishing cellular connections with extracellular matrix elements[40].

The function of Kindlins in integrin activation was first demonstrated in C. elegans, where Kindlins colocalize with integrins and mediate integrin-dependent cell-matrix adhesion[8]. In mammalian systems, Kindlin-1 overexpression has been proven to enhance integrin activation and downstream signaling. For example, Kindlin-1 overexpression induces sensory axon regeneration by counteracting the inhibitory effects of chondroitin sulfate proteoglycan in adult rat dorsal root ganglion (DRG) neurons, known to inactivate integrins. This is achieved by increasing integrin activation, as evidenced by elevated levels of phosphorylated focal adhesion kinase. Notably, Kindlin-2, despite being the primary isoform in the nervous system, fails to promote axon growth under similar conditions, highlighting isoform-specific functional differences in integrin signaling[41,42]. Kindlin-3 knockout mice exhibit severe phenotypes (defects in hemostasis and inflammation) resembling Kindlin-3 loss in humans. The bleeding stems from defective activation of platelet integrin αIIbβ3, while platelet morphological transformation remained unaffected, highlighting a specific disruption in inside-out integrin signaling[11,43].

Kindlins alone cannot induce robust integrin activation but play a crucial role as co-activators in synergy with talin[44]. Kindlin and talin interact with distinct motifs on the integrin β-subunit cytoplasmic tail, with Kindlin binding the membrane-distal NxxY motif and talin the membrane-proximal NPxY motif to regulate integrin activation. The C-terminal rod domain of talin not only dimerizes activated talin, amplifying its activity but also bridges the N-terminal head domain of talin to the integrin co-activator Kindlin-2 via the adaptor protein paxillin. This cooperation between talin and Kindlin creates a robust activation mechanism, and promotes integrin clustering, cell adhesion, and downstream signaling[45]. In summary, Kindlins are essential for inside-out integrin signaling, where they modulate integrin activation and play diverse roles depending on the isoform and cellular context.

4.1.2 Kindlins in outside-in integrin signaling pathway

Kindlins, traditionally known for their various functions in mediating inside-out integrin pathways, are also increasingly characterized as essential regulators of outside-in signaling. Although integrins function as dual-directional signaling mediators, utilizing their CT as molecular platforms for diverse cytoskeletal proteins and signaling effectors, Kindlins contribute to both directions of integrin activation[21]. In keratinocytes, Kindlin-1 helps regulate RhoGTPase activity through integrin β1 in outside-in signaling, revealing that Kindlin-1 activates Rho family GTPases (Rac1, RhoA, Cdc42) and their downstream effectors, including cofilin, LIM kinase and p21-activated kinase 1[46]. Furthermore, Kindlin-1 also is reported to upregulate αvβ6 and β1-class integrins to induce the release of TGF-β from latency-associated protein (LAP) and cell adhesion. The liberated TGF-β subsequently engages with its cognate receptors (TβRI/II), triggering a signaling cascade that results in Smad2/3 phosphorylation and nuclear accumulation, ultimately maintaining stem cell populations in a quiescent state[47].

Genetic manipulation of Kindlin-2 expression levels, either through knockdown or overexpression, differentially regulates the phosphorylation states of AKT and FAK signaling molecules[48]. Additionally, Kindlin-2 facilitates cytoskeletal organization through its regulation of the integrin β1-mediated signaling cascade involving FAK activation and RhoA GTPase signaling, which enhances cytoskeletal tension, leading to the activation and yes-associated protein (YAP) nuclear translocation. YAP, functions as a nuclear transcriptional co-regulator in the nucleus, is essential for promoting osseous differentiation[49]. Furthermore, Kindlin-2 is implicated in cancer progression and therapeutic resistance by modulating outside-in integrin signaling. miR-138 targets and inhibits Kindlin-2 expression, regulating a miR-138/Kindlin-2/integrin β1 axis in metastatic castration-resistant prostate cancer, with significant implications for modulating chemotherapeutic sensitivity[50]. In esophageal squamous cell carcinoma (ESCC), miR-200b downregulates PI3K-AKT signaling through suppression of the Kindlin-2/integrin β1 regulatory axis, thereby reducing cell invasiveness[51]. Meanwhile, Kindlin-2, in cooperation with Kindlin-3 and talin, enhances integrin α4β1-mediated cell adhesion, a process further enhanced by Rac1, which is functionally linked to the talin/Kindlin-3 complex. This cooperation contributes to stronger cell attachment, highlighting Kindlin-2's critical role in regulating integrin-dependent cell-matrix interactions and signaling in both vascular and cancer contexts[52].

Kindlin-3 is essential for mediating outside-in integrin signaling, particularly for integrins like αLβ2 and αMβ2. Kindlin-3 deficiency impairs cell adhesion, as demonstrated in LAD-III EBV-transformed B lymphoblasts, which fail to adhere to densely coated ICAM-1, and in K562 cells with reduced Kindlin-3 expression, which is defective in spreading on ICAM-1 or fibrinogen, despite overexpression of constitutively activated αIIbβ3 or αLβ2 integrins[53]. Moreover, Kindlin-3 is involved in the micro-clustering of integrin αLβ2 and interacts with a scaffold protein called receptor for activated C kinase 1 (RACK1), a scaffold protein, upon engagement of integrin αLβ2 with ICAM-1[54]. This interaction promotes cell adhesion and spreading. Additionally, Kindlin-3 plays

an indispensable role in facilitating αMβ2 integrin-dependent cellular adhesion and morphological spreading in K562 cells that naturally express Kindlin-3 but are deficient in integrin β2[55]. Moreover, the tension on syndecan-4 triggers PI3K-mediated activation of Kindlin-2/integrin β1/RhoA axis, which further supports YAP activation at the cell-extracellular matrix interface. This highlights the critical involvement of Kindlin-3 in integrin-dependent cell adhesion, signaling, and cytoskeletal regulation, emphasizing its importance in outside-in signaling across different integrin types[56].

Kindlin-3, on the other hand, is implicated in the dysregulation of TGF-β signaling, particularly in microglial cells. In the absence of Kindlin-3, high microglial contractility and excessive TGF-β1 expression led to aberrant vasculature and malformations in photoreceptor areas, demonstrating the role of Kindlin-3 in modulating TGF-β signaling through cytoskeletal regulation and ERK signaling[57]. In summary, Kindlins, including Kindlin-1, Kindlin-2, and Kindlin-3, play essential roles in outside-in integrin signaling by regulating integrin activation, cell adhesion, migration, and cytoskeletal dynamics, with implications in various biological processes such as stem cell quiescence, vascular hyperplasia, cancer progression, and therapeutic resistance.

4.2 Kindlins in integrin-independent signaling pathway

Kindlins are essential proteins that play dual roles in regulating cellular functions, both through integrin-dependent and integrin-independent mechanisms, and emerging evidence has revealed that Kindlins also mediate integrin-independent pathways, further broadening their functional repertoire[3,58]. Here, we delve into the significant roles of Kindlins in integrin-independent signaling pathways, exploring their diverse regulatory mechanisms and functional implications (Fig. 2).

4.2.1 NF-κB signaling pathway

NF-κB signaling cascade represents a fundamental intracellular pathway that controls the transcriptional regulation of genes mediating immune system activation, inflammatory processes, cellular survival mechanisms, and programmed cell death pathways[59]. Emerging research has demonstrated that Kindlin family proteins regulate NF-κB pathway activity through multiple

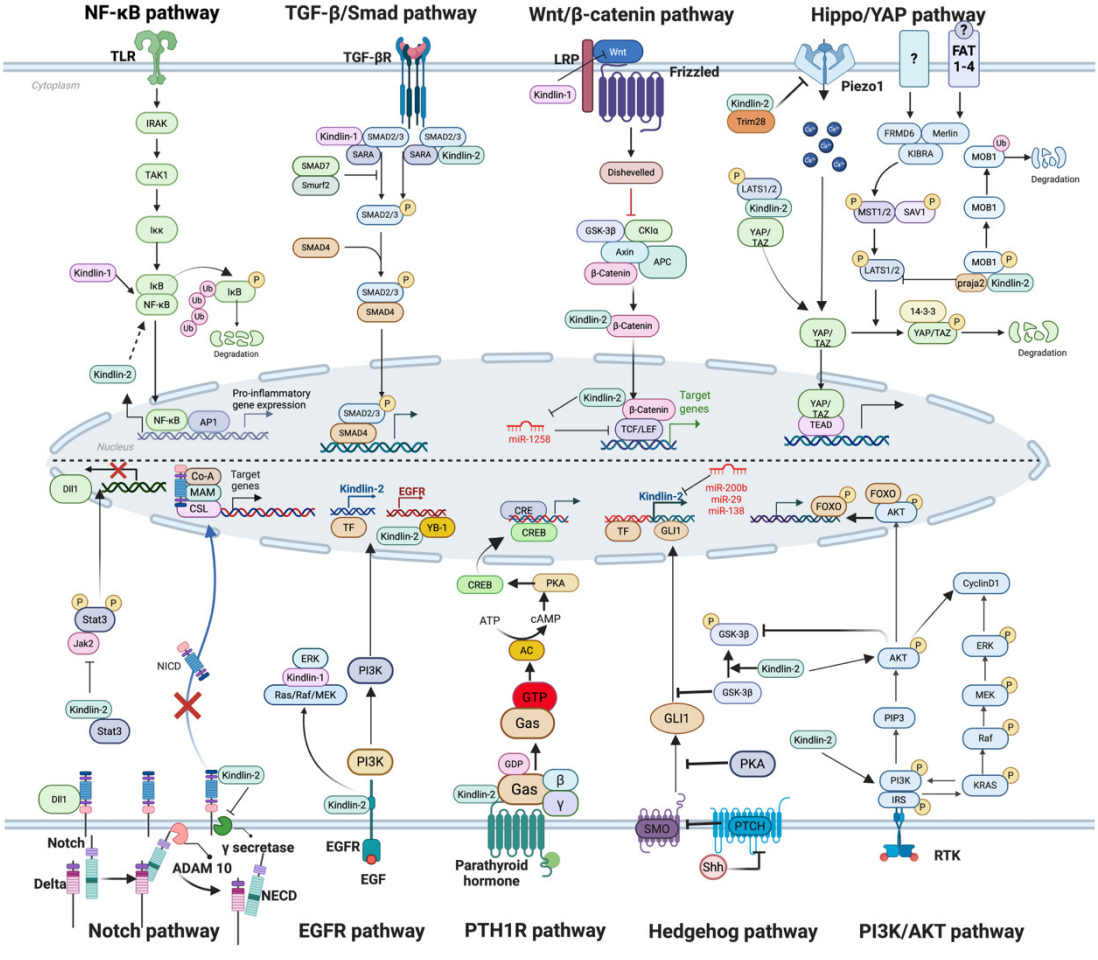

Figure 2 The roles of Kindlins in various integrin-independent signaling pathways. Kindlins are depicted as integral components that modulate several key pathways, including the NF-κB, TGF-β/Smad, Wnt/β-catenin, Hippo/YAP, Notch, EGFR, PTH1R, Hedgehog, and PI3K/AKT pathways (Created with BioRender.com).

molecular mechanisms, impacting both normal physiological functions and disease states. Experimental evidence indicates that Kindlin-1 stimulates NF-κB signaling by facilitating IκBα proteasomal degradation, which subsequently enables NF-κB nuclear translocation. This mechanism has been implicated in the promotion of gastric cancer progression[60]. Conversely, Kindlin-1 downregulation attenuated microglial inflammation and brain damage induced by intracerebral hemorrhage by inhibiting the NLRP3/NF-κB pathway. Specifically, Kindlin-1 knockdown prevents NF-κB p65 nuclear translocation and reduces NLRP3 inflammasome, consequently attenuating inflammatory activation in microglia[61].

Kindlin-2 also exhibits bidirectional regulatory effects on NF-κB signaling. In hepatocytes, it inhibits the TNF/NF-κB-Caspase 8 inflammatory signaling cascade, maintaining liver development and function[62]. However, in cancer contexts, Kindlin-2 overexpression activates NF-κB signaling, enhancing the expression of matrix metalloproteinases, MMP-2 and MMP-9, to promote tumor invasiveness. Silencing Kindlin-2 leads to reduced NF-κB activity and downregulation of MMPs, while inhibiting NF-κB with pyrrolidine dithiocarbamate or co-transfection with MMP siRNA nearly abolishes Kindlin-2-induced cancer cell invasiveness. This highlights the critical involvement of Kindlin-2 in modulating NF-κB-dependent tumor progression[63]. Furthermore, in gastric cancer cells, tumor-associated macrophages secrete TGF-β2, which downregulates Kindlin-2 expression by inhibiting NF-κB transcriptional activity. Collectively, these findings reveal that Kindlins regulate NF-κB signaling in context-dependent manners, influencing inflammation, tissue development, and cancer progression.

4.2.2 TGF-β/Smad signaling pathway

TGF-β/Smad signaling is initiated through the binding of TGF-β ligands to TGF-β receptor I (TβRI), leading to the phosphorylation and activation of Smad2/3 proteins, that subsequently undergo nuclear translocation to modulate downstream gene expression[64]. Kindlins participate in regulating TGF-β/Smad signaling by acting as mediators in the interaction between TβRI and Smad proteins, thereby enhancing Smads phosphorylation and nuclear translocation. Kindlin-1, for instance, physically interacts with TβRI, Smad3 and Smad anchor for receptor activation, facilitating their binding and promoting Smad3 phosphorylation. This interaction is crucial for activating TGF-β/Smad3 signaling, which is involved in multiple pathological processes including tissue fibrosis and cancer progression[65].

