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**Adipokines regulate mesenchymal stem cell osteogenic differentiation**

Xu ZH *et al*. Adipokines regulate MSCs

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**Abstract**

Mesenchymal stem cells (MSCs) can differentiate into various tissue cell types including bone, adipose, cartilage, and muscle. Among those, osteogenic differentiation of MSCs has been widely explored in many bone tissue engineering studies. Moreover, the conditions and methods of inducing osteogenic differentiation of MSCs are continuously advancing. Recently, with the gradual recognition of adipokines, the research on their involvement in different pathophysiological processes of the body is also deepening including lipid metabolism, inflammation, immune regulation, energy disorders, and bone homeostasis. At the same time, the role of adipokines in the osteogenic differentiation of MSCs has been gradually described more completely. Therefore, this paper reviewed the evidence of the role of adipokines in the osteogenic differentiation of MSCs, emphasizing bone formation and bone regeneration.

**Key Words:** Mesenchymal stem cells; Adipokines; Adipose tissue; Osteogenic differentiation; Osteogenesis; Bone regeneration

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**Core Tip:** Bone tissue supports and protects the organs of the human body. There is a close relationship between the immune system and bone homeostasis. Adipose tissue is an essential accessory tissue around bone tissue, which regulates bone homeostasis through the secretion of adipocytokines. There are many types of adipokines, but only some have been studied in detail. Different adipokines affect the behavior and differentiation of mesenchymal stem cells under different local microenvironments and surrounding inflammation, thus coordinating and participating in the regulation of bone homeostasis.

**INTRODUCTION**

Adipose tissue is currently considered an endocrine organ[1] and comprises adipose cells, endothelial cells, fibroblasts, and immune cells[2]. Adipokines are factors secreted by adipose tissue and have multiple functions[3] involving various biological processes including immune responses, inflammation, glucose metabolism, insulin secretion, sensitivity regulation, regulation of blood pressure and myocardial contractility, blood vessel growth, and lipid metabolism[3,4]. Therefore, adipokines regulate different biological processes in different organs including the brain, liver, muscles, blood vessels, heart, and pancreas[5]. The function, characterization, molecular targets, and potential clinical disease correlation of adipokines are still unclear and the main focus of future adipokine research.

Mesenchymal stem cells (MSCs), pluripotent stem cells derived from the mesoderm, were identified by surface markers such as CD29, CD37, CD44, CD90, CD105, and CD166[6]. MSCs can be readily extracted from many tissues including bone marrow, umbilical cord, placenta, fat, liver, and skin[7]. However, the most well-studied source is bone marrow. MSCs have been shown to differentiate into mature cells of various tissues including cartilage, bone, tendon, ligament, and adipose tissue[8]. Due to its multipotential nature, MSCs have been used to treat many diseases including tumors, central nervous system disease, liver disease, graft-versus-host disease, inflammation, immune system disease, and bone regeneration[9-12]. In this review, we focus on the osteogenic differentiation of MSCs.

Bone is a rigid organ that supports and protects the other vital organs in the body. In adults, bones are renewed approximately every 7 years[13], and bone formation by osteoblasts and bone resorption by osteoclasts play a significant role. Osteoclasts originate from hematopoietic stem cell precursors, and osteoblasts originate from MSCs[14]. The dynamic balance of the two processes maintains the stability of bone metabolism, whereas the destruction of balance leads to various diseases including osteoporosis[15], osteopenia[16], and bone nonunion[17]. Osteoblasts promote the deposition of calcium salts in the bone matrix and stimulate bone remodeling and osteoblast differentiation of MSCs. It can be verified by the detection of runt-related transcription factor 2 (RUNX2), alkaline phosphatase (ALP), and osteopontin (OPN). Therefore, the biological characteristics of MSC osteogenic differentiation have been widely used in bone tissue engineering to treat bone defects caused by trauma, infection, and tumor surgery[18-20]. As a common progenitor of both adipocytes and osteoblasts, MSCs are in a delicate equilibrium state during differentiation, whereas adipose-inducing factors inhibit the osteogenic differentiation of MSCs. In contrast, bone-inducing factors inhibit the adipogenic differentiation of MSCs[6]. As an important active secretion of fat, the position and role of adipokine in the osteogenic differentiation of MSCs are worth further consideration. Therefore, we reviewed the role of adipokines in the osteogenic differentiation of MSCs.

