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METHODS ARTICLE

Tissue Regeneration from Mechanical Stretching of Cell–Cell Adhesion

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Cell–cell adhesion complexes are macromolecular adhesive organelles that integrate cells into tissues. This mechanochemical coupling in cell–cell adhesion is required for a large number of cell behaviors, and perturbations of the cell–cell adhesion structure or related mechanotransduction pathways can lead to critical pathological conditions such as skin and heart diseases, arthritis, and cancer. Mechanical stretching has been a widely used method to stimulate the mechanotransduction process originating from the cell–cell adhesion and cell-extracellular matrix (ECM) complexes. These studies aimed to reveal the biophysical processes governing cell proliferation, wound healing, gene expression regulation, and cell differentiation in various tissues, including cardiac, muscle, vascular, and bone. This review explores techniques in mechanical stretching in two-dimensional settings with different stretching regimens on different cell types. The mechanotransduction responses from these different cell types will be discussed with an emphasis on their biophysical transformations during mechanical stretching and the cross talk between the cell–cell and cell-ECM adhesion complexes. Therapeutic aspects of mechanical stretching are reviewed considering these cellular responses after the application of mechanical forces, with a focus on wound healing and tissue regeneration.

Keywords: cell–cell adhesion, mechanical stretching, mechanotransduction, wound healing, tissue regeneration, regenerative medicine

Impact Statement

Mechanical stretching has been proposed as a therapeutic option for tissue regeneration and wound healing. It has been accepted that mechanotransduction processes elicited by mechanical stretching govern cellular response and behavior, and these studies have predominantly focused on the cell-extracellular matrix (ECM) sites. This review serves the mechanobiology community by shifting the focus of mechanical stretching effects from cell-ECM adhesions to the less examined cell–cell adhesions, which we believe play an equally important role in orchestrating the response pathways.

Introduction

Tissues in the human body are formed by the physical linkage among individual cells through cell–cell and cell-extracellular matrix (ECM) connections. These physical structures provide mechanical integrity by transmitting physical forces across cytoskeletal networks within individual cells. In the same capacity, they also possess mechanosensors that can feel physical forces and orchestrate a proper biochemical response of different types and timescales. This process has long been known as mechanotransduction, a phenomenon that was discovered in ion channels and later expanded to include mechanochemical processes from many other cell and tissue types.[1] Exploration of mechanotransduction has uncovered many molecules with mechanosensing capabilities at the cell-ECM and cell–cell connections, most noteworthy of which are at the focal adhesion and cadherin based cell–cell adhesion sites.[2]

Studies in cellular level mechanotransduction use many physical methods to apply a force or strain to cell adhesions, the only physical structures of a cell that can take mechanical input as a stimulus. In a two-dimensional (2D) cell culture model, mechanical stretching represents the most convenient way of applying this mechanical input,[3] among

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others such as fluid shear. Mechanical stretching normally uses a flexible substrate where cells can grow and form a monolayer. An actuation mechanism induces an in-plane deformation of the flexible substrate and thus causes a strain on the cell monolayer as a whole and, at the molecular level, a strain on the mechanosensing molecules. Different regimens of strains, including static, cyclic, uniaxial, and biaxial, have been proposed to elicit a variety of biochemical responses.[4] Through this simple mechanism, researchers have witnessed a host of discoveries that provide understanding on how cells in different tissues connect and interact with one another in tissue morphogenesis,[5] grow and proliferate,[6] and, most importantly, probe the microenvironment through mechanosensing to direct their own fate.[7]

Linker molecules between cadherin molecules and the cytoskeleton at the cell–cell contact, such as α-catenin, generally serve as the mechanosensing elements at cell–cell adhesion sites,[8] in a similar manner to focal adhesion kinases (FAKs) at the cell-ECM adhesion sites. They experience straining from external stimuli in the form of a conformational change, which exposes binding sites for molecules in downstream pathways. This series of events subsequently leads to strengthening of the cell–cell adhesion or dissipation of tissue level stresses within cytoskeleton elements.[9] These responses normally are achieved by forming adhesion bond clusters or by enhancing existing cell–cell adhesion connections.[10] Following mechanotransduction, cells will exhibit various physiological behaviors, and the majority of cell stretching studies are aimed at cellular proliferation and tissue regeneration.