Similarly, Kindlin-2 also plays a key role in modulating TGF-β/Smad signaling. In primary fibroblasts from a mouse Peyronie's disease model, Kindlin-2 mediates Smad3-TβRI interaction, promotes Smad3 phosphorylation, and enhances TGF-β1 target genes, leading to tissue fibrosis[66]. Additionally, Kindlin-2 is upregulated by TGF-β1 and contributes to liver fibrosis by promoting Smad2 and Smad3 phosphorylation in hepatic stellate cells (HSCs)[67]. In chondrocytes, Kindlin-2 localizes to both focal adhesions and the nucleus, where it regulates the expression of Sox9, which is crucial for chondrocyte differentiation and TGF-β1-induced Smad2 phosphorylation[68]. In pancreatic ductal adenocarcinoma (PDAC) pathogenesis, Kindlin-2 increases TβRI levels, creating a reinforcing signaling loop that amplifies TGF-β pathway activity[69]. Furthermore, Kindlin-2 promotes TGF-β/Smad pathway through recruiting Smad3 to TβRI, contributing to tubulointerstitial fibrosis in kidney tubular epithelial cells[70]. Notably, Kindlin-2 deficiency impairs TGF-β-induced Smad3 phosphorylation and inhibits the activation of the Smad pathway in keloid fibroblasts (KFs)[71] and osteocytes[72], highlighting its essential role in regulating fibrosis and differentiation. Overall, Kindlins are critical modulators of TGF-β/Smad signaling, influencing fibrosis, differentiation, and disease progression through their interactions with TGF-β receptors and Smad proteins.

4.2.3 Wnt/β-catenin signaling pathway

Wnt/β-catenin signaling is activated by the binding of Wnt ligands to Frizzled receptors, which represses glycogen synthase kinase-3β (GSK-3β) activity, leading to β-catenin stabilization and accumulation in the cytoplasm. Stabilized β-catenin then translocates into the nucleus, and subsequently it interacts with T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) transcription factors, thereby regulating the target genes involved in cell cycle progression and developmental processes[73]. Experimental evidence demonstrates that Kindlin-1 regulates Wnt/β-catenin pathway activity in a chronic pain model by modulating astrocyte activation and inflammatory mediator release. It interacts with Wnt10a, affecting the expression of Wnt signaling components including both ligands and receptors[74,75]. Moreover, Kindlin-1 inhibits the Wnt/β-catenin pathway by regulating the transcription of Wnt ligands and receptors autonomously in cells, independently of integrins. Depletion of Kindlin-1 causes β-catenin to move into the nucleus, boosting Wnt/β-catenin signaling and inflammation[47].

In hepatocellular carcinoma (HCC), Kindlin-2 boosts Wnt/β-catenin pathway by enhancing β-catenin levels, mainly the dephosphorylated variant. This process involves the epigenetic silencing of miR-1258, which enhances TCF4 and a reciprocal regulatory circuit between Kindlin-2 and TCF4[76]. Additionally, Kindlin-2 also upholds β-catenin steadiness by blocking its breakdown via GSK-3β interaction and stimulates Axin2 gene transcription by creating a trimeric structure with TCF4 and β-catenin[47,77]. In colon cancer, Kindlin-2 knockdown downregulates the level of β-catenin and nuclear localization, consequently suppressing the transcriptional activation of β-catenin-dependent target genes like cyclin D1, C-MYC and Snail-1[78]. Moreover, Kindlin-2 has been shown to enhance Wnt/β-catenin pathway via promoting the interaction between active TCF4 and β-catenin, which is an indispensable factor for myogenic differentiation in C2C12 cells[79]. In vascular smooth muscle cells, Kindlin-2 also facilitates cell proliferation and migration through Wnt signaling[80]. Similarly, in renal cell carcinoma, Kindlin-2 facilitates cell proliferation, migration, and invasion through activating Wnt signaling, independent of its interaction with ILK[81]. In summary, Kindlins, especially Kindlin-1 and Kindlin-2, are key modulators of the Wnt/β-catenin signaling, influencing various cellular processes, such as inflammation, differentiation, cancer progression, and fibrosis.

4.2.4 Hippo/YAP signaling pathway

Hippo/YAP signaling is primarily controlled by the Hippo kinase cascade, with large tumor suppressor kinase 1 (LATS1) acting as a key kinase that phosphorylates YAP1, thereby inducing its cytoplasmic retention and degradation. YAP1's nuclear translocation is essential for activating gene transcription related to cell proliferation and organ size regulation[82]. So far, only Kindlin-2 is showed to regulate the Hippo/YAP pathway, influencing cell fate

decisions, particularly in mesenchymal stem cells (MSCs). In MSCs, Kindlin-2 depletion triggers adipogenesis while inhibiting osteogenesis both *in vitro* and *in vivo*. Kindlin-2 mechanistically binds to myosin light-chain kinase, in response to mechanical signals, enhancing myosin light-chain phosphorylation. Consequently, RhoA is activated, leading to stress fiber generation and focal adhesion formation. This cascade ultimately inhibits YAP1 phosphorylation at Ser127, thereby blocking its nuclear expulsion and degradation[83]. In the absence of Kindlin-2, YAP1 undergoes enhanced phosphorylation at Ser127, leading to its cytoplasmic sequestration and degradation through the ubiquitin ligase atrophin-1 interacting protein 4 (AIP4). Furthermore, Kindlin-2 impedes the interaction between YAP and LATS1, promoting YAP nuclear import by inhibiting LATS1's phosphorylation of YAP. In contrast, Kindlin-2 loss promotes the interaction between YAP and LATS1, resulting in elevated YAP phosphorylation and impaired nuclear import, ultimately suppressing downstream gene transcription[83].

Notably, Kindlin-2 also interacts with MOB1, facilitating its interaction with the E3 ligase Praja2, thereby inhibiting LATS1 phosphorylation and further promoting YAP1 nuclear translocation[84]. In Sertoli cells, the loss of Kindlin-2 results in YAP activation, contributing to altered cell growth and biological function, emphasizing the importance of Kindlin-2 in the Hippo/YAP pathway regulation[85]. Moreover, in human umbilical vein endothelial cells (HUVECs), Kindlin-2 knockdown increases piezo type mechanosensitive ion channel component 1 (Piezo1) stability by disrupting the interaction between Piezo1 and E3 ligase tripartite motif-containing 28 (Trim28)[86]. And, elevated Piezo1 activates YAP/TAZ into the nucleus by increasing intracellular Ca^{2+} concentration, which finally contributes to Hippo/YAP signaling pathway[87,88]. These findings suggest that Kindlin-2 is a critical regulator of YAP1 activity and cell fate by modulating Hippo signaling and myosin light-chain phosphorylation, influencing cellular responses to environmental cues and developmental processes.

4.2.5 Notch signaling pathway

Notch signaling is a highly conserved pathway essential for cell fate determination, differentiation, proliferation, and angiogenesis. Activation occurs through interactions between Notch receptors on cell surfaces and neighboring cell ligands, resulting in receptor cleavage by γ-secretase. Subsequently, the Notch intracellular domain (NICD) is released and translocates to the nucleus to control the expression of target genes, including Hey1 and Hes1[89,90]. Kindlin-2 regulates Notch signaling, particularly by maintaining the structural integrity of the Notch1 receptor. Kindlin-2 interacts with NICD and prevents the cleavage of Notch1, thereby inhibiting the release of NICD. This interaction is critical during processes like angiogenesis, where endothelial Notch1 cleavage by γ-secretase is necessary for NICD-mediated transcription. In contrast, Kindlin-2 deficiency facilitates Notch1 cleavage, enhancing Notch signaling activity[91].

Additionally, Kindlin-2 deficiency in various cell types has been linked to dysregulation of Notch signaling through complementary mechanisms. In myoepithelial cells, the depletion of Kindlin-2 activates the Jak2-Stat3-Dll1 axis, leading to increased Notch signaling in luminal progenitor cells. This upregulation inhibits their differentiation and maturation during gestation[92]. Similarly, in ATDC5 chondrocyte-like cells, Kindlin-2 deficiency promotes mitochondrial oxidative stress and activates Stat3, which drives Runx2-mediated chondrocyte catabolism[92]. Overall, Kindlin-2 serves as a negative regulator of Notch signaling by stabilizing Notch1 and inhibiting its cleavage, while its deficiency disrupts this control, leading to increased Notch activity and downstream cellular effects. These findings highlight Kindlin-2's critical role in maintaining the balance of Notch signaling in diverse biological contexts.

4.2.6 EGFR signaling pathway

Epidermal Growth Factor Receptor (EGFR) signaling, a member of the ERBB tyrosine kinase receptor family, is involved in key cellular functions like proliferation, differentiation, migration, survival, and tumor invasion[93]. When stimulated by its ligand, EGFR triggers several signaling pathways like AKT, ERK, and β-catenin, which play a role in cell growth, survival, and movement. Abnormal EGFR signaling is commonly associated with conditions such as cancer and impaired tissue regeneration[94]. Kindlin-1 and Kindlin-2 have emerged as important modulators of EGFR signaling. In KS, keratinocytes exhibit significantly reduced EGFR expression, leading to defective EGF-dependent migration and signaling. Mechanistically, Kindlin-1 directly interacts with EGFR in an EGF-dependent, integrin-independent manner, protecting EGFR from lysosomal degradation and ensuring its stability[95]. This interaction is critical for normal keratinocyte migration and suggests that Kindlin-1 also regulates EGFR activity in other contexts, such as breast cancer, where EGFR signaling upregulates Kindlin-1 expression, forming a feedback loop[96]. In HCC, Kindlin-1 promotes tumor progression through the EGFR/AKT/β-catenin and EGFR/ERK pathways. Silencing Kindlin-1 inhibits these pathways, confirming their role in Kindlin-1-mediated tumor growth and invasion[97].

Similarly, Kindlin-2 interacts with the kinase domain of EGFR, independent of its association with integrins, and prevents EGFR from ubiquitination and degradation. By stabilizing EGFR protein levels, Kindlin-2 enhances EGF-induced migration in cancer cells[98]. Furthermore, Kindlin-2 promotes EGFR transcription by forming a tripartite transcriptional complex with Y-box binding protein-1 (YB-1) and β-catenin. This complex binds to the EGFR promoter, increasing EGFR mRNA expression and driving downstream signaling, such as the EGFR/AKT/β-catenin and EGFR/ERK pathways. These pathways are essential for Kindlin-2-mediated glioma cell proliferation and motility[99]. In summary, Kindlin-1 and Kindlin-2 act as key regulators of EGFR signaling by ensuring EGFR stability, enhancing its transcription, and promoting downstream signaling pathways. Their involvement highlights potential therapeutic targets for diseases characterized by aberrant EGFR signaling, including cancer and chronic tissue repair disorders.

4.2.7 PTH1R signaling pathway

Parathyroid hormone 1 receptor (PTH1R) is a G protein-coupled receptor (GPCR) responsible for transmitting the actions of parathyroid hormone (PTH) and PTH-related protein (PTHrP). PTH1R activation initiates signaling pathways that involve Gsα-dependent cyclic AMP (cAMP) generation and phosphorylation of cAMP-response element-binding protein (CREB), essential for the regulation of bone metabolism, osteoblast differentiation, and mineralization[100,101]. Kindlin-2 has been identified as a key regulator of PTH1R signaling in bone. Kindlin-2 directly interacts with the C-

terminal cytoplasmic domain of PTH1R via amino acids 474-475 and with Gsα, facilitating the coupling of PTH1R to its downstream signaling pathways. This interaction enhances PTH-induced cAMP production and CREB phosphorylation, crucial steps for osteoblast function and bone formation. The loss of Kindlin-2 suppresses these signaling events, impairing osteoblast activity and reducing bone remodeling efficiency[102].

In addition to modulating PTH1R activity, Kindlin-2 plays a direct role in osteogenesis. It stimulates the expression of osteocalcin (OCN), a non-collagenous protein (NCP) that regulates intrafibrillar hydroxyapatite alignment and mineralization. This regulation is critical for maintaining proper bone structure and mechanical properties[103]. Intriguingly, PTH signaling upregulates Kindlin-2 expression, creating a positive feedback loop that amplifies both PTH1R signaling and osteoblast function[102]. To sum up, Kindlin-2 serves as a pivotal mediator of PTH1R signaling by enhancing receptor activity, downstream signal transduction, and osteogenesis-related gene expression. This interplay between Kindlin-2 and PTH1R underscores its critical role in bone metabolism and highlights potential therapeutic targets for bone-related disorders.

4.2.8 Other integrin-independent signaling pathways

Kindlin proteins, beyond the above well-characterized roles in integrin-independent signaling pathways, also exhibit diverse regulatory functions across multiple others, for example, Kindlin-1 is crucial for fully activating ERK signaling in response to oxidative stress, thereby protecting cells from DNA damage[104]. In human cervical cancer cells (SiHa), Kindlin-2 promotes autophagy by inactivating the AKT/mTOR signaling pathway, suggesting a tumor-suppressive role under specific contexts[105]. Conversely, Kindlin-2 activates mTOR/VEGFA signaling to promote melanoma progression and angiogenesis[106]. Kindlin-2 influences cell fate through multiple mechanisms. For instance, its depletion increases Fas and FasL expression in KFs, activating the Fas/FasL-mediated exogenous apoptotic pathway[71]. Additionally, Kindlin-2 negatively regulates cellular senescence by modulating p53-dependent transcriptional activity, repressing senescence-associated genes like SerpinB2 and p21[107]. Ding *et al.* also demonstrate loss of Kindlin-2 enhances miR-29-mediated upregulation of p53, promoting the senescence-associated secretory phenotype (SASP) and impairing skeletal homeostasis[107].

