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Review

Cellular mechanotransduction

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Abstract: Cell adhesion and cell–cell contacts are pre-requisites for proper metabolism, protein synthesis, cell survival, and cancer metastasis. Major transmembrane receptors are the integrins, which are responsible for cell matrix adhesions, and the cadherins, which are important for cell-cell adhesions. Adherent cells are anchored *via* focal adhesions (FAs) to the extracellular matrix, while cell-cell contacts are connected *via* focal adherens junctions (FAJs). Force transmission over considerable distances and stress focusing at these adhesion sites make them prime candidates for mechanosensors. Exactly which protein(s) within FAs and FAJs or which membrane component of ion channels sense, transmit, and respond to mechano-chemical signaling is currently strongly debated and numerous candidates have been proposed.

1. Introduction

Mechanotransduction is a process where cells detect, interpret, and respond to mechanical signals converting them into biochemical signals. This is a poorly understood process, which often involves mechanosensing. Much work has recently displayed that the nuclear linkage *via* the cytoskeleton (actin, microtubules, and intermediate filaments, IFs) is important in cellular mechanotransduction and that ion channels play a central role in sensory systems. Based on this observation, it was initially assumed that a sensing protein might be involved in the signaling

process. However, it is now becoming obvious that there might be numerous mechanosensors in a cell, ranging from stretch-sensitive channels in the plasma membrane to cytoplasmic proteins, and the nucleus itself that undergo conformational changes in response to force. With regard to the nucleus, the question today: Is it a true mechanosensor or does it serve as a central processor for a variety of mechanotransduction signals converging from all parts of the cell? While signaling pathways mediating mechanotransduction are still being elucidated, important subcellular structures have been identified, which include cell-type specific differences in mechanotransduction signaling pathways. For instance, membrane stress can lead to protein activation and changes in transport [1–7].

A number of computational modeling studies have focused on the effects of membrane tension on mechanotransduction-related structural and dynamical properties of the bilayer. They provided quantitative insight into some of the well-studied bilayer properties (e.g., bilayer thickness and diffusion coefficients) that led to novel hypotheses related to membrane-mediated mechanotransduction in cells, which can be tested experimentally. To enable observations that determine the molecular basis of mechanotransduction over large time and length scales, researchers have integrated methods such as total internal fluorescence microscopy (TIRF), epifluorescence and -differential interference contrast (DIC) microscopy as well as 3D deconvolution with optical traps into their technical repertoire [8,9].

Considerable efforts have also been directed to determine how the various mechanical processes in the cell eventually lead to the regulation of gene expression. Within this context, the operant mechanics between the cell and its microenvironment that results in differences in cell architecture and signaling and influences numerous human diseases (*via* mechanotransduction signals where cells transduce mechanical stimuli into a biochemical response) were addressed. Further, changes in the mechanical nature of the microenvironment, which is critically important in many prevalent and poorly understood human pathological conditions, were also investigated. The assumption that applied cellular loads alter protein structure leading to novel functions has revealed some of the molecular mechanisms mediating mechanotransduction, particularly in adhesion biology.

1.1. Cell membrane

Much of the mechanotransduction work in mammalian cell culture has focused on the role of integrins (heterodimeric transmembrane receptors) that connect the extracellular matrix to the cytoskeleton. Since focal adhesions (FAs) are membrane-attached anchoring platforms for the actin cytoskeleton, recent findings are consistent with a role for FAs in this process. Complexes of more than 100 different proteins, including integrin receptors that link the cell's actin cytoskeleton and plasma membrane to the underlying extracellular matrix (ECM), have been reported. A wide range of signaling molecules and structures, including the plasma membrane, membrane-associated (adaptor) proteins [talin, vinculin, p130Cas, focal adhesion kinase (FAK), etc.), receptors (integrins, G-protein-coupled receptor (GPCR), cadherins], platelet endothelial cell adhesion molecules (PECAMs), vascular cell adhesion proteins (VCAMs), intercellular adhesion molecules (ICAMs), and ion channels as well as actin filaments, microtubules, and IFs have been identified to play important roles in converting stresses into biochemical signaling cascades. For example, the modulation of plasma membrane fluidity changes stress-induced mitogen-activated protein kinase (MAPK) signaling pathways, supporting the importance of the plasma membrane in