**Cytokine and cytokine-like proteins**

Interleukin (IL) is an essential inflammatory adipokine that plays a vital role in the differentiation of MSCs in the early stage of bone reconstruction[21]. Lacey *et al*[22] found that low-dose IL-1β (0.001-1 ng/mL) inhibited ALP activity, reduced RUNX2 and procollagen expression, and inhibited the degree of mineralization of MSCs in mice. IL-6 is a multifunctional lymphoid factor with pro-inflammatory and anti-inflammatory effects[23]. At the same time, it can be secreted by osteoblasts to stimulate the secretion of osteoclasts and participate in bone homeostasis. IL-6 induces osteogenic differentiation in human bone marrow-derived MSCs (BMSCs) *via* mitogen-activated protein kinase signaling[24]. IL-10 can reduce the synthesis of pro-inflammatory cytokines and chemokines and inhibit the expression of IL-1 and tumor necrosis factor alpha (TNF-α)[25]. In mice, IL-10 inhibits the osteogenic differentiation of MSCs prior to ALP expression[26]. IL-17 cytokines act by binding to the IL-17 receptor family[27]. In the early stage of bone injury, IL-17 secretion increases, promoting the transformation of MSCs into bone progenitor cells or osteoblasts. In some cases, IL-17 can also act as an anti-osteoblast factor, leading to bone loss[28,29].

TNF-α is a pro-inflammatory cytokine that can bind to the TNF receptor superfamily and participate in the regulation of a variety of biological processes. Different doses of TNF-α showed different osteogenic differentiation activity of MSCs. Wang *et al*[30] showed that a high dose of TNF (50 ng/mL) could stimulate the upregulation of some osteogenic factors in MSCs, including vascular endothelial growth factor and insulin growth factor. Lacey *et al*[22] cultured BMSCs with different doses of TNF-α and found that low-dose TNF-α (0.1-10 ng/mL) inhibited the mineralization and activation of ALP and OPN in cultured MSCs.

Monocyte chemotactic protein 1 (MCP-1), also known as C-C motif chemotactic factor ligand 2, can influence monocyte migration and subsequent macrophage polarization[31]. Xie *et al*[32] showed that in the process of osteogenic differentiation, MSCs from patients with ankylosing spondylitis secreted more MCP-1 than MSCs from healthy people. Enhanced MCP-1 secretion promoted monocyte migration, increased classical macrophage polarization, and enhanced TNF-α secretion[32]. Other adipokine-related cytokines, such as progranulin and resistin, have not been reported to correlate with MSC osteogenic differentiation.

Transforming growth factor b (TGF-β) has a unique correlation with the differentiation of adult MSCs[33]. Through the precise matching of ligands, receptors, and cell signaling molecules, TGF-β is involved in the lineage transformation process of the differentiation of various stem cells such as lipids, osteoblasts, chondrogenic and myogenic cells[34]. Tang *et al*[35] confirmed that TGF-β1 induced the migration of MSCs to the bone resorption site of mice by activating the activin receptor-like kinase 5-Smad2/3-Smad4 pathway and restricted the further recruitment of osteoclasts but did not induce osteogenic differentiation. However, other studies have reported that TGF-β inhibits osteogenic differentiation through Wnt signaling interactions and inhibits RUNX2 through the activation of Smad3[36,37]. However, TGF-β has also been reported to promote the osteogenic differentiation of MSCs[38,39]. However, further research needs to be carried out in the future.

Chemerin is a secreted protein derived from adipocytes and liver cells involved in physiological processes including inflammation, angiogenesis, and calcium mobilization[40,41]. Epidemiological studies have reported that patients with osteoporosis have higher circulating chemerin[42], and the knockout of chemerin or its receptor CMKLR1 inhibits lipogenesis and promotes the osteogenic differentiation of MSCs[43]. Li *et al*[41] showed that chemerin promoted the osteogenic differentiation of C3H10T1/2 cells and MSCs through Akt/Gsk3β/β-catenin signaling. However, Akt inhibitors (MK2206) inhibited chemerin’s promotion of osteogenic differentiation and active β-catenin.

**Proteins of the fibrinolytic system**

Plasminogen activator inhibitor-1 (PAI-1) is a serine protease inhibitor of the fibrinolytic system[44]. Adipose-derived PAI-1 is associated with various pathologic conditions including inflammation, diabetes, cancer, and obesity[44]. Takafuji *et al*[45] studied the role of PAI-1 in the osteogenic differentiation of MSCs using wild-type and PAI-1-deficient mice and found that the loss of PAI-1 significantly weakened the expression of BMSC osteogenic genes, such as bone morphogenetic protein 2 (BMP-2) and ALP.

