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Decoding force-transmission linkages for therapeutic targeting and engineering

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ABSTRACT

Mechanosensing and mechanotransduction enable cells to perceive and respond to mechanical forces, underpinning essential physiological processes and disease pathways. Central to these phenomena are force-transmission supramolecular linkages, which undergo structural transitions and regulate signaling proteins in response to mechanical stimuli. This review examines the mechanisms of these force-bearing linkages, focusing on force duration, dictated by the stability of protein–protein interfaces, and force-dependent mechanical structural changes of force-bearing domains in the linkage, which activates or deactivates mechanosensing domains. We discuss the emerging potential of these linkages as pharmaceutical targets, exploring drugs and peptides designed to modulate these mechanical properties. In addition, we highlight the application of artificial intelligence in protein engineering to enhance therapeutic precision by dynamically tuning these mechanosensing characteristics. Our synthesis of current findings and future perspectives aims to inform novel approaches to drug design and inspire future research in the field of mechanomedicine.

I. MECHANOSENSING AND MECHANOTRANSDUCTION

Mechanosensing and mechanotransduction are fundamental cellular processes that enable cells to perceive and respond to mechanical cues in their surrounding environment. Mechanosensing refers to the ability of cells to detect mechanical forces or changes in the physical properties of their microenvironment, including neighboring cells, the extracellular matrix (ECM), and fluid flow. These mechanical signals are transduced into biochemical pathways that regulate a wide range of cellular functions such as cell spreading, migration, differentiation, and tissue development.[1–8]

Importantly, dysregulation of mechanotransduction pathways has been implicated in diverse pathologies. In cancer, abnormally stiff ECM and altered integrin signaling potentiate oncogenic pathways, fostering tumor invasion and metastasis.[9,10] In muscular dystrophy, mutations that weaken the dystrophin–glycoprotein complex impair force transmission across the sarcolemma, triggering progressive muscle degeneration.[11,12] Similarly, in cardiomyopathies, defects in nuclear- or sarcomere-based mechanosensors (for example, LMNA or titin) compromise contractile remodeling and precipitate heart failure.[13,14] These examples underscore how perturbations in mechanical signal sensing and transmission can drive disease pathogenesis, highlighting the therapeutic potential of targeting force-transmission linkages.[15–21]

Mechanotransduction refers to the mechanisms by which mechanical signals are converted into biochemical signals that regulate cellular behavior.[1–3,7,22] This process encompasses the transmission of mechanical forces across the exterior and interior of the cell, leading to biochemical responses and structural remodeling. Mechanotransduction relies on a network of proteins, signaling pathways, and cellular structures that coordinate these mechanical responses.

Surface receptors play a pivotal role in cell mechanosensing and mechanotransduction by directly interacting with the local extracellular environment, including the ECM and neighboring cells. By engaging with external mechanical cues, surface receptors facilitate the conversion of extracellular signals into intracellular responses.[23–27]

The cytoskeleton also serves as a key component in mechanosensing and mechanotransduction. This dynamic network of interlinking protein filaments in the cytoplasm is composed of actin filaments, microtubules, and intermediate filaments.[28,29] During cytoskeletal

processes, such as filament polymerization and depolymerization, actomyosin contraction, and deformation during migration, dynamic forces are generated and transmitted across the cell. Force-bearing proteins that organize the cytoskeleton are critical to sensing and responding to mechanical stimuli.

Importantly, many plasma membrane receptors are directly or indirectly linked to the cytoskeleton through their intracellular domains, mechanically coupling extracellular and intracellular mechanosensing and mechanotransduction.[23,30] Furthermore, the cytoskeleton connects to the nuclear membrane through nesprin–LINK complexes, establishing a mechanical connection between the cytoplasm and the nucleus.[31,32] This coupling suggests that both the nucleus and the cytoplasm participate in integrated mechanosensing and mechanotransduction processes, enabling coordinated responses to mechanical cues.

