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REVIEW

Integrins and extracellular matrix in mechanotransduction

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Abstract: Integrins are a family of cell surface receptors which mediate cell–matrix and cell–cell adhesions. Among other functions they provide an important mechanical link between the cells external and intracellular environments while the adhesions that they form also have critical roles in cellular signal-transduction. Cell–matrix contacts occur at zones in the cell surface where adhesion receptors cluster and when activated the receptors bind to ligands in the extracellular matrix. The extracellular matrix surrounds the cells of tissues and forms the structural support of tissue which is particularly important in connective tissues. Cells attach to the extracellular matrix through specific cell-surface receptors and molecules including integrins and transmembrane proteoglycans. Integrins work alongside other proteins such as cadherins, immunoglobulin superfamily cell adhesion molecules, selectins, and syndecans to mediate cell–cell and cell–matrix interactions and communication. Activation of adhesion receptors triggers the formation of matrix contacts in which bound matrix components, adhesion receptors, and associated intracellular cytoskeletal and signaling molecules form large functional, localized multiprotein complexes. Cell–matrix contacts are important in a variety of different cell and tissue properties including embryonic development, inflammatory responses, wound healing, and adult tissue homeostasis. This review summarizes the roles and functions of integrins and extracellular matrix proteins in mechanotransduction.

Keywords: ligand binding, α subunit, β subunit, focal adhesion, cell differentiation, mechanical loading, cell–matrix interaction

An introduction to integrins and the extracellular matrix (ECM)

Integrins are a family of αβ heterodimeric receptors which act as cell adhesion molecules connecting the ECM to the actin cytoskeleton. The actin cytoskeleton is involved in the regulation of cell motility, cell polarity, cell growth, and cell survival.[1] The integrin family consists of around 25 members which are composed of differing combinations of α and β subunits.[2] The combination of αβ subunits determines binding specificity and signaling properties.[3] In mammals around 19 α and eight β subunits have been characterized. Variants of some of the subunits exist which are formed from differential splicing (eg, four variants of the β1 subunit exist).[4] Some integrin subunits are ubiquitously expressed, while other subunits are expressed in a tissue- or stage-restricted manner.[5]

Both α and β integrin subunits contain two separate tails, which penetrate the plasma membrane and possess small cytoplasmic domains which facilitate the signaling functions of the receptor. There is some evidence that the β subunit is the principal

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site for binding of cytoskeletal and signaling molecules, whereas the α subunit has a regulatory role.[6] The integrin tails link the ECM to the actin cytoskeleton within the cell and with cytoplasmic proteins, such as talin, tensin, and filamin.[7] The extracellular domains of integrin receptors bind the ECM ligands. Integrins can also associate laterally in the plasma membrane with other cell surface proteins, including tetraspanins, growth factor receptors, matricellular proteins, and matrix protease receptors.[8]

The ECM is a complex mixture of matrix molecules, including glycoproteins, collagens, laminins, glycosaminoglycans, proteoglycans, and nonmatrix proteins, including growth factors. These can be categorized as insoluble molecules within the ECM, soluble molecules, and/or matrix-associated biochemicals, such as systemic hormones or growth factors and cytokines that act locally.

The ECM contains many types of insoluble molecules which form a meshwork of structural proteins to which adhesive proteins, proteoglycans, and glycosaminoglycans are associated.[9] This provides rigidity and support for the tissue. Common insoluble structural matrix molecules include members of the collagen family. There are many types of collagen present in the ECM of tissues, including type I, III, IV, V, and the glycosaminoglycan-containing type XI.[10] Elastin is another common structural protein found in the ECM.[11] The glycoprotein families, including proteoglycans and tenascins,[12,13] can be present in the ECM as free soluble molecules or bound to substrates; the presentation of these molecules in the tissue as soluble or bound can result in differing cellular responses upon ligand binding.

ECM proteins are involved in various biological functions through their ability to bind multiple interacting partners such as other ECM proteins, growth factors, signal receptors, and other adhesion molecules. ECM proteins are secreted from cells and then integrate themselves into the matrix through binding via specific protein domains to form multiprotein interactions which regulate the structure and function of the tissue.[14]

Binding of integrins to the ECM

Some integrins show a high specificity for ligand binding, whereas most are more promiscuous and bind several different types of ligands. Most integrins recognize several ECM proteins, and several matrix proteins such as fibronectin and collagens bind to several different integrins.[15] There are four collagen receptor integrins (α1β1, α2β1, α10β1, and α11β1)[16] and around ten different fibronectin receptor integrin receptors.[17] Integrin receptors and their ligands are summarized in Table 1.[18] The composition and proportion of molecules in the ECM can be tissue specific; collagen II is present only in hyaline cartilage. This diverse tissue specific expression of ECM results in different expression profiles of integrin receptors within the cellular membranes of tissues.