The latest research results also show that Kindlin-2 promotes peroxisome proliferator-activated receptor gamma (PPARγ) activity by stabilizing fatty acid synthase (FAS), enhancing fatty acid binding protein 4 (FABP4) expression. This axis suppresses insulin expression and decreases bone mass. Inhibiting Kindlin-2 accelerates FAS degradation, reduces FABP4 expression, and reverses these effects, highlighting its role in metabolic regulation and bone remodeling[108]. Recently, Kindlin-2 established a regulatory loop with GLI1, an effector of the Hedgehog pathway. GLI1 transcriptionally represses Kindlin-2, while Kindlin-2 promotes GLI1 expression via GSK-3β inactivation in a Smoothened-independent manner[109]. Additionally, Kindlin-2 modulates Rho GTPase activity by interacting with Rho GDP-dissociation inhibitor α (RhoGDIα) and Rac1, maintaining cytoskeletal dynamics and cellular motility. Its loss in podocytes leads to Rac1 hyperactivation, cytoskeletal defects, and increased motility[110].

Researchers also pay attention to the roles of Kindlins in gene transcription and epigenetic Modulation. Kindlin-2 interacts with histone methyltransferase SUV39H1 to repress GATA4 expression via H3K9 di- and tri-methylation, attenuating cardiac hypertrophy[111]. It also associates with RNA helicase DDX3X, facilitating c-Myc mRNA translation to drive glycolysis and pancreatic ductal adenocarcinoma (PDAC) progression, demonstrating its involvement in transcriptional and translational control[112]. These findings collectively reveal that Kindlin proteins act as versatile regulators of non-integrin signaling pathways, orchestrating cellular responses to environmental and intracellular cues. Their dysregulation contributes to diverse pathological conditions, including cancer progression, oxidative stress, fibrosis, metabolic disorders, and aging. These insights not only underscore the broad biological importance of Kindlin proteins but also highlight their potential as therapeutic targets across a wide range of diseases (Table 1).

Table 1 Kindlins in integrin-independent signaling pathway.

Isoform	Signaling pathway	Cell/Tissue type	Mechanism	Function	Ref
Kindlin-1	Kindlin-1/Wnt/β-catenin	Primary keratinocytes, KS patient specimens	Kindlin-1 loss activates Wnt-β-catenin signaling by regulating transcription of Wnt ligands and receptors in a cell autonomous and integrin-independent manner	Hyperthickened epidermis↑, KS-like defects↑, skin tumor incidence↑	[47]
	Kindlin-1/NF-κB	Human GC cell lines, human GC specimens	Kindlin-1 activates NF-κB signaling by promoting the degradation of IκBα	Overall survival rate↓, proliferation, invasion, metastasis and EMT↑	[60]
	Kindlin-1/NF-κB/NLRP3	BV2 microglial cells, rat brain	Kindlin-1 knockdown prevents NF-κB p65 from entering the nucleus and decreased NLRP3 inflammasome activation	Microglial inflammation and brain damage↓, intracerebral hemorrhage↓	[61]
	Kindlin-1/TGF-β1/Smad3	Human CRC lines, human and mouse CRC specimens	Kindlin-1 interacts with TβRI, SARA and Smad3 to activate TGF-β/Smad3 signaling pathway	Cell proliferation↑, tumor growth↑	[65]
	Kindlin-1/Wnt-10a/β-catenin	Primary astrocytes, rat brain specimens	kindlin-1 interacts with Wnt10a to activate Wnt10a/β-catenin signaling	GFAP↑, hyperalgesia↑, inflammatory mediators↑	[74,75]
	Kindlin-1/EGFR	Immortalized keratinocytes, KS patient specimens	Kindlin-1 and EGFR interacts directly to restrict c-Cbl–EGFR association and thus protects EGFR from lysosomal degradation	Cell migration↑	[95]
	Kindlin-1/EGFR/AKT/β-catenin	Human normal liver cells and hepatoma cell lines, human HCC specimens	Kindlin-1 activates EGFR/AKT/β-catenin and EGFR/ERK pathways	Cell viability, invasion, migration, and EMT↑	[97]

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Isoform	Signaling pathway	Cell/Tissue type	Mechanism	Function	Ref
Kindlin-2	Kindlin-2/TNF/NF-κB/Caspase 8	HepG2 and Huh7 cells, mouse liver injury	Kindlin-2 inhibits TNF/NF-κB-Caspase 8 inflammatory pathway	Hepatocyte apoptosis↓, liver fibrosis and injury↓	[62]
	Kindlin-2/NF-κB/MMPs	Human prostate cancer cell lines	Kindlin-2 overexpression activates NF-κB-dependent signaling and upregulate the expression of MMPs	Cell invasion↑	[63]
	Kindlin-2/TGF-β1/Smad3	Mouse primary fibroblasts cells, mouse skin specimens	Kindlin-2 mediates Smad3-TβRI interaction, activates p-Smad3, and enhances TGF-β1 target gene expression	Tissue fibrosis↑	[66]
	Kindlin-2/TGF-β/Smad	Human HSC cell line, human and mouse liver specimens	Kindlin-2 promotes TGF-β signaling through upregulation of Smad2 and Smad3 phosphorylation	Hepatic stellate cells activation ↑, liver fibrogenesis↑	[67]
	Kindlin-2/TGF-β/Smad	Limb MSCs, mouse bone specimens	Kindlin-2 ablation inhibits TGF-β1-induced Smad2 phosphorylation	Chondrocyte differentiation↓	[68]
	Kindlin-2/TGF-β1/HOXB9	PDAC cell lines, human PDAC specimens	Kindlin-2 is upregulated by TGF-β1 and upregulates TβRI to inhibit HOXB9	Cell growth, migration and invasion↑	[69]
	Kindlin-2/TGF-β/Smad	Human kidney TECs, human and mouse kidney specimens	Kindlin-2 facilitates activation of TGF-β/Smad signaling via recruiting Smad3 to TβRI	Renal fibrosis↑	[70]
	Kindlin-2/Smad/SOST	MLO-Y4 cells, mouse bone specimens	Kindlin-2 decreases SOST by downregulating Smad2/3	Osteopenia and mechanical property defects↓	[72]
	Kindlin-2/miR-1258/TCF4	Human HCC cell lines, human and mouse HCC specimens	Kindlin-2 upregulates TCF4 expression by epigenetically suppressing miR-1258	Cell migration and metastasis↑	[76,77]
	Kindlin-2/Wnt/β-catenin	Human colon cancer cell lines, human RCC cell lines	Kindlin-2 silencing directly reduces the expression, and nuclear localization of β-catenin, and decreases β-catenin target genes	Cell proliferation, invasion, and migration↓	[78,81]
	Kindlin-2/TCF4/β-catenin	C2C12 cells	Kindlin 2 forms a tripartite complex with active β-catenin and TCF4, and hence co-occupied on the promoter of myogenin to enhance its expression	myogenic differentiation↑	[79]
	kindlin-2/Wnt/β-catenin	Primary VSMCs, rat VSMC specimens	kindlin-2 upregulats Wnt/β-catenin signaling and thereby modulates the expression of β-catenin target genes	Cell proliferation, migration and intimal hyperplasia↑	[80]
	Kindlin-2/YAP/TAZ	Human MSCs, mouse bone specimens	Kindlin-2 loss inhibits RhoA activation and reduces myosin light-chain phosphorylation, resulting in increased Ser127-phosphorylation and nuclear exclusion of YAP1, and ubiquitin ligase atrophin-1 interacting protein 4-mediated degradation of YAP1/TAZ	MSC differentiation↑, adipogenesis↑, osteogenesis↓	[83]
	Kindlin-2/Hippo/YAP	Human renal tubular epithelial and human embryonic kidney cell lines, human and mouse kidney specimens	Kindlin-2 inhibits Hippo signaling by interacting with and degrading MOB1 and promoting the interaction between MOB1 and the E3 ligase praja2, and thus inhibits the phosphorylation of LATS1 and YAP and promotes YAP translocation into the nucleus	Tubular degeneration↑, renal fibrosis↑	[84]
	Kindlin-2/Hippo/YAP	Sertoli cell lines, mouse epididymis tissues	Kindlin-2 depletion enhances LATS1 interaction with YAP, increases YAP phosphorylation and decreases its nuclear translocation	Severe testis hypoplasia↑, cell proliferation↓, apoptosis↑, phagocytosis↓	[85]
	Kindlin-2/Piezo1/TGF-β/Runx2	HUVECs	Kindlin-2 knockdown increases Piezo1 stability by disrupting the interaction between Piezo1 and Trim28.	EC-to-OSB↑, bone mass↑	[86]
	Kindlin-2/Notch1	HUVECs, rat kidney vasculature specimens	Kindlin-2 interacts with NICD and prevents the cleavage of Notch1	Cell migration, matrix proteolysis, morphogenesis and sprouting↑	[91]
	Kindlin-2/STAT3/Dll1/Notch	Human breast cancer and human embryonic kidney cell lines, mouse mammary glands	Kindlin-2 depletion in myoepithelial cells promotes Stat3 activation and upregulates Dll1, which activates the Notch pathway	Luminal cell differentiation and maturation↓, alveologenesis↓	[92]
	EGFR/PI3K/Kindlin-2	Human cell lines HeLa, HEK-293T	EGF upregulates Kindlin-2 expression via EGFR–PI3K signaling cascade, and Kindlin-2 prevents EGFR from degradation via decrease of EGFR ubiquitination	Cell migration↑	[98]
	Kindlin-2/β-catenin/YB-1/EGFR	Human glioma cell lines, human and mice glioma specimens	Kindlin-2 forms a transcriptional complex with YB-1 and β-catenin that bound to the EGFR promoter and enhanced transcription	Cell proliferation and motility↑, glioma cell growth↑	[99]

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Isoform	Signaling pathway	Cell/Tissue type	Mechanism	Function	Ref
	Kindlin-2/Gsa/PTH1R	MC-4 cells, mouse bone specimens	Kindlin-2 interacts with the C-terminal cytoplasmic domain of PTH1R via aa 474-475 and Gsα.	PTH anabolic activity↑, bone mass accrual and homeostasis↑	[102]
	Kindlin-2/PTH1R/OCN	Rat BMSCs, rat bone specimens	Kindlin-2 activates PTH1R and stimulates the excretion of OCN	Osteogenesis↑, bone mass↑	[103]
	miR-29/Kindlin-2/p53	Primary BMSCs, 3T3-E1 cells, human and mouse OP specimens	miR-29 promotes senescence by upregulating p53 via targeting Kindlin-2 mRNA in MSCs to increase SASP levels	Skeletal senescence↑, cortical bone thickness↓, trabecular bone mass↓	[107]
	Kindlin-2/GSK-3β/GLI1	Human prostate cancer cell lines	Kindlin-2 promotes GLI1 expression through a mechanism involving GSK-3β inactivation	Cell viability↑	[109]
	Kindlin-2/SUV39H1/GATA4	Primary rat neonatal cardiomyocytes and HEK293A cells, mouse heart specimens	Kindlin-2 interacts with SUV39H1 and recruits it to GATA4 promoter leading to the occupancy of histone H3K9 di- and tri-methylation to suppresses GATA4 expression	Cardiomyocyte hypertrophy↓	[111]
	Kindlin-2/DDX3X/c-Myc	HEK 293T cells and MIA PaCa-2 cells, mouse PDCA specimens	Kindlin-2 facilitates DDX3X interaction with c-Myc mRNA 5'UTR and thereby promotes c-Myc translation	Tumor cell glycolysis and progression↑, tumor growth↑	[112]
	Kindlin-2/p53/SerpinB2	Breast cancer cell lines, mouse tumor specimens	Kindlin-2 negatively regulates cellular senescence in part through its interaction with p53, whereby it regulates the expression of SerpinB2 at the promoter level	Cellular senescence↓	[127]
	TGF-β2/NF-κB/Kindlin-2	Human GC cell lines, mouse GC specimens	TGF-β2 secreted by TAMs up-regulated the expression of Kindlin-2 through activating NF-κB	Overall survival↓, cell invasion and metastasis↑	[133]
	miR-200b/Kindlin-2	Human ESCC cell lines, human and mouse ESCC specimens	miR-200b binds to the 3′-UTR of Kindlin-2 and decreases Kindlin-2	Cell proliferation and migration↓, apoptosis↑, cell cycle arrest↑	[151]
	Kindlin-2/Stat3/Runx2	ATDC5 cells, human and mouse OA specimens	Kindlin-2 deficiency promotes mitochondrial oxidative stress and activates Stat3, leading to Runx2-mediated chondrocyte catabolism	Spontaneous OA↑, OA lesions↑	[180]
	Kindlin-2/GSK-3β/β-catenin	Primary human pancreatic islets, mouse pancreatic specimens	Kindlin-2 loss activates GSK-3β and downregulates β-catenin	β-cell proliferation and mass↓, diabetic phenotypes↑	[228]

"↑": upregulation; "↓": downregulation.