In this review, we will provide a focused overview of the 2D cell stretching practices on different cells with an emphasis on the molecular pathways in mechanotransduction, which lead to cell proliferation, tissue regeneration, and wound healing. We will review cell–cell adhesive junctions and the biophysical processes in their adaptation to external strain. We will subsequently discuss different modes and regimes of cell stretching, which is followed by an overview of mechanotransduction responses to these different types of stretching. The effect of mechanical stretch on the cross talk between the cell–cell and cell-ECM adhesion complexes is also discussed, in addition to physiological effects that arise from the responses, such as tissue regeneration and wound healing. Then, a concluding remark and future perspective will be provided to suggest potential new niche areas of research on mechanotransduction.

Cell–Cell Adhesion

Cell–cell adhesion junctions

There are four types of cellular junctions at the cell–cell contact: tight junctions, gap junctions, adherens junctions (AJs), and desmosomes. Tight junctions seal the paracellular space, limiting the passage of molecules and ions through intercellular spaces and preventing the movement of membrane proteins between the upper and lower portions of the cell. Therefore, the apical and basolateral parts of the cell membrane with different functions can be preserved.[11] Gap junctions function as pores between adherent cells, allowing small molecules, ions, and electrical current to pass directly between cells.[12] This facilitates the passage of potential through a tissue. For example, moving action potential in heart muscles flows across cells, causing the heart to pulse rhythmically.[13]

AJs and desmosomes, on the other hand, have the key role in maintaining tissue mechanical integrity. AJs are composed of classical cadherins at the extracellular area as adhesion molecules and armadillo family proteins at the intracellular region as linker molecules.[14] At the extracellular domain, E-cadherin molecules from neighboring cells form catch bonds, resisting tension and maintaining tissue integrity. E-cadherin continues through the cell membrane to the cytoplasmic domain. At this point, E-cadherin is linked to linker molecules, p120- and β-catenin, which are further connected to actin filaments (AFs) through another linker molecule, α-catenin (Fig. 1A). It has been shown that both E-cadherin and α-catenin at AJs serve as mechanosensors in different types of cells in the skin and cardiovascular tissues.[15] Desmosomes are cadherin-based adhesive junctions and have a molecular organization similar to AJs.[16] Desmosomes are composed of desmosomal cadherin, desmogleins (Dsg), and desmocollins (Dsc), as well as linker proteins from the armadillo family and the plakin family of cytolinkers.[17] The cytoplasmic tails of the cadherins connect to the intermediate filament network through the linker molecules (Fig. 1B). Molecules in the desmosome junction are yet to be revealed as mechanosensors, although some studies have suggested that plakophilin serves as binding scaffolds for RhoA, which potentially regulates cell contractility.[18]

Biophysics of cadherin-based AJ and desmosome cell–cell adhesions

Cells adhere to their neighboring cells physically through cellular junctions with cadherin adhesion molecules, transmembrane molecules that have a key role in cell–cell adhesion. They function as a cell–cell adhesion regulator and

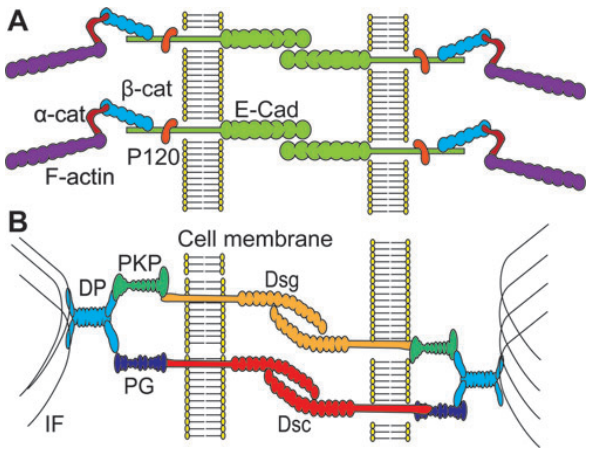

FIG. 1. Molecular complex of the AJ and desmosome. **(A)** AJ complex includes a chain of E-Cad at the extracellular domain and α-cat, β-cat, and P120 at the intracellular domain. β-cat links the cadherin to F-actin through α-cat. **(B)** Desmosome is a combination of three protein families. Dsc and Dsg are the molecules at the extracellular domain. PKP and PG are connected to Dsg and Dsc, respectively. These two molecules are then connected to intermediate filament through desmoplakin (DP). α-cat, α-catenin; β-cat, β-catenin; AJ, adherens junction; Dsc, desmocollins; Dsg, desmogleins; E-Cad, E-cadherin; PG, plakoglobin; PKP, plakophilin. Color images are available online.