Tissue factor, another adipokine that plays a crucial role in the clotting process[46], whose overexpression in the body can lead to multiple forms of thrombosis[47]. In a study aimed at improving coagulation activity, Rangasami *et al*[48] found that pluronic micelle-mediated tissue factor silencing could effectively induce the higher differentiation of MSCs in osteogenic and lipid-forming media.

**Complement and complement-related proteins**

Adipsin was the first adipocyte-secreted protein to be identified[49] and is currently named complement factor D[50]. Fat cells produce it through the activation of peroxisome proliferator-activated receptor gamma[51]. More recently, adipsin was shown to promote insulin secretion by pancreatic b cells and prevent b-cell death[52]. By activating Wnt signaling, adipsin initiates adipogenesis from BMSCs[53]. Experiments on BMSCs of adipsin knockout mice showed the increased expression of mineralized nodules and osteoblast markers including RUNX2, COL1A1, and osteocalcin compared with MSCs of normal origin[53].

Complement and complement-related proteins from adipose tissue include complement component 1q and TNF-related protein family, complement factor B, and acylating simulation protein[3,54]. However, it has not been reported whether they induce or inhibit the osteogenic differentiation of MSCs.

**Adipokines**

Leptin, a hormone derived from adipose tissue, is involved in pathophysiological processes such as food absorption, energy metabolism, inflammation, immunity, and bone homeostasis[55-58]. Leptin binds to its leptin receptor, a marker specific to BMSCs[59]. Leptin has been shown to cross-regulate BMP-9 signaling through the JAK/STAT signaling pathway in MSCs, thereby enhancing BMP-9-induced osteogenesis[60].

Adiponectin plays a vital role in anti-inflammation, glucolipid metabolism, and insulin resistance regulation[61,62]. Wang *et al*[63] reported that adiponectin regulates BMSC osteogenic differentiation and osteogenesis through the Wnt/β-catenin pathway. Similar results have also been reported in other studies[64-66].

Visfatin is commonly produced by visceral adipose tissue and is also known as nicotinamide phosphoribosyltransferase (Nampt) or pre-B cell cluster enhancer. It is strongly expressed in osteogenic differentiation[67] and promotes the proliferation and mineralization activity of osteoblasts[68]. Visfatin induces the secretion of IL-6, IL-8, and MCP-1 during the osteogenic differentiation of MSCs and significantly increases matrix mineralization during osteogenic differentiation, while the expression of type I collagen is decreased[69].

Nicotinamide adenine dinucleotide (NAD) is involved in energy metabolism and protein modification[70]. Nampt has recently been identified as a novel adipokine[71]. Nampt is a rate-limiting enzyme and participates in all-around MC3T3 E1-osteogenesis prior to the cell differentiation process of NAD salvage pathways. Knocking out Nampt, or adding its specific inhibitor, Fk866, resulted in decreased intracellular NAD concentration and decreased osteogenic ability[67]. Thus, Nampt can be used as a specific marker for the osteogenic differentiation of MSCs[72].

Visceral adipose tissue-derived serine protease inhibitor (vaspin), an adipose-derived hormone, attenuates osteogenic differentiation of the preosteoblast cell line MC3T3-E1[73] and antagonizes the osteogenic differentiation of rat osteoblasts. However, the role of vaspin in the osteogenic differentiation of MSCs has not been reported[74].

BMPs, the largest component of the TGF-β ligand family, regulate multiple organogenetic pathways, fat formation, and energy metabolism[75,76]. BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, and BMP-7 all strongly promote osteogenesis. Short-term addition of BMP-2 increases osteocalcin expression[77], and BMP-7 induces the increased expression of ALP, a marker of osteoblast differentiation, and accelerates calcification[78]. The absence of BMP-2 and BMP-4 results in severely impaired osteogenic function, but the limb skeleton still develops normally without BMP-4[79]. BMP-3 regulates adult bone mass by limiting the differentiation of bone progenitor cells into mature osteoblasts[80]. It is important to note that BMP-7 has been marketed and used in surgery to aid fracture healing, with no reported local or systemic adverse events[81]. The effects of BMP-5[82,83] and BMP-6[84,85] on the osteogenic differentiation of MSCs have also been reported.