5 Kindlins in development and diseases

5.1 Kindlins in cancer progression and metastasis

While earlier reviews laid the groundwork for understanding Kindlins in cancer[113,114], the massive recent findings underscore their broader and deeper impact. These advances reveal not only novel regulatory mechanisms and pathways but also the potential of Kindlins as biomarkers for cancer prognosis and as therapeutic targets for intervention (Fig. 3). A thorough examination of genetic alterations across more than 10,000 patients with 33 cancer types demonstrated that kindlin mutations and alterations occur frequently across various malignancies. These genetic variations are not merely incidental but are closely associated with tumor progression, metastasis, and dysregulation of key cancer hallmark pathways. This highlights their multifaceted roles in oncogenesis, cancer progression and metastasis[115].

5.1.1 Kindlins in breast cancer

Recent studies have highlighted the pivotal roles of Kindlin-1 in breast cancer progression, metastasis, and immune regulation. Kindlin-1 promotes anti-tumor immune evasion by modulating the tumor microenvironment; its deletion in breast cancer models leads to tumor regression, reduced tumor-infiltrating regulatory T cells (Tregs), and increased IL-6 secretion, which impairs Treg-mediated $CD8^+$ T cell suppression[116]. Additionally, Kindlin-1 has been identified as a clinically relevant mediator of breast cancer[117], Kindlin-1 also enhances early steps of metastasis, including local invasion and pulmonary dissemination, through β-integrin activation and α4 integrin-mediated adhesion to endothelial VCAM-1. This facilitates early pulmonary arrest and metastasis, partly mediated by Kindlin-1-dependent secretion of factors like tenascin-C[118,119]. Collectively, these findings establish Kindlin-1 as a crucial regulator of breast cancer metastasis and immune modulation, presenting potential therapeutic targets for intervention.

Kindlin-2 has emerged as a critical regulator in breast cancer progression and metastasis, influencing multiple oncogenic pathways and cellular processes. It plays a pivotal role in mammary morphogenesis, alveologenesis, and lactation by mediating the Kindlin-2-Stat3-Dll1 signaling cascade, which regulates luminal progenitor commitment[92]. In triple-negative breast cancer, Kindlin-2 interacts with β1-integrin and TβRI, forming a complex that stabilizes oncogenic signaling, promoting tumor progression and metastasis[120]. Kindlin-2 contributes to an aggressive tumor microenvironment by modulating TGF-β/CSF-1 signaling employed by breast cancer cells, which recruits macrophages to support tumor progression[121]. Additionally, it facilitates androgen receptor (AR) signaling by forming a supramolecular complex with AR and Src, driving AR phosphorylation and enhancing breast

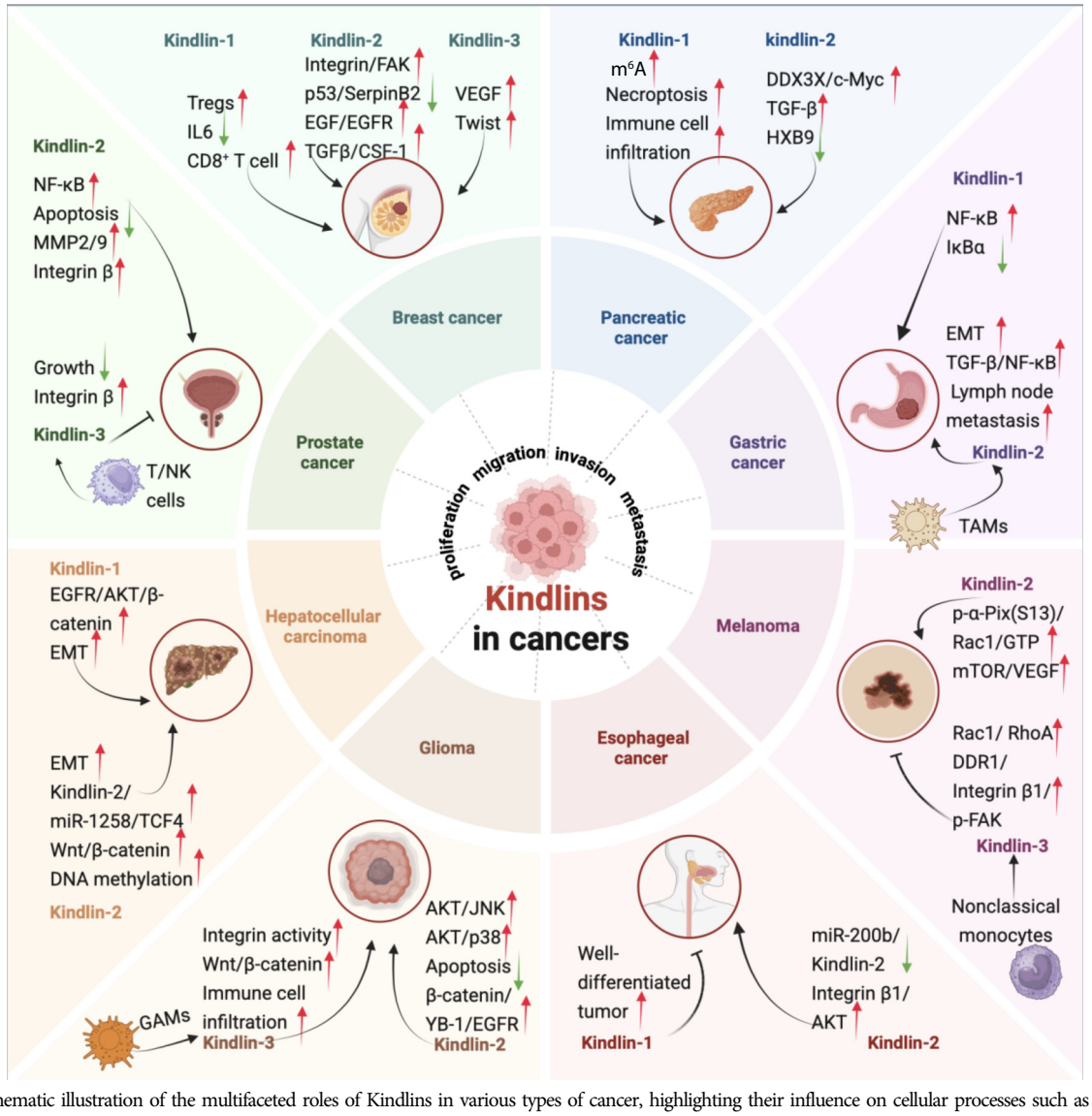

Figure 3 Schematic illustration of the multifaceted roles of Kindlins in various types of cancer, highlighting their influence on cellular processes such as proliferation, migration, invasion, and metastasis (Created with BioRender.com).

cancer cell proliferation and migration[122]. It stabilizes EGFR by inhibiting its ubiquitination and degradation, thereby amplifying EGF-induced breast cancer cell migration. Moreover, Kindlin-2 regulates breast cancer stiffness and invasion through its interaction with HIF-1α, influencing collagen biogenesis via the integrin/FAK pathway[123].

Epigenetically, Kindlin-2 enhances DNMT1 and DNMT3A activities, leading to silencing of tumor suppressors such as E-cadherin and miR-200 through CpG island hypermethylation. These changes facilitate breast cancer epithelial-mesenchymal transition (EMT), invasion, and metastasis[124]. The loss of Kindlin-2, conversely, increases miR-200 expression, suppressing EMT and metastasis[125,126]. Furthermore, Kindlin-2 interacts with p53 to regulate SerpinB2 and p21 expression, inhibiting cellular senescence and promoting tumor survival[127]. Its high expression also induces genome instability and enhances tumor growth in xenograft models, contributing to breast cancer progression *in vivo*[128]. Importantly, Kindlin-2 expression correlates with poor survival outcomes in breast cancer patients and mice, highlighting its potential as a therapeutic target[129,130]. Collectively, these findings underscore Kindlin-2's diverse and critical roles in breast cancer, from tumor initiation and progression to metastasis and therapy resistance.

Although Kindlin-3 is not expressed in breast tumor epithelial cells, it is highly expressed in tumor-infiltrating leukocytes, correlating with poor patient prognosis[131]. Moreover, elevated Kindlin-3 mRNA levels were observed in human breast tumors, with its overexpression enhancing primary tumor growth and lung metastasis in mouse models. Mechanistically, Kindlin-3 upregulates vascular endothelial growth factor (VEGF) secretion via integrin β1 activation and increased Twist expression, a transcription factor that drives angiogenesis[132]. These findings highlight the critical role of Kindlin-3 in modulating tumor-stromal interactions and its potential as a therapeutic target in aggressive breast cancers.

5.1.2 *Kindlins in gastric cancer*

Kindlin-1 and Kindlin-2 have been reported to be involved in gastric cancer progression, influencing tumor behavior through

distinct molecular pathways. Kindlin-1 is significantly overexpressed in gastric cancer tissues compared to normal tissues and is associated with poor overall survival. Mechanistically, Kindlin-1 activates NF-κB signaling by promoting IκBα degradation, driving proliferation, invasion, metastasis, and EMT. Knockdown of Kindlin-1 inhibits these oncogenic behaviors, suggesting its critical role in tumor progression[60]. Kindlin-2 is similarly implicated in advanced gastric cancer, with elevated expression linked to worse clinical outcomes, deeper tumor invasion, and lymph node metastasis. Kindlin-2 fosters EMT by activating fibroblasts and promoting M2 macrophage polarization. The TGF-β2/NF-κB/Kindlin-2 axis, driven by tumor-associated macrophages (TAMs), enhances invasion and progression, particularly under hypoxic conditions[133,134]. Additionally, Kindlin-2 induced by macrophages regulates the expression of interleukins (e.g., IL-8, IL-11, IL-22), further promoting gastric cancer cell invasion and tumor microenvironment remodeling[135].

Kindlin-2 also plays a crucial role in integrin signaling, enhancing the phosphorylation of β1 and β3 integrins to facilitate adhesion to the endothelium and ECM components like collagen IV. Its high expression in metastatic gastric cancer cell lines correlates with increased proliferation, invasion, and angiogenesis[136], alongside poor survival outcomes[137]. Both Kindlin-1 and Kindlin-2 are significantly upregulated in gastric cancer tissues, with their expression levels correlating with tumor stage, metastasis, and survival, highlighting their importance as biomarkers and therapeutic targets.

5.1.3 Kindlins in pancreatic cancer

In pancreatic adenocarcinoma (PAAD), Kindlin-1 is significantly upregulated and correlates with tumor stage, histologic grade, and poor prognosis, making it a valuable diagnostic and prognostic marker. Its expression is linked to N6-methyladenosine (m^6A) modification and methylation at specific CpG sites, which also influence prognosis. High Kindlin-1 expression may also increase sensitivity to chemotherapy drugs such as Palbociclib, AM-5992, and TAE-226, offering potential therapeutic avenues[138]. The Kindlin-1 protein is found in the cytoplasm and membrane of cancer cells, further functional assays revealed that silencing Kindlin-1 in PAAD cell lines, such as AsPC-1 and KP-2, significantly reduced their migration and invasion capabilities, though proliferation remained unaffected[139].

Kindlin-2 is also reported to deeply contribute to pancreatic cancer progression by regulating multiple signaling pathways[140,141]. It is upregulated by TGF-β1, which enhances pancreatic ductal adenocarcinoma (PDAC) cell growth, migration, and invasion. Kindlin-2 and TGF-β signaling creates a positive feedback loop, where Kindlin-2 also upregulates TβRI, further promoting PDAC progression[69]. Mechanistically, Kindlin-2 contributes to tumor advancement by downregulating key proteins such as HOXB9 and E-cadherin, which are involved in tumor suppression and epithelial integrity[69]. Moreover, Kindlin-2 has been implicated in the regulation of glucose metabolism and tumor growth through the DDX3X-c-Myc signaling axis, as loss of Kindlin-2 inhibits this axis, reducing c-Myc translation and glycolysis[112]. Additionally, Kindlin-2 is essential for the migration and invasion of PDAC cells *in vitro* and *in vivo*, with the knockdown of Kindlin-2 inhibiting pancreatic stellate cell-mediated effects on tumor progression[142]. Clinically, elevated Kindlin-2 expression is associated with poor prognosis in PDAC patients[69], indicating its potential as a biomarker for tumor aggressiveness and a therapeutic target for intervention.

5.1.4 Kindlins in prostate cancer

Kindlin-2 is significantly upregulated in prostate cancer (PCa) cells, particularly in androgen-independent cell lines such as PC3 and DU145. Kindlin-2 regulates integrin-mediated adhesion, migration, and invasion of PCa cells, facilitating their ability to invade surrounding tissues and metastasize[143]. Its overexpression in metastatic castration-resistant prostate cancer cells has been linked to enhanced cell survival and chemoresistance, particularly to chemotherapy agents like docetaxel and cisplatin. Mechanistically, Kindlin-2 protects PCa cells from apoptosis by modulating the expression of anti-apoptotic proteins like Bcl-xL and inhibiting β1-integrin signaling pathways, which are crucial for cell survival and migration[144]. In contrast, knocking down Kindlin-2 in PCa cells significantly reduces their invasiveness, suggesting its key role in promoting tumor progression through NF-κB activation and subsequent upregulation of matrix metalloproteinases (MMP-2 and MMP-9), enzymes that degrade the extracellular matrix and enhance invasive capabilities[63]. Additionally, Kindlin-2's role extends beyond cell adhesion and migration. Overexpression of Kindlin-2 in androgen-sensitive LNCaP cells confers resistance to cisplatin-induced cell death[144], while silencing Kindlin-2 in androgen-independent PCa cell lines such as PC3 enhances chemotherapy sensitivity[50,109]. *In vivo* studies also reveal that disruption of Kindlin-2 signaling impairs PCa growth and metastasis[143], highlighting its potential as a therapeutic target.

