



Mechanistic Insight Into the Roles of Integrins in Osteoarthritis

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Osteoarthritis (OA), one of the most common degenerative diseases, is characterized by progressive degeneration of the articular cartilage and subchondral bone, as well as the synovium. Integrins, comprising a family of heterodimeric transmembrane proteins containing α subunit and β subunit, play essential roles in various physiological functions of cells, such as cell attachment, movement, growth, differentiation, and mechanical signal conduction. Previous studies have shown that integrin dysfunction is involved in OA pathogenesis. This review article focuses on the roles of integrins in OA, especially in OA cartilage, subchondral bone and the synovium. A clear understanding of these roles may influence the future development of treatments for OA.

Keywords: integrin, osteoarthritis, cartilage, subchondral bone, mechanical signal conduction, synovial membrane

INTRODUCTION

As the most common degenerative joint disease, OA can destroy both cartilage and subchondral bones, causing progressive degeneration of the articular cartilage and subchondral bone, as well as the synovium (Chen et al., 2017). The unique composition and structure of the cartilage extracellular matrix (ECM) allows for the long-term load-bearing capabilities of the joint, playing important roles in joint function. OA can affect the ECM, causing increased catabolic activity and inflammation changes in the mechanical function of the ECM in the joint (Guilak et al., 2018). There is evidence that metabolic changes in the ECM play an vital role in the pathological process of OA (Rahmati et al., 2017). As participants in an integral membrane complex, integrins play important roles in the transmembrane association, which are involved in the ECM and the cytoskeleton interactions and take part in transmembrane signals conduction. Previous studies have shown that integrin dysfunction is involved in OA pathogenesis. This review article focuses on the roles of integrins in OA, especially in OA cartilage, and subchondral bone, as well as the synovium. A clear understanding of these roles may influence the future development of treatments for OA.

WHAT ARE INTEGRINS?

Integrins, comprising a heterodimeric transmembrane protein family, contain two subunits (the α subunit and β subunit). There are eighteen α subunits and eight β subunits. All these can combine into twenty-four integrin molecules (Ansari and Byrareddy, 2016). The integrin molecules can act as transmembrane receptors to bind ECM proteins, which can regulate essential physiological

functions of cells, such as adhesion, migration, the inflammatory response, and mechanical signal conduction. Depending on the types of ligands, integrins can be divided into two categories: Arg-Gly-Asp (RGD)-binding receptors and non-RGD-binding receptors. Non-RGD binding receptors include collagen-binding receptors, laminin-binding receptors, and leukocyte-binding receptors (Margadant and Sonnenberg, 2010; Finney et al., 2017). As transmembrane molecules, integrins play important roles in the physiological function of cells. Integrins can mediate adhesion between cells and their surroundings. Integrin-based adhesion is formed mainly between the cytoskeleton and the ECM. For example, lamellipodia and filopodia, the bumps of the cell surface and cytoskeleton, can attach to the ECM through integrin-based adhesions (Geoghegan et al., 2019). By combining with intracellular proteins, like α -actinin, vinculin, and paxillin, integrins can connect the inner cytoskeleton to the ECM (Zaidel-Bar et al., 2004). Cell signaling mediated by integrins can regulate the functions of cells, including their matrix remodeling, adhesion, migration, and mechanical signal conduction (Loeser, 2002). In addition, integrins, working in concert with the cytoskeleton, can receive external mechanical stimulation and transmit information on the mechanical status of the ECM into the cell. As mechanical sensors, integrins play important roles in facilitating cell movement, generating tension on the ECM, activating intracellular signaling pathways, and producing biological reactions (Humphries et al., 2019; Sun et al., 2019).

More and more results showed that the dysregulated function of integrins was implicated in OA pathogenesis. Animal experiments showed that $\alpha 4$, $\alpha 5$, and $\alpha 2$ integrin expression was increased in cartilage and that the content of proteoglycan and fibronectin was also changed (Almonte-Becerril et al., 2014). High levels of $\alpha 1\beta 1$ and $\alpha 3\beta 1$ were detected in OA cartilage tissues, potentially facilitating the modulation of ECM deformation and promoting chondrocyte hypertrophy (Häusler et al., 2002). The components of the ECM play important roles in maintaining chondrocyte homeostasis. For example, the stiffness of collagen in cartilage is associated with the occurrence and development of OA, not only on the joint surface but also at the interface between cartilage and bone (Wen et al., 2012). Collagen type II (COLII) can suppress chondrocyte hypertrophy and deterioration of OA by promoting the interaction between $\beta 1$ integrin and drosophila mothers against decapentaplegic protein 1 (SMAD1) (Lian et al., 2019). Because of the crosstalk between the cartilage and subchondral bone, the subchondral bone of OA patients is also changed. Compared to controls, subchondral osteocytes showed a series of changes in cell morphology, such as rough cell surfaces, unorganized dendrites, and so on (Jaiprakash et al., 2012). Studies have also shown that culturing bone cells on the ECM of OA specimens leads to reduced expression of integrin $\beta 1$ and inactivation of the FAK cell signaling pathway (Prasad et al., 2013). The changes of $\alpha V\beta 3$ integrin level can vary with the degree of cartilage degeneration in patients with OA (Wang et al., 2018). Dysfunction of integrin $\alpha v\beta 3$ and integrin-associated protein (CD47) signaling pathways have been proved that can promote the occurrence and progression of OA

(Wang et al., 2019). We will discuss the role of integrins in OA in detail in the following text.

