Talin-1 interaction network in cellular mechanotransduction (Review)

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Abstract. The mechanical signals within the extracellular matrix (ECM) regulate cell growth, proliferation and differentiation, and integrins function as the hub between the ECM and cellular actin. Focal adhesions (FAs) are multi-protein, integrin-containing complexes, acting as tension-sensing anchoring points that bond cells to the extracellular microenvironment. Talin-1 serves as the central protein of FAs that participates in the activation of integrins and connects them with the actin cytoskeleton. As a cytoplasmic protein, Talin-1 consists of a globular head domain and a long rod comprised of a series of α-helical bundles. The unique structure of the Talin-1 rod domain permits folding and unfolding in response to the mechanical stress, revealing various binding sites. Thus, conformation changes of the Talin-1 rod domain enable the cell to convert mechanical signals into chemical through multiple signaling pathways. The present review discusses the binding partners of Talin-1, their interactions, effects on the cellular processes, and their possible roles in diseases.

Contents

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1. Talin-1 structure overview

Cells can sense the rigidity of the extracellular matrix (ECM) through integrin adhesions, which have been reported to be a significant factor in various processes, including tissue repair, maintenance and formation (1,2). The mechanical signals of the extracellular microenvironment regulate cell growth, proliferation, differentiation and integrin activity (3). The physical connection between cells and the ECM is based on multi-component molecular complexes that are controlled by integrins, known as the core structure of transmembrane proteins (4). Through integrins, the mechanical signals of the extracellular microenvironment can be transmitted intracellularly (4). Integrins are transmembrane heterodimeric glycoprotein receptors consisting of α- and β-heterodimers, providing a connection between the ECM and intracellular actin cytoskeleton through their large extracellular domains, via adapter proteins, including Talin-1 and vinculin (5-7). As the main activator of integrin, Talin-1 has been reported to connect the cytoplasmic domain of integrin with the cytoskeleton of actin to form focal adhesions (FAs) (8). FAs are the congregates of the intracellular proteins that function as tension-sensing anchoring points, integrating cells with the extracellular microenvironment (9,10). In addition, FAs have been reported to promote intracellular reorganization, leading to dynamic alterations in cell morphology and function (9-12). In recent years, researchers have discovered that the specific structure of Talin-1 with mechanical sensitivity plays a defining role in mechanical properties and interaction networks in cellular mechanotransduction.

Talin-1 is mainly expressed in the liver, kidneys, stomach, spleen, lungs and vascular smooth muscle, and is a large, 270-kDa protein with 18 domains, containing a 50-kDa globular head, a long rod comprised of 62 helices forming 13 helical bundle domains (R1-R13) (13,14) and a dimerization (DD) motif at the C-terminus (15). A schematic view of Talin-1 structure is illustrated in Fig. 1. The head four-point-one, ezrin, radixin, moesin (FERM) domain consists of four subdomains

(F0-F3), being a common structural feature of several integrin tail-binding proteins, while the rod domain includes 13 helical bundles (R1-R13), forming an extendible and flexible chain with a dimer domain (DD) at the end of the structure, through the connection with short linkers. The unique conformation of Talin-1 allows it to function as a 'spring' and unfold into a 60-100 nm linear rod (16-18). This conformational change is responsible for binding to various FA components, including actin and vinculin (19).

The rod part of Talin-1 is the main structure, with the ability to sense mechanical forces and regulate the assembly and maturation of the FA complexes (FACs). R9 and R12 shield the binding sites of integrin and phosphatidylinositol-4,5-bisphosphate (PIP2) of the FERM structure (11). R3 is extremely sensitive to mechanical forces (20). As the 'goalkeeper' of FAC, it is the first to release the folded four-helix bundle under the action of relatively low-intensity mechanical force (5 pN), and the compact structure of Talin-1 begins to collapse (19-21). The second messenger, PIP2, promotes Talin-1 binding to integrin, subsequently stretching Talin-1 conformation further and binding to actin, while exposing vinculin binding sites (VBS) (22,23). Moreover, R3 can also directly bind Rap1-GTP interacting protein (RIAM), which results in VBS exposure (24). Talin-1 contains up to 11 VBS, rendering vinculin a crucial regulator for the performance of signal transformation (25). Vinculin has been identified to trigger the phosphorylation and nuclear localization of the transcription factor, Yes-associated protein (YAP) (26).

Subdomains F0 and F1 of Talin-1 have been reported to bind to Ras-associated protein 1 (Rap1) or RIAM and participate in integrin activation (27). F3 binds to integrin cytoplasm domains and related proteins, including FA kinase (FAK), Layilin, T-cell lymphoma invasion and metastasis 1 (TIAM1), phosphatidylinositol phosphokinase Iγ (PIPKIγ) and RIAM, as well as F1-F3 contain actin-binding site (ABS1), R4-R8 (ABS2) and R13-DD (ABS3) (19,28). Corresponding to F3, R8 can also bind to deleted in liver cancer 1 (DLC1), RIAM, vinculin and paxillin (19,29), being able to form a competitive interaction network. Among these, DLC1 is the Rho GTPase activation protein (RhoGAP), being able to inhibit the contraction of actin and promotes the refolding of Talin-1 (30). The combination of DLC1 and TIAM1 has been reported to provide the capability to balance Rac and Rho when they are involved in forming tension fibers (30). Subsequently, this combination plays a counter-regulatory role in the process of FA maturation driven by actin polymerization (30). Therefore, under the promotion of multiple factors, Talin-1 functions as a 'spring' at the core of FA transmitting tension between the ECM and actin (26,29). Based on its unique structure, Talin-1 is able to sense and respond to mechanical signals from the matrix and transmit mechanical forces to the surrounding cells (19). The matrix, in turn, can convert forces into intracellular biochemical signals, thereby regulating nuclear transcription (26,31). Furthermore, mechanotransduction is triggered due to Talin-1 unfolding above the mechanical threshold (26). Integrins have been reported to unbind and release forces before Talin-1 unfolding, provided that stiffness remains below the mechanical threshold; in contrast, when the stiffness supersedes the threshold, Talin-1 unfolds and binds to vinculin, leading to adhesion growth and YAP nuclear translocation (26,31). Thus, it has been reported that the combination of Talin-1 unfolding dynamics with a theoretical clutch model could quantitatively predict cell response (26,31). Overall, the specific structure of Talin-1 including the active and inactive forms provides the possibility for proteins to convert mechanical signals into chemical signals. In the inhibited state, the rod structure folds into a closed spherical conformation with a diameter of 15 nm, based on charge interaction (11). The inhibition of Talin-1 is crucial to cell function and development, and its disruption has been reported to greatly contribute to the migration of metastatic cancer cells (32-34). The active form of Talin-1 has been well-characterized; however, its inhibited state has not been extensively studied.

2. Role of Talin-1 in mechanotransduction

Interactions between cells and the ECM are fundamental features of multicellular organisms (35). All living cells are constantly subjected to various mechanical signals from the surrounding cells or from the ECM (36). Mechanotransduction is a process that helps cells to adapt to changes in the microenvironment by transforming the physical signals into biological ones (36). In recent years, researchers have demonstrated a growing interest in mechanical forces as key regulators of cellular behavior. Mechanical forces can be directed on the cell externally from the ECM or generated internally from the active cytoskeleton (37). A number of intracellular molecules defined as mechanosensors have been discovered, which can react to mechanical stress, including Talin-1 and vinculin. Conformational changes of mechanosensors in response to mechanical stress can alter their binding partners, thereby revealing new potential binding sites. This switch of binding partners is the key to converting mechanical signals into intracellular biochemical signals (38). FAs are the major connection between ECM and cytoskeleton, with multiple components including scaffolding molecules, GTPases, and many enzymes, including kinases, phosphatases, proteases, and lipases (39-42). In FAs, integrins and proteoglycans mediate adherent junctions from the actin cytoskeleton to the actin cytoskeleton (43). The integrin family of type I transmembrane adhesion receptors has been reported to mediate cell-matrix attachment, as well as cell-cell attachment. Integrins are involved in cell anchorage to the ECM and its binding to the cytoskeleton and cytoplasmatic signaling, thus directly affecting tissue architecture (44).

The signals transmitted by integrins are bidirectional. Firstly, through 'inside-out' signaling, intracellular signals may induce the binding of Talin-1 and Kindlin to the cytoplasmic domains of integrin β subunits, thereby activating integrin ligand binding function (45-48). Conversely, a second type of signaling termed 'outside-in' signaling, is mediated by interactions between integrins and their multiple ligands across the membrane, enabling cells to sense and respond to the extracellular environment (49,50), including cell spreading, retraction, migration, proliferation and survival.

Talin-1 and vinculin are mechanosensitive cellular proteins that can be folded and unfolded via mechanical forces (51). This unfolding causes the disruption of the tertiary structure of the protein, revealing the cryptic sites for various ligand binding, molecule activation or domain cleavage by

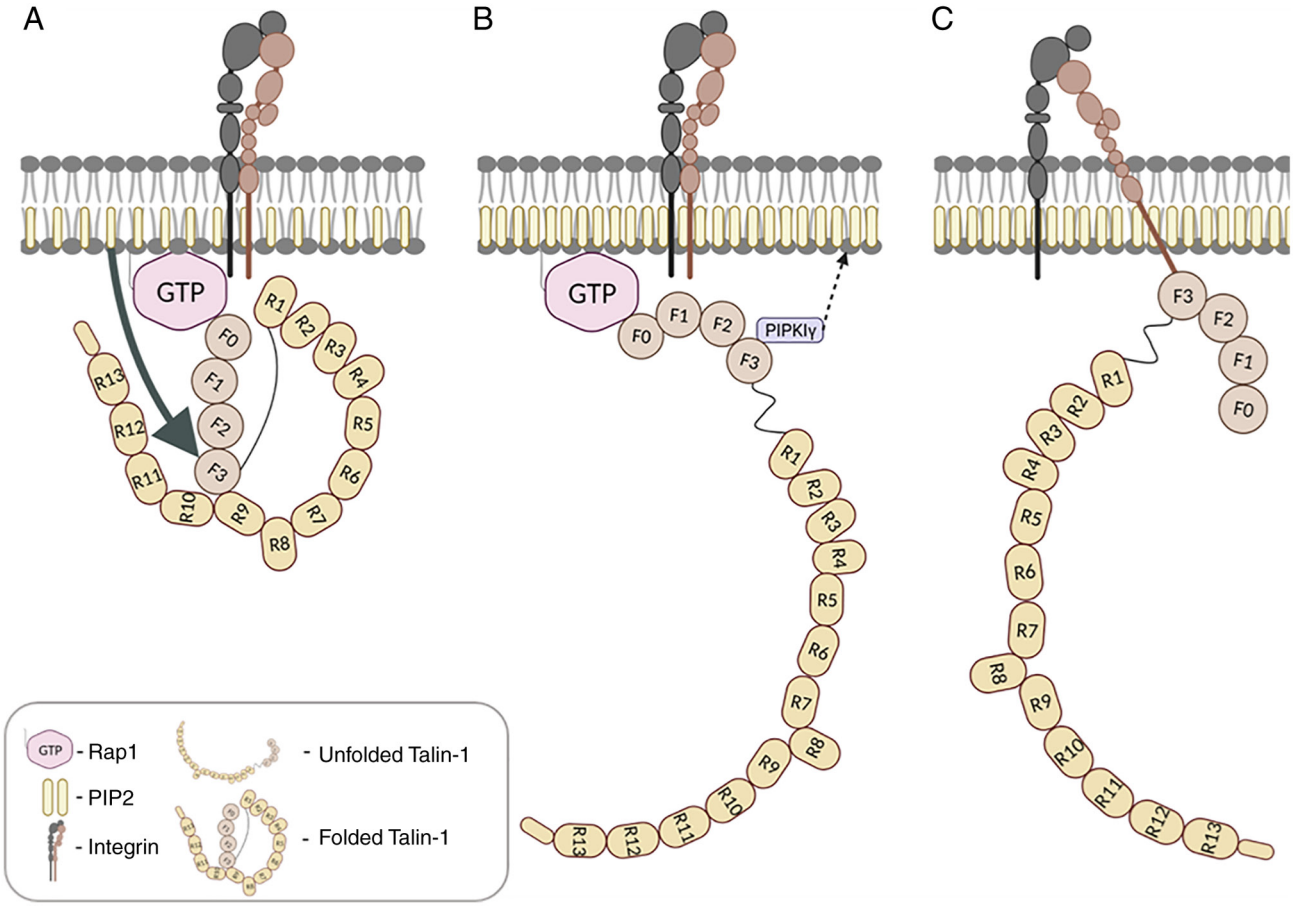

Figure 1. Activation of Talin-1 through interaction with Rap1 and PIP2. (A) Rap1 phosphorylation results in its activation, promoting the recruitment of Talin-1 to the plasma membrane. PIP2 interacts with Talin-1 F2 and F3 and induces the conformational change that reveals an integrin binding site in its F3 domain. (B) PIPKIγ co-localizes with Talin-1 F3, enzymatically promoting PIP2 production. (C) Fully activated, PIPKIγ-free Talin-1 binds and activates the integrin β subunit. Rap1, ras-proximate-1; PIP2, phosphatidylinositol-4,5-bisphosphate; PIPKIγ, type I phosphatidylinositol phosphate kinase γ.

proteases (52). In addition to its role as an integrin activator, Talin-1 also functions as a mechanosensor responsible for the transmission of tension between the actomyosin machinery and the ECM, within the FA (11). To perform its role as a mechanosensor, Talin-1 requires at least two anchorage points: ECM-anchored integrins and actin (the cytoskeleton). Talin-1 head domain binds to the integrin cytosolic tail with its tail binding to the actin, thus connecting integrins with the cytoskeleton (53). This bridging position allows Talin-1 to be folded and unfolded either by mechanical forces generated from the outside or internally by cytoskeletal contraction. Talin-1 participates in both 'inside-out' and 'outside-in' signaling, and is capable of transmitting mechanical forces imposed on cells externally, or generated internally (45,53-56). Through its binding to the cytoplasmic tail of integrin β subunits, Talin-1 controls integrin activation, linking the integrin β subunit to the actin bundles rod through by the C-terminal rod (14). The bridging position of the Talin-1 molecule leads to its unfolding and stretching due to the actomyosin contraction, and these conformation changes affect the affinity and interaction with its binding partners (57). Talin-1 is required for the initial weak connection between small clusters of integrins and the cytoskeleton (58), and for the reinforcement of integrin linkages to the cytoskeleton when cells encounter mechanical forces, again suggesting the role of Talin-1 in FA formation (42,59). Thus, similar to the activation and inactivation of integrins, the activation and inhibition of Talin-1 has been reported to play a crucial role in the regulation of FA dynamics and the transduction of mechanical signals.

3. Talin-1 interaction network

Interaction with Rap1 and RIAM. Rap is a part of the Ras family of small GTPases with five isoforms reported: Ras-associated protein 1A (Rap1A), Rap1B, Rap2A, Rap2B and Rap2C, expressed in mammalian cells (60). Rap2A and Rap2C are considered as the central membrane-associated small GTPases, which recruit proteins to the plasma membrane for the modulation of various cellular responses (61-64), such as exocytosis (65), junction formation (66-68), cell adhesion (69,70), migration and invasion (71), cell proliferation (72), apoptosis (73) and polarity (74,75). Consequently, they are also important for cardiovascular function (76), carcinogenesis (77,78) and liver physiopathology regulation (79). The mechanisms responsible for the recruitment of Talin-1 to the plasma membrane remain to be clearly elucidated. As suggested in a previous study, Talin-1 is recruited to the plasma membrane through the Rap1 GTPase and its effector, RIAM (80). However, even though RIAM binding to F3 of the Talin-1 head domain helps the process of Talin-1 activation (81),

the function of the Rap1-RIAM-Talin-1 pathway appears to be leukocyte-specific (82-84). Nevertheless, RIAM is still an important factor for cell signaling, which also binds to the folded R3 of the Talin-1 rod (13). When exposed to forces, R3 structure is disrupted, leading to the exposure of cryptic VBS and the disruption of RIAM binding (21). This exchange of ligands thus functions as a mechanochemical switch for Rap1 signaling, with RIAM binding to Talin-1 in the absence of force and to vinculin in the presence of force (19). Recent studies have suggested that membrane recruitment can be controlled via the direct binding of Rap1 to the ubiquitin-like F0 and F1 Talin-1 domains (60,85-88). Even though Talin-1 F0 and F1 both bind to Rap1 very weakly in solution, Talin-1 F0 and F1 may bind intracellularly to membrane-anchored Rap1 and lead to strong binding and efficient recruitment of Talin-1 to the membrane (60,85-88). The phosphorylation of membrane-bound Rap1 and its activation promotes Talin-1 binding and its recruitment to initiate FA formation (Fig. 1A). Mutations interfering with either Rap1/Talin-1-F0 or Rap1/Talin-1-F1 interaction lead to impaired FA assembling, decreased integrin activation in CHO cells and malfunctioning leukocytes and platelets in mouse models (89). In case both interactions are disrupted, more severe defects in FA assembly, cell spreading and adhesion may be observed (60,85-88).

Interaction with PIP2 and type I phosphatidylinositol phosphate kinase γ (PIPKIγ). The amount of PIP2 present in membrane phospholipids is very low (0.1 to 5% of inner plasma membrane bilayer lipids) (90). However, it has been reported to play a crucial role in the regulation of various cellular activities, including vesicle trafficking, actin polymerization, and integrin signaling complex formation (91-94). PIP2 can recognize multiple motifs, including epsin N-terminal homology (ENTH), phosphotyrosine binding (PTB), pleckstrin homology (PH), and can assist the recruitment of different proteins to the membrane (95). During the cell attachment to the ECM via integrins, PIP2 functions as a scaffolding molecule, recruiting various molecules to the activated integrin site and as a signaling molecule, regulating target molecule activities (96-100). It has been previously revealed that PIPKIγ interacts with Talin-1 N-terminal head PTB domain and is recruited to the FA sites (Fig. 1B) (95,101). When PIP2 binds to Talin-1, it induces a change in the conformation of the Talin-1 head domain, further leading to the unmasking of the integrin-binding site (Fig. 1C) (89). By contrast, the F3 domain of Talin-1 has been reported to directly bind to the integrin β cytoplasmic tail through the same PTB domain. Even though PIPKIγ may appear to impede Talin-1 F3 PTB domain binding to integrin, it has been reported that PIPKIγ requires only small quantities of Talin-1, being abundant in cells, to be recruited (89). As a kinase, the concentration of PIPKIγ has been reported to be usually decreased (102). However, it is capable of enzymatically producing PIP2, for the activation of the PIPKIγ-free Talin-1 (89). Thus, the interaction between PIPKIγ and Talin-1 promotes PIP2 production, binding and activating in turn Talin-1, leading to the enhanced Talin-1-integrin binding (Fig. 1C) (89). It has been reported in a previous study that in migrating cells, integrins reassembled FAs polarized towards the leading edge, and PIPKIγ, together with Talin-1 and FAK, regulating endocytosed integrin activation-induced FA assembly polarization (103).

Integrin activation by Kindlin and Talin-1. In recent years, there is an increasing interest in Kindlin, a FERM-domain-containing protein, that may play a crucial role in integrin activation (104,105). The Kindlin family consists of three members, Kindlin-1, Kindlin-2 and Kindlin-3. Kindlin-2 is expressed in the majority of cell types, whereas Kindlin-1 and -3 are mainly expressed in hematopoietic and epithelial cells (89). The loss of Kindlin-1 may lead to the blistering and fragility of the skin in humans and mice, while Kindlin-2 plays an essential role in embryonic development. The lack of Kindlin-3 has been suggested to cause various immune problems and bleeding disorders (89). The head domain of Kindlin consists of four subdomains, ubiquitin-like F0, F2 subdomain with an inserted PH domain and FERM domain comprised of three subdomains F1, F2 and F3 (89). β-integrin tails, Kindlin, and Talin-1 head form a ternary complex *in vitro* (Fig. 2A) (89,106,107). The direct Kindlin-integrin interaction is essential for maximal integrin activation (108). Kindlin is recruited to the cell membrane by binding directly to the anionic membrane phospholipids (PIP2) utilizing its positively charged residues in F0 domain and the second NPXY motif in the β-integrin tails using F3 head subdomain The inhibition of Kindlin binding leads to the disruption of Talin-1-mediated integrin activation (106,107,109). Nevertheless, a recent study revealed that Kindlin binding disruption still allows integrins to be activated via Talin-1; however, the enhancing effect of Kindlin is obstructed (110). Thus, the cooperative interaction of Talin-1 and Kindlin leads to the stable active conformation of integrin and promotes ligands binding and clustering (89). The binding of Kindlin with Paxillin, which, in turn, binds to FAK, giving rise to an interesting 'Kindlin-Paxillin-FAK' pathway that can regulate FAK activation, and can participate in dynamic cell adhesion and FA assembly (111-113).

Interaction with FAK and paxillin. Paxillin is a 68-kDa cytoskeletal protein and its main function is the recruitment of FAK to the FA site, further promoting in turn the tyrosine phosphorylation of paxillin and rendering Paxillin an important docking protein for the integrin signal transduction (114). Paxillin is recruited to the FA site mainly through its interaction with the Kindlin and Talin-1 R8 domain (Fig. 2A) (89) and its head domain, and a recent study suggested that it may bridge Kindlin and Talin-1 (115). There is evidence to suggest that the interaction between paxillin and FAK markedly contributes to cell motility and FA assembly and disassembly (116,117). FAK is 125-kDa non-receptor tyrosine kinase that is expressed throughout the human body and participates in signal transduction from the adhesions for the modulation of diverse biological cellular functions, including cell migration, survival and cancer cell invasion (118-120). FAK has been also reported to be involved in binding various proteins and in their recruitment into larger protein complexes (121), thus functioning as an adaptor protein utilizing its multiple domains, including the FERM domain (122). There are multiple pathways associated with FAK activation, including bioactive lipids, growth factors and mitogenic neuropeptides (118). Following its recruitment to the FA site, FAK interacts with the PIP2-rich membrane to relieve the autoinhibitory interaction between its FERM and kinase domains (123). This results in the exposure of the autophosphorylation site, allowing FAK to function as a molecular

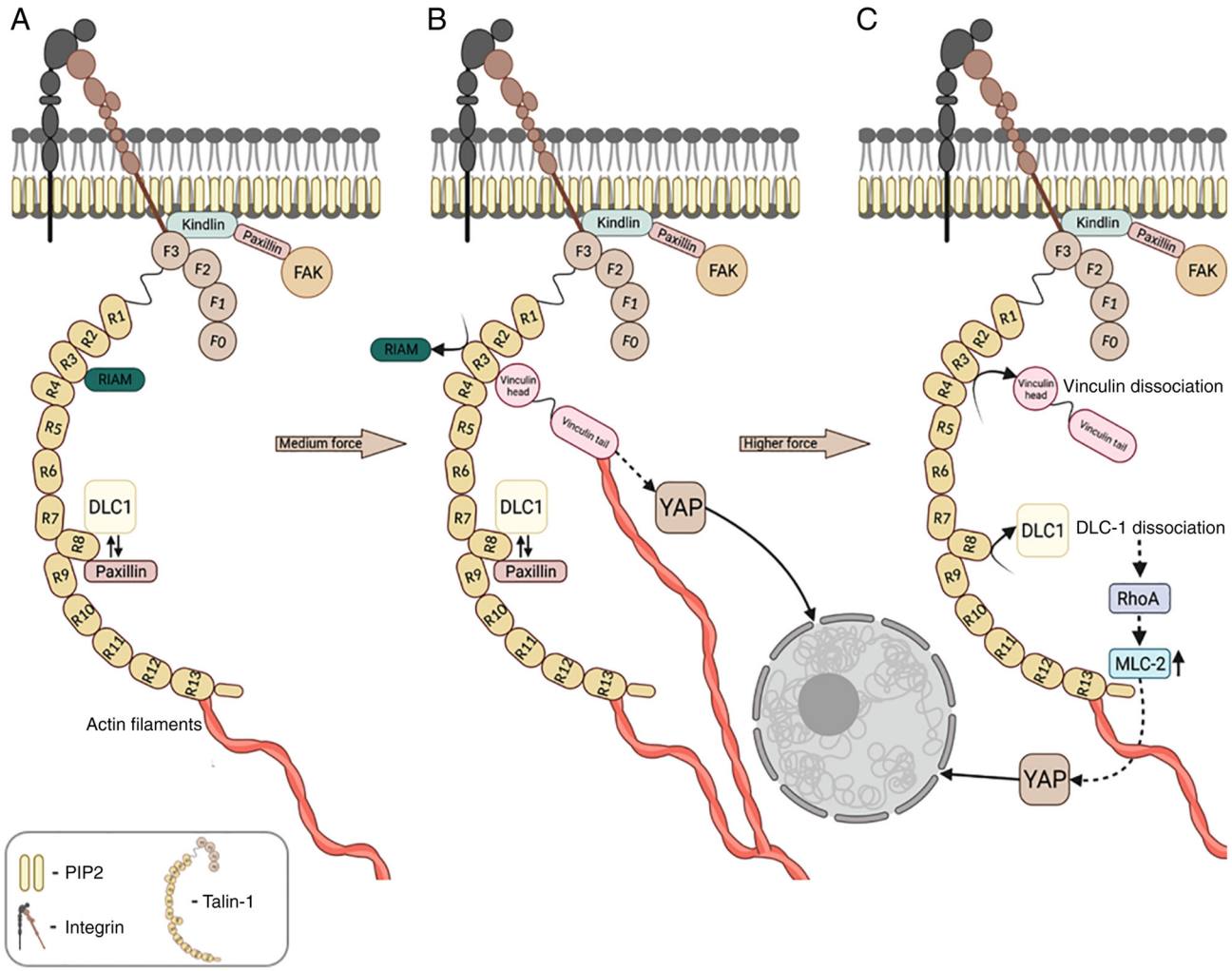

Figure 2. Talin-1 interaction network in cellular mechanotransduction. (A) Kindlin is recruited to the plasma membrane via its interaction with membrane PIP2, reveals its autoinhibited conformation, binding to the integrin tail and promoting more stable active integrin conformation and enhanced ligand binding. The tail of the Kindlin recruits FAK via paxillin binding to its tail domain. Completely unfolded Talin-1 tail begins to interact with its various binding partners, R3 binds to the RIAM, and R8 interacts with DLC1, subsequently regulating the RhoA and paxillin activity. DLC1 and paxillin form a competitive interaction network, since both bind to the R8 domain. Talin-1 R13 binds to the actin. (B) With the exertion of medium intensity force, Talin-1 R3 unfolds, causing the dissociation of RIAM and exposure of the cryptic VBS, culminating in vinculin binding to unfolded R3, and actin binding to the vinculin tail. Increased protein levels of cytoskeleton-associated vinculin result in an increase in nuclear-localized YAP/TAZ levels. (C) In the presence of higher intensity force, unfolding of Talin-1 R8 causes the dissociation of DLC1 and promotes RhoA activity, consequently affecting the MLC-2 signaling pathway and YAP nuclear translocation. R3 domain unfolds completely at high intensity force and becomes a polypeptide chain that cannot bind vinculin. PIP2, phosphatidylinositol-4,5-bisphosphate; FAK, focal-adhesion kinase; RIAM, rap1-GTP interacting protein; DLC-1, deleted in liver cancer 1; RhoA, ras homolog family member A; VBS, vinculin binding site; YAP, yes-associated protein; TAZ, transcriptional coactivator with PDZ-binding motif; MLC-2, myosin light chain-2.

scaffold and recruit SRC kinases to further phosphorylate its main activation loop inside the kinase domain (123). FAK may also act as a scaffold for the nuclear transcriptional regulatory complexes affecting the expression of target genes, including chemokine encoding genes which are responsible for anti-tumor immunity and microenvironment (124,125).

Interaction with DLC1. The Talin-1 rod has been reported to respond to mechanical force, as well as adjusting the contractility of FAC through the Rho-GTPase signaling pathway (126). This pathway is responsible for the regulation of FA assembly and contractility, and can be affected by the tension on Talin-1 (127). Originally, the members of the Rho branch were considered only as actin cytoskeleton regulators. However, a wide range of other functions including expression, morphogenesis, motility and proliferation have been discovered (128-130). In human cancers, the activity of Rho-GTPase is often altered and may have an effect on tumor invasiveness and growth (131,132). In an active state, it has been suggested that Rho proteins may activate various effector molecules, including phospholipases, lipid and protein kinases (128-130). Additionally, Rho family proteins may function as a molecular switch via a nucleotide-controlled conformational change (133,134). There are two classes of regulatory proteins that are controlling the GTP-GDP cycle of Rho: Guanine nucleotide exchange factors (GEFs) stimulate the binding of GTP to activate the protein, and GTPase activating proteins (GAPs), which are responsible for inactivation and GTP hydrolysis (135). It has been suggested that, both RhoGEFs and RhoGAPs are regulated through interactions with different molecules. Some of the RhoGEFs can be activated as a response to the stimulation of receptors on the cell

Table I. Binding partners of Talin-1 and the functions.

Binding partners	Function	(Refs.)
Rap1	Recruits Talin-1 to the cell membrane.	(55,81-84)
PIPKI γ	Enzymatically produces PIP2 at the cell membrane	(21)
PIP2	Acts as a scaffolding molecule, interacts with Talin-1 head domain and induces the conformation change that reveals an integrin binding site. In addition, it recruits kindlin to the cell membrane and promotes vinculin activation	(21,91-95,101,102,104,158)
Kindlin	Enhances the stable active conformation of integrin	(21,103)
Paxillin	Recruits FAK to the focal adhesion site	(109,111,112)
DLC1	When DLC1 binds to Talin-1, regulates RhoA signaling and decreases the contractility of myosin-driven machinery	(27,28,146)
RIAM	Regulates Rap1 signaling	(11,17,80)
Vinculin	Links integrin-Talin-1 complexes to the actin cytoskeleton and participates in the nucleation and polymerization of actin	(159)

Rap1, Ras-associated protein; PIPKIγ, type I phosphatidylinositol phosphate kinase γ; PIP2, phosphatidylinositol-4,5-bisphosphate; DLC1, deleted in liver cancer 1; RIAM, Rap1-interacting adapter molecule.

surface, while other GEFs form various complexes with scaffolding proteins and Rho effectors, elevating specificity and efficiency of Rho signaling (136,137). Although the RhoGAP signaling pathways have not been studied in detail, it has been suggested that they are linked to normal cell function alterations in diverse human diseases (138). One of the RhoGAP family members is DLC1, which has been of increased interest as a potential tumor suppressor and cytoskeletal organization and cell proliferation (138). It has been reported that DLC1 mRNA is expressed in the majority of tissues in adults; however, it is completely absent or downregulated in various human cancers, including gastric (140), ovarian (141,142), lung (135,141,143,144), pancreatic (145), renal (141), prostate (146), colon (141), breast tumors (141,147,148) and hepatocellular carcinoma (HCC) (149-151). DLC1 is a negative regulator of Ras homolog family member A (RhoA) signaling, binding the unstretched form of Talin-1 and decreasing the contractility of myosin-driven machinery (Fig. 2A) (29,30,152), and released in response to tension (29). Provided that DLC1 is localized to the FA site through interaction with Talin-1-R8, it may function as a RhoGTPase regulator and affect cellular function (152). Since the tension on large adhesions is often much weaker than tension on smaller adhesions (54,153), FAs growth promoted by contractility and tension on Talin-1 results in the redistribution of force between increased numbers of FA components, consequently decreasing the level of tension experienced by single Talin-1 molecule. The reduction of mechanical stress may facilitate the refolding of the Talin-1 domain bound by DLC1, thus decreasing the contractility by inhibiting RhoA (29). Subsequently, the second important molecular switch is revealed, thus being able to convert mechanical signals to the chemical with subsequent effect on downstream signaling, including myosin light chain 2 (MLC-2), with its activation being directly proportional to the quantities of active RhoA (29).

Interaction with vinculin. Adherent cells are anchored to the ECM via FA proteins, whereas cell-cell contacts connect via FA junction proteins. A previous study revealed that myosin-driven cell contractility or externally applied stresses greatly contribute to the strengthening of these connections (154). The mechanisms through which the proteins involved in these connections sense, transmit and respond to mechanical signals have not yet been fully elucidated. Vinculin is one of the potential candidate molecules for the role of key cell-matrix and cell-cell adhesion protein, establishing a strong physical connection for force transmission between ECM and cytoskeleton (154).

Vinculin and Talin-1 play crucial roles in cell-matrix mechanosensing (155). Both proteins exist an autoinhibited form, and in order for it to be activated, it has been suggested that vinculin should bind to a mechanically activated Talin-1 (156). Vinculin is a 116-kDa protein, consisting of head domains D1, D2, D3, D4, and a tail domain linked to the head domain through the proline-rich linker (7,156). The head of vinculin forms a pincer-like structure via inter-domain interactions (157,158). Vinculin D1 binds to the eleven VBS on the Talin-1 rod and other signaling proteins, as well as the F-actin through its tail domain (159,160). In order to bind Talin-1, vinculin requires the exposure of the cryptic VBS buried inside α-helical bundles of Talin-1 rod domains, subsequently unfolding when exposed to a mechanical force, and the forces within the biological range are adequate for the exposure of the VBS (13,21,51,161). In the absence of force, Talin-1 R3 is folded and binds to RIAM. However, when a medium-intensity force is exerted, it easily unfolds, revealing cryptic VBS promoting the dissociation of RIAM and vinculin binding (Fig. 2B) (19). The Talin-1-vinculin interaction is of low affinity (162). However, with the presence of phosphatidylinositol 4,5-bisphosphate [PtdIns(4,5)P2] affinity has been reported to increase significantly (163).

Thus, the binding of PIP2 decreases the interaction intensity between vinculin head and tail domains and secures an open conformation of vinculin, allowing the binding of additional proteins, including F-actin (164). Thus, it was deduced that vinculin plays a crucial role in the regulation of integrin adhesions. Additionally, FA dynamics are likely to be regulated by vinculin-Talin-1-integrin-ECM interactions (154). Vinculin has been suggested to link integrin-Talin-1 complexes to the actin cytoskeleton and to also participate in the nucleation and polymerization of actin (165). Vinculin and Talin-1 can also bind paxillin even with both proteins inactive. Adhesions containing paxillin and vinculin can be formed without the interaction of Talin-1 and integrins (166). Talin-1 binding to the integrins has been suggested to result in the engagement of mechanical forces and adhesion maturation (34). Hence, vinculin is a crucial protein for the formation of cell adhesion, turnover and maturation (167).

Influence on YAP/transcriptional co-activator with PDZ-binding motif (TAZ) through vinculin. Hippo effectors YAP and TAZ are proteins with a molecular weight of 65 and 43 kDa, respectively, and have been reported to act as transcription factors responsive to the changes in ECM mechanics and composition (168,169). YAP contains a coiled-coil domain, an Src homology domain-3 binding motif (SH3-BM), an WW domain and a tea domain transcription factor (TEAD). In its C-terminus, YAP has a PDZ-binding motif (PDZ-BM) and, in contrast to TAZ, YAP contains a proline rich region in the N-terminus (170). Since YAP lacks a DNA-binding site, it has been reported to bind to the TEAD DNA-binding transcription factors in order to take effect in antiapoptotic, cell fate, and growth promoting genes (171). Moreover, YAP/TAZ plays a vital role in cell shape, polarity and cytoskeletal organization (171), YAP nuclear expression is connected to Rho signaling (Fig. 2C) and the presence of vinculin spikes in the FA (169). FAs act as a bridge between ECM-integrin connection and cytoskeleton and may be crucial for cellular mechanosensing (172). FA formation is controlled by cell spreading and RhoA GTPase activity, in order to stabilize the anchorage of the actin cytoskeleton to the cell membrane, requiring also YAP co-transcriptional function (169). Therefore, YAP mechanosensing activity may be the key determinant of cell mechanics in response to ECM stimuli.

According to previous reports, the nuclear localization of Yap is significantly increased in cells on rigid substrates compared with cells on soft substrates (173). On the rigid ECM, YAP/TAZ accumulation within the nucleus becomes transcriptionally active, while on the soft ECM, the accumulation occurs within the cytosol (173). An increased ECM stiffness positively affects the amount of cytoskeleton-associated vinculin and elevates the levels of nuclear-localized transcriptional coactivator paralogs, YAP and TAZ, and their activity. On the rigid ECM, vinculin participates in nuclear translocation and the activity regulation of YAP/TAZ. The process of YAP/TAZ nuclear translocation has been reported to be partly regulated by vinculin, through the organization of the actin cytoskeleton. Talin-1 molecule only unfolds when a certain stiffness threshold is surpassed. Above this threshold, Talin-1 molecule unfolds and binds to various binding partners, including vinculin, leading to YAP nuclear translocation and adhesion growth (169). Even though the actin organization and intracellular tension appears to take part in the regulation of this process, the mechanisms through which ECM stiffness regulates YAP/TAZ remain to be elucidated. The explanation of the interaction between Talin-1 and Yap will further broaden the understanding of the cellular mechanotransduction role of Talin-1.

4. Conclusions and future perspectives

As the main integrin-activating and mechanosensing protein, Talin-1 is important for FA assembly, as well as for various cellular events. Although Talin-1 itself is a protein with a vast interaction network, its interactions with vinculin, DLC1, Rap1 and RIAM, paxillin, and FAK subsequently affect multiple signaling pathways inside the cell. Through interactions with its binding targets (Table I), Talin-1 converts mechanical signals into chemical, consequently affecting a plethora of cellular responses.

Recent discoveries in the field of mechanobiology have a marked effect on other disciplines. It has previously been revealed that even the alterations in the physical environment of the cell, ECM in particular, can cause a malignant phenotype in the cancer cells (174). The presence of Talin-1 is insufficient for proper cell function. It must be subjected to force, either through cell contraction or through the application of shear stress (34). The function of Talin-1 in cancerous phenotypes is not limited on the influence on adhesion and motility. In contrast, it also depends on downstream signaling, as emphasized by Talin-1 overexpression in nonadherent cells. Until recently, the role of Talin-1 has been studied in oral squamous cell (175), colon (176) and prostate carcinoma (177). Studies have revealed that Talin-1 could be used as a biomarker for HCC infiltration and metastasis (178,179). Moreover, the co-localization of Talin-1 and Vinculin has been determined to be in the liver infected by Ebola virus (180). In the process of HBV-induced liver fibrosis, the increase in PIP2 levels increases the risk for liver fibrosis (181), and additionally, HBV X protein (HBx) can mediate the decrease of Talin-1 protein monomer levels (182). However, no evidence has yet been reported in relation to the regulatory role of Talin-1 in liver pathophysiological processes, at least to the best of our knowledge. Although Talin-1 has been found to promote tumor formation, migration and metastasis in liver cancer and colon cancer (33,183,184), the role of Talin-1 remains controversial, particularly in HCC (185). Even though, to the best of our knowledge, there is no evidence available to date of the direct regulatory role of Talin-1in pathogenesis, understanding its interaction network in cellular mechanotransduction is of utmost significance for disease diagnosis and prevention.

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Authors' contributions

YZ and CT conceived the research idea. YZ and NL wrote and reviewed the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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