mechanotransduction. Further, lamins, which associate with numerous proteins/structures in the nuclear interior and membranes, modulate intracellular force propagation and signaling. Figure 1 highlights the mechanical and chemical interplay of intracellular, extracellular, and membrane components. Membrane molecular organization and dynamics modulate cell growth, differentiation, signal transduction, transport, and migration through biochemical signaling pathways. As an example, lateral membrane tension can cause conformational changes in integral membrane proteins, affecting membrane permeability, lipid lateral diffusion, and organization of lipid rafts. A relation between membrane mechanics and protein activation can be assumed by bringing them together, or by changing their conformation. Therefore, the general big question is whether forces on membranes are the origin of changes in the transport of membrane components and whether differences in integral membrane protein conformation are equivalent to those caused by ligand binding, a process that is well known in biochemical signaling. To be able to answer these questions will have significant ramifications in the field of mechanobiology because many of the important proteins that transduce external cellular signals into intracellular changes in signaling pathways and genetic expression reside in the plasma membrane [10–17].
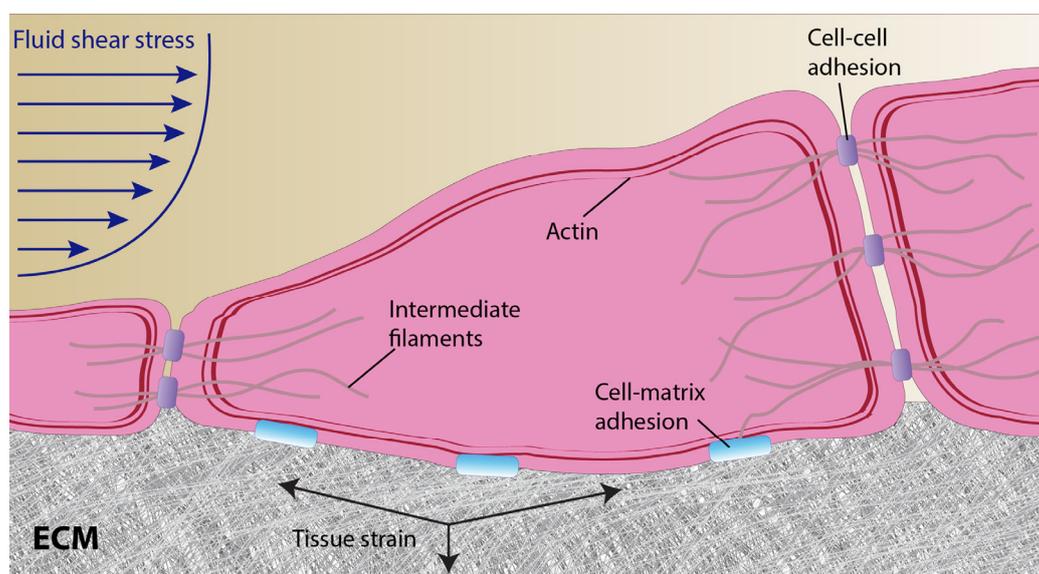

Figure 1. Shear stress on cell-matrix and cell-cell adhesions.

1.2. Integrins and the ECM

Potential mechanosensors include integrins, mechanosensitive ion channels, and stretch sensitive focal adhesion proteins, such as p130Cas [18]. Integrins, for instance, can act as sensors by responding to cues from the ECM, along with other signaling molecules such as kinases, phosphatases, and adaptor proteins. Seminal observations, using a magnetic tweezer and a twisting device to transfer force directly from integrins to the local cytoskeleton suggest that mechanical deformation of one or more FA proteins is the proximal step in an intracellular signaling cascade that leads to global cytoskeletal rearrangements and mechanotransduction at multiple, distant sites within a cell [19,20]. Despite the requirement of integrins and matrix attachment, for example, productive

muscle contraction, and the role of the ECM in the process by which muscle contractions stimulate the remodeling of hemidesmosome-like junctions, very little is known about the role of integrins and the ECM in mechanotransduction [21,22].

1.3. Ion channels

Mechanical stimuli can open ion channels, alter binding of proteins in FAs, and cause changes in overall cell morphology. Classic examples are the unfolding or stretching of molecules or the opening of ion channels under mechanical forces that transduce a signal to downstream-signaling pathways. Ion channels play a central role for mechanotransduction in the sensory systems, but the situation at FAs is very different, since speed of response is not an issue at FAs under force. Intriguingly, recent evidence reveals a direct link between Rho/ROCK and TRP-mediated signaling, suggesting that cross-talk may exist between mechanical signaling through integrins and through mechanosensitive ion channels [23,24,25]. More detailed information is presented in the following review article.

1.4. Molecular mechanisms

Mechanotransduction in the cell can typically be described as (a) transmission of the applied load to specialized structures, (b) transduction of the force into a biochemically detectable signal, and (c) the subsequent response of the cell. These are commonly referred to as mechanotransmission, mechanosensing, and mechanoresponse, respectively. Cells can sense and translate extracellular mechanical cues into intracellular biochemical signals to regulate cellular processes; however, their conversion into a biochemically detectable signal is the least understood [18].

As we know today, the remodeling of, for instance, bone in response to loading is achieved *via* a cascade of different steps including mechano- and biochemical coupling, signal transmission, and cell response, which are part of the mechanotransduction pathway. Mechanotransduction must therefore be viewed as a force-induced process initiating biochemical responses (for instance, changing binding affinity, altering phosphorylation state, and/or conformation change) and initiating signal pathways leading to gene expression, protein synthesis, and cellular phenotype change [26,27,28].

Recent reports suggest that the cell nucleus may also be directly involved in this cellular mechanotransduction process. These findings portray the nucleus as a central hub in cellular mechanotransduction, both structurally and biochemically, with important implications in physiology and disease. Consequently, the role of the nucleus in mechanotransduction includes the modulation of biochemical signals arriving at the nucleus. For instance, the MAPK pathway has been shown to be directly involved in cellular mechanotransduction. Finding suitable conditions that recapitulate both the mechanical and biochemical environment of the nucleus in isolation may therefore prove challenging. Answering these points will help to determine whether the nucleus is a true mechanosensor or mostly serves as a central processor for a variety of mechanotransduction signals converging from all parts of the cell. While many ground-breaking studies have enumerated the changes in cell signaling or protein expression after mechanical stimulation, relatively few have focused on determining the relationship between protein deformation and alterations in biochemical properties, such as differential enzymatic activity or binding lifetimes, in living cells. For example,

each of the sarcomeric components are critical in regulating how muscle perform mechanical work, maintain passive tension, undergo biochemical signaling, and facilitate mechanotransduction [29,30].

1.5. Signaling molecules and cascades

Signaling molecules are involved in mechanosensing and mechanotransduction. FAs and their components are not only structural proteins and mechanosensors, but also important signaling molecules, capable of relaying signals to the intracellular space *via* a range of signaling cascades. Since the nucleus has also been suggested to be a cellular mechanosensor, besides being a key player in the physical signaling pathway, it is possible that the linker of nucleoskeleton and cytoskeleton (LINC) complex is involved in chemical signal transduction pathways as well [31,32].

However, in recent years, an intricate complex of force sensing and signaling molecules has been identified, and many of these proteins have critical roles in development and disease. This is particularly relevant to Z-discs that were once thought only to be a static architectural support for the myofilaments, responsible for anchoring and transversely cross-linking adjacent thin filaments. In cardiomyocytes, integrin expression and signaling as well as focal adhesion and integrin-linked kinase activities and mechanotransduction are particularly complex, i.e., individual muscle cells respond to externally applied mechanical forces and generate internal loads that are transmitted to adjacent cells and to the surrounding ECM [33,34].

1.6. Biochemical signals and cross-talk

While mechanotransduction only describes the immediate process of converting a mechanical signal into a biochemical signal, the term "mechanotransduction" is often also understood to include the downstream biochemical signaling from a mechanosensor [35]. Normally, the term "mechanotransduction/sensoring/signaling" includes both the initial mechanosensing event as well as the biochemical signaling downstream of the mechanosensor. Based on this definition, a number of proteins can be involved in mechanotransduction. To avoid confounding factors from cytoplasmic mechanotransduction signals, experiments should be complemented by assays involving isolated nuclei subjected to mechanical stimulation. The development of new sensors has addressed this point to better understand the force-sensitive regulation of FA dynamics and signaling cross-talk between Wnt and the mechanosensitive integrins and yes-associated protein/transcriptional coactivator with PGZ-binding motif (YAP/TAZ) pathways. Recent observations demonstrated that integrin engagement with the ECM and subsequent activation of integrin-linked kinase lead to the nuclear accumulation of β-catenin and the activation of the growth factor receptor-bound protein2/focal adhesion kinase/c-Jun N-terminal kinase (Grb2/FAK/JNK) connection [36–39].

1.7. Force transmission to the nucleus

Force transmission over considerable distances and stress focusing at the focal FA sites make them prime candidates for mechanotransmisson. Although the nucleus may not directly sense mechanical stimuli, it certainly has a key role in regulating the cellular mechanoresponse *via* both physical force transmission and biochemical signal processing. For example, changes in the nuclear envelope protein composition not only affect nuclear deformability but might also disrupt force

transmission between the nucleus and cytoskeleton. Although the specific function of the nucleus in cellular mechanotransduction is still unknown, it is well established that mutations in numerous nuclear envelope proteins cause both defects in mechanotransduction signaling and force transmission. This suggests that these proteins might be involved in cellular functions, such as force transmission, mechanical stability, or mechanotransduction, and highlights the importance of intact force transmission and mechanotransduction pathways in cellular function. An improved understanding of the role of the nucleus would not only lead to better insights into normal cell biology but may also pave the way for novel therapies for the many diseases caused by mutations in nuclear (envelope) proteins. It would therefore be pertinent to find out which are the primary disease drivers. Are changes in the mechanical environment, in which cellular mechanotransduction signaling functions normally but responds to an altered input, or physical defects in cellular structure, resulting in altered force transmission solely responsible? Or is direct physical damage in response to mechanical stress and/or altered mechanotransduction signaling at the origin? So far, only a few pharmaceutical interventions are available to restore normal signaling. It remains to be established whether the defects in signaling are caused by altered nuclear mechanics and impaired force transmission to the nucleus or by disrupted interactions. For instance, are lamins/emerin and binding partners involved in transcriptional regulation? Regardless of the mechanism, the impaired signaling may not only weaken muscle adaptation to mechanical stress but could also affect stem cell differentiation [40,41].

1.8. Focal adhesions (FAs) and adaptor proteins

Many molecules function at the plasma membrane or FAs at the interface between the cell and the extracellular environment. FAs not only serve as mechanosensors that reorganize their composition in response to the diverse environmental cues but also function as mechanotransducers that mediate specific cellular signaling pathways that regulate FA turnover and cytoskeletal organization, thereby controlling cell behavior and driving cell migration. They combine membrane mechanics, membrane composition, lateral transport, and mechanotransduction. In muscle development, FAs are important in mechanotransduction, which plays a leading role in contractility and mechanical induction of myogenic differentiation. Although the mechanism of mechanotransduction *via* FAs is still not clear, it could involve protein stretching that reveals cryptic-binding sites for additional actin-binding proteins [42].

Integrins respond to cues from the ECM along with other signaling molecules such as kinases, phosphatases, and adaptor proteins. Pyk2, like FAK, acts as an important scaffolding protein and transduces signals from GPCRs to downstream MAPK signaling pathways depending on which signaling kinase and adaptor protein bind to the phosphorylated enzyme. Both talin and vinculin can exist in closed and open conformations, a fact which might point in the direction of a mechanosensor function at FAs [43].

Interfering with linker proteins of the FAs, the cytoskeleton and the nucleus cause defects in cell mechanosensing and function. Recent work in this area highlighted the role of this linkage. It has been suggested that force-induced unbinding of fibronectin on the extracellular side and force-induced unbinding of certain cytoplasmic adaptor proteins (e.g., vinculin) in FAs might be involved in mechanosensory processes of tissue cells [12,44,45]. The distinction between tension and conformation sensors in dynamic FAs, like for vinculin, will lead to a better molecular scale

understanding of mechanotransduction. Activation of the FAK/*Src*/p130Cas/vinculin complex *via* phosphorylation, which can be triggered mechanically, leads to the induction of the MAPK and PI3K signaling pathways, which are crucial regulators of stem cell behavior.

Shear stress (tension or bending) on the membrane can also influence the conformation of transmembrane and receptor proteins that leads to the activation of MAPK, Rac, Rho, etc. or constrains autocrine signaling. Stresses applied to a layer of epithelial cells grown on a porous membrane resulted in changes in gene expression, signaling, and ERK1/2 phosphorylation in lungs. Notably, physical manipulation of calcium signaling has been used to control mesenchymal stem cell (MSC) differentiation. Elevated tension induces integrin clustering and focal adhesion formation and consequently activates the Rho and ERK1/2 signaling pathways that promote cell division. For instance, in some transformed cells, this regulatory pathway is attenuated, thereby leading to uncontrolled cell proliferation [10,46–48].

2. Mechanosensor and Force Sensing

FA mechanosensors might also be regarded as a network of tightly interconnected molecular units that operate in a coordinated fashion in response to mechanical forces [49]. The signal transduction pathways that are activated in response to mechanical forces include many unique components as well as elements shared by other signaling pathways. Intrinsically generated and externally applied mechanical forces are usually transmitted bi-directionally to internally situated sarcomeres of the rod-shaped cardiomyocytes [50,51].

A key challenge is defining the unknown molecular mechanisms by which cells sense and respond to mechanical forces in the living animal. Mechanical forces are also thought to guide tissue growth. For example, the mechanotransduction pathway allowing cells of the shoot apical meristem to sense and respond to mechanical forces involves microtubule (MT) dynamics, thus resulting in their self-organization [52].

2.1. Pressure and tension

Signaling pathways leading to shear stress–induced vasodilation and blood pressure regulation require integrin–matrix interactions at FAs. In the heart, the process by which cells sense external forces and translate them into biochemical signals that change cell function is regulated by a diverse array of factors operating at different length scales. Externally, arterial blood pressure, valve compliance, passive stiffness, adhesivity of the cellular niche, and ventricular wall stress have all been shown to impact the form and function of the heart [53].

Proteins such as zyxin and p130Cas are well-known focal adhesion proteins that have been described as tension sensors. Recently, a new class of biosensors has been developed that reports the deformation within or the tension across specific proteins in living cells. This revealed some of the molecular mechanisms mediating mechanotransduction in adhesion biology. The analysis of the spatio-temporal dynamics of the tension across a specific FA protein has also advanced our understanding of cell signaling. Cytoskeletal tension triggers nuclear translocation and targets gene expression by transcription factors such as myocardin-related transcription factor (MRTF-A4) and YAP/TAZ. A detailed picture of the molecular events that underlie MRTF-A-mediated mechanotransduction has emerged. To effectively use force as a signal to coordinate cell behavior in

tissues, cells must sense different types of stress or strain, such as compression, tension, or shear [12,30,54,55,56].

2.2. Mechanical work, forces, and protein stability

In principle, there are many different physical mechanisms that might be at work as mechanosensors at focal adhesions. In addition to its contributions to mature sarcomere stability in muscle, myosin associates with actin during the earliest stages of sarcomerogenesis, suggesting that it is crucial for performing mechanical work given the few proteins present in these early contractile structures. Recent work using super-resolution microscopy with enhanced resolution in the vertical direction has shown that the proteins within FAs are arranged in a weakly stratified structure, comprising an integrin signaling layer, a force transduction layer, an actin regulatory layer, and finally actin-based stress fibers. Ultimately, how the nuclearskeleton integrates mechanical stimuli with complex intracellular signaling pathways and gene regulatory networks will require a systems biology approach that seeks to understand cells in a compact manner. To date, researchers have not yet pieced together a full picture of how mechanosensing and mechanotransduction work but a number of possible mechanisms are starting to emerge [57,58].

A clearer understanding of these processes and of the mechanical mechanisms that mediate cell–cell interactions will open up new avenues in the development of biological and medical science. Some of these factors, such as ERK1/2 and c-Fos, have well-established roles in signaling. Thus, tension could also modulate upstream signaling pathways, such as the activation of the small GTPase RhoA. The aim of a recent computational modeling study was to determine the effects of membrane tension on mechanotransduction-related structural and dynamic properties of the bilayer [59].

Moreover, considerable efforts are aimed at elucidating the mechanisms of mechanotransduction, namely how the various mechanical processes in the cell eventually lead to regulation of gene expression. Among the different proposed routes are integrin signaling, stretch-activated ionic channels, and nuclear deformation. For example, inside the vasculature, cyclic blood flow leads to dynamic shear stresses on endothelial cells and alterations in blood pressure, stretching the vessel wall. Other forms of mechanotransduction can be (a) stretch-activated ion channel activation, (b) membrane mechanotransduction (*via* G-protein and GPCRs), and various other proteins that connect to focal adhesion/adherence junctions and the cytoskeleton [60,61]. It is conceivable that different sensors are required to gage transverse versus longitudinal stretch, perhaps accounting for differential signaling and cellular phenotype resulting from pressure versus volume overload.

3.   Skeletal and Cardiac Muscles and Diseases

Complementary to the intracellular propagation of biochemical signals is the process of propagating physical forces through the cell. Endothelial cells, for instance, are constantly exposed to chemical and mechanical microenvironment in vivo [62].

Shear stress at the membrane mediates processes by an array of signaling cascades in the cell. For example, the modulation of plasma membrane fluidity can alter the shear stress-induced MAPK signaling pathway that underscores the importance of the plasma membrane in mechanotransduction. Both atrial and ventricular cardiomyocytes, for instance, not only regulate the *beat-to-beat* cardiac

performance but also affect the proliferation, differentiation, growth, and survival of the cellular components that comprise the human myocardium. Some evidence now indicates that integrin-based cell–matrix contacts act as local mechanosensors that change mechanical information about the environment directly into cellular decision-making answers. The mechanosensory properties of the cells themselves and their cell–cell and cell–matrix adhesions have a central function in these processes. For instance, integrin–matrix interactions at FAs are required to initiate the signaling pathway leading to shear stress–induced vasodilation and blood pressure regulation. Cardiomyocytes are composed of several sub-compartments involved in mechanotransduction, which include the contractile sarcomeres, the cytoskeletal filament networks, transmembrane cell–cell and cell–matrix junctions, stretch-sensitive membrane structures, and calcium-handling machinery [11].

Possible explanations include cell-type specific differences in signaling pathways or the fact that skeletal muscle has a higher potential for repair and regeneration compared to cardiac tissue. In this context, the mechanotransduction pathway is required for tissue elongation and coordination of epidermal and muscle tissue morphogenesis. Molecules in the sarcomere are capable of acting as stress sensors that are capable of nuclear signaling, allowing the myocyte to respond and localize at the Z-disc, thus further suggesting a critical sensory role for these types of proteins. Sarcomeres are also known to respond to alterations in the mechanical forces being presented to the heart, that is "outside-in" mechanotransduction. Thus, sarcomerogenesis and maintenance of sarcomeric protein quality may depend upon the ability of the sarcomeres to act as a stress/strain sensor and perturbations of this structure could impair the resultant signaling [63,64].

By dissecting the effector and affected pathways of cardiac mechanotransduction, we hope that the reader will appreciate how mechanics regulates cardiac differentiation. To improve our understanding of the precise timing of mechanotransduction and its downstream pathways during the lifespan of the heart is absolutely essential. Also better understanding of cardiac differentiation from stem cells and the mechanotransductive signaling that enables this may reveal indirect therapeutic targets and/or enable better direct engineering of cells and tissue for repair and regeneration [65].

Disruption of FA dynamics that leads to loss of functions of protein components in the complexes is related to heart disease. There are many examples of mechanotransduction that lead to diseases forms such as arteriosclerosis, the hardening and narrowing of the arteries, mainly causing shear flow changes in which endothelial cells sense the level of stress and regulate their behavior concomitantly. Revealing the cellular and molecular basis for mechanotransduction is, therefore, central to our overall understanding of cardiac structure and function in the normal and diseased heart. Like a mechanic fixing a car without understanding how the engine is built and connected to the rest of the car, attempting to decipher the role of the nucleus in mechanotransduction and disease necessitates an understanding of nuclear structure and its connection to the cytoskeleton [66,67,68].

Other diseases, including progeria, that are caused by mutations in nuclear envelope proteins, such as lamins A/C and emerin, are examples of how defects in nuclear envelope proteins can affect cellular mechanics and mechanotransduction. Since the discovery of the first disease-causing mutations in nuclear envelope proteins 20 years ago, research on nuclear mechanics and nuclear mechanotransduction has been a rapidly growing field. Ultimately, insights gained from these studies will not only enhance our understanding of normal cellular processes and mechanotransduction but may also provide important novel therapeutic targets for diseases ranging from deafness to muscular dystrophy, heart disease, and cancer [40,69].

4. Conclusions

In this review, we focused on the molecular mechanotransduction in cells. Force transduction through cell-matrix (FAs) and cell-cell contacts (FAJs) controls the maturation or assembly/disassembly of these adhesions and triggers intracellular signaling cascades that influence cellular behaviors. The dynamic connection of actin at these adhesion sites as well as protein tyrosine phosphorylation/dephosphorylation is closely related to cellular mechanotransduction, sensing, and signaling. Understanding the interplay between biochemical and mechanical interactions of the actin-FAs and actin-FAJs linkages will bring important insight into molecular and biophysical mechanisms of cell migration, proliferation, and differentiation in both physiological and pathological processes [68].

Acknowledgements

Conflict of Interest

The authors declare that there is no conflict of interests.

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