II. FORCE-TRANSMISSION LINKAGES

Mechanosensing and mechanotransduction rely on the dynamic assembly of force-transmission supramolecular linkages, which span from force-generating to force-resisting cellular structures.[33] Here, we define a linkage as a linear chain of interacting proteins that physically transmits mechanical forces across a defined molecular axis. These linkages often bridge force-generating elements (such as actomyosin contractile networks) and force-resisting anchors (such as the extracellular matrix or the nuclear lamina) and typically include a transmembrane receptor as a structural and signaling interface. Each linkage consists of multiple serially connected proteins held together by noncovalent protein–protein interactions (Fig. 1). These proteins frequently contain tandem arrays of structured domains and intrinsically disordered regions, some of which function as mechanosensitive switches or as binding sites for cytoplasmic signaling factors.[34]

The mechanical properties of a cell's local environment are closely coupled to the forces transmitted through these supramolecular linkages.[35–37] By responding sensitively to force levels, these linkages facilitate mechanosensing and mechanotransduction via force-dependent dynamics, including the assembly and disassembly of the linkages, conformational changes in structural domains, and alterations in unstructured regions.[38–42] These processes, in turn, modulate the binding of cytoplasmic factors to the linkage.[41,43–45]

In particular, force-induced structural changes in specific domains act as mechanical switches, regulating their interactions with cytoplasmic factors. Using talin—an extensively studied mechanosensing protein—as an example to illustrate key concepts: in response to tensile force built during dynamic stretching, domains within talin may undergo unfolding, leading to the dissociation of existing binding partners and the exposure of new binding sites for alternative factors[43,46–49] (Fig. 2).

Similar force-dependent behaviors are shared by many proteins that coordinate cytoskeletal architecture and adhesion signaling. Filamin A immunoglobulin-like repeats unfold under piconewton forces, unveiling cryptic integrin- and signaling-partner binding sites that guide focal-adhesion dynamics.[50] In adherens junctions, α-catenin undergoes reversible force-induced unfolding that exposes a vinculin-binding helix and strengthens cadherin-catenin linkages to F-actin.[47,51] Vinculin itself is mechanosensitive: force triggers large-scale domain rearrangements that regulate its affinity for talin, actin, and other partners.[47,52] Within the sarcomere, intrinsically disordered segments of titin's I-band respond to a few-piconewton loads with compaction and unfolding;[53] these transitions modulate binding to four-and-a-half LIM domain protein-2 (FHL2).[45] In addition, the GAIN domains of adhesion G-protein-coupled receptors (GPCRs) undergo force-dependent conformational changes and dissociation, which play a crucial role in their mechanical activation.[54,55] Collectively, these examples underscore that force-sensitive conformational switching is a broadly conserved mechanism for converting mechanical cues into biochemical signals across diverse protein families.

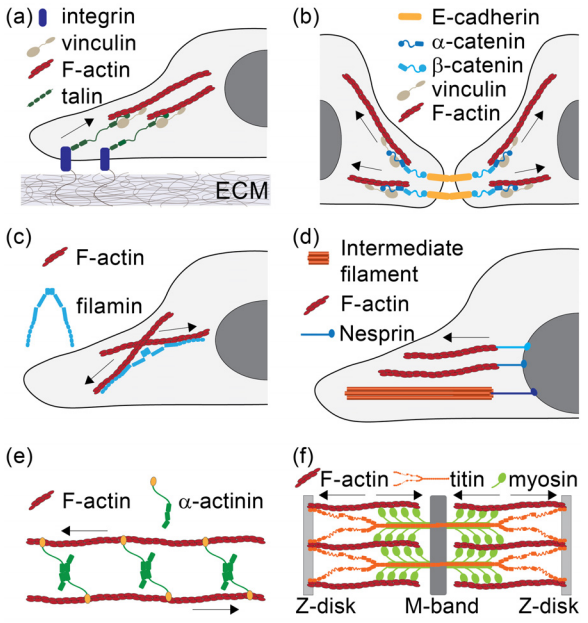

FIG. 1. Force transmission linkages from top left to bottom right: (a) molecular linkages formed by integrins/talin/vinculin in focal adhesions; (b) linkages involving cadherins/catenins in cell–cell junctions; (c) actin cross-linking mediated by filamins; (d) cytoskeleton–nucleus connections facilitated by nesprins; (e) actin cross-linking by alpha-actinins in sarcomeres; and (f) titin linking and aligning myosin and actin filaments in sarcomeres. Forces are indicated by black arrows.

The critical force (F_c), force-dependent unfolding rate (k_u), and refolding rate (k_f) are three key mechanical parameters that characterize the behavior of a force-bearing domain. At the critical force, the unfolding and refolding rates are equal ($k_u = k_f$), resulting in equal probabilities of occupying the folded and unfolded states. Within a force window approximately defined by $F_c - \frac{k_B T}{\Delta} \leq F \leq F_c + \frac{k_B T}{\Delta}$, the rates k_u and k_f remain comparable, and the domain stochastically fluctuates between the two states. Here, Δ represents the extension difference between the folded and unfolded conformations. Outside this range, the equilibrium shifts: above the upper bound, the domain predominantly adopts the unfolded conformation; below the lower bound, it remains mostly folded.

Another important physical parameter governing a force-transmission linkage is its lifetime under force during a stretching process. This duration influences both the persistence and magnitude of the downstream mechanotransduction signaling cascade.

Developing strategies to externally modulate these mechanical parameters offers exciting opportunities to advance both fundamental mechanobiology and pharmaceutical applications.

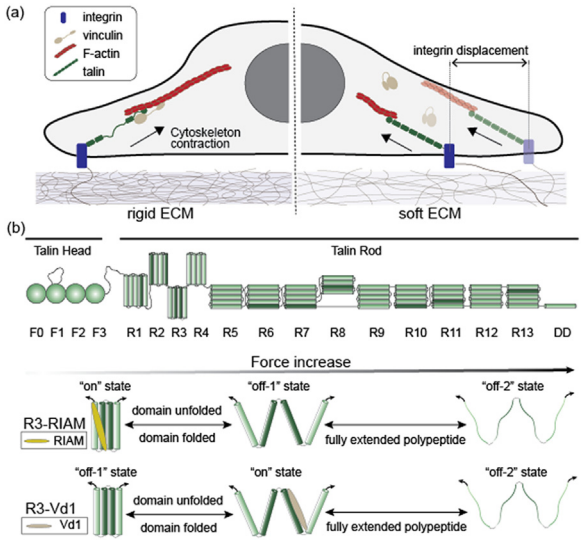

FIG. 2. Cell rigidity sensing (a) Integrin, talin, and vinculin form a multi-protein linkage from the extracellular matrix (ECM) to the actin cytoskeleton. Talin serves as a mechanosensitive hub, transmitting external forces into biochemical signals, enabling cells to sense and respond to ECM rigidity.[87,88] The tension threshold for talin domain unfolding and exposure of vinculin-binding sites (VBSs) critical for FA maturation typically falls within a few piconewtons (pN).[39,41,47,89–92] Forces on the linkage are higher on more rigid ECM, promoting domain unfolding that exposes vinculin binding and FA maturation. (b) Talin comprises an N-terminal FERM domain (F0–F3) linked to 13 rod domains (R1–R13), nine of which contain VBSs (deep green).[93] The binding sites for various partners can exist in either folded talin domains or unfolded structures, enabling downstream signaling. For example, RIAM binds to the folded R3 domain but dissociates when forces unfold R3.[94] Conversely, the vinculin head domain (Vd1) binds to unfolded R3 under mechanical force, but dissociates at higher forces when R3 fully extends.[47]

III. PHARMACEUTICAL TARGETING

Dysregulated mechanosensing and mechanotransduction are implicated in a range of diseases, including cancer, muscular dystrophy, and cardiomyopathies.[15,16,18–21] Current pharmacological strategies targeting these pathways have largely focused on modulating cellular contractility, employing agents such as Rho-associated protein kinase (ROCK) inhibitors, myosin II inhibitors, and cardiac myosin inhibitors.[56–59] In addition, extracellular matrix (ECM) rigidity has emerged as a therapeutic target.[60] While these approaches modulate intracellular force generation or extracellular stiffness, they do not directly address the structural linkages responsible for force transmission.

Recently, force-bearing proteins located at force-transmission linkages or on the cell membrane have garnered increasing attention as potential drug targets. Prominent examples include agents that disrupt the physical connections between integrins and the extracellular matrix (ECM),[61,62] small-molecule agonists and antagonists of mechanosensitive ion channels that stabilize a channel either in a constitutively activated or in an inactive closed conformation,[63–65] and engineered T-cell receptors (TCRs) exhibiting catch-bond kinetics.[66] These approaches have demonstrated substantial pharmaceutical promise. Representative pharmacological agents that modulate mechanotransduction are summarized in Table I.

Building on the recent trend of pharmacologically targeting force-bearing mechanosensing proteins and protein–protein interfaces, we propose that targeting force-transmission linkages offers a broader and more selective means of modulating mechanosensing and mechanotransduction processes. In particular, both the magnitude and duration of force exerted on these linkages are crucial for their functional responses.[40,76–83] By leveraging pharmaceutical interventions to precisely regulate these mechanical parameters, we envision a novel therapeutic approach for tuning mechanotransduction in a disease-specific manner (Fig. 3).

Force-transmission linkages undergo dynamic stretching during various cellular processes. The duration of force depends on the lifetime of the linkage under stretching, which is largely determined by its mechanical stability—specifically, the force-dependent lifetime of force-bearing protein–protein interfaces (PPIs) within the linkage.[44,54,55,81,84–86] The mechanical stability of a PPI can be enhanced by a large molecule that acts as a "glue," binding both domains that form the PPI. A molecule can also be designed targeting the binding interface of a PPI, suppressing the rate of assembly of the PPI, thereby decreasing the overall magnitude of the mechanotransduction signaling associated with a specific type of linkage.

A molecule can also be designed to target crucial force-bearing domains within a linkage that serve as binding sites for other factors. Increasing evidence suggests that such domains can bind multiple factors depending on their structural state, which is itself force-dependent[41,47,50,88,95,96] (Fig. 2). The mechanical stability of a domain can be characterized by a critical force F_c, where the folded and unfolded states are equally probable, and by the rate of transition k near the critical force. Both properties can be modulated pharmaceutically. A molecule designed to bind the folded conformation is expected to both increase the critical force and reduce the unfolding rate, whereas a molecule designed to bind the unfolded or partially unfolded state could decrease the critical force and reduce the refolding rate under force.

In summary, the pharmaceutical modulation of force-transmission linkages offers a promising novel strategy to address diseases linked to dysregulated mechanosensing and mechanotransduction. By targeting the mechanical stability of force-bearing protein–protein interfaces or key force-responsive domains, molecules can precisely tune the magnitude and duration of forces experienced by these linkages. Molecules designed to stabilize or destabilize specific structural states provide a means to modulate critical mechanical parameters, such as the critical force and transition rates, enabling control over the mechanosensing and mechanotransduction processes. This approach holds significant potential for developing targeted therapies for mechanobiology-related diseases.

IV. AI-DRIVEN DESIGN OF PEPTIDE AND SMALL-MOLECULE BINDERS FOR FORCE-TRANSMISSION LINKAGES

Targeting force-bearing PPIs and structural domains presents significant opportunities for therapeutic and mechanobiological research. However, discovering high-affinity, selective binders for these targets remains a major challenge due to the dynamic nature of mechanosensing proteins and their force-dependent conformational changes. Traditional experimental approaches for binder discovery are often labor-intensive and limited by the availability of structural data. Recent advancements in artificial intelligence (AI) have introduced transformative tools that significantly enhance the design of both peptide and

TABLE I. Key pharmacological agents that modulate mechanotransduction.

Class/Example	Primary molecular target	Clinical status[a]	Mechanistic/Therapeutic notes
ROCK inhibitors (fasudil, ripasudil, Y-27632)	ROCK1/2 kinase domain	Approved in Asia (cerebral vasospasm, glaucoma); phase II in fibrosis	Decrease MLC phosphorylation → reduced actomyosin tension; vasodilatory and anti-fibrotic benefits, but systemic hypotension limits chronic dosing[67–69].
Non-muscle myosin II ATPase inhibitors (blebbistatin, para-nitro-blebbistatin)	Myosin II motor domain	Pre-clinical/tool compounds	Lower contractile force, ablate rigidity sensing; phototoxicity and poor solubility hamper translation[70].
Cardiac myosin inhibitors (mavacamten, aficamten)	β-cardiac myosin (super-relaxed-state stabilization)	FDA-approved 2022 (obstructive HCM)	Reduce cross-bridge duty ratio → sarcomere de-stiffening; improve LV outflow but risk systolic dysfunction if overdosed[59,71].
ECM cross-linking inhibitors (β-aminopropionitrile, PXS-5153A)	Lysyl oxidase (LOX/LOXL)	PXS-5153A: phase I (NASH fibrosis)	Soften matrix, indirectly lowering mechanosignals; long dosing times needed for matrix turnover[72–74].
Integrin antagonists (cilengitide, volociximab)	α v β 3/α v β 5 integrins (RGD pocket)	Phase III (oncology) terminated	Block adhesion-site force transmission; integrin redundancy and adaptive signaling undercut efficacy[61,62].
Piezo/TRP channel modulators (GsMTx4, Yoda1, GSK2798745)	Stretch-activated channels (Piezo1/2, TRPV4)	GsMTx4: phase I topical; Yoda1: probe; TRPV4 antagonists: phase II (pulmonary edema)	Directly tune mechanosensitive ion flux; specificity and delivery (peptide vs small molecule) remain challenges[63–65].
Engineered T-cell receptors (MAGE-A3 variants)	Peptide–MHC (TCR–pMHC interface)	Pre-clinical (proof-of-concept; IND enabling)	Force-tuned catch bonds prolong bond lifetimes under load, enhancing antigen discrimination and reducing off-target toxicity[66,75].

[a]Highest regulatory or clinical stage as of April 2025.

small-molecule binders, enabling precise targeting of these mechanosensitive elements.[97–99]

AI-driven approaches have revolutionized protein binder design by providing computational frameworks that accelerate and optimize the discovery process. A wide range of AI-based tools have been developed to predict protein structures, model interactions, and generate binders with high specificity.[100–109] Notably, AlphaFold-Multimer[101] and RFdiffusion[104,105] have demonstrated significant capabilities in modeling protein–protein interactions (PPIs) and designing novel peptide binders. AlphaFold-Multimer excels at predicting binding interfaces, while RFdiffusion generates structural backbones for de novo binders and predicts protein–peptide interactions using the ProteinMPNN algorithm.[104–106] The integration of these tools enables a systematic workflow for designing peptides that selectively engage force-bearing protein domains, optimizing their binding affinity and specificity.

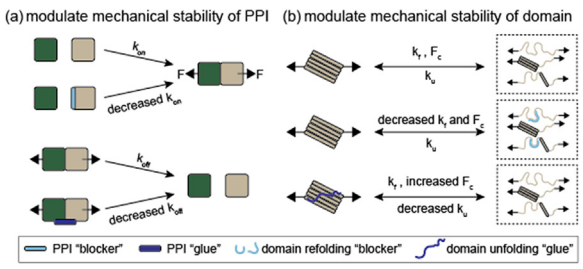

FIG. 3. Approaches to regulate mechanosensing and mechanotransduction. (a) Drug design for modulating the mechanical stability of force-bearing PPIs or domains. The PPI "blockers" and "glues" are designed to modulate the kinetics between two interacting protein domains. Specifically, the PPI "blockers" decrease the binding rate (k_{on}), while the PPI "glues" decrease the dissociation rate (k_{off}). (b) Similarly, domain refolding "blockers" bind to unfolded or partially unfolded domain structures, reducing the refolding rate (k_f) and lowering the critical force (F_c) of the targeted protein domain. In contrast, domain unfolding "glues" bind to folded protein structures, decreasing the unfolding rate (k_u) and increasing the critical force (F_c) of the targeted protein domain.

For small-molecule binder design, AI-based generative models and molecular docking platforms offer complementary capabilities. Tools, such as ChemProp[110] and OpenChem,[111] leverage large molecular datasets to predict key properties, including binding affinity, pharmacokinetics, and toxicity, streamlining the early stages of drug discovery. In addition, AI-assisted docking algorithms like DiffDock[112] automate the identification of optimal binding sites, allowing for the rapid screening and optimization of small molecules tailored to force-transmission linkages. By integrating these computational approaches, researchers can efficiently design and refine small-molecule inhibitors or stabilizers that modulate mechanotransduction pathways with high precision.

AI-driven binder design offers a versatile strategy for targeting force-bearing protein–protein interactions (PPIs) and structural domains, regardless of whether their conformations are well-characterized or poorly defined. For structured domains, AlphaFold2 or AlphaFold3[100,113] can generate high-confidence structural models that serve as templates for AI-assisted binder design. In cases where the target domain is unfolded or partially unfolded under force, steered all-atom molecular dynamics (MD) simulations can be used to generate conformational ensembles that guide the design of binders specific to transient mechanosensitive states.

However, due to the high computational cost of all-atom molecular dynamics (MD) simulations, the accessible timescales are typically several orders of magnitude shorter than those of experimental observations. Consequently, caution is required when using steered MD to identify structural intermediates. Key guidelines include: (i) initiating simulations from a near-equilibrium conformation, which may be derived from an experimentally solved structure or, when unavailable, from an AI-predicted model (e.g., AlphaFold3), and (ii) applying small, incremental stretching steps to minimize conformational perturbation, with sufficient relaxation after each step. This can be implemented by initially applying a stiff spring to deform the native structure by less than 10% extension, followed by an immediate switch to a softer spring to allow rapid relaxation toward a new near-equilibrium state. Because each deformation is small and promptly followed by relaxation, these simulations effectively probe near-equilibrium behavior. This approach has been validated by reproducing the DNA overstretching plateau[114] and DNA bending rigidity.[115] The main limitation of this method lies in its scalability: as the size of the protein domain increases, the computational cost grows substantially, making simulations of large domains challenging.

These AI-assisted workflows potentially provide a powerful approach to selectively modulate force-transmission linkages, either by blocking specific interactions or stabilizing desired structural states. As AI tools continue to advance, their application in targeting mechanosensitive elements will further expand, paving the way for novel therapeutic strategies in mechanobiology.

V. SUMMARY AND FUTURE PERSPECTIVES

This review highlights the central role of force-transmission linkages in mechanosensing and mechanotransduction, emphasizing their potential as therapeutic targets. By integrating AI-driven binder design with advanced computational and experimental tools, we propose strategies to modulate the mechanical stability of force-bearing protein–protein interfaces and domains, enabling precise control over crucial mechanical properties. These approaches not only advance our understanding of mechanobiology but also pave the way for novel therapies targeting diseases linked to dysregulated mechanotransduction, such as cancer and cardiomyopathies.

While mechano-modulation holds promise for diseases in which aberrant force transmission and downstream mechanotransduction pathways are primary drivers—such as certain fibrotic disorders, cardiomyopathies, and myopathies—its therapeutic utility is likely confined to these force dependent contexts. In complex, multifactorial diseases involving metabolic, genetic, or inflammatory components, mechano-modulation alone may not suffice as a stand alone therapy. Future studies should therefore focus on identifying the disease models most amenable to mechanical intervention and on designing combination strategies that integrate mechano-modulation with conventional treatments.

Looking ahead, additional hurdles remain. Improving AI predictions for dynamic, force-dependent protein conformations and translating binder designs into *in vivo* applications will be essential. Real-time monitoring of mechanotransduction in live tissues, coupled with AI-assisted off-target prediction, will help fine-tune dosage and delivery of the next-generation mechanotherapeutics. Interdisciplinary collaboration—spanning biophysics, machine learning, and translational medicine—will be critical to unlocking the full therapeutic potential of mechanomodulators and establishing mechanobiology as a cornerstone of precision medicine.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Jingzhun Liu: Conceptualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Yunxin Deng:** Conceptualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Jie Yan:** Conceptualization (lead); Supervision (lead); Writing – original draft (equal); Writing – review & editing (equal).

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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