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Roles and Regulatory Mechanisms of Integrins in Osteogenic Differentiation of Mesenchymal Stem Cells

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Abstract: *Bone defect repair remains a core research focus and tough challenge in regenerative medicine, and the osteogenic differentiation of mesenchymal stem cells (MSCs) is a crucial prerequisite for successful bone regeneration. As transmembrane cell adhesion molecules, integrins mediate interaction between MSCs and the extracellular matrix (ECM) via bidirectional signal transduction and play a central regulatory position during osteogenic differentiation. This review systematically summarizes the structural features, biological functions and subtype expression patterns of integrins. We further elaborate the underlying mechanisms by which integrins modulate MSC osteogenic differentiation through three core signaling cascades, including FAK/PI3K-Akt pathway, Wnt/β-catenin pathway and mechanochemical signal transduction. Meanwhile, this paper clarifies the upstream regulatory roles of integrins in ECM microenvironment perception, biomaterial interface response and epigenetic modification, as well as downstream effector processes involving RUNX2/OSX transcriptional cascade activation, cytoskeleton rearrangement and expression of matrix mineralization-related genes. Current controversies regarding the functional specificity and redundancy of different integrin subtypes are also discussed, and prospective applications of integrins in the development of intelligent biomaterials and precise regulation of bone tissue engineering are highlighted. In conclusion, this review comprehensively expounds the regulatory mechanisms of integrins, aiming to provide novel theoretical references and promising therapeutic strategies for bone defect regeneration and repair.*

Keywords: *Integrin, Mesenchymal stem cells, Osteogenic differentiation, Signaling pathway, Bone tissue engineering*

1. Introduction

Bone defect repair has long been a core focus and challenging issue in regenerative medicine. Autologous bone grafting, allogeneic bone transplantation and artificial bone substitute materials have achieved favorable outcomes in repairing small-scale bone defects [1, 2]. Nevertheless, the repair of large bone defects still faces enormous clinical obstacles, mainly restricted by insufficient tissue sources, secondary donor site trauma and unsatisfactory degradation characteristics of bone substitutes [3]. As an emerging therapeutic strategy, bone tissue engineering, which consists of seed cells, biological scaffolds and signaling molecules, provides a promising avenue for bone regeneration and reconstruction [4].

Mesenchymal stem cells (MSCs) possess potent multi-lineage differentiation potential and are regarded as ideal seed cells, whose osteogenic differentiation capacity is the core determinant of bone defect repair efficacy [5]. Under physiological conditions, MSCs derived from various tissues respond to microenvironmental cues and differentiate into osteoblasts, participating in bone matrix synthesis and mineralization processes [6, 7]. In pathological states, dysfunction of MSCs is closely correlated with the occurrence and progression of multiple skeletal disorders [8-10].

Integrins are glycosylated heterodimeric transmembrane cell adhesion molecules widely distributed on the cell membrane, which mediate cell-extracellular matrix (ECM) and cell-cell interactions.

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Serving as pivotal signaling mediators, integrins exert indispensable regulatory effects in bone tissue engineering [11, 12]. Via extracellular domains, integrins specifically recognize ECM components to facilitate MSC adhesion and spreading, thereby establishing physical anchoring sites for osteogenic differentiation [13]. Meanwhile, their intracellular domains bind to downstream regulatory proteins and initiate multiple signaling cascades, further modulating a series of biological behaviors including cell metabolism, survival, immune surveillance, proliferation and differentiation.

At present, the molecular mechanisms governing MSC osteogenic differentiation remain incompletely elucidated, and the inability to recapitulate optimal osteogenic microenvironments severely hinders the clinical translation of bone tissue engineering. Clarifying the precise molecular regulatory networks underlying MSC osteogenesis will greatly promote the advancement of bone tissue engineering and facilitate the development of novel therapeutic strategies for bone regenerative repair. This review systematically summarizes the research progress regarding the regulatory roles and molecular mechanisms of integrins during MSC osteogenic differentiation.

2. Structural Characteristics and Biological Functions of Integrins

Integrins are heterodimeric type I transmembrane proteins composed of α and β subunits, each containing an extracellular domain, a single-pass transmembrane domain and an intracellular cytoplasmic domain. To date, 18 α subunits and 8 β subunits have been identified in the integrin superfamily, which can assemble into more than 24 distinct integrin subtypes via diverse combinations.

Notably, integrins exhibit unique bidirectional signaling activity and dynamically switch between active and inactive conformations. Under physiological circumstances, integrins predominantly exist in an inactive state on the cell surface. Upon receiving intracellular activating signals, cytoplasmic regulatory proteins bind to the intracellular segments of α and β subunits, triggering inside-out signaling and converting integrins into active conformations. Subsequently, activated integrins recognize and bind to ECM ligands through extracellular domains, inducing further conformational changes and integrin clustering on the plasma membrane. Clustered membrane integrins further recruit intracellular adaptor proteins to initiate downstream signaling events.

2.1. ECM Ligand Recognition Specificity Mediated by Extracellular Domains

The α subunit primarily determines the ligand-binding specificity of integrins. Integrin subtypes containing extracellular α I domains can specifically recognize the GFOGER sequence of type I, II and IX collagens, mediate cell-collagen adhesion, and modulate MSC differentiation and bone regeneration. In contrast, integrins lacking α I domains identify the RGD sequence of fibronectin, vitronectin and TGF-β through the junction region between the β-propeller domain of α subunits and β I domain of β subunits, thereby regulating cell proliferation, migration, mechanical sensing and signaling pathway activation [14]. Distinct integrin subtypes recognize specific ECM ligands and activate divergent downstream signaling cascades, ultimately directing the lineage commitment and differentiation fate of MSCs [14-16].

2.2. Intracellular Domains: Structural Basis for Signal Transduction

The intracellular domains of integrins connect cytoskeletal proteins and signaling adaptors, constructing the structural framework for mechanotransduction. Cytoplasmic tails of integrins interact with multiple downstream effectors such as talin and focal adhesion kinase (FAK) to form mechanotransduction complexes [16, 17]. Following ECM ligand binding, intracellular integrin domains undergo conformational rearrangement, which triggers FAK phosphorylation and subsequent downstream signaling cascades, converting extracellular mechanical stimuli into biochemical signals that regulate osteogenic differentiation [11, 16, 17]. In addition, intracellular integrin domains interact with cytoskeleton remodeling-related molecules to modulate cell morphology and polarity, thus participating in the spatial regulation of MSC osteogenic differentiation [16, 17].

2.3. Expression Profiles of Integrin Subtypes in MSCs

The expression patterns of integrin subtypes display dynamic alterations during MSC osteogenic differentiation. Accumulating evidence has demonstrated that the expression level of integrin α2 is markedly downregulated, while integrin α3 and αV are significantly upregulated along with increased

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osteogenic marker expression during osteogenic induction of human bone marrow-derived MSCs [18]. Similar expression trends of α3 and αV have also been verified in human periodontal ligament stem cells and dental pulp stem cells. Furthermore, flow cytometric sorting results confirm that MSCs with high integrin αV expression possess superior osteogenic potential [18]. Dynamic changes in integrin expression signatures are also observed in human umbilical cord Wharton's jelly-derived MSCs during osteogenic commitment [19].

3. Core Signaling Networks Regulated by Integrins

As essential transmembrane receptors, integrins precisely govern MSC osteogenic differentiation via activating multiple downstream signaling networks, among which three pivotal pathways are well-established.

3.1. FAK/PI3K/Akt Signaling Pathway

The binding of intracellular integrin domains to FAK induces FAK autophosphorylation and further triggers the activation of the PI3K/Akt signaling cascade. In osteogenically induced human MSCs, the expression levels of integrin α5 and β1 are positively correlated with those of FAK and phosphorylated Akt (p-Akt), which markedly upregulate the expression of osteogenic genes including bone gamma-carboxyglutamate protein (BGLAP) and runt-related transcription factor 2 (RUNX2), and accelerate extracellular matrix calcium deposition [20]. Topographical cues specifically activate the PI3K/Akt signaling axis via integrin α2, and knockout of integrin α2 abolishes material surface topography-mediated differential expression of osteogenic genes [21]. Multiple integrin subtypes exert osteogenic regulatory effects through this core pathway. Mechanistically, integrin α6 interacts with pluripotency factors OCT4 and SOX2 to form a positive feedback regulatory loop, sustaining persistent PI3K/Akt activation and maintaining the osteogenic differentiation potential of MSCs. Blockade of integrin activity or pharmacological inhibition of the PI3K/Akt pathway significantly impairs MSC osteogenic capacity, confirming that the FAK/PI3K/Akt axis serves as the core signaling cascade mediating integrin-regulated osteogenesis [22].

3.2. Wnt/β-catenin Signaling Pathway

The canonical Wnt/β-catenin pathway facilitates cytoplasmic accumulation and nuclear translocation of β-catenin, which further modulates target gene transcription and diverse cellular biological responses. As critical mechanical sensors, integrins mediate mechanical stimulation-induced activation of the Wnt/β-catenin pathway. Micro-nano structured titanium surfaces significantly upregulate the mRNA levels of integrin β1, β3 and β6, transduce mechanical signals to activate canonical Wnt ligands including Wnt1 and Wnt3a, and inhibit GSK-3β activity, thereby promoting β-catenin nuclear translocation and facilitating MSC osteogenic differentiation [23]. The activation of Wnt signaling is synergistically modulated by multiple upstream molecules. For instance, ligand-activated integrin α5β1 initiates Wnt/β-catenin signaling via the PI3K/Akt pathway, which promotes MSC osteogenesis independent of cell adhesion and ameliorates abnormal bone microstructure in aged osteoporotic mice [24]. Collectively, these findings indicate that the Wnt/β-catenin pathway acts as a central hub linking integrin activity to MSC osteogenic differentiation.

3.3. Mechanochemical Signal Transduction

Integrins function as molecular switches that convert extracellular mechanical cues into intracellular biochemical signals. Mechanical stimulation dramatically elevates the expression of integrin β1 and downstream integrin-linked kinase (ILK), accompanied by enhanced alkaline phosphatase (ALP) activity and upregulated RUNX2 expression in bone marrow mesenchymal stem cells [25]. Cyclic tensile stress activates integrin αVβ3 in MSCs, recruits FAK and ILK to assemble focal adhesion complexes, induces actin cytoskeleton rearrangement, promotes YAP nuclear translocation, and initiates the transcription of osteogenic genes to accelerate early-stage osteogenic differentiation [26]. As key cytoskeleton modulators, Rho GTPases are regulated by integrins to strengthen mechanotransduction and participate in osteogenic progression [17, 23]. Integrin-mediated dynamic assembly of focal adhesions relies on FAK and ILK adaptor proteins to coordinate cytoskeleton remodeling and osteogenic gene expression, forming a complete mechanochemical signal transduction system [17, 25, 26].

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4. Upstream Regulatory Mechanisms Mediated by Integrins

MSC osteogenic differentiation is precisely modulated by multi-layered upstream regulatory mechanisms, including ECM microenvironment sensing, biomaterial interface response and epigenetic modification, in which integrins play a central bridging role.

4.1. Dual Sensing of ECM Microenvironmental Signals by Integrins

The ECM constitutes a dynamic microenvironment that dominates cellular biological behaviors. Integrins are capable of sensing both biochemical and physical properties of the ECM and transducing mechanical stimuli into intracellular biochemical signals. Distinct integrin subtypes recognize ECM physical characteristics and respond to specific mechanical stimuli, activating downstream cascades such as PI3K/Akt, Wnt/β-catenin, FAK/ERK and mTOR to orchestrate osteogenic progression [17].

In addition to physical properties, ECM biochemical components are indispensable regulators of osteogenesis. Collagens, vitronectin, osteopontin and other ECM proteins bind to specific integrin subtypes to fine-tune MSC osteogenic potency [27, 28]. Moreover, the ECM serves as a reservoir of various cytokines involved in integrin-mediated osteogenic regulation. For example, integrin α5 interacts with the IGF-2/IGFBP-2 signaling axis to synergistically induce MSC osteogenic differentiation [29]. As a pivotal osteogenic cytokine in the TGF-β superfamily, BMP-2 coordinates with integrin receptors to amplify intracellular signaling transduction, and its pro-osteogenic effects have been validated in murine bone defect models and canine non-union fracture models [30]. In summary, integrins integrate dual biochemical and mechanical ECM signals to modulate MSC osteogenic differentiation.