The integrin receptor formed from the binding of α and β subunits is shaped like a globular head supported by two rod-like legs (Figure 1). Most of the contact between the two subunits occurs in the head region, with the intracellular tails of the subunits forming the legs of the receptor.[6] Integrin recognition of ligands is not constitutive but is regulated by alteration of integrin affinity for ligand binding. For integrin binding to ligands to occur the integrin must be primed and activated, both of which involve conformational changes to the receptor.[2] The integrins are composed of well-defined domains[19] used for protein–protein interactions. The α-I domains of α integrin subunits comprise the ligand binding sites. X-ray crystallography has identified an α-I domain within the β subunit and a β propeller domain within the α subunit which

Table 1 Integrin receptors and their ligands; adapted from Barczyk et al[18]

Integrins	Ligands
α1β1	Collagen (I, IV, IX), laminin
α2β1	Collagen (I, IV, IX), laminin
α3β1	Laminin
α4β1	Fibronectin, VCAM-1
α5β1	Fibronectin
α6β1	Laminin
α7β1	Laminin
α8β1	Fibronectin, vitronectin, nephronectin
α9β1	Tenancin C, VEGF-C VEGF-D
α10β1	Collagen (II, IV, VI, IX)
α11β1	Collagen (I, IV, IX)
αDβ2	ICAM-3 VCAM-1
αLβ2	ICAM-1,2,3,5
αMβ2	iC3b, fibrinogen
αXβ2	iC3b, fibrinogen
αVβ1	Fibronectin, vitronectin
αVβ3	Fibronectin, vitronectin, fibrinogen
αVβ5	Vitronectin
αVβ6	Fibronectin, TGF-B-LAP
αVβ8	Vitronectin, TGF-B-LAP
αIIBβ3	Fibronectin, fibrinogen
α6β4	Laminin
α4β7	MadCAM-1, fibronectin, VCAM-1
αEβ7	E-cadherin

Notes: Collagen receptors are highlighted yellow, laminin receptors are highlighted gray, RGD receptors are highlighted aqua, and leukocyte-specific receptors are highlighted pink. With kind permission from Springer Science+Business Media: *Cell and Tissue Research, Integrins*, 339, 2010, 269–280, Barczyk M, Carracedo S, Gullberg D, tables 1 and 2.

Abbreviations: ICAM, intercellular adhesion molecule; iC3b, proteolyticly inactive product of the complement cleavage fragment C3b; VCAM, vascular cell adheson molecule; MadCAM, mucosal addresion cell adhesion molecule; VEGF, vasular endothelial growth factor; TGF, transforming growth factor; LAP, latency-associated peptide.

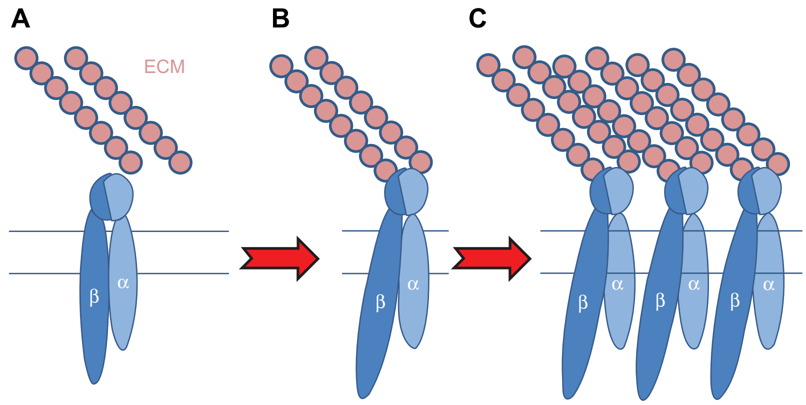

Figure 1 Integrin binding to extracellular matrix (ECM). Conformational changes to integrin structure and clustering of subunits which allow enhanced function of the receptor. (**A**) No binding; (**B**) after binding to ECM integrin subunits, the knee of the receptor is bent to allow exposure of intracellular binding sites; and (**C**) clustering of subunits allows enhanced activity of receptors.

complex to form the ligand-binding head of the integrin.[20,21] The use of activating and conformation-specific antibodies also suggests that the β chain is extended in the active integrin.[22] It has since been identified that the hybrid domain in the β chain is critical for integrin activation, and a swing-out movement of this leg activates integrins.[23]

The β subunit regulates integrin activation though conformational changes at the "knee" of the β subunit leg. The knee is located between the plexin-semaphorin-integrin/I-epidermal growth factor-1 and I-epidermal growth factor-2 domains; this bend in the β subunit results in the ligand-binding head pointing towards the membrane, which is unfavorable for ligand binding.[24] During integrin activation a "knee-jerk" extension occurs to give the high-affinity/active conformation with the ligand-binding head repositioned away from the membrane in a more favorable position for ligand binding.[24,25] The affinity of the receptor is dependent on the conformation of the receptor. Low affinity occurs when the headpiece is closed and bent, with the N-terminal ligand-binding pocket close to the membrane. Intermediate affinity occurs when the headpiece is closed but extended; high affinity occurs when the headpiece is open and extended,[19] resulting in the ligand-binding pocket moving away from the membrane. RGD peptides and small ligands can bind integrins that are not fully activated, whereas larger ligands such as fibrinogen and fibronectin cannot.[26,27] Clustering of low-affinity receptors enhances both the strength of ligand binding and the formation of adhesion complexes.[28]

Signaling that occurs with binding of integrins and ECM

Integrin extracellular binding activity is regulated from inside the cell and binding to the ECM induces signals that are transmitted into the cell.[15] This bidirectional signaling requires dynamic, spatially, and temporally regulated formation and disassembly of multiprotein complexes that form around the short cytoplasmic tails of integrins. Ligand binding to integrin family members leads to clustering of integrin molecules in the plasma membrane and recruitment of actin filaments and intracellular signaling molecules to the cytoplasmic domain of the integrins.[24] This forms focal adhesion complexes which are able to maintain not only adhesion to the ECM but are involved in complex signaling pathways which include establishing cell polarity, directed cell migration, and maintaining cell growth and survival. Initial activation through integrin adhesion to matrix recruits up to around 50 diverse signaling molecules to assemble the focal adhesion complex which is capable of responding to environmental stimuli efficiently.[29,30] Mapping of the integrin adhesome binding and signaling interactions identified a network of 156 components linked together which can be modified by 690 interactions.[31]

The binding of the adaptor protein talin to the β subunit cytoplasmic tail is known to have a key role in integrin activation.[7] This is thought to occur through the disruption of inhibitory interactions between α and β subunit cytoplasmic tails.[32] Talin also binds to actin and to cytoskeletal and signaling proteins.[33] This allows talin to directly link activated integrins to signaling events and the cytoskeleton. Other molecules which may participate in integrin activation alongside talin include members of the kindlin family.[34] Inhibition of kindlin binding inhibits integrin activation, whereas coexpression of kindlin and talin activates integrins.

After the initial activation resulting from binding of the integrin to ECM, the focal adhesions mature into multiprotein complexes at the cytoplasmic face of the clustered, ligand-bound integrins. The binding of a ligand to integrins results in a rise in intracellular calcium ion concentration. This leads to the activation of various kinase families including tyrosine kinases, such as focal adhesion kinase (FAK) and Fyn, and Src family kinases (SFKs).[35] FAK is ubiquitously expressed and is phosphorylation regulated. FAK interacts with the adaptor proteins talin and paxillin, which recruit FAK to focal adhesion.[36,37] FAK is autophosphorylated during integrin clustering and allows the presentation of docking sites for Src homology 2 domain-containing proteins.[38] These include SFKs which become activated on docking and phosphorylate FAK, promoting its kinase activity. SFKs are rapidly activated following integrin-ligand interactions. SFKs then activate downstream kinases and adaptors during these initial events.[39] SFKs can bind directly to β integrin tails which contributes to the activation of kinase activity.[40] Integrin-linked kinase has a major role as a signaling scaffold at integrin adhesions. Kinase activities of integrin-linked kinase are uncertain as the kinase domain lacks catalytic residues that are normally conserved among protein kinases; however in vitro studies suggest there may be some catalytic activity, though this has not been identified in vivo.[41]