mechanotransducer during tissue morphogenesis. Cadherin regulates cell–cell adhesion with three mechanisms as follows: (1) providing catch bonds that strengthen when pulled, (2) varying the interfacial tension between cell surfaces through adhesion tension, and (3) initiating mechanosensing to regulate the cytoskeletal network.[19] Adhesion tension, like surface tension in liquids, gives rise to the circular shape of cells; at the cell–cell contact, cadherin causes a reduction in adhesion tension and, as a result, increases the surface contact area.[20] In addition to reducing adhesion tension to decrease the interfacial tension between cells, cadherin signaling also helps increase the cell contact area, which is achieved by reorganizing the actomyosin cytoskeleton in the contact area.[20]

Studies show that contractile actomyosin exerts pulling forces on the cadherin bonds, which resist the pulling by forming catch bonds to prevent bond rupture.[21] Forces are subsequently transmitted through cadherin bonds to the entire cytoskeletal network. The anchor points of cadherin to the cytoskeleton are mediated by α- and β- catenin, and, if forces increase, vinculin and other molecules are recruited to this complex in parallel.[22,23] Researchers determined that the weakest component resides in the cytoplasmic domain rather than the extracellular domain.[24–26]

Diseases related to AJs and desmosomes

In normal tissues, cells tightly attach and maintain tissue integrity. In the diseased state, on the other hand, tissues frequently have cells with detachment or abnormal integrity in cell–cell adhesion. In atherosclerosis, when plaque builds up inside blood vessels, reduction of cell adhesion strength results in the detachment of the plaque, which can lead to a stroke or heart attack.[27] In malignant tumors, a significant decrease in cell–cell adhesion is often exhibited.[28,29] Immunostainings of various tumor types with antibodies targeting specific proteins in the AJs have shown a correlation between the changes in the proteins' expressions and pathological conditions.[30] In breast cancer, for instance, cadherin expressions are often downregulated, and the overall loss of heterozygosity of cadherin is common.[30] Loss-of-function mutations in α- and β-catenin proteins have also been reported in cell lines derived from human epithelial tumors.[31] However, the prevalence of these mutations in primary tumors remains to be fully understood.[31]

Desmosomes have the primary role in resisting external strain. They are prominent in the epidermis and heart, tissues often subjected to considerable mechanical stresses in the human body. Mutations in, or autoantibodies directed at, desmosomal proteins lead to compromised cardiac or cutaneous function and sometimes both. An autoimmune attack on Dsg causes pemphigus and staphylococcus.[32] Ablation of the plakoglobin gene results in mouse embryonic lethality owing to mechanical fragility of the myocardium.[33] Desmoplakin mutations can cause an array of diseases in the heart and skin with varying severity.[34]

Monolayer Based Stretching

Interrogating cells in a monolayer is the most convenient way to study cell–cell adhesion and the effect of mechanotransduction in healthy and diseased conditions. In these methods, cells are seeded and grown on a flexible substrate, which is then stretched through the application of a load. These loads are transduced to biochemical signals through different pathways depending on the nature of the load.[35–37] Different cell types behave in different ways to the same stimulation, which is yet to be fully studied.[38] Investigators have cultured various cell types on these flexible substrates, such as bone cells,[39] lung cells,[40] and neurons,[41] to study cell responses to the stretching force, including cell proliferation, migration, differentiation, cytoskeleton rearrangement, and other mechanotransduction responses.

Two common load types have been used to investigate cell–cell adhesion using flexible substrates. The simplest is static loading, in which a fixed strain is applied to the substrate and held. Viscoelastic properties of cells such as relaxation time can be investigated with this load type. Conversely, dynamic loading is used to subject the substrate to a time-varying strain. The effect of strain amplitude and frequency on tissue behavior of melanocytes has been explored with this load shape.[42] In-plane uniaxial and biaxial stretching is commonly used as methods to apply a uniformly distributed force to cells. To apply the load, the substrate is attached to a mechanism, which stretches the substrate upon actuation. Bone cells and embryonic osteoblasts were investigated using this stretching method[43,44] (Fig. 2A, B). Uniaxial and biaxial stretching methods are mainly used to study the effect of load on bone tissue.[38,45,46] A similar in-plane technique uses vacuum pressure to apply strain to the substrate of cultured HEK293 cells (Fig. 2C) and offers a uniform equiaxial strain on cells.[47] Four-point bending[48,49] is an out-of-plane technique for applying strain to the substrate (Fig. 2D). This method offers a low strain and uniform longitudinal and lateral stresses on cells. Curved template method is another out-of-plane stretching technique, in which the substrate is pressed on a curved template which deforms the substrate out of plane (Fig. 2E). By controlling the shape of the curved template, uniform strain can be achieved.[50]

The main advantage of the 2D substrate deformation methods compared to other techniques such as fluid flow and 3D cell culture is that the amount of force can be precisely adjusted. Determining the force in fluid flow induced shear requires rigorous calculations, and the force in 3D culture is directed in three dimensions, making the exact amount of force on cells difficult to be calculated. Stiffness of the substrate is a parameter that plays an important role in the resolution of the applied load. Substrate stiffness is controlled by changing the substrate's thickness or chemical composition. By altering the substrate stiffness, researchers can get different force resolutions, allowing for even more control of the force. However, obtaining a fine resolution through control of substrate stiffness is still an issue. Another advantage of 2D substrate deformation methods is the variety of load conditions that can be applied to the substrate. Compared to fluidic flow and 3D stretching, more options for load application are available for substrate deformation.

Aside from these advantages, the 2D stretching method has some limitations. Since the load is applied to a cell monolayer, it is almost impossible to directly and quantitatively measure the adhesion forces at either the cell–cell or cell-ECM adhesions. Although there is some statistical analysis that can be done on these data, the exact amount of the adhesion force is not obtainable. In addition, stretching

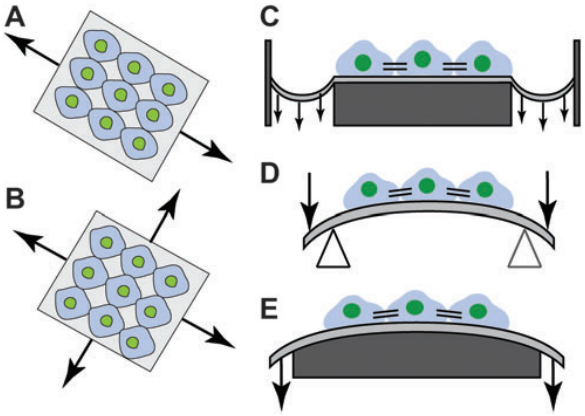

FIG. 2. Mechanical stretching of a monolayer of cells. **(A)** Uniaxial stretching. **(B)** Biaxial stretching. **(C)** Equiaxial stretching with vacuum suction. **(D)** Four points bending substrate flection; **(E)** Stretching with curved template. Color images are available online.

cell monolayers cannot reveal the underlying mechanotransduction cross talk between cell–cell and cell-ECM adhesions.[48] Studies have shown the interplay between integrin and cadherin based adhesions when cells are stimulated by external load or fluid shear.[51–53] Since monolayer stretching applies stress and strain to both adhesion complexes at the cell–cell and cell-ECM contacts, it is difficult to decouple the mechanotransduction pathways originating from the two interfaces. A detailed discussion of this cross talk from recent cell stretching studies is presented in the following section.

Mechano-Sensation of Cell–Cell Stretching

Mechanical stretching induces an external strain to a layer of cells in the 2D substrate deformation scheme. At the tissue level, cells within the layer reorganize their cytoskeleton structures to dissipate the additional stress. At the cellular level, contractile forces generated from the AF network will be balanced at the cell–cell adhesion sites with the external force from the stretch. Mechanosensory processes respond to the external stress by strengthening the cellular junctions through the recruitment of adhesion molecules to the cell–cell contact.[10]

Strengthening of the junction

Cells can strengthen cell–cell adhesion with different mechanisms. When subjected to external load, cadherin bonds can switch to long-lived, force-induced bonds with a tighter contact,[54] commonly referred to as catch bonds (Fig. 3A).[21,55,56] Catch bonds play important roles in cell migration and wound healing as they allow cells to grasp each other strongly when pulled and to release in the absence of external stimuli.[57] In addition, mechanosensors at the AJ and the desmosome initiate a cascade of signaling processes, which results in the strengthening of the linker molecules.[58] For instance, α- and β-catenin at the cytoplasmic tail of the junction can recruit vinculin to the complex.[59] As a result, the force is divided between the two chains, and the junction can strengthen (Fig. 3B).[60] Furthermore, when mechanosensors at the junction detect stress increase at a specific location, the signaling pathway leads to an increase in the number of bonds,[61] and therefore, the average force within each bond drops (Fig. 3C).[62–64] In epithelia, E-cadherin is concentrated at regions of greatest tension within the AJ,[65] suggesting the presence of several mechanisms that couple the spreading of cadherins to cortical actomyosin. These may include moving cadherins linked to the cytoskeleton toward sites of higher contractile stress,[66] clustering of cadherin by F-actin[67] and myosin,[68] and regulating cortical actin.[69]

Stress dissipation within the cell layer

The molecular complex at the cell–cell junction behaves like a spring. The force stretches the bond and can rupture it at the yield point. To mitigate the effect of applied stress, cells can align their orientation along the principle direction of the load,[70] divide along the direction of the load,[71] or reorganize the cytoskeleton (Fig. 4).[72] When cells are subjected to force, they can divide and proliferate in the direction of the applied force to alleviate stress within each cell (Fig. 4A). Another mechanism is through cell intercalation, in which cells can exchange their positions with neighbors so that the resting length increases and the force dissipates (Fig. 4B).[71–74] Rearranging the tissue in this manner leads to additional mass in the direction of the load. Intercalation requires a combination

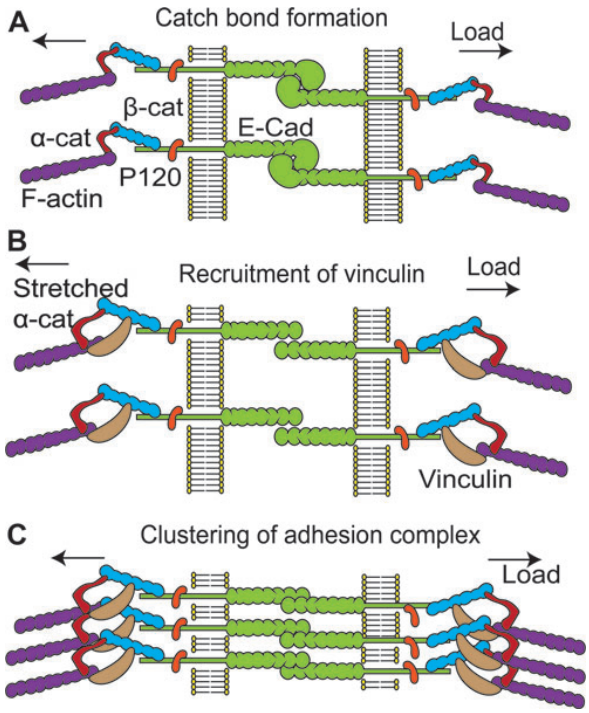

FIG. 3. Strengthening the adhesion bonds occurs when cells are subjected to an external force. **(A)** Catch bond formation of the cadherin bonds enables them to live longer and strengthen. **(B)** Recruitment of vinculin and other molecules to the junction complex parallel to α-cat can reduce the force on the junction. **(C)** Clustering the adhesion bonds at the concentrated stress region can decrease the amount of force on each cell. Color images are available online.

of mechanisms, including adhesive changes at the cell–cell and cell-ECM adhesion sites that allow cells to reposition, cytoskeletal events through which cells exert the forces needed for cell neighbor exchange, and cell polarity changes to regulate these processes.[75] Moreover, molecular remodeling of the cytoskeleton inside the cell by the upregulation of filaments and cross linker molecules also dissipates the internal stress (Fig. 4C).[76–80] Consequently, the rest length increases and the stress on the cytoskeleton decreases.[81] Furthermore, the fluid-like behavior of the actin cytoskeleton allows extrinsic stresses to be dissipated by molecular turnover of cytoskeletal components,[82] hence reducing the load on each adhesion complex at the cell–cell junction.[83]

Cross talk between cell–cell and cell-ECM adhesion under mechanical stretch

It has been shown that modulation of cell–cell and cell-ECM adhesions is coordinated during tissue morphogenesis.

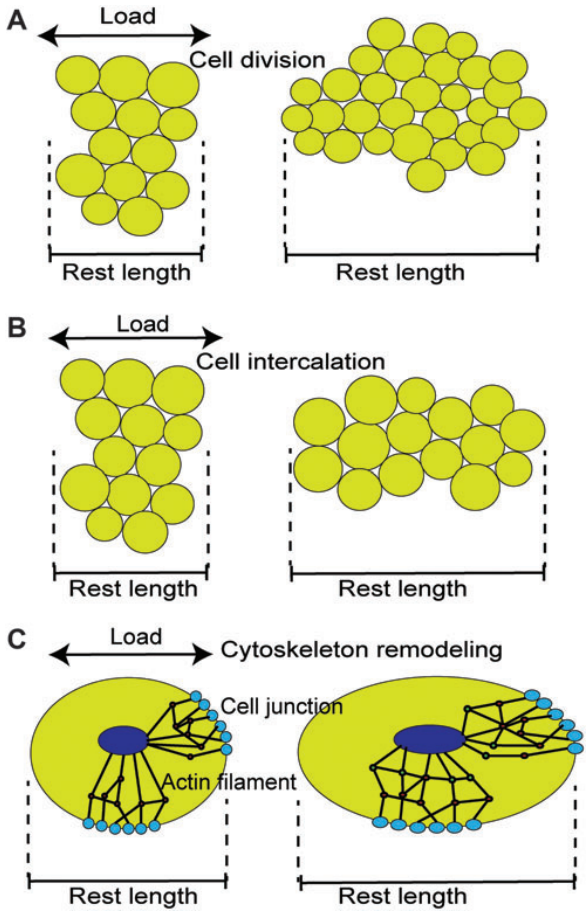

FIG. 4. Cells can dissipate the force at the cell junction in three ways. **(A)** Oriented division of cells in the direction of the principal stress, which adds mass to this direction and increases the rest length. **(B)** Reorganization of cells through intercalation. **(C)** Molecular remodeling of the cytoskeleton which decreases the stress on the fibers. Color images are available online.

Increasing the number of cell-ECM adhesion complexes leads to a decrease in the expression of cell–cell adhesion molecules, especially E-cadherin, during mouse lung morphogenesis.[84,85] The adhesion of osteoblasts to collagen in bone formation promotes cell–cell adhesion on the apical surface.[86] The formation of cell-ECM adhesions in cancer cells hinders formation of cell–cell adhesion, as was demonstrated by the negative feedback between the two adhesions when cells were cultured on surfaces coated with both types of adhesion molecules.[87] In contrast, cell–cell adhesion can locally disrupt the formation of cell-ECM adhesion. A study on epithelial cells showed that cadherin formation prevents cell-ECM adhesion formation, which arrests cell migration[88] and results in the disassembly of cell-ECM adhesion in the contact region.[89] On the contrary, disruption of cell–cell adhesion can promote the formation of cell-ECM adhesion complex to facilitate cell migration.[90,91]

Mechanical stretch affects mechanosensors at the cell–cell junctions in association with mechanosensors at the focal adhesion sites. Integrins and cadherins are both connected to AFs. Therefore, the same set of molecules is recruited in these junctions when they are subjected to external forces. Interaction of integrin and cadherin causes an upregulation in the expression of RhoA to reorganize the cytoskeleton in response to the mechanical force.[92] Actomyosin contractility is one of the major responses to mechanical forces induced at AJs and focal adhesions.[53] In fact, the role of AJs at the cell–cell contact to communicate with cell-ECM adhesions has been well documented.[53] These signaling activities include the vinculin signaling facilitated by α-catenin, stress sensing initiated by E-cadherin,[93] and the transcriptional activities through β-catenin nucleus translocation[15] (Fig. 5).

At the tissue level, these integrated networks of AFs form a strong connection between neighboring cells and between cells and the ECM. These connections lead to a global transmission of the mechanical force across the tissue when stretched to facilitate collective migration and tissue homeostasis.[53] Furthermore, when an external force is applied, since both adhesion types sense the force, a force balance between these junctions is established to maintain tissue integrity. As a result, activating the FAK leads to deactivating VE-cadherins.[94] Conversely, weak cell attachment to the substrate results in the aggregation of cells and an increase in cell–cell adhesion.[94]

Mechanical Stretching as a Candidate for Therapeutic Option

The biophysical processes of strengthening cell–cell adhesion and reducing the internal tissue stress lead to a wide variety of physiological phenomena, which allows the scientific community to contemplate whether mechanical stretching can become a suitable candidate for therapeutic options. These efforts resulted in a range of studies in correlating mechanical stretch with tissue regeneration and wound healing.

Wound healing

It is widely accepted that mechanical forces are involved in both wound healing and scar formation. Mechanically stretched engineered tissues in bioreactors may have excellent organization, functionality, and strength compared with

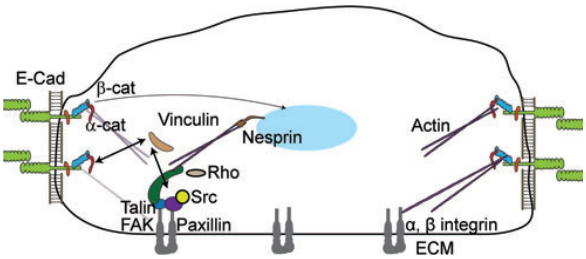

FIG. 5. Cross talk of cell–cell adhesion and cell-ECM adhesion mechanotransduction. Cadherin junctions at cell–cell adhesion site have cross talk with focal adhesion points. Vinculin can be recruited either at AJ in parallel with α-cat or at the focal adhesion junction in parallel with Paxillin. ECM, extracellular matrix. Color images are available online.

unstretched counterparts.[4] Fibroblasts have been extensively studied in biomechanical wound models, and physical forces are known to influence the expression of ECM genes and inflammatory genes involved in scar formation.[95–97] Increased mechanical stresses in the wound environment induce hypertrophic scarring through stimulation of mechanotransduction pathways, and, as a result, cell proliferation, angiogenesis, and epithelization are accelerated.[98]

Most wound healing processes occur as a result of the activation of mechanotransduction pathways.[99] Rapid embryonic repair of epithelial tissues involves collective migration of cells around the wound bed. This migratory behavior requires the generation and transmission of mechanical forces for the cells to move and coordinate their movements. Understanding the different aspects of wound healing requires an understanding of the mechanical signals involved in the process and the way these signals are modulated by the mechanical properties of cells, as well as the way the signals are converted into biochemical cues that affect cell behavior.[100] Mechanical stimulation modulates integrin, wingless-type (Wnt), protein kinase B, FAK, and several other key molecules downstream of FAK.[95] For instance, when mechanical stretch is applied, Src kinase interacts with integrin intracellular domains[101] and FAK[102] at the focal adhesion site, and this further promotes signaling events at the cytoplasmic domain, including talin, paxillin, and vinculin production[103] (Fig. 5). These signaling events promote the assembly of adhesion complexes and facilitate cell migration. For instance, talin is one of the most important proteins, which plays a vital role in cell migration.[104] In addition, the dynamic interactions of paxillin with α5 integrin and α-actinin have been implicated in the formation of protrusive regions during cell migration.[105]

Tissue regeneration

Cyclic loading and inducing mechanical stresses are ways of improving the mechanical properties of engineered tissues and also help in accelerating regeneration of cells.[106] It is necessary to understand biomechanical stimuli in cells as they may hold the key to prepare tissues with adequate mechanical integrity for implantation purposes. This has been demonstrated in muscle and cardiac tissues. It was shown that mechanical strain affects the maturation of cardiac tissue, cell–cell interaction, and gap junctions.[107] In addition, *in vivo*-like forces were applied to human bio-artificial muscles (HBAMs) as they differentiated. By applying a cyclic load, the HBAMs acquired improved tissue elasticity and therefore an increased myofiber diameter compared to unstretched HBAMs.[108] Moreover, cyclic mechanical stretching stimulates proliferation of cardiomyocytes within engineered early embryonic cardiac tissue, and this increase is blocked by p38MAPK inhibitor.[109] Furthermore, a bioreactor was used to investigate the influence of mechanical stresses and strains on properties of mature arteries.[110] In the study, cells were subjected to mechanical stress while they were cultured on a substrate, and they adapted to surrounding functional demands while growing to obtain cohesive regenerated tissues.[110]

Stem cell differentiation under mechanical stretching

Recently, researchers have focused on applying mechanical stimulation to stem cells in regenerative medicine. Several studies have reported the effects of mechanical stretch on stem cell differentiation toward cardiovascular cell types, since they are under continual strain in nature.[111] In one study, mechanical loading showed to improve myocardium regeneration and reduced apoptosis during cardiomyocyte differentiation.[112] It was also demonstrated that mesenchymal stem cell commitment and differentiation to ligament cells could be stimulated by mechanical stretch loading.[113] A comprehensive review on the effect of mechanical loads associated with F-actin on differentiation of stem cells revealed that the fate decision of stem cells was mostly governed by mechanical and chemical cues correlated with microfilament proteins and intercellular adhesion molecules.[114] For instance, it was documented that cyclic mechanical stretching sped up ECM-induced osteogenic differentiation along with promoting the overall expression.[115] In addition, the RhoA/ROCK, cytoskeletal organization, and FAK were shown to regulate mechanical stretch-induced realignment of human mesenchymal stem cells.[116]

Mechanical stretch can further induce the migration of stem cells, such as bone marrow derived stem cells and mesenchymal stem cells (MSCs), resulting in their production of expanded skin tissue and skin regeneration.[117] For instance, application of cyclic loading on bone marrow stromal cells promotes cell migration through the FAK-ERK1/2 pathway.[118] In addition, MSCs have been transplanted into animal models of skin tissue to investigate the effect of mechanical loading on migration of these cells to regenerate the skin.[119] Furthermore, cyclic mechanical loading can be used to increase cardiomyocyte proliferation in early embryonic cardiac tissue.[109]

Future Perspectives

In this review, the basics of cell–cell junctions were discussed, and different types of such junctions and their role in cell–cell adhesion under static and stretched conditions were introduced. Some diseases that impact the functionality of AJs and desmosomes, the most important cell–cell junctions to maintain tissue integrity and resist mechanical forces, were reviewed.[10,32,120] However, the mechanotransduction role of these junctions and their pathways in regulating disease conditions needs to be better elucidated. Some studies show that desmosomes also have some mechanosensory roles in

addition to classical AJs.[120] Furthermore, there is some evidence suggesting that when cells are subjected to external forces, AJs and desmosomes have some cross talk in both the mechanics of force distribution and signaling pathways in mechanotransduction.[52,53,121,122] Studies have been mainly about AJs and there is little investigation on desmosomes; thus, more studies on desmosomes and their potential interaction with AJs should be conducted.

Researchers have used some techniques to interrogate the adhesion forces in a cell pair. However, there is no method currently available to measure the cell–cell adhesion force directly. With emerging new technologies in microfabrication, a single cell pair stretch device may be fabricated, which can directly measure the cell–cell adhesion force. In making such a device, repeatability and accountability of the mechanical measurement, as well as biocompatibility and mechanical properties of the device such as stiffness, may be the most important parameters that should be considered. To visualize the mechanotransduction events and related signaling mechanisms, advanced imaging techniques such as Förster resonance energy transfer can be adopted with *in situ* cell stretching. The effect of mechanical forces in tissue growth, repair, and remodeling has been studied for more than several decades. However, the mechanobiology research in relation to regenerative medicine is still young, and the exact mechanisms by which these forces interact with cell–cell adhesion and ways to use them to stimulate tissue regeneration can be very promising research topics.

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