On the other hand, Kindlin-3 plays a complementary role in PCa progression, particularly in immune cells such as T cells and natural killer (NK) cells. It has been shown that loss of Kindlin-3 in these immune cells promotes tumor growth, suggesting its involvement in immune-mediated suppression of tumor development[145]. Moreover, interference with the interaction between Kindlin-3 and integrins in tumor-associated immune cells accelerates tumor growth, indicating that Kindlin-3 contributes to the tumor-suppressive activity of immune cells in the prostate cancer microenvironment[145]. Together, these findings underscore the pivotal roles of both Kindlin-2 and Kindlin-3 in regulating PCa progression, metastasis, and response to chemotherapy.

5.1.5 Kindlins in glioma

Kindlin-2 and Kindlin-3 have emerged as significant regulators in glioma progression, with distinct roles in cell motility, proliferation, and chemoresistance. High expression of Kindlin-2 in glioma tissues correlates with higher pathological grade and worse prognosis. Kindlin-2 promotes glioma cell motility and proliferation through activation of the EGFR pathway and the formation of a transcriptional complex with YB-1 and β-catenin, which upregulates EGFR transcription[99]. Furthermore, Kindlin-2's role in attenuating cisplatin-induced apoptosis in glioma cells has been demonstrated through AKT/JNK and AKT/p38 signaling pathways, with its F3 subdomain being critical for this effect[146].

Also, Kindlin-3 is highly expressed in glioblastoma tissues, particularly in high-grade gliomas, and is an independent prognostic factor for glioma. It enhances glioma cell proliferation and chemoresistance, particularly to temozolomide, through integrin-mediated activation of Wnt/β-catenin signaling[147]. Kindlin-3 is primarily expressed in glioma-associated microglia/macrophages (GAMs) and plays a crucial role in immune response and cytokine production, correlating with immune cell infiltration

and immune checkpoint gene expression. Moreover, Kindlin-3 overexpression has been associated with improved responses to anti-PD1 therapy[148]. These findings suggest that Kindlin-2 and Kindlin-3 play pivotal roles in glioma biology, influencing both tumor growth and therapeutic resistance, making them potential targets for novel glioma treatments.

5.1.6 Kindlins in esophageal cancer

In esophageal cancer (EC), both Kindlin-1 and Kindlin-2 show elevated expression compared to normal esophageal tissues, but their roles differ depending on tumor differentiation. Kindlin-1 is predominantly expressed in well-differentiated tumors, while Kindlin-2 is more prevalent in poorly differentiated tumors[149]. These observations suggest that Kindlin-1 may serve as a negative regulator of EC progression, potentially inhibiting tumor growth and metastasis, whereas Kindlin-2 appears to play a more supportive role in promoting tumor aggressiveness and progression. Recent studies further elucidate the regulatory mechanisms involving microRNAs in EC. Specifically, miR-200b has been shown to negatively regulate Kindlin-2 expression in esophageal squamous cell carcinoma (ESCC) cells. Overexpression of miR-200b reduces Kindlin-2 levels, leading to decreased cell protrusions, focal adhesion (FA) formation, and reduced invasiveness. Conversely, knockdown of miR-200b or enforced expression of Kindlin-2 abrogates the inhibitory effects of miR-200b on cell migration and invasiveness[150]. In addition, the long non-coding RNA lnc-ATB has been found to regulate the miR-200b/Kindlin-2 axis, as silencing of lnc-ATB significantly inhibits both cell proliferation and Kindlin-2 expression, thereby suppressing tumor growth *in vivo*[151]. Mechanistically, miR-200b targets Kindlin-2, leading to the suppression of integrin β1-mediated signaling and AKT activation, which further mitigates the invasive capabilities of ESCC cells[51]. These findings suggest that Kindlin-2 is a key player in EC progression, with its expression being tightly regulated by miR-200b and lnc-ATB, making it a potential therapeutic target for the treatment of ESCC.

5.1.7 Kindlins in hepatocellular carcinoma

In hepatocellular carcinoma (HCC), epigenetic modification of Kindlins genes plays a crucial role rather than genetic factors in hepatocarcinogenesis among the Chinese population. Kindlin-2 expression also correlates with aggressive clinicopathological features of HCC, including tumor encapsulation, microvascular invasion, extrahepatic metastasis, and poor prognosis[152]. High Kindlin-2 levels are associated with EMT in HCC cells, promoting invasion and metastasis through the activation of Wnt/β-catenin signaling. Additionally, a novel Kindlin-2-miR-1258-TCF4 feedback loop, identified in a recent study, has been found to promote HCC cell invasion and metastasis in an integrin-independent manner[76]. Furthermore, Kindlin-2 has been identified as an independent prognostic factor for both overall and disease-free survival in HCC patients[153]. These findings suggest that Kindlin-2 could serve as a potential biomarker for predicting poor prognosis in HCC and may be targeted for therapeutic intervention.

5.1.8 Kindlins in melanoma

Kindlin-2 is highly expressed in melanoma and correlates with advanced tumor stages, metastasis, and recurrence[149]. Clinically, high kindlin-2 expression is associated with advanced melanoma stages and predicts poor patient prognosis. Specifically, in experimental studies, elevated kindlin-2 enhances melanoma cell migration, invasion, and EMT without affecting proliferation *in vitro*. Mechanistically, Kindlin-2 upregulation activates the mTOR pathway, leading to increased VEGFA secretion and angiogenesis, which promotes tumor growth and lung metastasis *in vivo*[106].

Kindlin-3 has a more complex role. Although it regulates integrin-mediated cell adhesion, aberrant expression of Kindlin-3 disrupts RhoGTPase signaling, leading to impaired cell migration in melanoma[154,155]. Kindlin-3 is also involved in collagen-related signaling through its interaction with the DDR1 receptor, affecting β1-integrin activation. Knockdown or mutation of Kindlin-3 enhances the oncogenic properties of $BRAF^{V600mut}$ melanoma, promoting proliferation and migration while impairing the anti-proliferative effects of DDR1 inhibition[156]. Furthermore, Kindlin-3-deficient nonclassical monocytes, which are crucial for patrolling the vasculature and preventing tumor metastasis, exhibit defective tumor cell interaction, leading to increased lung metastasis in melanoma models[157]. Together, both proteins are potential therapeutic targets for melanoma treatment, offering opportunities to modulate tumor growth, metastasis, and immune responses.

5.1.9 Kindlins in other cancers

In addition to the cancers mentioned above, Kindlin proteins play significant roles across various other cancers, influencing tumor progression, metastasis, and patient prognosis. In chronic myeloid leukemia (CML), Kindlin-3 deficiency triggers the release of leukemia stem cells from the bone marrow, impairing their proliferation and survival in secondary organs, thus curbing disease progression and metastasis[158,159]. A similar role for Kindlin-3 has been observed in acute myeloid leukemia (AML), where its overexpression correlates with tumor proliferation and invasion, and its inhibition via miR-4792 suppresses these processes[160]. In renal cell carcinoma (RCC), Kindlin-2 promotes tumor progression by enhancing migration, invasion, and Wnt signaling activation, while higher Kindlin-2 levels correlate with poor prognosis[81,161]. In colorectal cancer (CRC), both Kindlin-1 and Kindlin-2 are implicated in promoting cell proliferation, migration, and invasion through TGF-β/Smad3 and Wnt/β-catenin pathways. Kindlin-1 is also associated with poor prognosis in CRC[65,78,162]. Similarly, in cutaneous squamous cell carcinoma (SCC), Kindlin-1 loss leads to tumor growth through a hypoxic environment and increased MMP13 expression[163,164]. In lung cancer, Kindlin-1 inhibits EMT, while Kindlin-2 promotes it, particularly in large cell lung cancer[165]. Additionally, in ovarian cancer, low Kindlin-2 expression is linked to poor prognosis, as it suppresses peritoneal dissemination and enhances EMT[166].

Kindlin-2 and Kindlin-3 have also been shown to play significant roles in lung adenocarcinoma[30], lymphoma[167], osteosarcoma[168], and cervical cancer[105] through their involvement in tumor growth, metastasis, and prognosis. Given the rapidly expanding evidence base, kindlins have emerged as key players in cancer biology beyond their previously recognized roles. This updated review integrates new insights into the diverse mechanisms by which Kindlins influence cancer progression and metastasis, providing a more comprehensive understanding of their importance in oncogenesis (Table 2).

5.2 Kindlins in bone biology and skeletal diseases

Kindlin-2 and Kindlin-3 are critical regulators of skeletal development and bone homeostasis, influencing processes such as

Table 2 Kindlins in cancer progression and metastasis.

Cancer	Isoform	Experimental cell/Model system	Treatment in vivo	Signaling pathway	Function	Ref
Breast cancer	Kindlin-1	Met-1 cells, mouse breast cancer model	Kindlin-1 mutant	Kindlin-1/IL6	Tumor infiltrating Tregs↓, IL-6 secretion↑, tumor regression↑	[116]
	Kindlin-1	Met-1 cells, 168FARN cells, 4T1 mouse model	Kindlin-1 mutant	Kindlin-1/Integrin β1	Cell invasion and metastasis↓, early pulmonary arrest	[118,119]
	Kindlin-2	Human cell lines HeLa, HEK-293T	Kindlin-2 siRNA	EGFR/PI3K/Kindlin-2	Cell migration and invasion↓	[98]
	Kindlin-2	MDA-MB-231, 4T1, and HEK293 cells, mouse breast cancer model	Kindlin-2 KO	Kindlin-2/Integrin β1/TβRI	Cell invasion and metastasis↓, tumor growth↓	[120]
	Kindlin-2	Human BT549 cells and HEK 293T cells,	Kindlin-2 KO, Kindlin-2 shRNA	Kindlin-2/AR/Src	Tumor metastasis↓, cancer progression↓	[122]
	Kindlin-2	MDA-MB-231 cells, human breast cancer specimens, MMTV-Kindlin-2 mice	MMTV-Kindlin-2	Kindlin-2/DNMT1/E-cadherin	Cell proliferation and migration↑	[124,131]
	Kindlin-2	Human breast cancer cell lines, mouse breast cancer model	Kindlin-2-deficient	miR-200b/Kindlin-2	EMT and cell metastasis↓	[125,126]
	Kindlin-2	Breast cancer cell lines, mouse tumor xenografts	Kindlin-2 shRNA	Kindlin-2/p53/SerpinB2	Cellular senescence↑, tumor growth↓	[127]
	Kindlin-3	Human breast cancer cell lines, human breast cancer specimens, mouse breast cancer model	N/A	Kindlin-3/Twist/VEGF	Primary tumor growth and lung metastasis↑	[132]
Gastric cancer	Kindlin-1	Human gastric cancer cell lines, human gastric cancer specimens	N/A	Kindlin-1/NF-κB	Overall survival rate↓, proliferation, invasion, metastasis and EMT↑	[60]
	Kindlin-2	Human gastric cancer cell lines, nude mouse oncogenesis model	N/A	TGF-β2/NF-κB/Kindlin-2	Overall survival rate↓, cell invasion↑	[133]
	Kindlin-2	Human gastric cancer cell lines, human gastric cancer specimens	N/A	Kindlin-2/EMT/macrophage	Overall survival rate↓, cell invasion, metastasis and EMT↑	[134,135]
	Kindlin-2	Human gastric cancer cell lines, human gastric cancer specimens	N/A	Kindlin-2/Integrin β	Overall survival rate↓, cell proliferation, adhesion, invasion, metastasis and EMT↑	[136]
Pancreatic cancer	Kindlin-1	Pancreatic cancer cell lines, human PAAD specimens	N/A	Kindlin-1/m^{6}A	Cell migration and invasion↑, poor prognosis↑	[138,139]
	Kindlin-2	HEK 293T cells and pancreatic cancer cell lines, mouse PDAC model	Kindlin-2 KO	Kindlin-2/DDX3X/c-Myc	Tumor cell glycolysis↓, tumor growth↓	[112,140]
	Kindlin-2	PDAC cell lines, human PDAC specimens	N/A	Kindlin-2/TGF-β1/HOXB9	Cell growth, migration and invasion↑	[69,141]
Prostate cancer	Kindlin-2	Human prostate cancer cell lines	N/A	Kindlin-2/NF-κB/MMPs	Cell invasion↑	[63,143]
	Kindlin-2	Human prostate cancer cell lines	Kindlin-2 siRNA	Kindlin-2/GSK-3β/GLI1	Cell viability↓	[109]
	Kindlin-2	Human prostate cancer cell lines	Kindlin-2 siRNA	miR-138/Kindlin-2/Integrin β1	Cell apoptosis↑, drug sensitivity↑	[50,144]
	Kindlin-3	Mouse xenograft model	Kindlin-3 knock-in	N/A	Tumor growth↓	[145]
Glioma	Kindlin-2	Human glioma cell lines, human glioma specimens, experimental metastasis mouse model	N/A	Kindlin-2/β-catenin/YB-1/EGFR	Cell proliferation and motility↑, glioma cell growth ↑	[99,148]
	Kindlin-2	Human glioma cancer cell lines	Kindlin-2 siRNA	Kindlin-2/AKT/JNK/p38	Cell apoptosis ↑	[146]
	Kindlin-3	Human glioma cancer cell lines, human glioma specimens	Kindlin-3 siRNA	Kindlin-3/Integrin/Wnt/β-catenin	Cell survival and chemoresistance↓	[147]
Esophageal cancer	Kindlin-1	Human esophageal cancer specimens	N/A	N/A	Tumor growth↓	[149]
	Kindlin-2	Human ESCC cell lines, human and mouse ESCC specimens	N/A	miR-200b/Kindlin-2/Integrin β1/AKT	Cell proliferation and migration↓, apoptosis↑, cell cycle arrest ↑	[51,150, 151]
Hepatocellular carcinoma	Kindlin-1	Human normal liver cells and hepatoma cell lines, human HCC specimens	Kindlin-1 siRNA	Kindlin-1/EGFR/AKT/β-catenin	Cell viability, invasion, migration, and EMT↓	[97,152]
	Kindlin-2	Human HCC cell lines, human and mouse HCC specimens	Lentivirus-Kindlin-2 shRNA	Kindlin-2/miR-1258/TCF4	Cell migration and metastasis↓	[76]
	Kindlin-2	Human HCC cell lines, human HCC specimens	N/A	Kindlin-2/Wnt/β-catenin	Cell invasion, metastasis and EMT↑, HCC clinicopathological features↑	[153]