INTEGRINS IN ARTICULAR CARTILAGE AND CHONDROCYTE HOMEOSTASIS

Integrins in Chondrocytes Adhesion

Articular cartilage, composed mainly of water, collagen, proteoglycans, and cells, provides a smooth surface for joints and facilitates the transmission of loads (Ulrich-Vinther et al., 2003; Carballo et al., 2017). The articular cartilage lining the surface of the subchondral bone is multi-layered. The surface layer consists of collagen fibrils and chondrocytes, which parallels to the articular surface. In the deeper layer, the arrangement of collagen fibrils is more random and collagen fibrils are vertically inserted into the subchondral bone in the deepest layer (Silver et al., 2001). Chondrocytes, constituting the main cell group of adult articular cartilage cells, play important roles in maintaining the balance between the anabolism and catabolism of the ECM (Loeser, 2009; Kozhemyakina et al., 2015; Li et al., 2017; Liang et al., 2018; Kadry and Calderwood, 2020). Under normal physiological conditions, the ECM components are in a slow renewal state, which maintains homeostasis between chondrocyte catabolism and anabolism. Studies have confirmed that integrins, such as $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha V\beta 3$, $\alpha V\beta 5$, and so on, are expressed on chondrocytes (Loeser et al., 2000; Kurtis et al., 2003; Lahiji et al., 2004; Shattil et al., 2010). The interactions between chondrocytes and the ECM mediated by integrins are crucial for chondrocyte activity. ECM, as an “informative” environment, is made up of many molecules, including COLII, proteoglycans (PGs), hyaluronic acid (HA), and chondroitin sulfate (CS), etc., and the various components in the ECM are important for the structure and function of the ECM (Gao et al., 2014; Hansen, 2019). ECM changes in OA seem to be driven by the imbalance between anabolic and catabolic activities of chondrocytes, which are responsible for the occurrence and development of OA. The increase of catabolism in ECM was observed in OA pathology (Rahmati et al., 2017).

As a transmembrane molecule of chondrocytes, integrin plays an important role in cartilage homeostasis. Integrins act as a central regulator in multicellular biology, which can coordinate with multiple cellular functions. The integrins can mediate cell adhesion between chondrocytes and the ECM (Ginsberg, 2014; Dustin, 2019; Kadry and Calderwood, 2020). Integrins and their connections to the cytoskeleton play important roles in monitoring cell adhesion and the physical properties of the ECM (Romero et al., 2020). Cell adhesion can be achieved by binding the adhesion superstructures with integrins to the periphery of the non-collagenous fibril (Woltersdorf et al., 2017). Chondrocytes express several integrin protein families, like fibronectin ($\alpha 5\beta 1$), COLII and COLVI ($\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 10\beta 1$), laminin ($\alpha 6\beta 1$), osteopontin ($\alpha V\beta 3$), and so on (Loeser, 2000). Chondrocytes can be attached to various cartilage and bone proteins, which is mainly mediated by integrins, including members of the $\beta 1$ and $\beta 3$ subunit family. The regulation of chondrocyte adhesion is related to the activation or increase

of integrin expression (Loeser, 1993). Adhesions between cartilage oligomeric matrix protein (COMP) and chondrocytes occurs through α V β 3 integrin (Chen et al., 2005). α 10 β 1 integrin, expressed by normal adult chondrocytes, can bind COLII, and α 1 β 1 integrin can also bind COLII collagen but preferentially binds COLVI collagen (Camper et al., 1998; Loeser et al., 2000). Complex interactions between integrins and their extracellular ligands show that integrins play important roles in chondrocyte adhesion.

Integrins in Chondrocyte Mechanotransduction

Studies have shown that the mechanical stress environment of joints is an essential factor affecting or regulating chondrocyte activity *in vivo* (Loeser et al., 2000). Mechanical load plays an important role in the formation, differentiation, shaping, maturation and matrix synthesis of cartilage. Chondrocytes are exceedingly sensitive to mechanical changes in their surroundings. The stabilizing maintenance of articular cartilage can be regulated by stimulations, such as mechanical load, small soluble molecules in ECM and matrix components. Mechanical stimulation can be divided into dynamic compression, fluid shear, tissue shear, and hydrostatic stimulation (Sharifi and Gharravi, 2019). Integrins, as an important mechanical receptor, can affect the physiological function of chondrocytes by activating the mechanical signal pathway, a process known as mechanotransduction (Roca-Cusachs et al., 2012; Geoghegan et al., 2019).

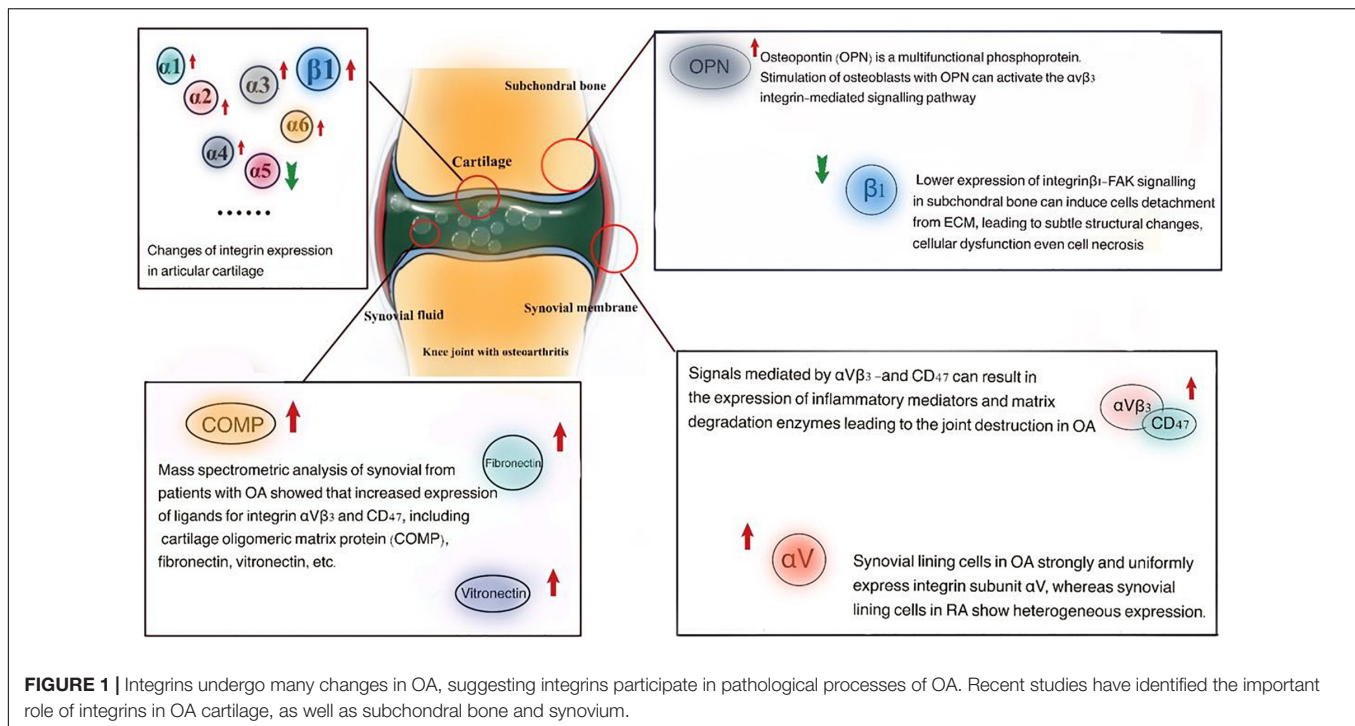
The integrin-mediated biochemical signals of extracellular mechanical stimuli are dependent on integrin-matrix interactions (Zhao Z. et al., 2020). Studies have shown that integrin α 1 β 1 is a crucial molecule for transducing mechanical load (Jablonski et al., 2014). The periodic mechanical load can significantly facilitate the fibronectin-integrin α 5 β 1 bond (Kong et al., 2013). Periodic mechanical load activates downstream protein kinase C (PKC) signals by stimulating chondrocytes α 5 β 1 integrin, which can cause hyperpolarization of chondrocyte membrane (Wright et al., 1997). Mechanical signal pathways mediated by integrins are involved in the proliferation and matrix synthesis of chondrocytes, such as integrin β 1- Src- GIT ArfGAP 1 (GIT1)- focal adhesion kinase (FAK) (Tyr576/577)- extracellular regulated protein kinase 1/2 (ERK1/2), integrin β 1-FAK(Tyr397)-ERK1/2, and integrin β 1- Ca²⁺/calmodulin dependent protein kinase II (CaMKII)- Proline-rich tyrosine kinase 2 (Pyk2)-ERK1/2 signal pathway (Liang et al., 2017; Ren et al., 2018). Studies suggested that the death signaling pathway mediated by integrins also participated in the process that excessive mechanical load acting on cartilage explants (Jang et al., 2014).

Integrins in Chondrocyte Transmembrane Signaling

In addition to being involved in mechanical signal transduction, integrin involvement in transmitting signals has attracted attention (Loeser, 2014; Prein and Beier, 2019). The cytoplasmic signaling within chondrocytes, called “inside-out signaling,”

can regulate the affinity of integrins for their ligands. The combination of the α subunit and β subunit cytoplasmic tails can maintain integrins in an inactive state. Signals from G-protein-coupled receptors can activate integrins, causing phosphorylation of the cytoplasmic domain of the β subunit, which can disrupt the combination of the α subunit and β subunit (Takada et al., 2007). Through “inside-out signaling,” the adhesion intensity and strength between integrins and the ECM can be regulated. Binding to specialized extracellular ligands, integrins can be activated by “outside-in signaling.” In this situation, integrins cluster on the surface of the cell and undergo conformational changes that activate cytoplasmic kinase and cytoskeletal signaling cascades. The cross-talking of signaling mechanism components in integrin-mediated “outside in” and “inside out” signaling pathways play a role in maintaining cartilage homeostasis (Attur et al., 2000). As a vital mediator of between chondrocytes and ECM in cartilage, integrins can regulate the response to signals emitted from the ECM, which play an important role in cell proliferation, survival, differentiation and matrix remodeling.

Studies have shown that integrin-mediated signaling pathways are involved in the gene expression of micro-molecules, like inflammatory mediators, chemokines, matrix metalloproteinases (MMPs), such as MMP-1, MMP-3, MMP-10, MMP-13, etc., (Werb et al., 1989). The α 5 β 1 integrin, an important cellular membrane receptor of chondrocytes, can be activated by proteins with RGD peptide, antibodies against α 5 β 1 integrin or fibronectin fragments (Fn-fs) in ECM. One reason for the imbalance between anabolism and catabolism of chondrocytes is that the combination of α 5 β 1 integrin with soluble Fn-fs. Fn-fs, generated by MMPs degrading fibronectin (Fn), have catabolic properties. The pro-catabolic response to matrix fragments may be particularly associated with the destruction of ECM. RGD-containing Fn-fs, when binds to α 5 β 1 integrin, was found to be the most active (Homandberg et al., 1993). PKC δ is the rate-limiting factor at the convergent points of signaling input from Fn-fs. PKC δ activation can cause the activation of nuclear factor kappa B (NF- κ B) in addition to MAP kinase (MAPK) (Lee et al., 2013). MAPK activation can lead to inhibition of anabolic signaling, suppression of PG production, and upregulation of catabolic proteases, like MMP-3, MMP-13, and so on. Many signaling pathways are interconnected, which can enhance cartilage destruction in OA. For example, MAP3-kinase TGF- β -activated kinase 1 (TAK1) can link MAPK signals to the activation of NF- κ B, which may play a role in OA pathogenesis (Cheng et al., 2016). The NF- κ B pathway, considered a typical proinflammatory signaling pathway, plays an important role in many inflammatory diseases (Lawrence, 2009). Both pathways work together to inhibit anabolic signaling and stimulate ECM degeneration (Figure 1). All these can stimulate chondrocytes to produce proinflammatory mediators, such as prostaglandin E2 (PGE2), reactive oxygen species (ROS), a disintegrin and metalloproteinase with thrombospondin motif (ADAMTS)-5, nitric oxide (NO), and MMPs (Arner and Tortorella, 1995; Homandberg, 1999; Forsyth et al., 2002; Gemba et al., 2002). The roles of integrins in pathological processes of OA will be discussed in detail in the following text.



CHANGES IN INTEGRIN EXPRESSION AND FUNCTIONAL BEHAVIOR IN OSTEOARTHRITIS

Cartilage surface defects are common changes in OA. Chondrocytes can be fixed to special positions by adhesion, which in turn can trigger the secretion of molecules that repair the defect and tissue. Eventually, chondrocytes adhere to the host tissue and become part of the cartilage. There are many important molecules involved in chondrocyte adhesion to the ECM, such as Annexins (mainly A5), CD44, and integrins. Studies found that there was an increased level of $\alpha 1\beta 1$, $\alpha 3\beta 1$, $\alpha 2\beta 1$, $\alpha 4\beta 1$, and $\alpha 6\beta 1$ in cartilage tissue of OA (Loeser et al., 1995; Lapadula et al., 1997; Ostergaard et al., 1998). These changes in integrins may be the result of feedback regulation from changes in the ECM. Growth factors and cytokines can stimulate integrin expression, which accounts for the change in integrins in OA (Loeser, 1997). Dysfunction of integrin $\alpha v\beta 3$ and CD47 signaling in chondrocytes has been confirmed to contribute to inflammation and joint destruction in OA (Wang et al., 2019).

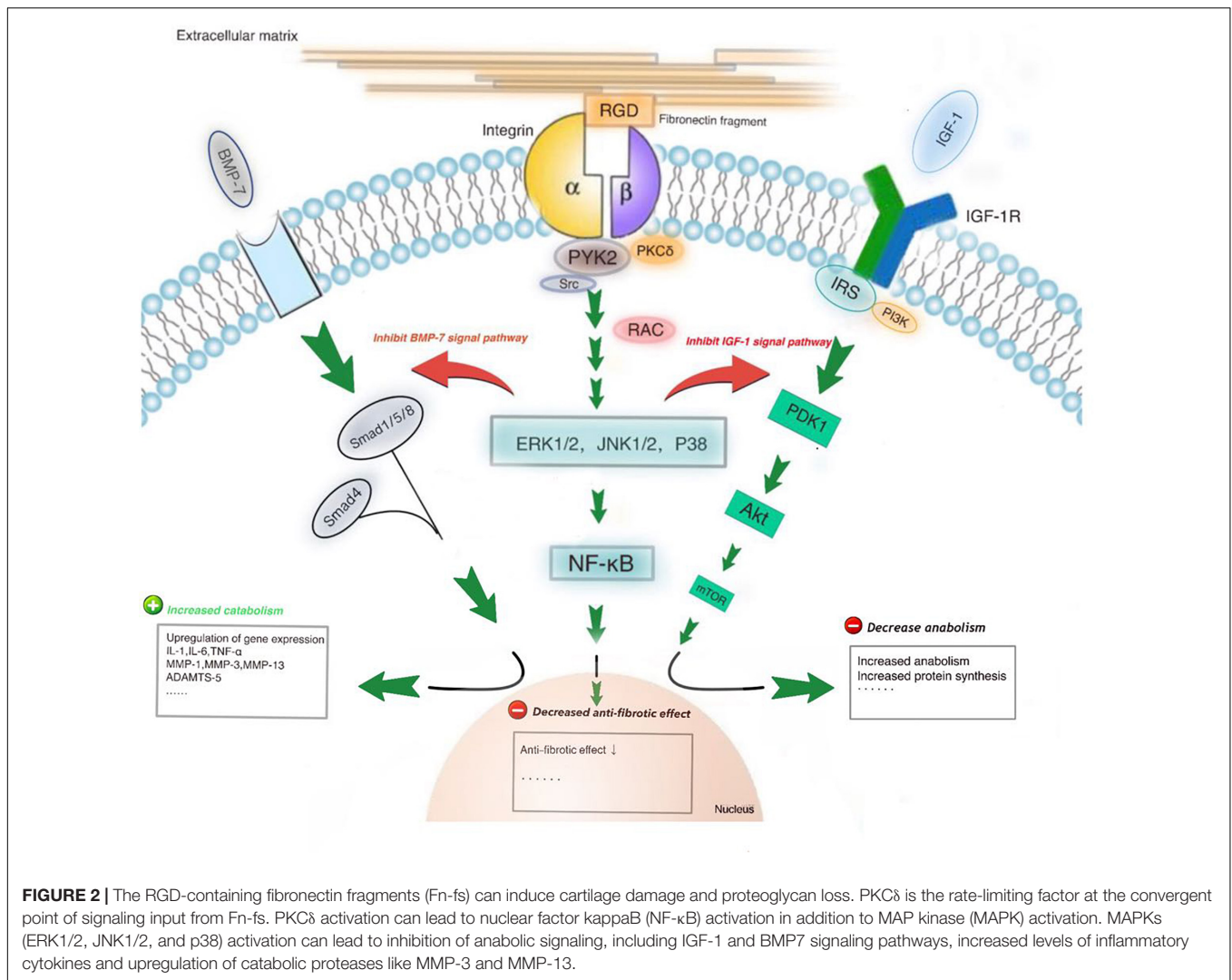
Integrin $\alpha 5$ is inferred to be a protective factor that inhibits hypertrophy, OA occurrence, and chondrocyte development. Evidence has shown that the expression of integrin $\alpha 5$ in chondrocytes was lower in an OA model of rats induced by surgery than in a normal group, suggesting that changes of ECM may lead to the imbalance of cartilage homeostasis and affects the repair ability of chondrocytes, finally deteriorating the pathological changes of OA (Castaño Betancourt et al., 2012; Bernhard et al., 2017). Lack of $\alpha 1$ integrin subunit was associated with early degradation of cartilage homeostasis and accelerated aging-dependent lesions. Compared with wild-type (WT) mice,

more severe degradation, glycosaminoglycan depletion, and higher expression of MMP-2 and MMP-3 in the cartilage of $\alpha 1$ -KO mice (Zemmyo et al., 2003). In addition, the increase of $\alpha 2$ and $\alpha 3$ subunits expression in cartilage tissue is related to the degree of fibrosis and a high expression of αv integrin was detected in hypertrophic chondrocytes of rats with OA. All these changes suggest that integrins play important roles in OA (Figure 2).

THE ROLES OF INTEGRINS IN OSTEOARTHRITIS

Integrins in Osteoarthritis Cartilage Changed ECM Components and Integrins

Changed ECM components in OA are a result of an imbalance of synthesis and catabolism, which can serve as initiating or progressive factors of OA (Guilak et al., 2018). Developmental and mature chondrocytes are constantly interacting with ECM and remodeling ECM. Various ECM components promote OA by stimulating receptors on chondrocytes membranes, such as endothelin-1 (ET-1), which induces chondrocyte senescence and cartilage damage by endothelin receptor B, so as integrins (Au et al., 2020). Integrin-mediated signaling pathways are key sources of the catabolic reactions critical for joint destruction in OA. Developmental chondrocytes can express a special molecule called integrin- β -like 1 (Itgbl1) at specific stages, which can inhibit integrin-mediated signal pathways and promote cartilage generation. However, the expression of Itgbl1 was decreased significantly in the chondrocytes of OA (Song et al., 2018). A rat model experiment suggested that Indian hedgehog



(Ihh) expression during the late stages of OA can inhibit the endochondral ossification induced by bone morphogenetic protein 7 (BMP-7) and α V integrin (Garcidiego-Cázares et al., 2015). During the procession of OA, ECM-degrading enzymes, such as urokinase-type plasminogen activator (uPA), ADAMTSs, and MMPs, can degrade components of the ECM (Pérez-García et al., 2019). Angiopoietin-like protein 2 (ANGPTL2) secreted by chondrocytes can induce the production of inflammatory factors through the integrin α 5 β 1/MAPKs, Akt, and NF- κ B signaling pathways (Takano et al., 2019). Another study found that the stimulation of the α V β 3 and α V β 5 integrins of chondrocytes can upregulate the gene expression of Interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), MMP-3, and MMP-13 (Hirose et al., 2020). Animal experiments have shown that ofloxacin can interfere with the β 1 integrin/ERK/MAPK signal pathway and thus induces apoptosis in young rabbit articular chondrocytes (Sheng et al., 2008). CD147, also called ECM metalloproteinase inducer (EMMPRIN), is a highly glycosylated transmembrane glycoprotein, which can interact with β 1 integrin (α 3 β 1 and α 6 β 1) in the

membrane of chondrocytes (Orazizadeh and Salter, 2008). Previous studies suggested that collagen type X (COLX) can interact with chondrocytes directly through major integrin α 2 β 1 (Leitinger and Kwan, 2006).

Excessive Mechanical Load and Integrins

The mechanical load can affect the cartilage matrix. Chondrocytes are constantly subjected to external mechanical load, thereby regulating remodeling. The optimal level of mechanical load is essential to maintain the dynamic balance of chondrocyte homeostasis (Vazquez et al., 2019). The mechanical load acting on joints can directly affect the production of matrix degradation enzymes and further affect cartilage homeostasis (Aigner et al., 2006; Goldring and Goldring, 2007). The moderate mechanical load can lead to hypertrophy. The excessive mechanical load can lead to collagen network damage, resulting in irreversible cartilage destruction (Jørgensen et al., 2017). Moreover, excessive mechanical load of cartilage also can cause cartilage tissue damage through necrosis (Arokoski et al., 2000). MAPKs, as central regulators of cell signaling

pathways, play important roles in cell physiological functions, which are considered potential targets for the treatment of OA (Loeser et al., 2008). MAPKs can mediate cell signaling pathways induced by the mechanical stimulation of integrins and then regulate chondrocyte gene expression and proliferation in response to the mechanical load acting on joints (Roca-Cusachs et al., 2012). After the stimulation of integrins by mechanical load, a signaling cascade is activated (Lee et al., 2000).

The homeostasis of articular cartilage depends partly on the mechanical load generated in daily activities. Appropriate joint load stimulates chondrocytes to maintain healthy cartilage by producing specific protein components. Conversely, excessive mechanical load alters cartilage composition and causes focal degeneration of cartilage, leading to disease (Smith et al., 2004; Monfort et al., 2006). Excessive mechanical load acting as signals from the ECM can activate integrins, which further promotes the progressive destruction of the cartilage matrix in OA (Fang et al., 2021). Under excessive mechanical load, integrins can regulate the responses of chondrocytes to mechanical stimulation through multiple pathways. Studies have shown that integrins can interact with the MAPK-ERK pathway. Articular chondrocytes respond to $\alpha 5 \beta 1$ integrin, acting as a mechanoreceptor. Animal experiments showed that mechanical load led to an increase in the number of $\alpha 5$ subunit in both immature cartilage and mature cartilage, but the number of $\beta 1$ subunit was not increased (Lucchinetti et al., 2004). Integrin-associated protein (CD47/IAP) can interact with $\alpha 5 \beta 1$ integrin to modulate chondrocyte responses to mechanical signals (Orazizadeh et al., 2008). The downstream signaling cascades and cell responses are different in OA chondrocytes. Excessive mechanical signals can regulate key molecules in MAPK signal cascades to maintain their efficacy in proinflammatory environments. For example, mechanical signals can affect gene expression and chondrocyte proliferation during proinflammatory environments through integrin-linked kinase and signal pathways (Perera et al., 2010). All these factors can progressively destroy the cartilage matrix in OA. Cellular communication network factor 2 (CCN2), a cysteine-rich secreted matricellular protein, is highly expressed and secreted into the ECM under mechanical load, regulating cell physiological functions. Integrins, the first receptor to perceive mechanical load on the cell membrane of chondrocytes, can enhance the gene expression of CCN2. CCN2 expression is increased when exposed to excessive mechanical stress, that further triggers cartilage fibrosis through the activation of integrin-mediated signal pathways (Huang et al., 2021). There were significant differences in signal events and cell responses when mechanical load acts on normal and OA chondrocytes (Millward-Sadler and Salter, 2004). Under excessive mechanical stress, integrins can respond to inflammatory activation in chondrocytes. High levels of $\alpha 1 \beta 1$ and $\alpha 3 \beta 1$ were observed in the cartilage tissues of OA patients, which may potentially contribute to ECM deformation and chondrocyte hypertrophy (Zhao Y. et al., 2020).

Cytokine Signals and Integrins

As the most common disease in the elderly, OA can damage the ECM of cartilage, leading to pain and dysfunction of

joints. There are many factors that can cause OA, including mechanical injury, cytokines, superoxide release, adipokines, etc., (Sofat, 2009; Zhang et al., 2018). The role of cytokines in OA has gradually drawn people's attention (Sofat, 2009). Integrins as key receptors on the cell surface can interact with cytokines secreted into the ECM, that may participate in the pathogenesis of OA. The gene expression of integrins can be regulated by cytokines like insulin-like growth factors-1 (IGF-1) and transforming growth factor-beta (TGF- β) (Loeser, 2000). Integrins can change their expression patterns under pathological conditions and promote the deterioration of OA by releasing active TGF- β and regulating various signals downstream of the integrins (Zhang et al., 2020). A high level of TGF- β can disrupt cartilage homeostasis and impair the metabolic activity of chondrocytes. Animal studies have shown that knockdown of αV integrin gene in mouse chondrocytes can reverse TGF- β activation and subsequent abnormalities in articular cartilage metabolism (Zhen et al., 2021). Cytokines in ECM are considered to have a variety of effects on cartilage. We listed some of the cytokines associated with integrins in this section. The chemokine CX3CL1 can induce chemotaxis of monocytes, neutrophils, and fibroblasts. CX3CL1 acts through its receptor CX3CR1. By stimulating CX3CR1, CX3CL1 can activate integrin-dependent migration of chondrocytes, which is evident in many articular cartilage diseases (Poniatowski et al., 2017). Angiopoietin-like 2 (ANGPTL2) secreted by chondrocytes can stimulate the integrin $\alpha 5 \beta 1$ /MAPKs, Akt, and NF- κB signaling pathways leading to ECM degradation and inflammatory response, which plays a negative role in the pathogenesis of OA (Shan et al., 2019). In addition, both growth differentiation factor 5 (GDF-5) and BMP-7 in chondrocyte could regulate the expression of integrins, that may participate in normal physiological function and OA progression (Garciaadiego-Cázares et al., 2015).

Integrins in Healthy and Osteoarthritic Subchondral Bone

Like the bones in other parts of our bodies, subchondral bone osteocytes are the main mechanical sensitive cells in bone. Increasing evidence showed that integrin-based adhesion could promote mechanical transduction and play an important role in forming subchondral bone (Geoghegan et al., 2019). During the formation of subchondral bone, Osteoblasts and osteocytes express $\beta 1$ subunit, that can combine with $\alpha 1$, $\alpha 2$, $\alpha 3$, $\alpha 4$, and $\alpha 5$ subunits. $\beta 3$ subunit connects with αv subunit in osteoblasts and osteocytes (Horton et al., 1991; Engleman et al., 1997; Geoghegan et al., 2019). All these integrin molecules are involved in cell-matrix adhesion and facilitate mechanical conduction. Integrin-mediated signaling pathways and their cross-talking with Wnt/ β -catenin signaling pathways are involved in osteoblast mechanical transduction (Marie et al., 2014). Mechanical load acting on joints can regulate the metabolism of healthy subchondral bone osteoclasts and cause gene expression of interleukin-6 (IL-6), interleukin-8 (IL-8), MMP-3, MMP-9, MMP-13, etc., (Sanchez et al., 2012). The structure of subchondral bone can determine the mode of mechanical load acting on cartilage and the mode of TGF- β

activation, which can regulate the metabolism of chondrocyte and cartilage homeostasis. Mechanical stress can trigger TGF- β activation through α V integrin-mediated signaling pathways. A high level of TGF- β activation has been detected in areas with high mechanical load in cartilage (Zhen et al., 2021).

In addition to degenerative changes in articular cartilage, OA also causes the destruction of subchondral bone. The role of subchondral bone in OA has been gradually recognized (Goldring and Goldring, 2010). The causes of the subchondral bone of OA, specially in non-load-bearing areas, include synovial fluid inflow, mechanical contusion, vascular lesion, etc., (Chan et al., 2017). Abnormal subchondral bone remodeling plays an important role in the pathological changes of OA. Osteocyte morphology was found to be altered in the subchondral bone of OA patients, the cell body became round and roughened by the degeneration of typical dendrites and the appearance of unorganized dendrites (Jaiprakash et al., 2012). OA can cause the destruction of subchondral bone, osteoblast dysfunction of subchondral bone at the cell level; and cystic lesions, sclerosis, and osteophytes at the tissue level (Weber et al., 2019). Risk factors for OA include aging, obesity, abnormal joint mechanical load, and joint sprain, which interact in a complex way (Palazzo et al., 2016). In particular, the excessive mechanical load of joints triggered a series of cell changes, including cartilage damage and subchondral bone adaptation changes (Adebayo et al., 2017). The imbalance between cartilage and subchondral bone destroys the normal physiological relationship between both tissues and further leads to the deterioration of OA. This section of this article focuses on integrins in the subchondral bone of OA.

Pathological changes of subchondral bone were found in OA, including microstructural damage, bone marrow edema-like injury, and bone-cyst formation (Li et al., 2013). Excessive mechanical load applied upon articulation may be critical for these changes. The sclerosis of the subchondral bone is widely regarded as one of the features of OA. Osteoblasts isolated from sclerotic areas of subchondral bone were found to express levels of α 5, α v, β 1, and β 3 integrins and CD44, which is similar to the levels in non-sclerotic osteoblasts under basal conditions (Sanchez et al., 2012). Subchondral bone is hypo-mineralized due to abnormal bone remodeling. Osteopontin (OPN), a multifunctional phosphoprotein, was found that highly expressed in OA tissues. Stimulation of osteoblasts with OPN can activate the α v β 3 integrin-mediated signaling pathway (Su et al., 2015). Culture of osteocytes on defective ECM tissue produced by OA subchondral bone osteoblasts caused a decreased gene expression of integrin β 1 and deactivation of the FAK signaling pathway. Many proteins containing the three amino acid sequence RGD in the ECM can be recognized by corresponding integrin β 1 receptors (Schaffner and Dard, 2003; Marini et al., 2017). The combination of integrins with these macromolecules can activate a series of downstream signals and initiate a cascade of phosphorylation events, which are essential for the function of subchondral bone cells, such as cell adhesion and proper cytoskeletal organization (Legate et al., 2009; Michael and Parsons, 2020). Lower expression of integrin β 1-FAK signaling in the subchondral bone can induce cell detachment from ECM, leading to subtle structural changes, cellular dysfunction even cell necrosis (Prasad et al., 2013).

Integrins in Osteoarthritic Synovium

The synovium can secrete synovial fluid to joint space, which contributes to the functional properties of articular surfaces and modulation of the state of chondrocytes. For example, hyaluronic acid (HA) secreted by synovial lining cells contribute to the integrity of the cartilage surface and reduce friction at cartilage surface (Hui et al., 2012). Synovitis in OA is characterized by increased angiogenesis and hypoxia (Liu et al., 2019). Fibroblasts and macrophages in the synovial lining are important sources of inflammatory mediators, such as IL-1, IL-6, TNF, etc., The destruction of cartilage can induce the inflammation of the synovium, causing the production of cytokines. The concentrations of cartilage-protecting factors in the synovial membrane decrease, and harmful factors are constantly generated (Scanzello and Goldring, 2012; Hügler and Geurts, 2017; Michael and Parsons, 2020). All these alterations can deteriorate OA by the degradation of the ECM and apoptosis of chondrocytes.

In synovium tissue, the gene expression of integrins depends on the specific cell location and cell type. Most gene expressions of integrins are similar in synovium tissue but differ in the synovial lining, where the fibroblasts and macrophages degrade ECM and invade the cartilage. α 6 β 1 integrin is expressed only by fibroblasts, while macrophages not. The expression levels of α 5, α v, and β 1 integrin in the synovium lining increased compared to the sub-lining areas (Pirilä et al., 2001; Lowin et al., 2009; Lowin and Straub, 2011). Synovial cells are involved in the protection and maintenance of the stability of joints. Studies on rabbit synovial fibroblasts showed that cooperative signaling mediated by α 5 β 1 and α 4 β 1 integrins plays a dominant role in regulating MMP expression signaling in response to FN. MMP expression can remove the damaged matrix, which is the first step in repairing the damaged matrix. The cross-talking of integrins makes it possible for synovial fibroblasts to identify whether the matrix is intact or damaged. The volume of synovial fluids is increased in the OA articular cavity. Synovial fluids obtained from OA tissue showed increased expression of ligands for integrin α v β 3 and CD47, including COMP, fibronectin, and vitronectin. Increased ligand binding affinity of α v β 3 and CD47 was found in the synovium of the OA rat model. Signals mediated by α v β 3 and CD47 can result in the expression of inflammatory mediators and matrix degradation enzymes, leading to joint destruction in OA (Wang et al., 2019). Integrin α v β 3 and α 5 β 1 are involved in synovial cell proliferation, differentiation, and migration. Both are overexpressed in damaged synovial cells, acting as inflammatory and angiogenic factors in the progression of rheumatoid arthritis (RA). Their roles in the OA synovial membrane need further study (Morshed et al., 2019). There is evidence that the synovial lining cells in OA strongly and uniformly express integrin subunit α v, whereas synovial lining cells in RA show heterogeneous expression. Both RA and OA cells fail to express the integrin subunit β 3. These results show different manifestations of the α v and β 3 integrin subunits in cytokine-stimulated fibroblast-like cells from the synovium of OA and RA *in vitro* (Rinaldi et al., 1997). All these results showed that integrins are not only play a significant role in synovial joint development, but also involved in the pathological changes of OA.

TABLE 1 | Recent experiments on treating OA by interfering with integrin-mediated signaling pathways.

Interventions	Interfered integrin-mediated signaling pathway	Results	References
Integrin- β -like 1 (Itgbl1)	Interact with integrins to down-regulate activity.	In patients with osteoarthritis (OA), the expression of Itgbl1 is greatly reduced. The ectopic expression of Itgbl1 can protect articular cartilage from the development of OA.	Song et al. (2018)
locus-1 (Del1)	Integrin α ν β $_3$ -ERK/AKT signaling pathway.	DEL1 protected chondrocytes from apoptosis induced by various activators through integrin α ν β $_3$ -mediated signal pathways.	Wang et al. (2018)
Mechanical exposure and diacerein treatment	Integrin-FAK/STAT3-MAPKs signaling pathway.	In OA chondrocytes a significant reduction in the expression of Piezo1 was detected following treatment with diacerein, even in the presence of mechanical stimulation.	Lohberger et al. (2019)
Collagen type II (COL2A1)	Promote the interactions between integrin β 1 and SMAD1.	COL2A1 can inhibit BMP-SMAD1-mediated chondrocyte hypertrophy.	Lian et al. (2019)
Cilengitide	Inhibit integrin α ν β $_3$ / α ν β $_5$ -FAK-MAPK signaling pathway.	Cilengitide can suppress inflammation in chondrocytes under excessive mechanical stress by interfering integrin-mediated signaling pathway	Hirose et al. (2020)
Cationic solid lipid nanoparticles loaded by integrin β 1 plasmid DNA	Enforce the expression of integrin β 1.	SLNs-pDNA treatment can reduce the apoptosis of rat chondrocytes and enhance tissue repair, which can be used as a potential non-drug in the treatment of OA.	Zhao Z. et al. (2020)
Exogenic TGF- β 1 and WISP1 protein	Interact with Integrin α 5 or Integrin α ν .	TGF- β 1 and WISP1 interact to induce CHs dedifferentiation, which was mainly mediated by integrin α ν . However, Integrin α ν showed a protective effect.	Zhang et al. (2020)
Vitronectin (VTN) fragment	Interact with α ν β $_6$ in human fibroblast-like synoviocytes.	VTN could prevent TGF- β 1 activation by interacting with α ν β $_6$ in human FLSs and increase the level of α -SMA.	Ciregia et al. (2021)
Angiopoietin-like proteins (ANGPTLs)	Integrin α 5 β 1- ERK/p38/JNK-NF- κ B signaling pathway.	ANGPTL2 enhanced the gene expression of inflammatory mediators, while pretreatment with anti-LILRB2 antibody for 12 h reduced the inflammatory response.	Nishiyama et al. (2021)

PROSPECTS FOR INTEGRIN RESEARCH IN THE TREATMENT OF OSTEOARTHRITIS

Osteoarthritis, with a high incidence in the elderly population, brings tremendous economic burdens to individuals and society. Pain and joint dysfunction are the main causes of decreased quality of life in patients with OA. Current clinical trials mainly include repairing defects of cartilage and bone, intra-articular injections of drugs, physical exercise, etc. However, all the therapies has been proven that don't significantly have improvement in disease progression and successfully prevent arthroplasty surgery (Grässel and Muschter, 2020). People are constantly looking for new ways of treating OA. Integrins, as important receptors on the cell surface, play important roles in OA, which may provide new targets for the therapies of OA. In this section, we discuss the application prospects for integrin research in the field of OA treatment.

Interfering with the integrin-mediated signaling pathway provides a novel therapeutic approach for OA. For example, osteopontin (OPN) can interact with the integrin α ν β $_3$ receptor, which participates in maintaining the homeostasis of articular cartilage. High expression of OPN was detected in cartilage and synovial fluid, which may be involved in the progression of OA. Recently, researchers have attempted to use this protein as a diagnostic marker of OA or a targeted drug against

OA (Cheng C. et al., 2014). Low-intensity pulsed ultrasound (LIPUS) can interfere with integrin - FAK-phosphatidylinositide 3-kinases(PI3K)/protein kinase B (Akt) mechanochemical transduction pathways and alter chondrocyte-induced ECM production. The effect of LIPUS on articular cartilage can be used as a new treatment for OA (Cheng K. et al., 2014). Mesenchymal stem cells (MSCs) with high expression of the α 10 subunit have been proven to improve chondrogenic potential. Research showed that intra-articular injections of MSCs with high integrin α 10 expression after joint damage may protect against posttraumatic OA (Delco et al., 2020). Another study showed that mechanical exposure at moderate intensity combined with diacerein treatment could modulate integrin-FAK-MAPK mechanotransduction in human osteoarthritis chondrocytes (Lohberger et al., 2019). In addition to the treatments mentioned above, we have summarized the results of recent experiments on the treatment of OA based on interference of integrin-mediated signaling pathways in the following table (Table 1).

CONCLUSION

As transmembrane molecules on the cell surface, integrins play important roles in cartilage homeostasis, including cell survival, cell differentiation, matrix remodeling, and responses to mechanical stimulation. Integrins undergo many changes in OA, which may suggest that integrins are involved in the pathological

procession of OA. Recent studies have proved that the important roles of integrins in OA cartilage, subchondral bone, and synovium. Integrin-mediated signaling pathways are key sources of the catabolic reactions critical for ECM destruction. Excessive mechanical loading can cause the destruction of the cartilage matrix, and abnormal mechanical signals from the ECM mediated by integrins work together to promote progressive destruction of the cartilage matrix in OA. Interactions between cytokines and integrins also contribute to the progression of OA. Changes in integrins also contribute to pathological changes in the subchondral bone and synovium. Integrin shows good application prospects for the treatment of OA. Interfering with integrin-mediated signaling pathways is a novel therapeutic approach to OA.

AUTHOR CONTRIBUTIONS

HJ, SJ, and RW conceptualized this review, decided on the content, wrote the manuscript, and prepared the figures. YL, JD, and YZ revised the manuscript. All authors approved the final

version of the manuscript and agreed to be accountable for all aspects of the work.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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