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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 β (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 β cells and prevent β-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.

**REFERENCES**

1 **Klöting N**, Blüher M. Adipocyte dysfunction, inflammation and metabolic syndrome. *Rev Endocr Metab Disord* 2014; **15**: 277-287 [PMID: 25344447 DOI: 10.1007/s11154-014-9301-0]

2 **Blüher M**. Adipose tissue dysfunction contributes to obesity related metabolic diseases. *Best Pract Res Clin Endocrinol Metab* 2013; **27**: 163-177 [PMID: 23731879 DOI: 10.1016/j.beem.2013.02.005]

3 **Fasshauer M**, Blüher M. Adipokines in health and disease. *Trends Pharmacol Sci* 2015; **36**: 461-470 [PMID: 26022934 DOI: 10.1016/j.tips.2015.04.014]

4 **Blüher M**. Adipokines – removing road blocks to obesity and diabetes therapy. *Mol Metab* 2014; **3**: 230-240 [PMID: 24749053 DOI: 10.1016/j.molmet.2014.01.005]

5 **Blüher M**, Mantzoros CS. From leptin to other adipokines in health and disease: facts and expectations at the beginning of the 21st century. *Metabolism* 2015; **64**: 131-145 [PMID: 25497344 DOI: 10.1016/j.metabol.2014.10.016]

6 **Chen Q**, Shou P, Zheng C, Jiang M, Cao G, Yang Q, Cao J, Xie N, Velletri T, Zhang X, Xu C, Zhang L, Yang H, Hou J, Wang Y, Shi Y. Fate decision of mesenchymal stem cells: adipocytes or osteoblasts? *Cell Death Differ* 2016; **23**: 1128-1139 [PMID: 26868907 DOI: 10.1038/cdd.2015.168]

7 **Zuk PA**, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, Alfonso ZC, Fraser JK, Benhaim P, Hedrick MH. Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell* 2002; **13**: 4279-4295 [PMID: 12475952 DOI: 10.1091/mbc.e02-02-0105]

8 **Pittenger MF**, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, Moorman MA, Simonetti DW, Craig S, Marshak DR. Multilineage potential of adult human mesenchymal stem cells. *Science* 1999; **284**: 143-147 [PMID: 10102814 DOI: 10.1126/science.284.5411.143]

9 **Li T**, Xia M, Gao Y, Chen Y, Xu Y. Human umbilical cord mesenchymal stem cells: an overview of their potential in cell-based therapy. *Expert Opin Biol Ther* 2015; **15**: 1293-1306 [PMID: 26067213 DOI: 10.1517/14712598.2015.1051528]

10 **Das M**, Mayilsamy K, Mohapatra SS, Mohapatra S. Mesenchymal stem cell therapy for the treatment of traumatic brain injury: progress and prospects. *Rev Neurosci* 2019; **30**: 839-855 [PMID: 31203262 DOI: 10.1515/revneuro-2019-0002]

11 **Li A**, Guo F, Pan Q, Chen S, Chen J, Liu HF, Pan Q. Mesenchymal Stem Cell Therapy: Hope for Patients With Systemic Lupus Erythematosus. *Front Immunol* 2021; **12**: 728190 [PMID: 34659214 DOI: 10.3389/fimmu.2021.728190]

12 **Ding DC**, Chang YH, Shyu WC, Lin SZ. Human umbilical cord mesenchymal stem cells: a new era for stem cell therapy. *Cell Transplant* 2015; **24**: 339-347 [PMID: 25622293 DOI: 10.3727/096368915X686841]

13 **Teitelbaum SL**. Bone resorption by osteoclasts. *Science* 2000; **289**: 1504-1508 [PMID: 10968780 DOI: 10.1126/science.289.5484.1504]

14 **Caplan AI**. Mesenchymal stem cells. *J Orthop Res* 1991; **9**: 641-650 [PMID: 1870029 DOI: 10.1002/jor.1100090504]

15 **Jiang Y**, Zhang P, Zhang X, Lv L, Zhou Y. Advances in mesenchymal stem cell transplantation for the treatment of osteoporosis. *Cell Prolif* 2021; **54**: e12956 [PMID: 33210341 DOI: 10.1111/cpr.12956]

16 **Akbar MA**, Lu Y, Elshikha AS, Chen MJ, Yuan Y, Whitley EM, Holliday LS, Chang LJ, Song S. Transplantation of Adipose Tissue-Derived Mesenchymal Stem Cell (ATMSC) Expressing Alpha-1 Antitrypsin Reduces Bone Loss in Ovariectomized Osteoporosis Mice. *Hum Gene Ther* 2017; **28**: 179-189 [PMID: 27802778 DOI: 10.1089/hum.2016.069]

17 **Loi F**, Córdova LA, Pajarinen J, Lin TH, Yao Z, Goodman SB. Inflammation, fracture and bone repair. *Bone* 2016; **86**: 119-130 [PMID: 26946132 DOI: 10.1016/j.bone.2016.02.020]

18 **Fu X**, Liu G, Halim A, Ju Y, Luo Q, Song AG. Mesenchymal Stem Cell Migration and Tissue Repair. *Cells* 2019; **8** [PMID: 31357692 DOI: 10.3390/cells8080784]

19 **Brown C**, McKee C, Bakshi S, Walker K, Hakman E, Halassy S, Svinarich D, Dodds R, Govind CK, Chaudhry GR. Mesenchymal stem cells: Cell therapy and regeneration potential. *J Tissue Eng Regen Med* 2019; **13**: 1738-1755 [PMID: 31216380 DOI: 10.1002/term.2914]