(To be continued on the next page)

(Continued)

Cancer	Isoform	Experimental cell/Model system	Treatment in vivo	Signaling pathway	Function	Ref
Melanoma	Kindlin-2	Human melanoma tissues, melanoma cell lines	Kindlin-2 overexpression	Kindlin-2/mTOR/VEGFA	Tumor growth and angiogenesis↑	[106]
	Kindlin-3	Melanoma cell lines, mouse xenograft model	N/A	EMMPRIN/Integrin β1/kindlin-3	Cell invasion and migration↓, cell adhesion and spreading↑	[154,155]
	Kindlin-3	Melanoma cell lines, human melanoma specimens, mouse xenograft model	Kindlin-3 knockdown or mutant	Kindlin-3/DDR1/Integrin β1	Cell proliferation and migration↑, melanoma prognosis↓	[156,157]

"↑": upregulation; "↓": downregulation; "N/A": not applicable.

chondrogenesis, osteoblastogenesis, osteoclast activity, and osteocyte mechanotransduction. Kindlin-2 is indispensable for osteogenesis, with its deletion in osteoprogenitors or chondrocytes resulting in impaired ossification, severe skeletal abnormalities, and altered chondrogenic differentiation[169]. Mechanistically, Kindlin-2 promotes chondrocyte proliferation and survival, stabilizes key signaling molecules like Sox9, and regulates Smad2/3 signaling in osteocytes to modulate responses to mechanical stress[49,68]. Furthermore, Kindlin-2 affects osteoblast function through integrin β1/Rac1/AP-1 signaling, and its deficiency in osteocytes disrupts the balance between bone formation and resorption, increasing sclerostin expression, osteoclast activity, and RANKL levels, while reducing osteoblast differentiation and β-catenin signaling[49,72,170,171]. Furthermore, Kindlin-2 promotes osteogenesis by regulating osteoblast differentiation, ECM remodeling, and mineralization. It enhances osteoblast function through the Kindlin-2/PTH1R/OCN signaling axis and supports collagen crosslinking[103].

On the bone resorption front, Kindlin-3 plays a pivotal role in osteoclast function by regulating integrin activation and cytoskeleton organization[172,173]. Deficiencies in Kindlin-3 result in defective podosome and sealing zone formation, leading to impaired bone resorption and osteopetrosis[174,175]. Remarkably, Kindlin-3 interacts with LC3B, modulating podosome dynamics via autophagy-mediated degradation and inside-out integrin signaling[176]. Studies on inflammatory bone disorders reveal that aberrant Kindlin-3 and Talin-1 expression in pathologically activated osteoclasts contributes to pathological bone destruction[177]. Collectively, Kindlins orchestrate bone homeostasis by tightly regulating osteoblast, osteoclast, and osteocyte functions, offering potential therapeutic targets for metabolic and structural bone diseases.

5.2.1 *Kindlins in osteoarthritis*

Recent work has identified Kindlin-2 as a key regulator in maintaining the integrity of articular cartilage and preventing the progression of osteoarthritis (OA). Its expression is significantly downregulated in the degenerated cartilage of aged mice and patients with OA, highlighting its importance in cartilage homeostasis[178-180]. Genetic deletion of Kindlin-2 in articular chondrocytes leads to spontaneous OA and worsens OA lesions induced by joint instability. This is due to the activation of mitochondrial oxidative stress and the downstream activation of Stat3, which triggers the expression of Runx2, a master regulator of chondrocyte catabolism. Runx2 upregulates matrix-degrading enzymes like Mmp13, leading to cartilage degradation[180]. In the temporomandibular joint (TMJ), Kindlin-2 loss causes severe OA-like lesions, including progressive cartilage loss, surface fissures, and ectopic cartilage and bone formation. This is accompanied by a reduction in anabolic extracellular matrix proteins, such as aggrecan, Col2a1, and proteoglycan 4 (Prg4), and an increase in catabolic markers like Runx2 and Mmp13. Furthermore, Kindlin-2 deficiency leads to impaired chondrocyte proliferation and promotes apoptosis via cytochrome c release and caspase 3 activation[178].

Pharmacological inhibition of Stat3 or genetic ablation of Stat3 in chondrocytes can reverse the pathological changes associated with Kindlin-2 deletion, suggesting that targeting the Kindlin-2/Stat3/Runx2 axis could be a potential therapeutic strategy for OA. Intra-articular injection of AAV5-kindlin-2 has been shown to slow the progression of aging- and instability-induced knee joint OA in mice, further supporting the importance of Kindlin-2 in OA prevention and treatment[180]. Overall, Kindlin-2 plays a central role in cartilage homeostasis and OA pathogenesis, making it a promising therapeutic target for OA intervention.

5.2.2 *Kindlins in osteoporosis*

In aging and high-fat diet-induced osteoporosis (OP), Kindlin-2 expression in adipose tissue increases, contributing to decreased bone mass by promoting PPARγ activation, which upregulates FABP4 and inhibits insulin expression. This process leads to decreased bone mass. Targeted inhibition of Kindlin-2 results in increased bone mass by accelerating FAS degradation, decreasing PPARγ and FABP4 expression, and enhancing insulin levels[108]. Additionally, Kindlin-2 is integral to the PTH1R signaling pathway in osteoblastic cells, where its deletion impairs both osteoblast and osteoclast formation, neutralizing the bone anabolic effects of intermittent PTH treatment. The interaction between Kindlin-2 and PTH1R is critical for cAMP production and CREB phosphorylation, driving bone mass accrual. In estrogen-deficient mice, Kindlin-2 loss abrogates PTH-induced bone anabolic activity, highlighting its role in estrogen-dependent bone homeostasis[102]. Furthermore, miR-29, which targets Kindlin-2, is upregulated in aged mice and osteoporotic patients, promoting MSC senescence and exacerbating bone loss[107].

A recent study demonstrated that haploinsufficiency of Kindlin-2 in endothelial cells results in increased bone mass due to enhanced endothelial-to-osteoblast conversion (EC-to-OSB), indicating that Kindlin-2 loss in endothelial cells increases Piezo1 stability by disrupting the interaction between Piezo1 and Trim28. Meanwhile, elevated Piezo1 enhances EC-to-OSB by increasing TGF-β expression and subsequent Runx2 expression, which finally contributes to bone mass increase during aging, and also in mice with OP[86]. Overall, Kindlin-2 influences bone metabolism through multiple pathways, making it a potential therapeutic target for osteoporosis and related skeletal diseases.

5.2.3 Kindlins in intervertebral disc degeneration

Kindlin-2 also participates in the maintenance of intervertebral disc (IVD) homeostasis, and its loss is strongly associated with intervertebral disc degeneration (IVDD). It is highly expressed in the nucleus pulposus (NP) but not in the annulus fibrosus or cartilaginous endplates of IVD tissues. In aged mice and severe IVDD patients, Kindlin-2 expression in NP cells is significantly reduced. Deletion of Kindlin-2 in NP cells leads to spontaneous IVDD-like phenotypes, accelerating degeneration under mechanical stress[181]. Mechanistically, Kindlin-2 loss activates the NLRP3 inflammasome, inducing IL-1β expression, which further downregulates Kindlin-2, creating a vicious cycle that promotes ECM catabolism and NP cell apoptosis. Meanwhile, AAV-mediated overexpression of Kindlin-2 in human NP cells and rat models alleviates ECM catabolism and reduces cell apoptosis[181], offering potential therapeutic strategies for IVDD.

5.3 Kindlins in keratinocyte biology and skin diseases

Kindlins, including Kindlin-1 and Kindlin-2, are integral components of the integrin signaling network in keratinocytes and crucial for maintaining skin integrity and function. Kindlin-1, plays a significant role in keratinocyte adhesion, migration, and proliferation, primarily by interacting with integrins and actin cytoskeletal components[47,182-184]. In KS, a rare autosomal recessive disorder caused by Kindlin-1 mutations, patients exhibit skin fragility, photosensitivity, mucocutaneous scarring, and an increased risk of skin cancer[185,186]. Studies show that Kindlin-1 binds to cyclin-dependent kinases (CDK1 and CDK2), influencing cell cycle regulation and enhancing DNA repair in response to oxidative stress in KS[187]. Loss of Kindlin-1 sensitizes cells to oxidative damage by disrupting ERK signaling and ROS management, leading to increased DNA damage and photosensitivity in KS patients[104]. Additionally, Kindlin-1 is essential for EGFR signaling and cell migration in response to EGF, and it prevents EGFR degradation, which is crucial for proper wound healing[95,188]. Moreover, it leads to premature senescence, characterized by the downregulation of stemness markers and upregulation of cell cycle inhibitors such as p16[189].

Kindlin-2, while also involved in integrin-mediated adhesion, appears to have distinct functions from Kindlin-1[190]. It plays a key role in dermal-epidermal adhesion, barrier function, and cytoskeletal organization in keratinocytes[71,191]. In KS, the overlap between Kindlin-1 and Kindlin-2 in focal adhesions suggests that these proteins have complementary roles in skin epithelial integrity. However, Kindlin-2 cannot fully compensate for Kindlin-1 deficiency, and vice versa, highlighting their non-redundant roles. Notably, Kindlin-1 specifically interacts with β6 integrins, while Kindlin-2 is involved in interactions with integrin β1s, indicating functional differences that affect keratinocyte behavior[190,192,193].

Recent studies also suggest that modulating the balance between Kindlin-1 and Kindlin-2 expression, or targeting specific integrin signaling pathways (such as RhoGTPase regulation), could offer potential therapeutic strategies for treating KS and other skin diseases[191]. Understanding the precise molecular mechanisms by which Kindlins influence oxidative stress responses, cell cycle regulation, and integrin activation provides valuable insights into the pathophysiology of KS and other skin fragility disorders.

5.4 Kindlins in blood biology and hematological diseases

Kindlin-3 plays a crucial role in platelet function, hemostasis, and thrombosis by regulating integrin αIIbβ3 activation[20,194]. It interacts with talin and paxillin to facilitate integrin activation, platelet spreading, aggregation, and clot retraction. Studies demonstrate that Kindlin-3 is essential for the bidirectional signaling of integrin αIIbβ3, and its deficiency leads to impaired platelet adhesion and aggregation, extended bleeding times, and resistance to arterial thrombosis[195,196]. Kindlin-3 interacts with integrin β3 CT, distinct from talin, to support integrin activation[11]. In patients with ST-elevation myocardial infarction, Kindlin-3 cleavage in platelets is linked to myocardial infarction, suggesting a potential therapeutic target for anti-thrombotic treatments[197]. Additionally, reduced Kindlin-3 levels during fetal development result in diminished platelet spreading and function[198]. The role of Kindlin-3 in platelet integrin activation has significant implications for understanding thrombosis and bleeding disorders.

Leukocyte adhesion deficiency-III (LAD-III) is a rare autosomal recessive disorder caused by mutations in the Kindlin-3 gene encoding Kindlin-3, a crucial regulator of integrin activation in leukocytes, platelets, and osteoclasts[172,199,200]. Kindlin-3 deficiency impairs β1, β2, and β3 integrin-mediated adhesion, leading to defective leukocyte migration, platelet aggregation, and bone resorption, manifesting as symptoms of Glanzmann thrombasthenia and leukocyte adhesion deficiency[12,13,201]. Identified mutations, such as E138K and others causing truncation or destabilization of Kindlin-3's FERM domain, result in reduced protein expression and functional deficits in hematopoietic cells[201]. Kindlin-3 is also essential for NK cell migration, adhesion, and cytotoxicity[202]. Studies reveal that Kindlin-3 deficiency causes hematopoietic stem and progenitor cell quiescence and abnormal distribution between bone marrow and circulation, contributing to LAD-III pathophysiology[203]. Notably, allogeneic bone marrow transplantation has been shown to restore Kindlin-3 expression and resolve clinical symptoms[172], highlighting its therapeutic potential. These findings underscore Kindlin-3's critical role in leukocyte adhesion, platelet function, and integrin-mediated cellular processes in LAD-III.