4.2. Modulation of Integrin Activation by Biomaterial Surface Properties

Biomaterial surface characteristics directly regulate integrin conformational changes and activation status. In the absence of chemical osteogenic inducers, graphene materials with different elastic moduli can directly activate integrins and recruit FAK to upregulate osteogenic marker expression [31]. Biphasic calcium phosphate ceramics activate integrin αvβ3 to induce M2 macrophage polarization, which further secretes TGF-β to indirectly promote MSC osteogenesis and bone regeneration [32].

Nanoscale sheet arrays activate integrin β2 and FAK to trigger the PI3K/Akt/mTOR pathway and facilitate osteogenesis via remodeling the immune microenvironment, while microscale sheet structures enhance MSC osteogenic capacity through the integrin-mediated ROCK-YAP/TAZ mechanotransduction axis [33]. These studies demonstrate that biomaterial interfaces alter integrin spatial conformation and clustering behavior to determine the specific activation of downstream signaling pathways, thereby regulating MSC osteogenesis in direct or indirect manners.

4.3. Epigenetic Regulation of Integrin Functions

Epigenetic modifications, including DNA methylation, histone modification and non-coding RNA regulation, are primary mediators governing gene expression during MSC osteogenic differentiation [34, 35]. In human umbilical cord MSCs, lncRNA ODIR1 inhibits osteogenic differentiation by promoting ubiquitination and degradation of FBXO25, subsequently relaxing chromatin conformation and suppressing the transcription of master osteogenic transcription factor Osterix (OSX) [36].

Emerging evidence reveals that epigenetic mechanisms directly or indirectly modulate integrin expression and downstream signaling. In zebrafish embryonic development models, Dnmt3ba regulates the expression of integrin α3β and α7 via DNA methylation to control Akt signaling activity [37]. MiR-637 suppresses the osteogenic potential of degenerative intervertebral disc endplate stem cells by targeting WNT5A [38], and crosstalk exists between Wnt signaling and integrin cascades during MSC osteogenesis [39]. Taken together, epigenetic networks not only directly regulate core osteogenic transcription programs, but also indirectly modulate osteogenic progression by targeting integrins and their downstream effectors.

5. Downstream Effector Systems Activated by Integrin Signaling

Integrin-initiated signal transduction ultimately regulates MSC osteogenic differentiation via multiple downstream effector systems, mainly involving hierarchical activation of core transcription

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factors, dynamic cytoskeleton remodeling and precise expression control of mineralization-related genes.

5.1. Hierarchical Activation of RUNX2/OSX Transcriptional Cascade

RUNX2 is the master transcription factor governing osteogenic differentiation, which regulates the transcription of numerous osteogenic genes and plays an irreplaceable role in bone matrix mineralization, rendering it a promising therapeutic target for bone-related diseases [40-42]. Integrin signaling activates RUNX2 through multiple distinct pathways. Mechanical cyclic stretch upregulates RUNX2 expression via the integrin αVβ3-YAP/TAZ axis to promote early osteogenesis [26]. Type II collagen activates RUNX2 through the integrin α2β1/FAK/JNK signaling cascade [43], while osteogenic activators upregulate integrin β1 and initiate the ERK/MAPK pathway to enhance RUNX2 activity [44].

As a downstream target of RUNX2, OSX synergizes with RUNX2 to facilitate bone matrix formation and maturation. During MSC differentiation, MSCs first commit into RUNX2-positive osteoprogenitors, which further differentiate into OSX-expressing pre-osteoblasts under the induction of RUNX2 [45]. Mature osteoblasts are ultimately generated under the combined regulation of RUNX2 and OSX [45]. Accumulative studies have confirmed that multiple pro-osteogenic interventions simultaneously elevate the expression of RUNX2 and OSX [46-48], verifying that the RUNX2/OSX transcriptional cascade is the central regulatory axis of MSC osteogenesis.

5.2. Cytoskeleton Remodeling and Cell Polarity Establishment

Cytoskeleton rearrangement and polarity formation are critical morphological alterations during MSC osteogenic differentiation. As core cytoskeleton regulators, Rho GTPases act as central hubs downstream of integrins to construct synergistic multi-pathway regulatory networks [23]. Activated integrin β1/β3/β6 induced by micro-nano titanium topography upregulates Cdc42 expression [23]. Activated Cdc42 binds to downstream WASP to accelerate actin polymerization and filopodia formation, determining the establishment of cell polarity axis [23]. Rac1 activation promotes lamellipodia formation and enhances actin network density via IRSp53-mediated signaling [23]. In addition, integrin-coupled RhoA modulates actin stress fiber assembly and stabilizes cell morphology by regulating cofilin activity and PIP5K function. Activated Rho GTPases further initiate downstream Wnt/β-catenin and MAPK cascades to upregulate osteogenic gene expression, linking integrin-mediated cytoskeleton remodeling to MSC osteogenic fate determination [23].

5.3. Expression Regulation of Matrix Mineralization-related Genes

Matrix mineralization represents the terminal stage of MSC osteogenic differentiation, which is strictly controlled by a panel of specific osteogenic genes. Core mineralization-related genes include osteopontin (OPN), osteocalcin (OCN), integrin-binding sialoprotein (IBSP) and type I collagen (COL-I) [46, 47, 49, 50]. As the master upstream regulator, RUNX2 directly or indirectly modulates the transcription of these mineralization genes to drive bone matrix maturation and extracellular mineralized nodule formation [46, 47, 49, 50].

Numerous in vitro studies have demonstrated that pro-osteogenic stimuli synchronously upregulate RUNX2, OSX and mineralization-related genes, accompanied by increased ALP activity and enhanced extracellular mineral deposition [46, 47, 49, 50]. Conversely, anti-osteogenic factors exert opposite inhibitory effects [47, 49, 50]. These findings confirm that the RUNX2/OSX transcriptional cascade is tightly positively correlated with the expression of mineralization genes and osteogenic functional maturation.

6. Summary and Future Perspectives

Great progress has been achieved in exploring integrin-mediated molecular regulatory mechanisms during MSC osteogenic differentiation. Integrins exert bidirectional signaling capabilities and dynamically switch between active and inactive states to trigger downstream signaling cascades, which reshapes the traditional understanding of cell-ECM interaction from simple physical adhesion to dynamic signal-mediated cell fate regulation [17]. Integrins participate in bidirectional mechanotransduction and interact with ion channels, cytoskeletons and nuclear mechanosensitive elements, providing novel insights into cell fate manipulation and mechanobiology research [17].

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Given the vital roles of integrins as mechanical molecular switches, integrin-based regulatory mechanisms possess broad application prospects in bone tissue engineering [16, 51]. In the future, intelligent biomaterials with temporospatially controllable ligand presentation can be designed to dynamically regulate integrin activation kinetics, accurately simulate physiological ECM dynamic characteristics and optimize integrin signaling transduction efficiency. Moreover, dual-responsive biomaterials integrating mechanical and chemical microenvironmental cues can be fabricated to modulate integrin conformational changes and further enhance the directional osteogenic differentiation efficiency of MSCs [17].

Nevertheless, existing research still has certain limitations. The functional specificity and compensatory redundancy among different integrin subtypes remain controversial. Most current studies focus on the independent regulatory effects of single integrin subtypes, while the functional compensation and synergistic interactions among various subtypes are rarely discussed. Further in-depth research is urgently required to resolve this debate. Multi-omics analysis platforms combined with machine learning algorithms can be adopted to systematically excavate integrin subtype-mediated gene transcription, epigenetic modification, signaling activation and cytoskeleton remodeling profiles, distinguish functionally specific and redundant integrin subtypes, and establish a global regulatory network model for predicting MSC osteogenic differentiation, so as to accelerate the clinical transformation of integrin-targeted bone regenerative therapies [16, 17].

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