Paxillin acts as an adaptor protein for α4,[42] β1,[43] and β3[44] subunits. Association of FAK with integrins in vivo is thought to be indirect, and most probably occurs through interactions with paxillin.[45,46] Paxillin is one of the earliest proteins to be detected in nascent adhesions where it is rapidly organized.[47] Therefore paxillin has an important role in the assembly of focal adhesions. Paxillin acts as a scaffold[48] through the many protein–protein interaction modules in its structure such as leucine-rich repeats LIM domains and a proline rich region. Paxillin also has multiple phosphorylation sites which can be involved in the regulation of protein-protein interactions. These sites are targeted by diverse kinases including p21-activated kinase, FAK-Src, receptor for activated C-kinase 1, and mitogen-activated protein kinase.[48] Paxillin has been shown to be a direct binding partner for the vinculin tail domain,[49] however in mature adhesions paxillin and vinculin appear to uncouple[50] with only transient interactions. In mature adhesions paxillin mediates the binding of kinases, phosphatases, actin-binding proteins (eg, vinculin and the parvins), and regulators and effectors of the Rho family of small guanosine triphosphatases.

Deactivation of integrins through negative regulators is important in controlling the appropriate expression of integrins and adhesion. Negative regulation can occur at any point in the integrin signaling process, if molecules which act as negative regulators are activated. The kinase properties of mitogen-activated protein kinases and extracellular-signal-related kinase 1 and 2 suppress integrin activation in many cell types when activated by HRas.[51] In the final stages of integrin activation the association of negative regulators with talin or either integrin tail can lead to disassociation of integrin and disruption in the adhesion complex. Phosphatidylinositol phosphate kinase type Iγ90 competes with β integrin tails for binding to talin-1, and is believed to act as a molecular switch which may regulate dynamic focal adhesion turnover.[52,53] Phosphorylation events which occur during integrin-mediated focal adhesion development lead to activation of kinases which can tyrosine phosphorylate the β integrin tail and lead to altered conformation of the receptor and/or altered affinity for interacting molecules. Phosphorylation of tyrosine in the membrane proximal asparagine-proline-X-tyrosine motif of β integrin tails promotes competition with phosphotyrosine-binding domain-containing proteins which do not activate integrins. Tyrosine phosphorylation in this region may reduce the affinity of interactions with talin-1.[54] Other mechanisms by which the interaction between β integrin tail and talin can be disrupted is through competition for binding which occurs with filamin A[55] or integrin cytoplasmic domain associated protein 1.[56] Thus binding of integrins to ECM initiates a series of signaling cascades resulting from the assembly of the focal adhesion complex (interactions summarized in Figure 2). These can be complementary or independent from each other since many cascades diverge into each other at different intervals and lead to alteration of gene expression.

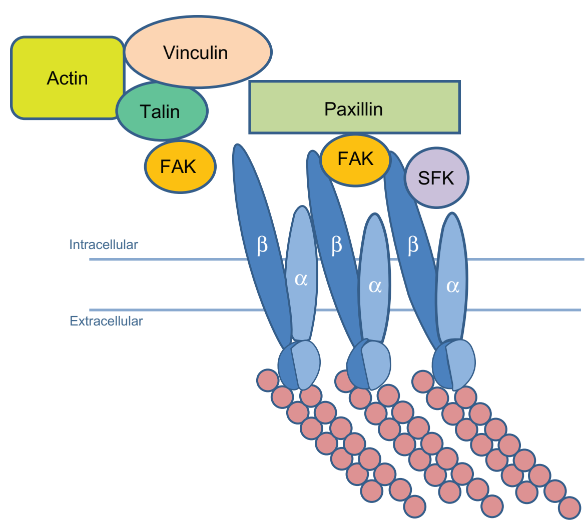

Figure 2 Simplified focal adhesion complex generated after integrin–extracellular matrix binding. Proteins shown are important molecules involved in focal adhesion development and intracellular signaling resulting from integrin–extracellular matrix interactions.
Abbreviations: FAK, focal adhesion kinase; SFK, Src family kinase.

Genetic programming that occurs with the binding of integrins to the ECM

Signal transduction pathway activation arising from integrin-ECM binding results in changes in gene expression of cells and leads to alterations in cell and tissue function. Various different effects can arise depending on the cell type, matrix composition, and integrins activated. One way in which integrin expression is important in genetic programming is in the fate and differentiation of stem cells.

Osteoblast differentiation occurs through ECM interactions with specific integrins to initiate intracellular signaling pathways leading to osteoblast-specific gene expression[57] and disruption of interactions between integrins and collagen; fibronectin blocks osteoblast differentiation and mineralization. Disruption of α2 integrin prevents osteoblast differentiation, and activation of the transcription factor osteoblast-specific factor 2/core-binding factor α1.[58] It was found that the ECM-integrin interaction induces a modification in osteoblast-specific factor 2/core-binding factor α1 to increase its activity as a transcriptional enhancer rather than increasing protein levels. It was also found that modification of α2 integrin alters induction of the osteocalcin promoter; inhibition of α2 prevents activation of the osteocalcin promoter,[58] while overexpression enhanced osteocalcin promoter activity.[59] It has been suggested that integrin-type I collagen interaction is necessary for the phosphorylation and activation of osteoblast-specific transcription factors present in committed osteoprogenitor cells.[60]

Generation of cartilage cells from stem cell differentiation (chondrogenesis) occurs through coordinated effects of growth, differentiation factors, and ECM components. In addition to hormone growth factors and transforming growth factor-β, many other factors drive the differentiation of mesenchymal stem cells towards cartilage, including ECM molecules, such as syndecans and glypicans or fibulins.[61] Thus integrin-mediated signaling appears to play an important role in the generation and maintenance of the chondrocytic phenotype during chondrogenic differentiation. During chondrogenesis there is a defined integrin expression pattern.[62]

The integrin-specific maturation of mesenchymal stem cells when plated on ECM ligands is being utilized in tissue repair. Adult mesenchymal stem cells are pluripotent progenitor/stem cells and can be differentiated into chondrocytes, tendonocytes, adipocytes, and osteoblasts.[63] Coating of engineered bioimplants with ECM, such as fibronectin fragments, can enhance integrin-mediated adhesion in vitro, osteogenic signaling, and differentiation in human mesenchymal stem cells which promote bone formation and functional integration of the implant into bone in rat tibiae.[64] Similar work with chondrocytes has been more difficult as stable cartilage can be formed in vitro, but has been less stable in vivo.[65]

Mechanotransduction: where integrins and ECM come together in physiology and pathophysiology

The process by which mechanical signals are converted into chemical activity and changes in cell behavior is termed mechanotransduction. Mechanical loading through movement of joints is essential in the maintenance of connective tissues. Movement and mechanical forces maintain healthy cartilage,[66] bone,[67] muscle,[68] and tendons[69] by regulating tissue remodeling. In tissues which are subject to mechanical loading, the relative amounts and organization of matrix molecules such as collagen and proteoglycan vary throughout the depth of cartilage reflecting the distribution and effect of load placed on the tissue. Integrins are one of a number of cell surface molecules which are able to sense deformation of the tissue resulting from mechanical loading, and are termed mechanosensitive receptors. Integrins are important molecules in mechanotransduction signaling in various tissues within the body,[69] and their location between the ECM and cell cytoskeleton is ideally suited for their role as a mechanoreceptor.

Deformation of the tissue during mechanical loading/stimulation alters the conformation of the ECM molecules and thus their availability to interact with cell surface receptors such as integrins as well as directly activating mechanosensitive receptors. Mechanical loading not only stimulates cells directly but there is also release of soluble mediators from cells such as chondrocytes which can stimulate cell surface receptors. During mechanotransduction, integrin expression and integrin-matrix affinity is modulated by these growth factors and cytokines, and by doing so may alter integrin signaling. This may result in altered matrix protein production,[70]stimulation of matrix metalloproteinases and aggrecanases,[71,72] or matrix degradation, which would affect cell–matrix interactions.[73] Similarly, a variety of growth factors and cytokines have been shown to be important in the regulation of integrin expression and function in chondrocytes.[3,74,75]

Mechanotransduction in chondrocytes occurs through several different receptors and ion channels including integrins.[76] During osteoarthritis the expression of integrins by chondrocytes is altered, resulting in different cellular transduction pathways which contribute to tissue pathology. In normal adult cartilage, chondrocytes express α1β1, α10β1 (collagen receptors), α5β1, and αvβ5 (fibronectin) receptors.[77,78] During mechanical loading/stimulation of chondrocytes there is an influx of ions across the cell membrane resulting from activation of mechanosensitive ion channels which can be inhibited by subunit-specific anti-integrin blocking antibodies or RGD peptides.[79] Using these strategies it was identified that α5β1 integrin is a major mechanoreceptor in articular chondrocyte responses to mechanical loading/stimulation.

When a ligand binds to integrin there is a rise in intracellular calcium ion concentration. This leads to the activation of tyrosine kinases and intracellular cell signaling pathways. In monolayer cultures of chondrocytes, normal cartilage mechanical loading/stimulation at 0.33 Hz results in α5β1-dependent tyrosine phosphorylation of FAK and paxillin and activation of protein kinase C.[80] This signaling can be interrupted by the use of integrin blocking methods. Function blocking β1 subunit antibodies inhibit cyclical compression induced gene expression of cartilage oligomeric protein in both calf articular cartilage explants as well as in alginate/chondrocyte constructs.[81] The use of RGD peptides were able to abolish dynamic compression induced cell proliferation, proteoglycan production, and nitric oxide inhibition in bovine three-dimensional agarose/chondrocyte culture.[82] Through a transforming growth factor-β3-dependent pathway, α5β1 integrins can also mediate signals from dynamic compression to enhance proteoglycan synthesis and chondrocyte proliferation.[83] More recently it has been identified that CD47 (integrin-associated protein) is involved in the membrane hyperpolarization, tyrosine phosphorylation, and elevation of aggrecan messenger ribonucleic acid induced by mechanical stimulation, and that this is mediated through interactions with α5β1 integrin.[84]

Although having important roles in maintaining cartilage in a healthy state it is widely accepted that mechanical forces, either abnormal loads acting upon healthy cartilage or normal loading of structurally abnormal cartilage, is involved in the pathophysiological processes that lead to osteoarthritis.[85] Injurious loading regimes in normal cartilage include static loading (inactivity of weight bearing joints) and high magnitude dynamic loading (high impact sports).

Chondrocytes from diseased cartilage show significant differences in cell phenotype, response to catabolic factors, and responses to mechanical stimuli. Loss of normal cartilage physiology means that the matrix is no longer able to protect the chondrocytes from mechanical loading. In an attempt to prevent tissue destruction, the chondrocytes try to produce new matrix to repair the damage. Osteoarthritis is a degenerative disease of cartilage, generally accepted to be secondary to the effects of mechanical forces on the joint. Articular cartilage is continually remodeled in response to both anabolic and catabolic stimuli, but during osteoarthritis inflammatory mediators are produced which alter normal cell signaling and lead to an increase in the production of catabolic molecules.[86] Similarly, chondrocytes derived from osteoarthritic cartilage show different cellular responses to mechanical stimulation in monolayer culture when compared to cells from normal joint.

Osteoarthritic chondrocytes show a depolarization response to 0.33 Hz stimulation in contrast to the hyperpolarization response of normal chondrocytes.[87] The mechanotransduction pathway in chondrocytes derived from normal and osteoarthritic cartilage both involve recognition of the mechanical stimulus by integrin receptors resulting in the activation of integrin signaling pathways leading to the generation of a cytokine loop.[88] Normal and osteoarthritic chondrocytes show differences at multiple stages of the mechanotransduction cascade (Figure 3). Early events are similar; α5β1 integrin and stretch activated ion channels are activated and result in rapid tyrosine phosphorylation events.[87] The actin cytoskeleton is required for the integrin-dependent mechanotransduction leading to changes in membrane potential in normal but not osteoarthritic chondrocytes.[87]

The composition of ECM is altered in osteoarthritis as a result of altered synthetic activity by chondrocytes and the production of proteases, which digest preexisting matrix molecules. Osteoarthritic cartilage is characterized by a decrease in proteoglycan content, disruption of the collagen II fiber network, increase in a variety of glycoproteins (including fibronectin, tenascin, and decorin), upregulation of collagen type VI expression, and altered integrin expression. In osteoarthritic chondrocytes there is additional expression of the integrin subunits α2, occasionally α4, and α3. In both normal and osteoarthritic chondrocytes, α1, α5, αV, β1, β4, and β5 subunits are present, with upregulated β1 integrin expression in chondrocytes from osteoarthritic cartilage.[78] These may result in changes in cell–matrix interactions that will influence how a chondrocyte perceives and responds to a mechanical load.

Integrin-ECM interactions in mechanotransduction are not limited to cartilage and connective tissue. There is evidence in many tissues for a role of integrins as mechanosensors and alterations in their expression and signaling can lead

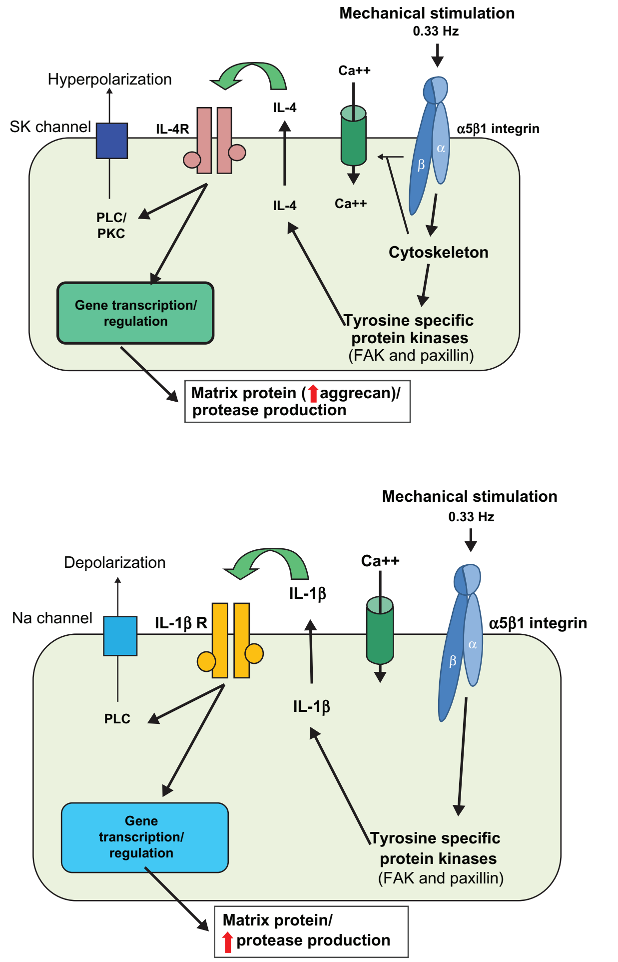

Figure 3 Mechanical signaling in normal chondrocytes (**A**) and in osteoarthritis (**B**). Mechanical stimulation is cyclical at 0.33 HZ. Activation of α5β1 integrin by mechanical loading/stimulation results in cell signaling via cytokine autocrine/paracrine loop, altered cell polarity, and initiates transcription of matrix proteins and proteases.

Abbreviations: Ca, calcium; FAK, focal adhesion kinase; IL, interleukin; Na, sodium; PLC/PKC, phospholipase C/protein kinase C; SK, small-conductance calcium-activated potassium.

to pathology. In cardiomyocytes, integrins are responsible for mechanotransduction. The main integrins expressed are α5β1 and αvβ3. Disruption or elimination of either β1 or β3 impedes pressure-induced hypertrophic signaling and leads to heart failure.[89] Other cardiovascular pathologies associated with altered integrin-mediated mechanics and loss of native contractility that can develop over time are hypertension and atherosclerosis.[90,91] Alteration in integrin sensitivity to mechanical loading/stimulation has been shown in cancer.[92,93] These altered integrin responses can facilitate metastasis and drive expression of the malignant phenotype.[94] Matrix stiffness and cytoskeletal stress are functionally linked through key signaling proteins during tumorigenesis which cooperate to drive focal adhesion assembly, contributing to a rigid tumor microenvironment.[95]

Conclusion

Cell–matrix interactions are essential for maintaining the integrity of tissues. An intact matrix is essential for cell survival and proliferation and to allow efficient mechanotransduction and tissue homeostasis. Cell–matrix interactions have been extensively studied in many tissues and this knowledge is being used to develop strategies to treat pathology. This is particularly important in tissues subject to abnormal mechanical loading, such as musculoskeletal tissues. Integrin-ECM interactions are being used to enhance tissue repair mechanisms in these tissues through differentiation of progenitor cells for in vitro and in vivo use. Knowledge of how signaling cascades are differentially regulated in response to physiological and pathological external stimuli (including ECM availability and mechanical loading/stimulation) will enable future strategies to be developed to prevent and treat the progression of pathology associated with integrin-ECM interactions.

Disclosure

The author reports no conflicts of interest in this work.

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