5.5 Kindlins in cardiovascular diseases

Kindlins, particularly Kindlin-2 and Kindlin-3, play essential roles in endothelial cell function and cardiovascular regulation. Kindlin-2 is critical for vascular stability and angiogenesis by regulating integrin β1 and β3 activity through FAK-PIK3 signaling and supporting VE-cadherin-based adherens junctions via actin cytoskeleton linkage[48,204,205]. Endothelial-specific deletion of Kindlin-2 causes embryonic lethality due to impaired angiogenesis and vascular hemorrhage, while partial loss reduces vessel growth and tumor angiogenesis[91,206]. Mechanotransduction studies reveal that Kindlin-2 arginine methylation regulates vascular stability via liquid-liquid phase separation[207]. In vascular smooth muscle cells (VSMCs), Kindlin-2 knockdown suppresses proliferation, migration, and intimal hyperplasia through Wnt signaling[80]. Kindlin-3, meanwhile, promotes vascular endothelial growth factor (VEGF) secretion via Twist-mediated transcription and supports integrin β1 activation, contributing to angiogenesis and vascular remodeling[132]. Notably, Kindlin-3 deficiency causes microvascular malformations linked to dysregulated TGF-β1 signaling[57]. These findings underscore Kindlins' therapeutic potential in vascular diseases, including atherosclerosis, hyperplasia, and angiogenic disorders.

Kindlin-2 is essential for cardiac development, structural

integrity, and function, playing a critical role in cardiomyocyte mechanotransduction and integrin-mediated signaling[192,208,209]. It is highly expressed in the heart, localized to intercalated discs, costameres, and Z-discs, where it interacts with integrin β1 and α-actinin-2. Loss of Kindlin-2 disrupts Z-disc integrity, reduces integrin β1 activation, and leads to disordered myocardial fibers, cardiac hypertrophy, fibrosis, and heart failure[210-213]. Studies in mice and zebrafish show that Kindlin-2 deficiency results in embryonic lethality, impaired myocardial development, and ventricular contractility[192,214]. In adults, postnatal deletion of Kindlin-2 exacerbates hypertrophic cardiomyopathy and accelerates pathological remodeling under stress (e.g., isoproterenol). Mechanistically, Kindlin-2 suppresses GATA4 expression, regulates cytoskeletal organization, and mediates myocyte elongation and differentiation during myogenesis[111]. In fibroblasts, Kindlin-2 modulates mechanosensing and extracellular matrix interactions, with its depletion linked to age-related cardiac dysfunction[208,215,216]. These findings highlight Kindlin-2 as a pivotal regulator of cardiac structure and function, with implications for therapeutic interventions in cardiovascular diseases.

5.6 Kindlins in axon regeneration and neurological diseases

Kindlins, particularly Kindlin-1 and Kindlin-2, contribute to axon regeneration and neurological diseases through their effects on integrin activation, inflammation, and intracellular signaling. Kindlin-1 is implicated in neuropathic pain by regulating astrocyte activation, neuroinflammation, and pain sensitivity via the glial fibrillary acidic protein (GFAP; biomarker for astroglial injury) and Wnt10a pathways[42,74,75]. Downregulation of Kindlin-1 reduces glial activation and inflammatory mediator release, alleviating pain hypersensitivity, whereas overexpression exacerbates neuropathic pain symptoms[217]. Hyperbaric oxygen (HBO) therapy effectively attenuates neuropathic pain by suppressing Kindlin-1 expression, suggesting a therapeutic link between Kindlin-1 and inflammation-mediated pain[74,218]. In intracerebral hemorrhage (ICH), Kindlin-1 contributes to microglia activation and neuroinflammation through the NLRP3 inflammasome and NF-κB pathways. Silencing Kindlin-1 reduces inflammatory factors (IL-1β, IL-18), alleviates hematoma, and improves neurological outcomes in ICH models[61].

Kindlin-2 is endogenously expressed in the nervous system and essential for axon guidance, neural crest formation, and amyloid precursor protein metabolism[219]. In sensory neurons, Kindlin-2 deficiency impairs axon growth, though this can be partially rescued by Kindlin-1. Remarkably, overexpression of Kindlin-1 promotes integrin activation, enhances axon regeneration in rat dorsal root injury models *in vivo*, and improves functional recovery, suggesting its potential as a therapeutic target for nervous system repair[42]. Kindlin-2 also regulates FGF signaling, supporting neural crest development independently of integrins[220]. Collectively, Kindlins, especially Kindlin-1, are critical modulators of axon regeneration, neural inflammation, and pain regulation, presenting promising targets for therapies in neurological diseases and injuries.

5.7 Kindlins in liver diseases

Kindlin-2 is a pivotal regulator of liver health and disease, mediating processes such as inflammation, oxidative stress, lipid metabolism, ischemia-reperfusion (I/R) injury, and fibrosis, making it a potential therapeutic target for a range of liver disorders. Loss of Kindlin-2 in hepatocytes disrupts liver homeostasis by downregulating glutathione-S-transferase P1, leading to excessive oxidative stress and reactive oxygen species (ROS) production, which in turn triggers inflammation, fibrosis, and hepatocyte apoptosis. These detrimental effects can be mitigated by antioxidant treatment (e.g., N-acetylcysteine) or inhibition of the TNF pathway, underscoring Kindlin-2's role in maintaining liver integrity[62,221]. In nonalcoholic fatty liver disease (NAFLD), Kindlin-2 is significantly upregulated and exacerbates disease progression by stabilizing Foxo1 through inhibition of its ubiquitination and degradation via the Skp2 E3 ligase. This stabilization promotes lipid metabolism disorders and hepatocyte inflammation. In contrast, Kindlin-2 haploinsufficiency or knockdown in hepatocytes alleviates NAFLD and glucose intolerance in mice, suggesting a protective role in reducing Kindlin-2 activity[62,222].

Kindlin-2 also plays a critical role in liver fibrosis, a common endpoint of chronic liver diseases. Elevated Kindlin-2 expression in hepatic stellate cells (HSCs) enhances TGF-β1 signaling by promoting Smad2 and Smad3 phosphorylation, driving HSC activation and collagen deposition. Experimental models demonstrate that Kindlin-2 deficiency significantly attenuates fibrosis progression, highlighting its potential as a target for antifibrotic therapies[67]. Moreover, in steatotic liver subjected to I/R injury, Kindlin-2 mediates the protective effects of irisin, an exercise-induced myokine, by improving mitochondrial function and reducing oxidative and endoplasmic reticulum stress. However, Kindlin-2 inhibition abolishes these protective effects, emphasizing its central role in hepatocyte resilience to stress[223].

5.8 Kindlins in intestinal diseases

Recent studies have highlighted the crucial roles of Kindlin-1 and Kindlin-2 in intestinal diseases, particularly in conditions such as ulcerative colitis (UC) and gastrointestinal dysfunctions. Kindlin-1 is localized to the plasma membrane of epithelial cells in the colon and rectum, and mutations in Kindlin-1 are associated with severe gastrointestinal symptoms in KS, including chronic diarrhea, failure to thrive, and UC[223-225]. In mouse models, deletion of Kindlin-1 in the intestine leads to epithelial dysfunction, barrier detachment, and inflammation, resembling human UC, with perinatal lethality due to defective integrin activation in intestinal epithelial cells[6]. Similarly, intestine-specific deletion of Kindlin-1 and -2 in mice causes tight junction degradation and mucosal inflammation, mirroring the pathophysiology of UC[226]. Additionally, Kindlin-2 depletion in smooth muscle cells impairs intestinal contractility, leading to hypoperistalsis, intestinal obstruction, and reduced blood pressure[227]. These findings underscore the importance of Kindlin proteins in maintaining intestinal epithelial integrity, smooth muscle function, and mucosal health, and suggest that Kindlin dysfunction contributes to severe gastrointestinal disorders.

5.9 Kindlins in islet function and diabetes

Kindlin-2 is emerging as a pivotal regulator in islet β-cell function, systemic glucose metabolism, and the pathogenesis of diabetes and its complications. In β-cells, Kindlin-2 maintains insulin secretion and β-cell mass via nuclear roles. It localizes to the nucleus, directly stabilizes transcription factor MafA, and enhances insulin expression. Its loss impairs both MafA-driven transcription and calcium-dependent secretion, while activating GSK-3β, downregulating β-catenin, and reducing proliferation. These disruptions collectively lead to β-cell mass loss and diabetic phenotypes[228]. Mechanistically study confirmed that this nuclear

translocation was facilitated by a putative NLS (TKKKKKK, aa 148-154) within Kindlin-2, as its deletion abrogated nuclear accumulation and pro-fibrotic functions[208]. Furthermore, the deletion of Kindlin-2 promotes NLRP3 inflammasome activation and increases pro-inflammatory cytokine levels, exacerbating β-cell dysfunction in diabetic conditions. Conversely, overexpression of Kindlin-2 improves insulin secretion, reduces inflammation, and alleviates hyperglycemia in high-fat diet and streptozotocin-induced diabetic models, highlighting its therapeutic potential[229].

In adipose tissue, Kindlin-2 regulates insulin sensitivity and systemic metabolism through its integrin-related and independent pathways. The loss of Kindlin-2 in adipocytes leads to an atypical lipodystrophic phenotype characterized by insulin resistance, preserved liver insulin sensitivity, and compensatory hyperinsulinemia[230]. Kindlin-2 also plays a significant role in mitigating diabetes-induced complications. In diabetic nephropathy, Kindlin-2 inhibition prevents podocyte EMT by downregulating TGF-β/Smad signaling, alleviating kidney damage[231]. Dong *et al.* also shows that Kindlin-2 regulates angiogenesis by maintaining Notch1 signaling integrity, with high glucose-induced hyperactive angiogenesis being counteracted by Kindlin-2 knockdown[91]. Collectively, these findings highlight Kindlin-2 as a multifaceted regulator of β-cell function, glucose metabolism, and diabetes-associated complications.

5.10 Kindlins in renal diseases

Kindlin-2 has been proven to be a crucial regulator in the pathogenesis of renal diseases, particularly in the development and progression of tubulointerstitial fibrosis (TIF) and diabetic nephropathy (DN). Its role in EMT, a key process in renal fibrosis, is well-documented[231]. Kindlin-2 promotes EMT in kidney tubular epithelial cells by activating major signaling pathways, including the TGF-β/Smad, Ras-ERK, and Akt pathways. By interacting with integrins, phosphoinositides, and directly binding to the TGF-β receptor (TβRI) and Smad3, Kindlin-2 facilitates the activation of TGF-β/Smad signaling, which is central to fibrosis development[70,232]. In particular, Kindlin-2 increases the deposition of ECM such as fibronectin, which exacerbates fibrosis in the kidney, and modulates podocyte-matrix adhesion, further contributing to glomerular injury[232].

In experimental models of renal fibrosis, including unilateral ureteral obstruction (UUO), Kindlin-2 depletion activates the Hippo/YAP signaling pathway, alleviating renal fibrosis. Kindlin-2 inhibits this pathway by promoting the degradation of MOB1, which correlates negatively with YAP activation and fibrosis in human samples. Targeting Kindlin-2 with siRNA effectively reduces UUO-induced fibrosis, suggesting that Kindlin-2 inhibition could be a potential therapeutic approach for renal fibrosis, providing a potential therapeutic avenue for managing kidney disease[84].

5.11 Kindlins in lung diseases

The involvement of Kindlin-2 in the pathogenesis of lung diseases such as acute lung injury (ALI) and pulmonary fibrosis offers a potential therapeutic target for these conditions. In ALI, Kindlin-2 expression is significantly upregulated, contributing to lung endothelial barrier disruption, inflammation, and pyroptosis. Specific deletion of Kindlin-2 in ALI models reduces pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), decreases pyroptosis-related proteins, and ameliorates lung injury by attenuating leukocyte infiltration and improving lung pathology[233]. In pulmonary fibrosis, Kindlin-2 promotes fibroblast activation and collagen matrix deposition by interacting with PYCR1, a key enzyme in proline synthesis. The Kindlin-2-PYCR1 complex and proline synthesis are elevated in fibrotic lungs and suppressed by antifibrotic drugs like pirfenidone and nintedanib. Ablation of Kindlin-2 in bleomycin-induced fibrosis models reduces PYCR1 expression, collagen deposition, and disease progression[234]. These findings highlight Kindlin-2 as a pivotal regulator of inflammation, fibroblast activation, and matrix remodeling in lung diseases (Fig. 4, Table 3).

6 Conclusions and future perspectives

Kindlins serve as critical molecular regulators of both integrin activation and signaling pathways, executing essential functions in multiple fundamental cellular activities such as cell-matrix adhesion, cellular proliferation, directed migration, and differentiation processes. Through their interactions with integrins, Kindlins mediate critical physiological functions across diverse systems, such as cardiovascular integrity, immune cell adhesion, bone resorption, angiogenesis, and tissue repair. Pathophysiological disruptions in Kindlin-integrin interactions are implicated in severe disorders, including leukocyte adhesion deficiency, cardiovascular diseases, osteoporosis, and other massive disorders.

However, emerging evidence highlights the growing significance of Kindlin functions beyond integrin activation, suggesting they act as versatile co-factors in non-integrin-dependent pathways that are pivotal for cellular homeostasis and disease progression. Kindlins integrate external mechanical cues into intracellular signaling cascades through their interactions with cytoskeletal proteins and signaling molecules independent of integrins. More importantly, Kindlins' integrin-independent roles are increasingly implicated in disease processes. For example, in cancer, elevated Kindlin expression drives tumor angiogenesis via Wnt signaling regulation and enhances tumor progression and metastasis[130,147]. In cardiovascular diseases, non-integrin-dependent effects on fibroblast function and mechanosensing contribute to pathological cardiac remodeling and heart failure[208,216]. In skeletal diseases, beyond its role in osteoclast-mediated bone resorption, Kindlin-2 impacts mesenchymal stem cell differentiation, linking it to bone regeneration and homeostasis[49,107,169].