Nesfatin-1 is a novel anorexia polypeptide that has a wide range of biological effects including energy metabolism, gastrointestinal function, anxiety and depression, and the regulation of cardiovascular and reproductive function[86-88]. The role of nesfatin-1 in the osteogenic differentiation of MSCs has not been reported, but it can promote the expression of osteogenic genes such as ALP and RUNX2 in newly derived rat stem cells[89]. Therefore, we speculate that Nesfatin-1 has a similar role in the osteogenic differentiation of MSCs, but this conclusion still needs to be confirmed by further studies.

Cathepsins are an important category of enzymes located within the lysosomes[90]. Cathepsins are produced by various tissues, which also include adipose tissue[91]. Cathepsin K is a crucial enzyme in the degradation of the organic bone matrix, and its expression in bone formation-related cells, including fibroblasts, osteoblasts, and MSCs, has also been confirmed[92,93]. Zhang *et al*[94] showed that knockout or inhibition of cathepsin K can promote the regeneration of BMSCs of jaw bone through glycolysis, thus promoting alveolar bone regeneration. Similarly, cathepsin S deficiency alters the balance between adipocyte and osteoblast differentiation, increases bone turnover, and alters bone microstructure[95].

Apelin is an endogenous ligand of the G protein-coupled apelin receptor[96]. Besides being an adipokine, apelin is also expressed in skeletal muscle, the central nervous system, the heart, and other tissues, and is involved in lipolysis, glucose metabolism, cell proliferation, and angiogenesis[97]. Exogenous addition of apelin protein or overexpression of apelin promotes postpositional MSC osteoblast differentiation by activating the Wnt/β-catenin signaling pathway[98].

Omentin-1 is the adipokine most commonly expressed in omental adipose tissue and is also abundant in plasma[99]. Omentin-1 is involved in the physiological processes of inflammation, insulin, and cardiovascular functions[99,100]. For bone effects, a study of postmenopausal women found a negative correlation between omentin-1 levels and lumbar bone density[101]. Tang *et al*[102] found that omentin-1 has a dose-dependent effect on the viability of MC3T3-E1 cells, which can significantly increase the expression of members of the TGF-β/Smad signaling pathway, and also significantly increase the expression levels of BMP-2, RUNX2, OPN, osteocalcin, and other proteins, thus promoting osteogenesis.

Lipocalin 2 (LCN2) is a protein involved in host defense, autoimmunity, insulin resistance, skin healing, tumor, and infection[103,104]. LCN2 disrupts osteoclast formation in bone tissue by negatively regulating the proliferation and differentiation of osteoclast precursors[105]. As a secretory bone factor, LCN2 positively affects the osteogenic differentiation and *in vivo* osteogenesis of MC3T3-E1[106].

Melatonin is an indoleamine that is synthesized and secreted primarily by the pineal gland in mammals but is also secreted by adipose tissue[107]. Melatonin mainly affects the circadian rhythm and sleep-wake cycle and is also involved in immune regulation and inhibition of tumor growth[108,109]. Melatonin is also involved in MSC differentiation, which is involved in developing and regenerating bone, muscle, and fat tissues. In BMSCs, melatonin enhances osteogenesis and inhibits lipogenesis. Melatonin also differentiates bone marrow progenitors from adipocytes to osteoblasts[110,111].

Gremlin-1 is a highly conserved glycoprotein, mainly distributed in the extracellular matrix, with a small amount in the endoplasmic reticulum[112]. As an adipokine, gremlin-1 plays an important role in adipose tissue homeostasis[113]. At the same time, studies have shown that gremlin-1 is a BMP protein inhibitor, which can inhibit their binding to BMP receptors on the cell membrane by binding to BMP-2, BMP-4, and BMP-7[112]. Specific overexpression of gremlin-1 in mouse bone tissue results in severe osteoporosis; however, conditional knockout of gremlin-1 increases trabecular volume and bone formation[114]. Gremlin-1 has also been shown to inhibit the viability and osteogenic differentiation of human BMSCs[115].