20 **Grayson WL**, Bunnell BA, Martin E, Frazier T, Hung BP, Gimble JM. Stromal cells and stem cells in clinical bone regeneration. *Nat Rev Endocrinol* 2015; **11**: 140-150 [PMID: 25560703 DOI: 10.1038/nrendo.2014.234]

21 **Liu L**, Shi Z, Ji X, Zhang W, Luan J, Zahr T, Qiang L. Adipokines, adiposity, and atherosclerosis. *Cell Mol Life Sci* 2022; **79**: 272 [PMID: 35503385 DOI: 10.1007/s00018-022-04286-2]

22 **Lacey DC**, Simmons PJ, Graves SE, Hamilton JA. Proinflammatory cytokines inhibit osteogenic differentiation from stem cells: implications for bone repair during inflammation. *Osteoarthritis Cartilage* 2009; **17**: 735-742 [PMID: 19136283 DOI: 10.1016/j.joca.2008.11.011]

23 **Majumdar MK**, Thiede MA, Haynesworth SE, Bruder SP, Gerson SL. Human marrow-derived mesenchymal stem cells (MSCs) express hematopoietic cytokines and support long-term hematopoiesis when differentiated toward stromal and osteogenic lineages. *J Hematother Stem Cell Res* 2000; **9**: 841-848 [PMID: 11177595 DOI: 10.1089/152581600750062264]

24 **Rezaee F**, Rellick SL, Piedimonte G, Akers SM, O’Leary HA, Martin K, Craig MD, Gibson LF. Neurotrophins regulate bone marrow stromal cell IL-6 expression through the MAPK pathway. *PloS One* 2010; **5**: e9690 [PMID: 20300619 DOI: 10.1371/journal.pone.0009690]

25 **Carmody EE**, Schwarz EM, Puzas JE, Rosier RN, O’Keefe RJ. Viral interleukin-10 gene inhibition of inflammation, osteoclastogenesis, and bone resorption in response to titanium particles. *Arthritis Rheum* 2002; **46**: 1298-1308 [PMID: 12115237 DOI: 10.1002/art.10227]

26 **Van Vlasselaer P**, Borremans B, Van Den Heuvel R, Van Gorp U, de Waal Malefyt R. Interleukin-10 inhibits the osteogenic activity of mouse bone marrow. *Blood*1993; **82**: 2361-2370 [PMID: 8400287 DOI: 10.1182/blood.V82.8.2361.bloodjournal8282361]

27 **Krstić J**, Mojsilović S, Mojsilović SS, Santibanez JF. Regulation of the mesenchymal stem cell fate by interleukin-17: Implications in osteogenic differentiation. *World J Stem Cells* 2021; **13**: 1696-1713 [PMID: 34909118 DOI: 10.4252/wjsc.v13.i11.1696]

28 **Ling L**, Nurcombe V, Cool SM. Wnt signaling controls the fate of mesenchymal stem cells. *Gene* 2009; **433**: 1-7 [PMID: 19135507 DOI: 10.1016/j.gene.2008.12.008]

29 **Chang J**, Wang Z, Tang E, Fan Z, McCauley L, Franceschi R, Guan K, Krebsbach PH, Wang CY. Inhibition of osteoblastic bone formation by nuclear factor-kappaB. *Nat Med* 2009; **15**: 682-689 [PMID: 19448637 DOI: 10.1038/nm.1954]

30 **Wang M**, Crisostomo PR, Herring C, Meldrum KK, Meldrum DR. Human progenitor cells from bone marrow or adipose tissue produce VEGF, HGF, and IGF-I in response to TNF by a p38 MAPK-dependent mechanism. *Am J Physiol Regul Integr Comp Physiol* 2006; **291**: R880-R884 [PMID: 16728464 DOI: 10.1152/ajpregu.00280.2006]

31 **Deshmane SL**, Kremlev S, Amini S, Sawaya BE. Monocyte chemoattractant protein-1 (MCP-1): an overview. *J Interferon Cytokine Res* 2009; **29**: 313-326 [PMID: 19441883 DOI: 10.1089/jir.2008.0027]

32 **Xie Z**, Wang P, Li J, Li Y, Wang S, Wu X, Sun S, Cen S, Su H, Deng W, Liu Z, Ouyang Y, Wu Y, Shen H. MCP1 triggers monocyte dysfunctions during abnormal osteogenic differentiation of mesenchymal stem cells in ankylosing spondylitis. *J Mol Med (Berl)* 2017; **95**: 143-154 [PMID: 27921117 DOI: 10.1007/s00109-016-1489-x]

33 **Crane JL**, Cao X. Bone marrow mesenchymal stem cells and TGF-β signaling in bone remodeling. *J Clin Invest* 2014; **124**: 466-472 [PMID: 24487640 DOI: 10.1172/JCI70050]

34 **Li SN**, Wu JF. TGF-β/SMAD signaling regulation of mesenchymal stem cells in adipocyte commitment. *Stem Cell Res Ther* 2020; **11**: 41 [PMID: 31996252 DOI: 10.1186/s13287-020-1552-y]

35 **Tang Y**, Wu X, Lei W, Pang L, Wan C, Shi Z, Zhao L, Nagy TR, Peng X, Hu J, Feng X, Van Hul W, Wan M, Cao X. TGF-beta1-induced migration of bone mesenchymal stem cells couples bone resorption with formation. *Nat Med* 2009; **15**: 757-765 [PMID: 19584867 DOI: 10.1038/nm.1979]

36 **Zhou S**. TGF-β regulates β-catenin signaling and osteoblast differentiation in human mesenchymal stem cells. *J Cell Biochem* 2011; **112**: 1651-1660 [PMID: 21344492 DOI: 10.1002/jcb.23079]

37 **Jian H**, Shen X, Liu I, Semenov M, He X, Wang XF. Smad3-dependent nuclear translocation of beta-catenin is required for TGF-beta1-induced proliferation of bone marrow-derived adult human mesenchymal stem cells. *Genes Dev* 2006; **20**: 666-674 [PMID: 16543220 DOI: 10.1101/gad.1388806]

38 **Du G**, Cheng X, Zhang Z, Han L, Wu K, Li Y, Lin X. TGF-Beta Induced Key Genes of Osteogenic and Adipogenic Differentiation in Human Mesenchymal Stem Cells and MiRNA-mRNA Regulatory Networks. *Front Genet* 2021; **12**: 759596 [PMID: 34899844 DOI: 10.3389/fgene.2021.759596]

39 **Igarashi Y**, Chosa N, Sawada S, Kondo H, Yaegashi T, Ishisaki A. VEGF-C and TGF-β reciprocally regulate mesenchymal stem cell commitment to differentiation into lymphatic endothelial or osteoblastic phenotypes. *Int J Mol Med* 2016; **37**: 1005-1013 [PMID: 26934950 DOI: 10.3892/ijmm.2016.2502]

40 **Bozaoglu K**, Bolton K, McMillan J, Zimmet P, Jowett J, Collier G, Walder K, Segal D. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. *Endocrinology* 2007; **148**: 4687-4694 [PMID: 17640997 DOI: 10.1210/en.2007-0175]

41 **Li J**, Zhang T, Huang C, Xu M, Xie W, Pei Q, Xie X, Wang B, Li X. Chemerin located in bone marrow promotes osteogenic differentiation and bone formation via Akt/Gsk3β/β-catenin axis in mice. *J Cell Physiol* 2021; **236**: 6042-6054 [PMID: 33492671 DOI: 10.1002/jcp.30290]

42 **Kadric L**, Zylla S, Nauck M, Völzke H, Friedrich N, Hannemann A. Associations Between Plasma Chemerin Concentrations and Bone Quality in Adults From the General Population. *Endocrinology* 2018; **159**: 2378-2385 [PMID: 29701774 DOI: 10.1210/en.2018-00157]

43 **Muruganandan S**, Roman AA, Sinal CJ. Role of chemerin/CMKLR1 signaling in adipogenesis and osteoblastogenesis of bone marrow stem cells. *J Bone Miner Res*2010; **25**: 222-234 [PMID: 19929432 DOI: 10.1359/jbmr.091106]

44 **Kaji H**. Adipose Tissue-Derived Plasminogen Activator Inhibitor-1 Function and Regulation. *Compr Physiol* 2016; **6**: 1873-1896 [PMID: 27783862 DOI: 10.1002/cphy.c160004]

45 **Takafuji Y**, Tatsumi K, Ishida M, Kawao N, Okada K, Matsuo O, Kaji H. Plasminogen activator inhibitor-1 deficiency suppresses osteoblastic differentiation of mesenchymal stem cells in mice. *J Cell Physiol* 2019; **234**: 9687-9697 [PMID: 30387130 DOI: 10.1002/jcp.27655]

46 **Drake TA**, Morrissey JH, Edgington TS. Selective cellular expression of tissue factor in human tissues. Implications for disorders of hemostasis and thrombosis. *Am J Pathol* 1989; **134**: 1087-1097 [PMID: 2719077]

47 **Nitori N**, Ino Y, Nakanishi Y, Yamada T, Honda K, Yanagihara K, Kosuge T, Kanai Y, Kitajima M, Hirohashi S. Prognostic significance of tissue factor in pancreatic ductal adenocarcinoma. *Clin Cancer Res* 2005; **11**: 2531-2539 [PMID: 15814630 DOI: 10.1158/1078-0432.CCR-04-0866]

48 **Rangasami VK**, Nawale G, Asawa K, Kadekar S, Samanta S, Nilsson B, Ekdahl KN, Miettinen S, Hilborn J, Teramura Y, Varghese OP, Oommen OP. Pluronic Micelle-Mediated Tissue Factor Silencing Enhances Hemocompatibility, Stemness, Differentiation Potential, and Paracrine Signaling of Mesenchymal Stem Cells. *Biomacromolecules* 2021; **22**: 1980-1989 [PMID: 33813822 DOI: 10.1021/acs.biomac.1c00070]

49 **Cook KS**, Min HY, Johnson D, Chaplinsky RJ, Flier JS, Hunt CR, Spiegelman BM. Adipsin: a circulating serine protease homolog secreted by adipose tissue and sciatic nerve. *Science* 1987; **237**: 402-405 [PMID: 3299705 DOI: 10.1126/science.3299705]

50 **Rosen BS**, Cook KS, Yaglom J, Groves DL, Volanakis JE, Damm D, White T, Spiegelman BM. Adipsin and complement factor D activity: an immune-related defect in obesity. *Science* 1989; **244**: 1483-1487 [PMID: 2734615 DOI: 10.1126/science.2734615]

51 **Choy LN**, Rosen BS, Spiegelman BM. Adipsin and an endogenous pathway of complement from adipose cells. *J Biol Chem* 1992; **267**: 12736-12741 [PMID: 1618777 DOI: 10.1016/S0021-9258(18)42338-1]

52 **Gómez-Banoy N**, Guseh JS, Li G, Rubio-Navarro A, Chen T, Poirier B, Putzel G, Rosselot C, Pabón MA, Camporez JP, Bhambhani V, Hwang SJ, Yao C, Perry RJ, Mukherjee S, Larson MG, Levy D, Dow LE, Shulman GI, Dephoure N, Garcia-Ocana A, Hao M, Spiegelman BM, Ho JE, Lo JC. Adipsin preserves beta cells in diabetic mice and associates with protection from type 2 diabetes in humans. *Nat Med* 2019; **25**: 1739-1747 [PMID: 31700183 DOI: 10.1038/s41591-019-0610-4]

53 **Aaron N**, Kraakman MJ, Zhou Q, Liu Q, Costa S, Yang J, Liu L, Yu L, Wang L, He Y, Fan L, Hirakawa H, Ding L, Lo J, Wang W, Zhao B, Guo E, Sun L, Rosen CJ, Qiang L. Adipsin promotes bone marrow adiposity by priming mesenchymal stem cells. *Elife* 2021; **10** [PMID: 34155972 DOI: 10.7554/eLife.69209]

54 **Bienertova-Vasku J**, Vinciguerra M, Buzga M, Villaroya F. Adipokines as Biomarkers in Health and Disease. *Dis Markers* 2018; **2018**: 5696815 [PMID: 30402169 DOI: 10.1155/2018/5696815]

55 **Reid IR**, Baldock PA, Cornish J. Effects of Leptin on the Skeleton. *Endocr Rev* 2018; **39**: 938-959 [PMID: 30184053 DOI: 10.1210/er.2017-00226]

56 **Park HK**, Ahima RS. Leptin signaling. *F1000Prime Rep* 2014; **6**: 73 [PMID: 25343030 DOI: 10.12703/P6-73]

57 **Yue R**, Zhou BO, Shimada IS, Zhao Z, Morrison SJ. Leptin Receptor Promotes Adipogenesis and Reduces Osteogenesis by Regulating Mesenchymal Stromal Cells in Adult Bone Marrow. *Cell Stem Cell* 2016; **18**: 782-796 [PMID: 27053299 DOI: 10.1016/j.stem.2016.02.015]

58 **Kelesidis T**, Kelesidis I, Chou S, Mantzoros CS. Narrative review: the role of leptin in human physiology: emerging clinical applications. *Ann Intern Med* 2010; **152**: 93-100 [PMID: 20083828 DOI: 10.7326/0003-4819-152-2-201001190-00008]

59 **Zhou BO**, Yue R, Murphy MM, Peyer JG, Morrison SJ. Leptin-receptor-expressing mesenchymal stromal cells represent the main source of bone formed by adult bone marrow. *Cell Stem Cell* 2014; **15**: 154-168 [PMID: 24953181 DOI: 10.1016/j.stem.2014.06.008]

60 **Zhang B**, Yang L, Zeng Z, Feng Y, Wang X, Wu X, Luo H, Zhang J, Zhang M, Pakvasa M, Wagstaff W, He F, Mao Y, Qin K, Ding H, Zhang Y, Niu C, Wu M, Zhao X, Wang H, Huang L, Shi D, Liu Q, Ni N, Fu K, Athiviraham A, Moriatis Wolf J, Lee MJ, Hynes K, Strelzow J, El Dafrawy M, Xia Y, He TC. Leptin Potentiates BMP9-Induced Osteogenic Differentiation of Mesenchymal Stem Cells Through the Activation of JAK/STAT Signaling. *Stem Cells Dev* 2020; **29**: 498-510 [PMID: 32041483 DOI: 10.1089/scd.2019.0292]

61 **Berg AH**, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med* 2001; **7**: 947-953 [PMID: 11479628 DOI: 10.1038/90992]

62 **Padmalayam I**, Suto M. Role of adiponectin in the metabolic syndrome: current perspectives on its modulation as a treatment strategy. *Curr Pharm Des* 2013; **19**: 5755-5763 [PMID: 23448486 DOI: 10.2174/13816128113199990360]

63 **Wang Y**, Zhang X, Shao J, Liu H, Liu X, Luo E. Adiponectin regulates BMSC osteogenic differentiation and osteogenesis through the Wnt/β-catenin pathway. *Sci Rep* 2017; **7**: 3652 [PMID: 28623357 DOI: 10.1038/s41598-017-03899-z]

64 **Chen T**, Wu YW, Lu H, Guo Y, Tang ZH. Adiponectin enhances osteogenic differentiation in human adipose-derived stem cells by activating the APPL1-AMPK signaling pathway. *Biochem Biophys Res Commun* 2015; **461**: 237-242 [PMID: 25892517 DOI: 10.1016/j.bbrc.2015.03.168]

65 **Pu Y**, Wu H, Lu S, Hu H, Li D, Wu Y, Tang Z. Adiponectin Promotes Human Jaw Bone Marrow Stem Cell Osteogenesis. *J Dent Res* 2016; **95**: 769-775 [PMID: 26961489 DOI: 10.1177/0022034516636853]

66 **Wang Y**, Du Y, Yuan H, Pan Y, Wu J, Du X, Hao S, Yan Z, Li X, Liu K, Xu F. Human amnion-derived mesenchymal stem cells enhance the osteogenic differentiation of human adipose-derived stem cells by promoting adiponectin excretion via the APPL1-ERK1/2 signaling pathway. *IUBMB Life* 2020; **72**: 296-304 [PMID: 31509344 DOI: 10.1002/iub.2165]

67 **Li Y**, He J, He X, Li Y, Lindgren U. Nampt expression increases during osteogenic differentiation of multi- and omnipotent progenitors. *Biochem Biophys Res Commun* 2013; **434**: 117-123 [PMID: 23537654 DOI: 10.1016/j.bbrc.2013.02.132]

68 **Otero M**, Lago R, Gomez R, Lago F, Dieguez C, Gómez-Reino JJ, Gualillo O. Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. *Ann Rheum Dis* 2006; **65**: 1198-1201 [PMID: 16414972 DOI: 10.1136/ard.2005.046540]

69 **Tsiklauri L**, Werner J, Kampschulte M, Frommer KW, Berninger L, Irrgang M, Glenske K, Hose D, El Khassawna T, Pons-Kühnemann J, Rehart S, Wenisch S, Müller-Ladner U, Neumann E. Visfatin alters the cytokine and matrix-degrading enzyme profile during osteogenic and adipogenic MSC differentiation. *Osteoarthritis Cartilage*2018; **26**: 1225-1235 [PMID: 29908226 DOI: 10.1016/j.joca.2018.06.001]

70 **Braidy N**, Berg J, Clement J, Khorshidi F, Poljak A, Jayasena T, Grant R, Sachdev P. Role of Nicotinamide Adenine Dinucleotide and Related Precursors as Therapeutic Targets for Age-Related Degenerative Diseases: Rationale, Biochemistry, Pharmacokinetics, and Outcomes. *Antioxid Redox Signal* 2019; **30**: 251-294 [PMID: 29634344 DOI: 10.1089/ars.2017.7269]

71 **Sommer G**, Garten A, Petzold S, Beck-Sickinger AG, Blüher M, Stumvoll M, Fasshauer M. Visfatin/PBEF/Nampt: structure, regulation and potential function of a novel adipokine. *Clin Sci (Lond)* 2008; **115**: 13-23 [PMID: 19016657 DOI: 10.1042/CS20070226]

72 **He X**, He J, Shi Y, Pi C, Yang Y, Sun Y, Ma C, Lin L, Zhang L, Li Y, Li Y. Nicotinamide phosphoribosyltransferase (Nampt) may serve as the marker for osteoblast differentiation of bone marrow-derived mesenchymal stem cells. *Exp Cell Res* 2017; **352**: 45-52 [PMID: 28159473 DOI: 10.1016/j.yexcr.2017.01.021]

73 **Liu Y**, Xu F, Pei HX, Zhu X, Lin X, Song CY, Liang QH, Liao EY, Yuan LQ. Vaspin regulates the osteogenic differentiation of MC3T3-E1 through the PI3K-Akt/miR-34c loop. *Sci Rep* 2016; **6**: 25578 [PMID: 27156573 DOI: 10.1038/srep25578]

74 **Wang H**, Chen F, Li J, Wang Y, Jiang C, Wang Y, Zhang M, Xu J. Vaspin antagonizes high fat-induced bone loss in rats and promotes osteoblastic differentiation in primary rat osteoblasts through Smad-Runx2 signaling pathway. *Nutr Metab (Lond)* 2020; **17**: 9 [PMID: 31993071 DOI: 10.1186/s12986-020-0429-5]

75 **Schulz TJ**, Huang P, Huang TL, Xue R, McDougall LE, Townsend KL, Cypess AM, Mishina Y, Gussoni E, Tseng YH. Brown-fat paucity due to impaired BMP signalling induces compensatory browning of white fat. *Nature* 2013; **495**: 379-383 [PMID: 23485971 DOI: 10.1038/nature11943]

76 **Schulz TJ**, Tseng YH. Emerging role of bone morphogenetic proteins in adipogenesis and energy metabolism. *Cytokine Growth Factor Rev* 2009; **20**: 523-531 [PMID: 19896888 DOI: 10.1016/j.cytogfr.2009.10.019]

77 **Huang Z**, Ren PG, Ma T, Smith RL, Goodman SB. Modulating osteogenesis of mesenchymal stem cells by modifying growth factor availability. *Cytokine* 2010; **51**: 305-310 [PMID: 20580248 DOI: 10.1016/j.cyto.2010.06.002]

78 **Gu K**, Zhang L, Jin T, Rutherford RB. Identification of potential modifiers of Runx2/Cbfa1 activity in C2C12 cells in response to bone morphogenetic protein-7. *Cells Tissues Organs* 2004; **176**: 28-40 [PMID: 14745233 DOI: 10.1159/000075025]

79 **Tsuji K**, Cox K, Bandyopadhyay A, Harfe BD, Tabin CJ, Rosen V. BMP4 is dispensable for skeletogenesis and fracture-healing in the limb. *J Bone Joint Surg Am*2008; **90 Suppl 1**: 14-18 [PMID: 18292351 DOI: 10.2106/JBJS.G.01109]

80 **Kokabu S**, Gamer L, Cox K, Lowery J, Tsuji K, Raz R, Economides A, Katagiri T, Rosen V. BMP3 suppresses osteoblast differentiation of bone marrow stromal cells via interaction with Acvr2b. *Mol Endocrinol* 2012; **26**: 87-94 [PMID: 22074949 DOI: 10.1210/me.2011-1168]

81 **Vaccaro AR**, Whang PG, Patel T, Phillips FM, Anderson DG, Albert TJ, Hilibrand AS, Brower RS, Kurd MF, Appannagari A, Patel M, Fischgrund JS. The safety and efficacy of OP-1 (rhBMP-7) as a replacement for iliac crest autograft for posterolateral lumbar arthrodesis: minimum 4-year follow-up of a pilot study. *Spine J* 2008; **8**: 457-465 [PMID: 17588821 DOI: 10.1016/j.spinee.2007.03.012]

82 **Rivera JC**, Strohbach CA, Wenke JC, Rathbone CR. Beyond osteogenesis: an in vitro comparison of the potentials of six bone morphogenetic proteins. *Front Pharmacol* 2013; **4**: 125 [PMID: 24101902 DOI: 10.3389/fphar.2013.00125]

83 **Tiaden AN**, Breiden M, Mirsaidi A, Weber FA, Bahrenberg G, Glanz S, Cinelli P, Ehrmann M, Richards PJ. Human serine protease HTRA1 positively regulates osteogenesis of human bone marrow-derived mesenchymal stem cells and mineralization of differentiating bone-forming cells through the modulation of extracellular matrix protein. *Stem Cells* 2012; **30**: 2271-2282 [PMID: 22865667 DOI: 10.1002/stem.1190]

84 **Zachos TA**, Shields KM, Bertone AL. Gene-mediated osteogenic differentiation of stem cells by bone morphogenetic proteins-2 or -6. *J Orthop Res* 2006; **24**: 1279-1291 [PMID: 16649180 DOI: 10.1002/jor.20068]

85 **Friedman MS**, Long MW, Hankenson KD. Osteogenic differentiation of human mesenchymal stem cells is regulated by bone morphogenetic protein-6. *J Cell Biochem* 2006; **98**: 538-554 [PMID: 16317727 DOI: 10.1002/jcb.20719]

86 **Goebel-Stengel M**, Stengel A. Role of Brain NUCB2/nesfatin-1 in the Stress-induced Modulation of Gastrointestinal Functions. *Curr Neuropharmacol* 2016; **14**: 882-891 [PMID: 27281021 DOI: 10.2174/1570159X14666160601153202]

87 **Levata L**, Dore R, Jöhren O, Schwaninger M, Schulz C, Lehnert H. Nesfatin-1 Acts Centrally to Induce Sympathetic Activation of Brown Adipose Tissue and Non-Shivering Thermogenesis. *Horm Metab Res* 2019; **51**: 678-685 [PMID: 31487748 DOI: 10.1055/a-0985-4272]

88 **Ranjan A**, Choubey M, Yada T, Krishna A. Nesfatin-1 ameliorates type-2 diabetes-associated reproductive dysfunction in male mice. *J Endocrinol Invest* 2020; **43**: 515-528 [PMID: 31691259 DOI: 10.1007/s40618-019-01136-0]

89 **Xu K**, Zhang Z, Chen M, Moqbel SAA, He Y, Ma C, Jiang L, Xiong Y, Wu L. Nesfatin-1 Promotes the Osteogenic Differentiation of Tendon-Derived Stem Cells and the Pathogenesis of Heterotopic Ossification in Rat Tendons via the mTOR Pathway. *Front Cell Dev Biol* 2020; **8**: 547342 [PMID: 33344440 DOI: 10.3389/fcell.2020.547342]

90 **Lecaille F**, Chazeirat T, Saidi A, Lalmanach G. Cathepsin V: Molecular characteristics and significance in health and disease. *Mol Aspects Med* 2022; **88**: 101086 [PMID: 35305807 DOI: 10.1016/j.mam.2022.101086]

91 **Fain JN**. Release of interleukins and other inflammatory cytokines by human adipose tissue is enhanced in obesity and primarily due to the nonfat cells. *Vitam Horm* 2006; **74**: 443-477 [PMID: 17027526 DOI: 10.1016/S0083-6729(06)74018-3]

92 **Liu F**, Zhou ZF, An Y, Yu Y, Wu RX, Yin Y, Xue Y, Chen FM. Effects of cathepsin K on Emdogain-induced hard tissue formation by human periodontal ligament stem cells. *J Tissue Eng Regen Med* 2017; **11**: 2922-2934 [PMID: 27401615 DOI: 10.1002/term.2195]

93 **Whitty C**, Wardale RJ, Henson FMD. The regulation of sclerostin by cathepsin K in periodontal ligament cells. *Biochem Biophys Res Commun* 2018; **503**: 550-555 [PMID: 29859187 DOI: 10.1016/j.bbrc.2018.05.160]

94 **Zhang W**, Dong Z, Li D, Li B, Liu Y, Zheng X, Liu H, Zhou H, Hu K, Xue Y. Cathepsin K deficiency promotes alveolar bone regeneration by promoting jaw bone marrow mesenchymal stem cells proliferation and differentiation via glycolysis pathway. *Cell Prolif* 2021; **54**: e13058 [PMID: 34053135 DOI: 10.1111/cpr.13058]

95 **Rauner M**, Föger-Samwald U, Kurz MF, Brünner-Kubath C, Schamall D, Kapfenberger A, Varga P, Kudlacek S, Wutzl A, Höger H, Zysset PK, Shi GP, Hofbauer LC, Sipos W, Pietschmann P. Cathepsin S controls adipocytic and osteoblastic differentiation, bone turnover, and bone microarchitecture. *Bone* 2014; **64**: 281-287 [PMID: 24780878 DOI: 10.1016/j.bone.2014.04.022]

96 **Fasshauer M**, Blüher M, Stumvoll M. Adipokines in gestational diabetes. *Lancet Diabetes Endocrinol* 2014; **2**: 488-499 [PMID: 24731659 DOI: 10.1016/S2213-8587(13)70176-1]

97 **Castan-Laurell I**, Dray C, Attané C, Duparc T, Knauf C, Valet P. Apelin, diabetes, and obesity. *Endocrine* 2011; **40**: 1-9 [PMID: 21725702 DOI: 10.1007/s12020-011-9507-9]

98 **Hang K**, Ye C, Xu J, Chen E, Wang C, Zhang W, Ni L, Kuang Z, Ying L, Xue D, Pan Z. Apelin enhances the osteogenic differentiation of human bone marrow mesenchymal stem cells partly through Wnt/β-catenin signaling pathway. *Stem Cell Res Ther* 2019; **10**: 189 [PMID: 31238979 DOI: 10.1186/s13287-019-1286-x]

99 **Yang RZ**, Lee MJ, Hu H, Pray J, Wu HB, Hansen BC, Shuldiner AR, Fried SK, McLenithan JC, Gong DW. Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action. *Am J Physiol Endocrinol Metab* 2006; **290**: E1253-E1261 [PMID: 16531507 DOI: 10.1152/ajpendo.00572.2004]

100 **Yamawaki H**, Tsubaki N, Mukohda M, Okada M, Hara Y. Omentin, a novel adipokine, induces vasodilation in rat isolated blood vessels. *Biochem Biophys Res Commun* 2010; **393**: 668-672 [PMID: 20170632 DOI: 10.1016/j.bbrc.2010.02.053]

101 **Tohidi M**, Akbarzadeh S, Larijani B, Kalantarhormozi M, Ostovar A, Assadi M, Vahdat K, Farrokhnia M, Sanjdideh Z, Amirinejad R, Nabipour I. Omentin-1, visfatin and adiponectin levels in relation to bone mineral density in Iranian postmenopausal women. *Bone* 2012; **51**: 876-881 [PMID: 22971441 DOI: 10.1016/j.bone.2012.08.117]

102 **Tang C**, Liang D, Qiu Y, Zhu J, Tang G. Omentin‑1 induces osteoblast viability and differentiation via the TGF‑β/Smad signaling pathway in osteoporosis. *Mol Med Rep* 2022; **25** [PMID: 35179221 DOI: 10.3892/mmr.2022.12648]

103 **Yan QW**, Yang Q, Mody N, Graham TE, Hsu CH, Xu Z, Houstis NE, Kahn BB, Rosen ED. The adipokine lipocalin 2 is regulated by obesity and promotes insulin resistance. *Diabetes* 2007; **56**: 2533-2540 [PMID: 17639021 DOI: 10.2337/db07-0007]

104 **Jung M**, Weigert A, Mertens C, Rehwald C, Brüne B. Iron Handling in Tumor-Associated Macrophages-Is There a New Role for Lipocalin-2? *Front Immunol* 2017; **8**: 1171 [PMID: 28979267 DOI: 10.3389/fimmu.2017.01171]

105 **Kim HJ**, Yoon HJ, Yoon KA, Gwon MR, Jin Seong S, Suk K, Kim SY, Yoon YR. Lipocalin-2 inhibits osteoclast formation by suppressing the proliferation and differentiation of osteoclast lineage cells. *Exp Cell Res* 2015; **334**: 301-309 [PMID: 25814363 DOI: 10.1016/j.yexcr.2015.03.008]

106 **Yin C**, Jia X, Zhao Q, Zhao Z, Wang J, Zhang Y, Li Z, Sun H, Li Z. Transcription factor 7-like 2 promotes osteogenic differentiation and boron-induced bone repair via lipocalin 2. *Mater Sci Eng C Mater Biol Appl* 2020; **110**: 110671 [PMID: 32204099 DOI: 10.1016/j.msec.2020.110671]

107 **Luchetti F**, Canonico B, Bartolini D, Arcangeletti M, Ciffolilli S, Murdolo G, Piroddi M, Papa S, Reiter RJ, Galli F. Melatonin regulates mesenchymal stem cell differentiation: a review. *J Pineal Res* 2014; **56**: 382-397 [PMID: 24650016 DOI: 10.1111/jpi.12133]

108 **Cardinali DP**, Srinivasan V, Brzezinski A, Brown GM. Melatonin and its analogs in insomnia and depression. *J Pineal Res* 2012; **52**: 365-375 [PMID: 21951153 DOI: 10.1111/j.1600-079X.2011.00962.x]

109 **Rodriguez-Garcia A**, Mayo JC, Hevia D, Quiros-Gonzalez I, Navarro M, Sainz RM. Phenotypic changes caused by melatonin increased sensitivity of prostate cancer cells to cytokine-induced apoptosis. *J Pineal Res* 2013; **54**: 33-45 [PMID: 22738066 DOI: 10.1111/j.1600-079X.2012.01017.x]

110 **Murdolo G**, Piroddi M, Luchetti F, Tortoioli C, Canonico B, Zerbinati C, Galli F, Iuliano L. Oxidative stress and lipid peroxidation by-products at the crossroad between adipose organ dysregulation and obesity-linked insulin resistance. *Biochimie* 2013; **95**: 585-594 [PMID: 23274128 DOI: 10.1016/j.biochi.2012.12.014]

111 **Zhang L**, Zhang J, Ling Y, Chen C, Liang A, Peng Y, Chang H, Su P, Huang D. Sustained release of melatonin from poly (lactic-co-glycolic acid) (PLGA) microspheres to induce osteogenesis of human mesenchymal stem cells in vitro. *J Pineal Res* 2013; **54**: 24-32 [PMID: 22712496 DOI: 10.1111/j.1600-079X.2012.01016.x]

112 **Topol LZ**, Bardot B, Zhang Q, Resau J, Huillard E, Marx M, Calothy G, Blair DG. Biosynthesis, post-translation modification, and functional characterization of Drm/Gremlin. *J Biol Chem* 2000; **275**: 8785-8793 [PMID: 10722723 DOI: 10.1074/jbc.275.12.8785]

113 **Grillo E**, Ravelli C, Colleluori G, D’Agostino F, Domenichini M, Giordano A, Mitola S. Role of gremlin-1 in the pathophysiology of the adipose tissues. *Cytokine Growth Factor Rev* 2023; **69**: 51-60 [PMID: 36155165 DOI: 10.1016/j.cytogfr.2022.09.004]

114 **Gazzerro E**, Smerdel-Ramoya A, Zanotti S, Stadmeyer L, Durant D, Economides AN, Canalis E. Conditional deletion of gremlin causes a transient increase in bone formation and bone mass. *J Biol Chem* 2007; **282**: 31549-31557 [PMID: 17785465 DOI: 10.1074/jbc.M701317200]

115 **Hu K**, Sun H, Gui B, Sui C. Gremlin-1 suppression increases BMP-2-induced osteogenesis of human mesenchymal stem cells. *Mol Med Rep* 2017; **15**: 2186-2194 [PMID: 28260028 DOI: 10.3892/mmr.2017.6253]

116 **Shore VG**, Shore B. Heterogeneity of human plasma very low density lipoproteins. Separation of species differing in protein components. *Biochemistry* 1973; **12**: 502-507 [PMID: 4345806 DOI: 10.1021/bi00727a022]

117 **Marais AD**. Apolipoprotein E and Atherosclerosis. *Curr Atheroscler Rep* 2021; **23**: 34 [PMID: 33970359 DOI: 10.1007/s11883-021-00933-4]

118 **Marais AD**. Apolipoprotein E in lipoprotein metabolism, health and cardiovascular disease. *Pathology* 2019; **51**: 165-176 [PMID: 30598326 DOI: 10.1016/j.pathol.2018.11.002]

119 **Huang Y**, Mahley RW. Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer’s diseases. *Neurobiol Dis* 2014; **72 Pt A**: 3-12 [PMID: 25173806 DOI: 10.1016/j.nbd.2014.08.025]

120 **Bächner D**, Schröder D, Betat N, Ahrens M, Gross G. Apolipoprotein E (ApoE), a Bmp-2 (bone morphogenetic protein) upregulated gene in mesenchymal progenitors (C3H10T1/2), is highly expressed in murine embryonic development. *Biofactors* 1999; **9**: 11-17 [PMID: 10221153 DOI: 10.1002/biof.5520090103]

121 **Lamers D**, Famulla S, Wronkowitz N, Hartwig S, Lehr S, Ouwens DM, Eckardt K, Kaufman JM, Ryden M, Müller S, Hanisch FG, Ruige J, Arner P, Sell H, Eckel J. Dipeptidyl peptidase 4 is a novel adipokine potentially linking obesity to the metabolic syndrome. *Diabetes* 2011; **60**: 1917-1925 [PMID: 21593202 DOI: 10.2337/db10-1707]

122 **Choi B**, Lee S, Kim SM, Lee EJ, Lee SR, Kim DH, Jang JY, Kang SW, Lee KU, Chang EJ, Song JK. Dipeptidyl Peptidase-4 Induces Aortic Valve Calcification by Inhibiting Insulin-Like Growth Factor-1 Signaling in Valvular Interstitial Cells. *Circulation* 2017; **135**: 1935-1950 [PMID: 28179397 DOI: 10.1161/CIRCULATIONAHA.116.024270]

123 **Lambert E**, Dassé E, Haye B, Petitfrère E. TIMPs as multifacial proteins. *Crit Rev Oncol Hematol* 2004; **49**: 187-198 [PMID: 15036259 DOI: 10.1016/j.critrevonc.2003.09.008]

124 **Lu P**, Takai K, Weaver VM, Werb Z. Extracellular matrix degradation and remodeling in development and disease. *Cold Spring Harb Perspect Biol* 2011; **3** [PMID: 21917992 DOI: 10.1101/cshperspect.a005058]

125 **Arpino V**, Brock M, Gill SE. The role of TIMPs in regulation of extracellular matrix proteolysis. *Matrix Biol* 2015; **44-46**: 247-254 [PMID: 25805621 DOI: 10.1016/j.matbio.2015.03.005]

126 **Jackson HW**, Defamie V, Waterhouse P, Khokha R. TIMPs: versatile extracellular regulators in cancer. *Nat Rev Cancer* 2017; **17**: 38-53 [PMID: 27932800 DOI: 10.1038/nrc.2016.115]

127 **Egea V**, Zahler S, Rieth N, Neth P, Popp T, Kehe K, Jochum M, Ries C. Tissue inhibitor of metalloproteinase-1 (TIMP-1) regulates mesenchymal stem cells through let-7f microRNA and Wnt/β-catenin signaling. *Proc Natl Acad Sci U S A* 2012; **109**: E309-E316 [PMID: 22223664 DOI: 10.1073/pnas.1115083109]

128 **Liang T**, Gao W, Zhu L, Ren J, Yao H, Wang K, Shi D. TIMP-1 inhibits proliferation and osteogenic differentiation of hBMSCs through Wnt/β-catenin signaling. *Biosci Rep* 2019; **39** [PMID: 30473539 DOI: 10.1042/BSR20181290]

129 **Jiang C**, Xia W, Wu T, Pan C, Shan H, Wang F, Zhou Z, Yu X. Inhibition of microRNA-222 up-regulates TIMP3 to promotes osteogenic differentiation of MSCs from fracture rats with type 2 diabetes mellitus. *J Cell Mol Med* 2020; **24**: 686-694 [PMID: 31691506 DOI: 10.1111/jcmm.14777]

130 **Lehr S**, Hartwig S, Sell H. Adipokines: a treasure trove for the discovery of biomarkers for metabolic disorders. *Proteomics Clin Appl* 2012; **6**: 91-101 [PMID: 22213627 DOI: 10.1002/prca.201100052]

131 **Kra G**, Daddam JR, Moallem U, Kamer H, Kočvarová R, Nemirovski A, Contreras GA, Tam J, Zachut M. Effects of omega-3 supplementation on components of the endocannabinoid system and metabolic and inflammatory responses in adipose and liver of peripartum dairy cows. *J Anim Sci Biotechnol* 2022; **13**: 114 [PMID: 36183098 DOI: 10.1186/s40104-022-00761-9]

132 **Cruz-López EO**, Uijl E, Danser AHJ. Perivascular Adipose Tissue in Vascular Function: Does Locally Synthesized Angiotensinogen Play a Role? *J Cardiovasc Pharmacol* 2021; **78**: S53-S62 [PMID: 34840262 DOI: 10.1097/FJC.0000000000001027]

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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-: Transforming growth factor beta; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor.



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