Recent studies reveal that Kindlins function as transcriptional co-regulators, modulating gene expression independent of their canonical integrin-binding domains. Kindlin-2, for example, binds directly to the GATA4 promoter, suppressing its expression and preventing stress-induced cardiac hypertrophy[111]. Additionally, Kindlin-2 influences the transcriptional activity of β-catenin/TCF4 complexes, thereby impacting skeletal muscle differentiation and fibrosis[79]. This highlights an underexplored but crucial aspect of Kindlins' role in transcriptional control, offering new therapeutic opportunities.

Future research should focus on elucidating the structural and biochemical underpinnings of Kindlins' non-integrin functions, particularly their roles in transcriptional regulation and signal transduction. Advanced structural biology approaches and single-cell multiomics will be instrumental in these efforts. The dual integrin-dependent and non-integrin functions of Kindlins offer unique therapeutic opportunities. It is important to note that, as adhesion scaffold proteins, Kindlins currently have no small-

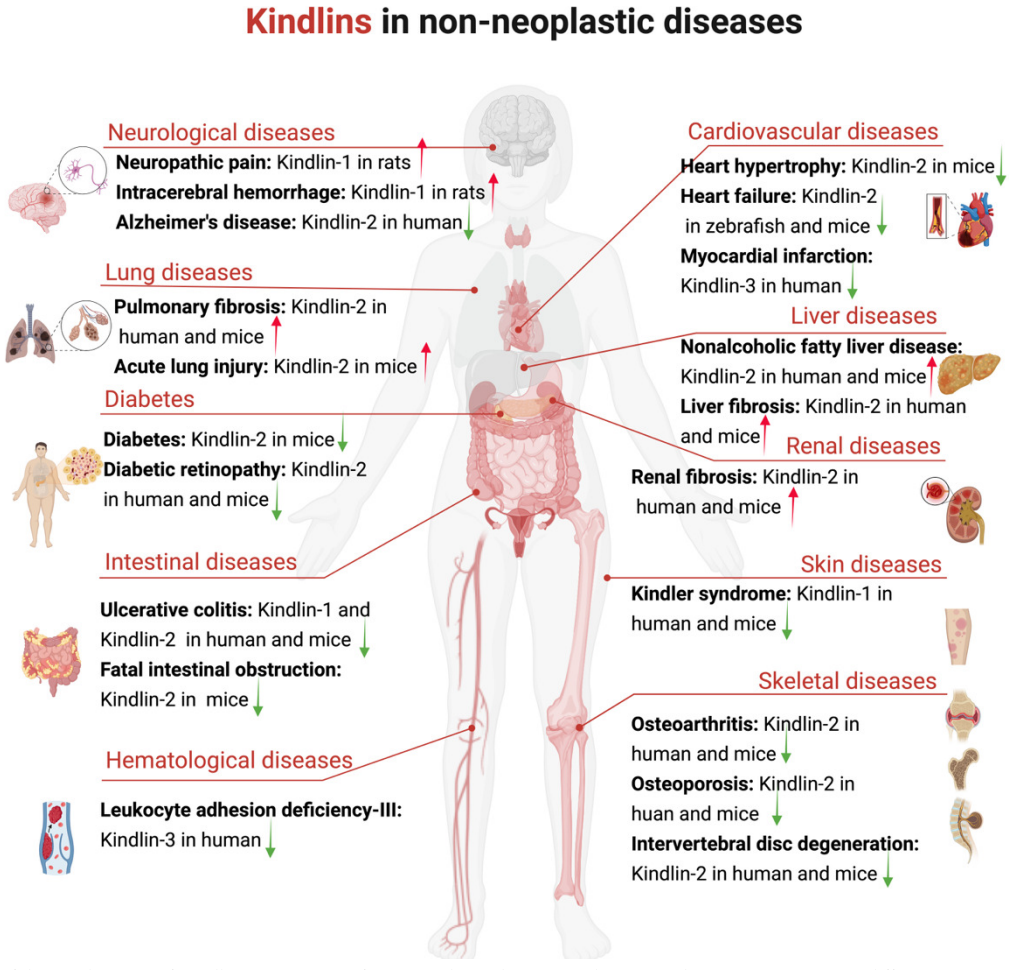

Figure 4 Overview of the involvement of Kindlins in a variety of non-neoplastic diseases, underscoring their association across different organ systems and the broad impact of kindlins on health and disease (Created with BioRender.com).

Table 3 Kindlins in non-neoplastic diseases.

Disease		Isoform	Experimental cell/Model system	Treatment in vivo	Signaling pathway	Function	Ref
Skeletal diseases	OA	Kindlin-2	ATDC5 cells, human OA specimens, mouse OA model	AAV5-Kindlin-2	Kindlin-2/STAT3/Runx2	OA lesions↓, articular cartilage integrity↑	[178-180]
	OP	Kindlin-2	HUVECs, mouse OVX model	Kindlin-2 knockdown	Kindlin-2/Piezo1/TGF-β/Runx2	Bone mass↑	[86]
	OP	Kindlin-2	MC-4 cells, mouse OVX model	Kindlin-2 KO	Kindlin-2/Gsa/PTH1R	PTH anabolic activity ↓, bone mass accrual and homeostasis ↓	[102]
	OP	Kindlin-2	Primary BMSCs, 3T3-E1 cells, human OP specimens, mouse OVX model	N/A	miR-29/Kindlin-2/p53	Skeletal senescence↑, cortical bone thickness↓, trabecular bone mass↓	[107]
	OP	Kindlin-2	Mouse primary BMSCs, mouse OVX model	Kindlin-2 knochdown	Kindlin-2/FAS/PPAR γ/FABP4	Bone mass↑, insulin expression↑	[108]
	IVDD	Kindlin-2	Primary human nucleus pulposus cells, human IVDD specimens, rat IVDs model	AAV5-Kindlin-2	Kindlin-2/NLRP3	ECM catabolism↓, cell apoptosis↓, IVDD progression↓	[181]
Skin diseases	KS	Kindlin-1	Primary keratinocytes, KS patient specimens	Kindlin-1 losss	Kindlin-1/Wnt/β-catenin	Hyperthickened epidermis↑, KS-like defects↑, skin tumor incidence↑	[47]
	KS	Kindlin-1	Immortalized keratinocytes, KS patient specimens	Kindlin-1 loss	Kindlin-1/EGFR	Cell migration↓, migratory behavior↓	[95]

(To be continued on the next page)

(Continued)

Disease		Isoform	Experimental cell/Model system	Treatment in vivo	Signaling pathway	Function	Ref
Hematological diseases	KS	Kindlin-1	Primary keratinocytes, KS patient specimens	Kindlin-1 loss	Kindlin-1/ERK	Oxidative stress↑, photosensitivity↑	[189]
	LAD-III	Kindlin-3	Human LAD-III specimens	Kindlin-3 loss	Kindlin-3/Integrin	Functional leukocyte defect↑, immune deficiency and bleeding ↑	[12,172,199]
Cardiovascular diseases	Heart hypertrophy	Kindlin-2	Primary rat neonatal cardiomyocytes and HEK293A cells, mouse heart specimens	Kindlin-2 KO	Kindlin-2/SUV39H1/GATA4	Cardiomyocyte hypertrophy↑	[111]
	Heart failure	Kindlin-2	Mouse and zebrafish heart specimens	Kindlin-2 KO	Kindlin-2/Integrin β1D	Premature death↑, heart and extensive fibrosis↑	[210-212,214]
	Myocardial infarction	Kindlin-3	Human myocardial infarction specimens	Kindlin-3 loss	N/A	Heart ischemic event↑	[197]
Neurological diseases	Intracerebral hemorrhage	Kindlin-1	BV2 microglial cells, ICH rat model	Kindlin-1 siRNA	Kindlin-1/NF-κB/NLRP3	Microglial inflammation and brain damage↓, intracerebral hemorrhage↓	[61]
	Neuropathic pain	Kindlin-1	Primary astrocytes, CCI neuropathic pain rat model	AAV- Kindlin-1 shRNA, hyperbaric oxygen	Kindlin-1/Wnt-10a/β-catenin	GFAP↓, hyperalgesia↓, inflammatory mediators↓	[74,75]
	Alzheimer's disease	Kindlin-2	Rat primary neuronal cells, human and mouse hippocampal specimens	Kindlin-2 siRNA	Kindlin-2/APP	Axonal growth, synaptic connectivity, and long-term potentiation↓	[219]
Liver diseases	Liver fibrogenesis	Kindlin-2	Human hepatoma cell lines, mouse liver injury model	AAV-Kindlin-2	Kindlin-2/TNF/NF-κB/Caspase 8	Hepatocyte apoptosis↓, liver fibrosis and injury↓	[62]
	Liver fibrogenesis	Kindlin-2	Human HSC cell lines, human and mouse liver specimens, mouse liver fibrogenesis model	Kindlin-2 depletion	Kindlin-2/TGF-β/Smad	Hepatic stellate cells activation↓, liver fibrogenesis↓	[67]
	NAFLD	Kindlin-2	Mouse primary hepatocytes, human NAFLD specimens, mouse NAFLD model	Kindlin-2 haploinsufficiency, AAV8- Kindlin-2 shRNA	Kindlin-2/Foxo1	glucose intolerance↓, lipid metabolism disorder and inflammation↓	[222]
Intestinal diseases	Ulcerative Colitis	Kindlin-1 and 2	Human and mouse colonic specimens	Kindlin-1 and 2 deletions	N/A	Intestinal inflammation↑, bloody stools↑	[226]
	Intestinal obstruction	Kindlin-2	Mouse primary smooth muscle cells, mouse intestinal specimens	Kindlin-2 KO	Kindlin-2/S100A14/STIM1	Cell apoptosis↑, smooth muscle development↓, intestinal hypoperistalsis↑	[227]
Diabetes mellitus	Diabetic retinopathy	Kindlin-2	HUVECs, mouse vascular specimens	Kindlin-2 KO	Kindlin-2/Notch	Angiogenesis↓, avascular retinas↑	[91]
	Type II diabetes mellitus	Kindlin-2	Rat BMSCs, rat type II diabetic model	N/A	Kindlin-2/PTH1R/OCN	Ion homeostasis↑, OCN↑, osteogenesis↑	[103]
	Diabetes	Kindlin-2	Primary human pancreatic islets, mouse pancreatic specimens	Kindlin-2 KO	Kindlin-2/GSK-3β/β-catenin	β-cell proliferation and mass↓, diabetic phenotypes↑	[228]
	Diabetes mellitus	Kindlin-2	Mouse insulinoma immortalized β-cell lines, mouse pancreas specimens	Kindlin-2 insufficiency	Kindlin-2/NLRP3	Inflammatory cytokines↑, β-cell dysfunction↑	[229]
	Diabetes mellitus	Kindlin-2	Mouse diabetic model	N/A	Kindlin-2/TGF-β/Smad	Structural injuries and functional variations↑	[231]
Renal diseases	Renal fibrosis	Kindlin-2	Human kidney TECs, human kidney specimens, UUO mice	Kindlin-2 siRNA	Kindlin-2/TGF-β/Smad	Matrix genes↓, renal fibrosis↓	[70]
	Renal fibrosis	Kindlin-2	Human renal tubular epithelial and human embryonic kidney cell lines, human kidney specimens, UUO mice	Kindlin-2 siRNA, Kindlin-2 KO	Kindlin-2/Hippo/YAP	Tubular degeneration↓, renal fibrosis↓	[84]
Lung diseases	Acute lung injury	Kindlin-2	Mouse cute lung injury model	Kindlin-2 siRNA	N/A	Lung injury severity↓, pro-inflammatory factors↓	[233]
	Pulmonary fibrosis	Kindlin-2	Human lung fibroblasts, mouse pulmonary fibrosis model	Kindlin-2 KO	Kindlin-2/PYCR1	Collagen matrix↓, pulmonary fibrosis↓	[234]

"↑": upregulation; "↓": downregulation; "N/A": not applicable.

molecule modulators or clinical-stage therapeutics directly targeting them. Their most advanced translational applications, including genetic modulation and biomarker validation, remain in the preclinical phase. To bridge this gap between mechanism and future application, the two following aspects of efforts are needed: (1) Developing more refined disease models, including patient-derived organoids and advanced animal models, will help clarify the contribution of non-integrin Kindlin functions to disease pathogenesis, enabling precision medicine approaches. (2) Given their role in multiple diseases, Kindlins hold potential as biomarkers for disease progression or therapeutic response, particularly in cancer, cardiovascular diseases, and immune dysfunction.

In conclusion, Kindlins are indispensable for cellular adhesion and integrin activation. They also function as multifunctional regulators through non-integrin-dependent roles in signal transduction, transcriptional regulation, and mechanotransduction, which are critical for cellular homeostasis and disease pathology. These non-canonical functions significantly broaden our understanding of Kindlins, positioning them as promising therapeutic targets and paving the way for innovative treatments in a wide spectrum of diseases. As our knowledge of Kindlins' integrin-independent mechanisms deepens, so too does their potential to revolutionize strategies for managing complex pathological conditions.

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Data available statement

N/A

Author contribution

H.C., G.M., and Y.C. conceived and designed the work. Y.C. prepared and wrote the draft of manuscript. Y.C., G.M., and F.W. visualized the figures and tables. H.C. supervised the project. All authors revised the manuscript and approved the final version.

Ethics approval and consent

N/A

Consent for publication

All authors agree to publish.

Conflicts of interest

The authors declare no conflicts of interest.

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