**Lipid transport**

Apolipoprotein E (ApoE), one of the main components of plasma very low-density lipoprotein[116], regulates lipid homeostasis by regulating lipid transport between tissues and cells. ApoE4 is associated with hyperlipidemia and hypercholesterolemia, leading to coronary heart disease, stroke, and atherosclerosis[117-119]. BMP-2 can upregulate the ApoE level of the mouse mesenchymal progenitor cell line (C3H10T1/2), leading to enhanced osteogenic differentiation. At the same time, ApoE is also expressed *in vitro* in mouse cranial primary osteoblasts with advanced osteoblast sequences[120].

**Enzymes**

Dipeptidyl peptidase 4 (DPP-4) is a protein secreted in the salivary glands, prostate, seminal vesicles, endometrium, small intestine, and decidual membrane, and has recently been identified in adipose tissue as well[121]. DPP-4 is an important drug target in type 2 diabetes and directly induces insulin resistance in adipocytes and skeletal muscle[121]. DPP-4 not only reflects but also promotes adipose tissue dysfunction. Choi *et al*[122] found that DPP-4, when overexpressed, could restrict the induction of osteogenic differentiation of heart artery flap-derived mesenchymal cells by the autocrine insulin-like growth factor-1 signaling pathway, but this result has not been verified on MSCs.

Tissue inhibitors of metalloproteinases (TIMPs) have four main members, TIMP-1, TIMP-2, TIMP-3, and TIMP-4, and are primarily responsible for degrading most proteins in the extracellular matrix[123,124]. TIMPs are generally considered to be inhibitors of matrix metalloproteinases (MMPs) through the action of their terminal N-domain[125]. Meanwhile, TIMPs exist in the extracellular matrix in a soluble form and preemptively bind to the extracellular matrix, thus inhibiting the effect of MMPs[126]. TIMPs can selectively inhibit different MMPs, metalloproteinase and a disintegrin and metalloproteinase with thrombospondin motifs[125,126]. Inhibition of endogenous TIMP-1 can inhibit the proliferation, metabolic activity, and osteogenic differentiation ability of MSCs by activating Wnt/β-catenin signaling[127]. However, Liang *et al*[128] found in the process of MSC osteogenic differentiation that TIMP-1 knockdown increased the deposition of calcium nodules, ALP activity, and the expression of osteocalcin protein by activating Wnt/β-catenin signaling. The conclusions here are contradictory and need further confirmation by other studies. Studies targeting TIMP-3 have shown that increased expression of TIMP-3 can significantly promote osteogenic differentiation of MSCs in the fracture model of diabetic rats[129].

**CONCLUSION**

The formation and regeneration of bone tissue usually require regulation of the local microenvironment. The balance between bone resorption and bone regeneration is essential for bone tissue regeneration. Adipokines are exogenous immune regulatory substances secreted by adipose tissue, and are widely involved in pathophysiological processes of surrounding tissues, including bone homeostasis and bone regeneration. Not all human adipokines have been identified, but the current literature has revealed that the surface adipose tissue secretes more than 600 factors or proteins involving many processes of human pathophysiology[130]. There are many types of adipokines, including cytokines[22], fibrinolysin[44], complement and related proteins[49], enzymes[121], lipid transport systems[116], endocannabinoids[131], and angiotensinogen[132] (Table 1).

In summary, this paper reviewed the current research on the regulation and influence of adipokine in the osteoblast differentiation of MSCs. However, this review did not include all currently discovered adipokines but only included published studies involving osteogenic differentiation of MSCs. Most of the included studies were conducted in BMSCs, with a small number involving osteoblast precursor cells, progenitor cells, and a small number of other tissue-derived stem cells. Our review suggests that different adipokines have different effects on the outcome of osteogenic differentiation, bone regeneration, and bone remodeling of MSCs. The progress of related research provides a good reference for subsequent preclinical and clinical studies and a new reference for treating osteogenic disorders and diseases of osteoblastic homeostasis.

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**Figure Legends**

**Table 1 Key activities of factors released by adipose tissue**

|  |  |  |  |
| --- | --- | --- | --- |
| **Classification** | **Appellation** | **Mechanism** | **Ref.** |
| Cytokine and cytokine-like proteins | Interleukin | IL-6 induces osteogenic differentiation in human bone marrow-derived MSCs *via* MAPK signaling. IL-10 inhibits osteogenic differentiation of MSCs prior to ALP expression. IL-17 promoting the transformation of MSC into bone progenitor cells or osteoblasts. | [24,26,28] |
| TNF-α | High dose of TNF could stimulate the upregulation of some osteogenic factors in MSCs, including VEGF and insulin-like growth factor. Low-dose TNF-α inhibited the mineralization and activation of ALP and OPN in cultured MSCs. | [22,30] |
| MCP-1 | Influencing monocyte migration and subsequent macrophage polarization. | [31] |
| TGF-β | Through the precise matching of ligands, receptors, and cell signaling molecules, TGF-β is involved in the lineage transformation process of the differentiation of various stem cells, such as lipid, osteoblast, chondrogenic, and myogenic. | [34] |
| Chemerin | Chemerin promotes lipogenesis and inhibits osteogenic differentiation of MSCs. | [42] |
| Proteins of the fibrinolytic system | PAI-1 | Loss of PAI-1 significantly weakened the expression of bone marrow-derived MSC osteogenic genes, such as BMP-2 and ALP. | [45] |
| Tissue factor | Tissue factor silencing could effectively induce higher differentiation of MSCs in osteogenic and lipid-forming media. | [48] |
| Complement and complement-related proteins | Adipsin | Adipsin initiates adipogenesis from bone marrow MSCs by activating Wnt signaling. | [53] |
| Adipokines | Leptin | Leptin has been shown to cross-regulate BMP-9 signaling through the JAK/STAT signaling pathway in MSCs, thereby enhancing BMP-9-induced osteogenesis. | [60] |
| Adiponectin | adiponectin regulates BMSC osteogenic differentiation and osteogenesis through the Wnt/β-catenin pathway. | [63] |
| Visfatin | Promoting the proliferation and mineralization activity of osteoblasts. | [68] |
| Nicotinamide | Nampt is a speed-limit enzyme and participates in the all-around MC3T3-E1. osteogenesis prior to the cell differentiation process of NAD salvage pathways. | [67] |
| Visceral | Attenuating the osteogenic differentiation of preosteoblast cell line MC3T3-E1. | [73] |
| Bone morphogenetic proteins | BMP-7 induced increased expression of ALP, a marker of osteoblast differentiation, and accelerated calcification. The absence of BMP-2 and BMP-4 resulted in severely impaired osteogenic function. BMP-3 regulates adult bone mass by limiting the differentiation of bone progenitor cells into mature osteoblasts. | [78-80] |
| Nesfatin-1 | Promoting the expression of osteogenic genes such as ALP and RUNX2 in rats’ newly derived stem cells. | [89] |
| Cathepsins | Knockout or inhibition of cathepsin K could promote the regeneration of bone marrow MSCs of jaw bone through glycolysis. Cathepsin S deficiency alters the balance between adipocyte and osteoblast differentiation, increases bone turnover, and alters bone microstructure. | [94,95] |
| Apelin | Promoting postpositional MSC osteoblast differentiation by activating the Wnt/β-catenin signaling pathway. | [98] |
| Omentin-1 | Increasing the expression of BMP2, RUNX2, OPN, and osteocalcin. | [102] |
| Lipocalin 2 | Disrupting osteoclast formation in bone tissue by negatively regulating the proliferation and differentiation of osteoclast precursors. | [105] |
| Melatonin | Differentiating bone marrow progenitors from adipocytes to osteoblasts. | [111] |
| Gremlin-1 | BMP protein inhibitor. | [112] |
| Lipid transport | ApoE | Enhancing osteogenic differentiation of the mouse mesenchymal progenitor cell line. | [120] |
| Enzymes | DPP-4 | Restricting the induction of osteogenic differentiation of heart artery flap-derived mesenchymal cells by the autocrine insulin-like growth factor-1 signaling pathway. | [122] |
| Tissue inhibitors of metalloproteinases | Inhibition of endogenous TIMP-1 can inhibit the proliferation, metabolic activity, and osteogenic differentiation ability of MSCs by activating the Wnt/β-catenin signal. | [127] |

ALP: Alkaline phosphatase; ApoE: Apolipoprotein E; BMP-2: Bone morphogenetic protein 2; DPP-4: Dipeptidyl peptidase 4; IL: Interleukin; JAK: Janus kinase; MAPK: Mitogen-activated protein kinase; MCP-1: Monocyte chemotactic protein 1; MSC: Mesenchymal stem cell; Nampt: Nicotinamide phosphoribosyltransferase; OPN: Osteopontin; PAI-1: Plasminogen activator inhibitor-1; RUNX2: Runt-related transcription factor 2; TIMP-1: Tissue inhibitors of metalloproteinase; TGF-b: Transforming growth factor beta; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor.