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MINIREVIEWS

Effect of adipokines on bone marrow mesenchymal stem cell function

Rui-Ming Wen, Hai-Xia Wang

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Rui-Ming Wen, School of Sports Health, Shenyang Sport University, Shenyang 110102, Liaoning Province, China

Hai-Xia Wang, College of Exercise and Health, Shenyang Sport University, Shenyang 110102, Liaoning Province, China

Co-first authors: Rui-Ming Wen and Hai-Xia Wang.

Corresponding author: Hai-Xia Wang, PhD, College of Exercise and Health, Shenyang Sport University, No. 36 Jinqiansong East Road, Shenyang 110102, Liaoning Province, China. whx1415@163.com

Abstract

During excessive adipose tissue accumulation, various adipokines such as visfatin, chemerin, vaspin, and adiponectin are released into systemic circulation, thereby influencing metabolic tissue function throughout the body. As multifunctional signaling molecules secreted by adipose tissue, adipokines play a pivotal role in metabolic regulation, inflammatory response, and tissue homeostasis. Recent studies have demonstrated that adipokines can influence skeletal system repair and regeneration by modulating bone marrow-derived mesenchymal stem cell (BMSC) proliferation, differentiation, migration, and immunomodulatory functions. However, different adipokines have distinct roles in regulating BMSC function, but their underlying molecular mechanisms are not fully understood. In this review, we systematically summarize the specific mechanisms of action and potential clinical applications of visfatin, chemerin, vaspin, and adiponectin on BMSC function in order to reveal new mechanisms of interaction between adipokines and BMSCs. The aim is to provide a theoretical basis for targeted treatment strategies for bone diseases targeting adipokines.

Key Words: Adipokine; Bone marrow-derived mesenchymal stem cells; Osteogenic differentiation; Adipogenic differentiation; Chondrogenic differentiation

Core Tip: Recent studies have shown that adipokines can play an important role in skeletal system repair and regeneration by regulating bone marrow-derived mesenchymal stem cell (BMSC) proliferation, differentiation, migration, and immune regulation. This review summarizes and elaborates on the specific mechanisms of action and potential clinical application prospects of the adipokines visfatin, chemerin, vaspin, and adiponectin on BMSC function. The aim is to reveal new pathways of interaction between adipokines and BMSCs and provide theoretical support for targeted adipokine-based bone disease treatment strategies.

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INTRODUCTION

As a group of stem cells with self-renewal ability and multipotent differentiation potential, bone marrow-derived mesenchymal stem cells (BMSCs) are widely present in various tissues such as bone marrow, adipose tissue, and umbilical cord blood[1,2]. Due to their self-renewal and multipotent differentiation potential, BMSCs play an important role in bone regeneration, cartilage repair, and immune regulation, maintaining tissue homeostasis, promoting injury repair, and participating in disease occurrence and development[3,4]. With the continued deepening of stem cell research, recent work has revealed that BMSC function is regulated by various paracrine factors in the microenvironment, including adipose tissue-derived adipokines[5,6].

As a crucial endocrine organ in the human body, adipose tissue not only acts as an energy storage reservoir, but more importantly, it can secrete molecules with a wide range of biological activities, collectively known as adipokines[7]. During obesity, excessive accumulation of adipose tissue is accompanied by abnormal adipokine release, which in turn has a profound impact on the body's glucose and lipid metabolism, inflammatory response, insulin resistance, and the occurrence and development of various metabolic diseases[8,9] (Figure 1). Adipokines are not only key regulators of energy metabolism, but have also been shown to be involved in determining stem cell fates. Numerous studies have identified a complex relationship between adipokines and BMSCs[6]. As signaling molecules, adipokines can finely regulate the core functions of BMSCs such as proliferation, differentiation, migration, and apoptosis by activating or inhibiting specific signaling pathways, thereby regulating the body's metabolic status and repair ability[10,11]. These findings provide new perspectives and ideas for using BMSCs in disease treatment. However, although the impact of adipokines on BMSC function has attracted widespread attention, the research is still in its infancy, and specific molecular mechanisms and regulatory pathways have not been fully elucidated. Therefore, this article focuses on four types of adipokines, visfatin, chemerin, vaspin, and adiponectin (APN), and explores their effects on BMSC function and elucidates their potential molecular mechanisms, aiming to provide new ideas and a basis for clinical treatment and the scientific exploration of tissue repair.

THE REGULATORY EFFECT OF VISFATIN ON BONE MARROW MESENCHYMAL STEM CELLS

Visfatin, also known as visceral fat factor, pre-B cell enhancing factor, and nicotinamide phosphoribosyltransferase (NAMPT) in its extracellular form, is a fatty factor with a wide range of biological activities[12,13]. Visfatin is mainly derived from visceral adipose tissue, but is also expressed in the placenta, skin, liver, stomach, pancreatic islet cells, and hypothalamus[14-16]. The visfatin gene is located between chromosomes 7q22.1 and 7q31.33, consisting of 491 amino acids and a 52 kD peptide. It forms two domains through 19β-turns and 13α-helices[17,18]. As a novel adipocyte cytokine, visfatin activates target cells by binding to insulin receptors, exerting insulin-like effects including promoting glucose uptake and triglyceride synthesis[19]. In addition, visfatin has NAMPT activity, which can catalyze the conversion of nicotinamide to nicotinamide adenine dinucleotide (NAD), the rate limiting step in nicotinamide mononucleotide biosynthesis[20,21]. These functions play an important role in regulating energy metabolism, inflammatory response, cell apoptosis, and immune response in the body.

In the context of BMSCs, visfatin exhibits complex and diverse effects. During osteoblast differentiation, visfatin expression increases over time. After treatment with the specific visfatin inhibitor FK866, the expression of the key transcription factor runt-related transcription factor 2 (Runx2) and osteoblast marker genes osteocalcin (OCN) and osteopontin (OPN) sharply decrease. This indicates that visfatin deficiency in BMSCs inhibits osteoblast differentiation. Further research has found that visfatin may reduce BMSC differentiation into osteoblasts through the NAD-sirtuin 1 (Sirt1) signaling pathway[22]. Consistent with the above, treatment of primary BMSCs with the visfatin inhibitor FK866 increased adipocyte formation and decreased osteogenic differentiation. In addition, visfatin knockout (KO) in the mouse C3H10T1/2 mesenchymal cell line caused a decrease in Sirt1 activity, leading to weakened osteoblast differentiation and enhanced adipogenesis[23]. Visfatin also induces the secretion of pro-inflammatory factors in osteogenesis and adipogenesis, increases matrix metalloproteinase levels, and causes an imbalance in matrix metalloproteinase/tissue metalloproteinase inhibitors during BMSC differentiation[24]. Visfatin plays a dual regulatory role between adipogenesis and

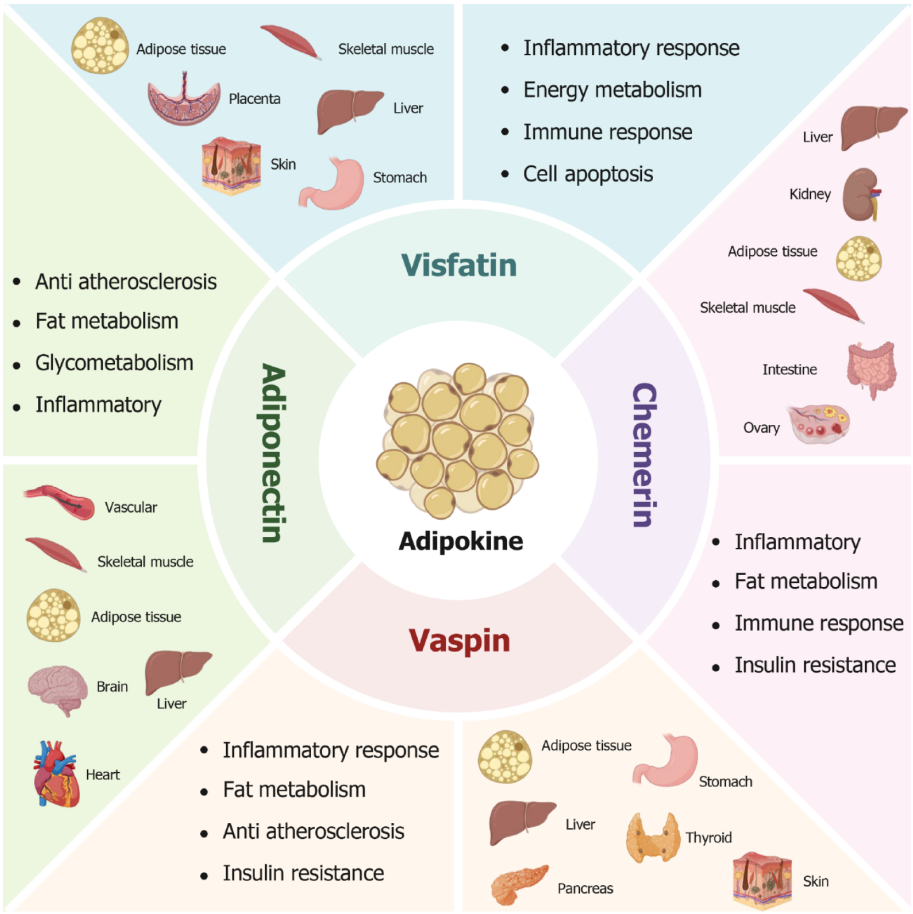

Figure 1 The distribution and biological roles of four adipokines (visfatin, chemerin, vaspin, and adiponectin) in human tissues and organs. Visfatin primarily comes from visceral adipose tissue, but it is also expressed in placenta, skin, liver, stomach and hypothalamus, and plays an important role in regulating energy metabolism, inflammatory reaction, apoptosis and immune response. Chemerin is mainly secreted by adipocytes, macrophages, dendritic cells and endothelial cells, showing multiple biological effects, such as regulating adipocyte differentiation, participating in immune response, and promoting cholesterol uptake by macrophages. Vaspin is composed of fat, liver, stomach, skin and other organs, which can participate in regulating inflammatory reaction, insulin resistance and adipocyte differentiation and other physiological processes, thus playing an important role in maintaining metabolic homeostasis of the body. Adiponectin is mainly secreted by blood vessels, fat, brain, skeletal muscle and so on to the whole body, which plays a role in lipid metabolism, inflammatory reaction and so on.

osteogenic differentiation, and this balance is crucial for maintaining bone health[25]. Visfatin also affects stem cell aging. Reducing visfatin levels in aging mesenchymal stem cells (MSCs) leads to a decrease in intracellular concentration of NAD^+ and downregulation of Sirt1 expression and activity. Similarly, treatment of young MSCs with the visfatin inhibitor FK866 induced senescence. On the contrary, visfatin overexpression alleviates cellular senescence in aging MSCs and significantly reduces senescence-associated β-galactosidase activity[26]. Other studies have also shown that visfatin can increase intracellular NAD^+ levels and activate Sirt1 deacetylase through NAMPT enzyme activity, thereby inhibiting p53-mediated cellular aging[27]. Therefore, in-depth research on the function and regulatory mechanism of visfatin is important for understanding the molecular mechanism of stem cell aging and developing anti-aging drugs (Figure 2).

These findings not only deepen our understanding of the biological functions of visfatin, but also provide new perspectives and ideas for exploring regenerative medicine strategies based on BMSCs. In the future, further exploration is needed to investigate the *in vivo* effects of visfatin, its interactions with other adipokines, its dual effects in different pathological microenvironments, and to verify its clinical safety through animal experiments.

THE REGULATORY EFFECT OF CHEMERIN ON BMSCs

Chemerin is an adipokine and chemotactic protein primarily secreted by adipocytes, macrophages, dendritic cells, and endothelial cells, among others. It is widely involved in obesity, metabolic syndrome, diabetes mellitus (DM), atherosclerosis, inflammation and other pathological processes[28-30]. Chemerin is encoded by the *RARRES2* gene and secreted in the form of an inactive precursor. It is activated by protease cleavage, and the full-length gene sequence is located on human chromosome 7q36.1, consisting of four exons. The encoded protein has a moderate molecular weight but contains strong biological activity[31,32]. By binding to receptors on the target cell membrane, chemerin exhibits multiple biological effects, such as regulating adipocyte differentiation, participating in immune responses, promoting ma-

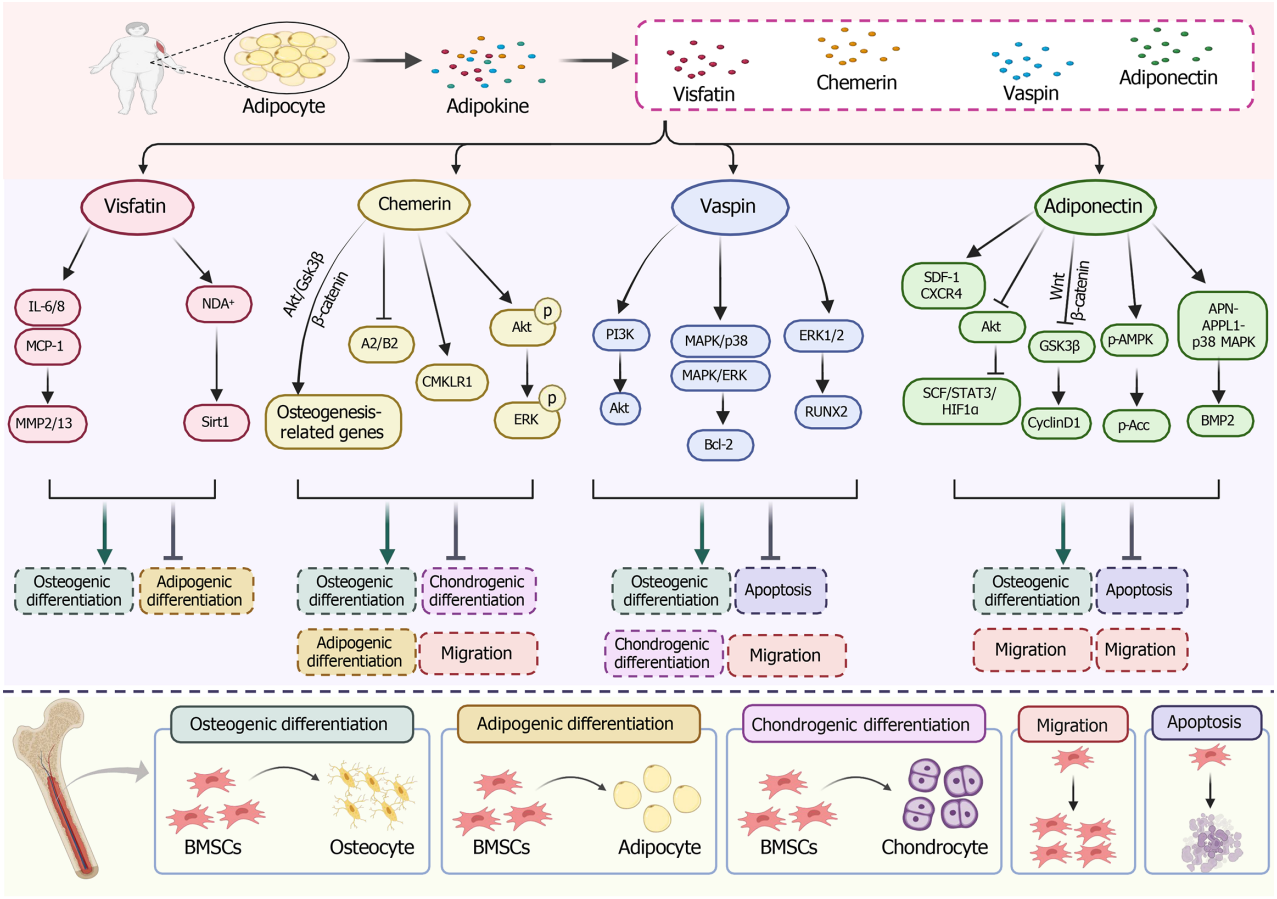

Figure 2 The mechanism by which adipokines regulate the proliferation, apoptosis, and differentiation of bone marrow-derived mesenchymal stem cells. Adipokines produced by adipose tissue regulate the osteogenic, adipogenic, and chondrogenic differentiation of bone marrow-derived mesenchymal stem cells (BMSCs) through various signaling pathways, and affect BMSC apoptosis and proliferation processes. Visfatin enhances osteogenic differentiation by up-regulating runt-related transcription factor 2 expression, and can delay cell aging through NAD+-sirtuin 1-p53. Chemerin regulates BMSC chemotaxis, proliferation, migration and osteogenic differentiation through chemerin chemokine-like receptor 1 and may regulate cartilage differentiation through extracellular regulated protein kinases 1/2 pathway. Vaspin specifically activates phosphoinositide-3 kinase/protein kinase B and extracellular regulated protein kinases 1/2 signaling pathways, inhibits inflammatory signaling pathways such as nuclear factor kappa B, and activates mitogen-activated protein kinase/p38 signaling pathways, thus enhancing BMSC viability, proliferation, differentiation, anti-apoptosis and anti-inflammatory ability. Adiponectin activates peroxisome proliferator-activated receptor γ pathway, stem cell factor/signal transducer and activator of transcription 3/hypoxia inducible factor 1α pathway, stromal cell-derived factor 1/CXC receptor 4, adenosine 5'-monophosphate-activated protein kinase pathway and Wnt/β-catenin through Adiponectin receptor 1 to promote BMSC migration, apoptosis and differentiation. IL-6/8: Interleukin-6/8; MCP-1: Monocyte chemotactic protein-1; MMP2/13: Matrix metalloproteinases 2/13; NAD: Nicotinamide adenine dinucleotide; Sirt1: Sirtuin 1; AKT: Protein kinase B; GSK3β: Glycogen synthase kinase 3 beta; CMKLR1: Chemokine-like receptor 1; ERK: Extracellular regulated protein kinases; PI3K: Phosphoinositide-3 kinase; MAPK: Mitogen-activated protein kinase; RUNX2: Runt-related transcription factor 2; Bcl-2: B cell lymphoma-2; SDF-1: Stromal cell-derived factor 1; CXCR4: CXC receptor 4; SCF: Stem cell factor; STAT3: Signal transducer and activator of transcription 3; HIF1α: Hypoxia inducible factor 1α; AMPK: Adenosine 5'-monophosphate-activated protein kinase; APN: Adiponectin; APPL1: Adaptor protein containing a PH domain, PTB domain and leucine zipper motif 1; Acc: Acetyl-CoA carboxylase; BMP2: Bone morphogenetic protein 2; BMSCs: Bone marrow mesenchymal stromal cells.

crophage uptake of cholesterol, *etc*[33,34]. More importantly, chemerin regulates inflammatory reactions, metabolic balance and tissue repair by binding its receptors chemerin chemokine-like receptor 1 (CMKLR1), G protein-coupled receptor 1 and C-C motif chemokine receptor like 2, and mediates downstream mitogen-activated protein kinase (MAPK)-extracellular regulated protein kinases 1/2 (ERK1/2), phosphoinositide-3 kinase (PI3K)/protein kinase B (AKT), adenosine 5'-monophosphate-activated protein kinase (AMPK) and nuclear factor kappa B signaling pathways[35-39]. The regulatory effect of chemerin on BMSCs is gradually being discovered.

Recent studies have shown that chemerin may guide the differentiation of osteoblasts, adipocytes, and chondrocytes by regulating the expression of related genes, thereby accelerating the repair and reconstruction of bone and cartilage tissues. In ovariectomized (OVX)-induced osteoporosis mice, endogenous chemerin can inhibit the formation of intraosseous blood vessels and osteoblast differentiation and proliferation[40], and reduce the expression of osteogenic markers Runx2, osteoprotegerin, and β-catenin by inhibiting Wnt/β-catenin signaling. Furthermore, it inhibits osteoblast differentiation and proliferation and enhances osteoclast differentiation by activating receptor activator of NF-κB signaling[41]. Surprisingly, during the osteogenic differentiation of BMSCs, the expression of chemerin was significantly upregulated with the increase of osteogenic genes alkaline phosphatase (ALP), Runx2, and OPN. It promotes osteogenic differentiation through the AKT/glycogen synthase kinase 3β (GSK3β)/β-catenin pathway, and *in vitro* administration has confirmed that chemerin can increase calcium deposition and osteogenic gene expression in C3H10T1/2 cells[42]. In

addition, *in vitro* studies have found that CMKLR1 deficiency leads to impaired osteoblast generation, causing BMSCs to transition from osteogenic differentiation to adipogenic differentiation[43]. From this, it can be seen that the effect of chemerin may depend on the action time/concentration of chemerin, receptor subtype, cell source and microenvironment, such as extracellular matrix (ECM), other cytokines, physical stimulation, *etc*., in which cells are located. In BMSCs, cells are in the early stage of multidirectional differentiation, and chemerin promotes osteogenic differentiation. In mature osteoblast/osteoclast precursor cells, their differentiation state is close to the terminal stage, and they are more sensitive to signaling pathways. C-C motif chemokine receptor like 2 or other receptors mediate Wnt inhibition and receptor activator of NF-κB activation, which leads to osteogenesis inhibition and osteoclast enhancement[44]. This mechanism may reflect the dynamic regulation of chemerin in bone homeostasis, but more complex regulatory mechanisms require further validation. Chemerin/CMKLR1 regulates typical Wnt signaling in BMSCs by affecting the expression, subcellular localization, and transcriptional activity of the central Wnt transducer β-catenin. CMKLR1 is a novel Wnt-responsive gene that acts in a negative feedback loop to limit Wnt signaling generated by osteoblasts. Mechanistically, this requires Notch-dependent changes in the expression and function of key adipogenic and osteogenic transcription factors, cell cycle proteins, and chromatin remodeling enzymes[44]. Research has found that chemerin can promote adipocyte differentiation, and loss of chemerin or CMKLR1 inhibits adipocyte differentiation, clonal expansion, and BMSC proliferation[45,46]. This inhibitory effect is achieved by increasing in G(2)/M phase cell cycle proteins (especially A2/B2), rather than reducing G(1)/S phase cell cycle protein D2[47]. The forced expression of the adipogenic transcription factor peroxisome proliferator-activated receptor γ (PPAR-γ) also promoted chemerin expression and reversed the loss of adipogenesis associated with chemerin or CMKLR1 knockdown in BMSCs[45]. However, simvastatin intervention inhibits BMSC adipogenesis by downregulating PPAR-γ, thereby blocking PPAR-γ-mediated chemerin/CMKLR1 signaling[35]. However, the fundamental mechanism by which chemerin/CMKLR1 affects lineage determination of BMSC differentiation has not been fully characterized.

Chemerin also seems to affect chondrocyte differentiation. At a dose of 5 μM, chemerin intervention significantly reduced chondrocyte proliferation by inducing chondrocyte metabolism and differentiation through AKT/ERK phosphorylation, thereby exacerbating osteoarthritis[48]. It is worth mentioning that chemerin may also mediate macrophage polarization and inflammatory bone destruction[49,50], but its regulation of BMSC immune function requires further research (Figure 2).

Chemerin regulates BMSC proliferation, differentiation, and immune regulatory function of through a multi-receptor multi-pathway network, but its effects are concentration - and microenvironment-dependent. Although the specific mechanism by which chemerin affects BMSC function is not yet fully understood, chemerin has broad application prospects in areas such as tissue repair, regeneration, and immune regulation.

THE REGULATORY EFFECT OF VASPIN ON BMSCs

Vaspin, also known as visceral adipose tissue derived serine protease inhibitor, is a type of adipokine belonging to the serpin family and is therefore named SERPINA12[51]. Its gene is located on human chromosome 10q23.31, and it encodes a protein with moderate molecular weight and significant biological activity[52]. As a serine protease inhibitor, vaspin has unique biochemical properties. By inhibiting specific serine protease activities, vaspin participates in regulating physiological processes such as inflammation, insulin resistance, and adipocyte differentiation, thus playing an important role in maintaining metabolic homeostasis throughout the body[53-55]. Similar to chemerin, vaspin originates from adipose tissue, especially visceral fat, and plays an important role in obesity, DM, metabolic syndrome and other metabolic diseases[54,56-58]. Multiple studies have shown that vaspin levels often exhibit abnormal changes in patients with metabolic disorders, suggesting that it may serve as a potential biomarker for disease diagnosis, disease monitoring, and prognosis evaluation[55,59,60].

It is worth noting that vaspin not only plays an important role in metabolic disease pathology and physiology, but also exhibits multidimensional biological effects in regulating BMSC function[61]. In terms of cell proliferation regulation, vaspin significantly enhances the survival ability of BMSCs and promotes their mitotic process by specifically activating the PI3K/AKT and ERK1/2 signaling pathways, providing necessary cellular reserves for tissue regeneration[62]. The results showed that the proliferation rate of BMSCs dramatically increased after 150 ng/mL vaspin treatment, accompanied by PI3K/AKT signal pathway activation. However, when the concentration increased to 300 ng/mL, cell proliferation rate decreased in a dose-dependent manner[62]. This indicates that there is not a concentration-dependent effect of vaspin on BMSC proliferation. To better understand this characteristic, future research should explore the optimal concentration range of vaspin and its mechanism of action under different experimental conditions. For example, by setting a detailed concentration gradient experiment, the optimal concentration threshold of vaspin for BMSC proliferation can more accurately determined. In addition, at the microenvironment regulation level, vaspin enhances BMSC adaptability through dual mechanisms. In terms of anti-inflammation, vaspin can reduce the inflammatory reaction at the site of tissue injury and create a more favorable microenvironment for BMSC proliferation and differentiation by inhibiting the activation of inflammatory signal pathways such as NF-κB[63]. Vaspin inhibits the apoptosis of BMSCs and osteoblasts induced by oxidative stress by activating MAPK/p38 and MAPK/ERK signaling pathways[64]. In addition, vaspin can up-regulate the expression of the anti-apoptosis protein B-cell lymphoma-2 and enhance the survival rate of BMSCs in hypoxic microenvironments. At the same time, understanding the role of vaspin in different growth factors, nutrients or oxygen concentrations will help reveal its regulatory mechanism in different microenvironments. Similarly, vaspin is also important in regulating BMSC differentiation. Vaspin can affect the differentiation direction of BMSCs by activating Smad2/3-Runx2, transforming growth factor-β1/Smad and other signaling pathways, thus participating in the

reconstruction process of bone and adipose tissue[65,66]. Specifically, vaspin can upregulate the expression of osteogenic differentiation related genes such as ALP, Runx2, osterix, and collegen alpha 1, and promote osteoblast proliferation and differentiation[67]. Vaspin also promotes Runx2 and osterix expression through the ERK1/2 pathway, increases ALP activity, and promotes calcium nodule formation. Vaspin promotes chondrogenic differentiation and chondrocyte survival of BMSCs by activating the AKT pathway, increasing the expression of cartilage formation and ECM secretion related markers (SRY-box transcription factor 9, collagen type II alpha 1 chain, and COMP), and delaying ECM degradation[68]. In addition, vaspin can antagonize PPAR-γ signaling and reduce lipid droplet accumulation, suggesting that it may have a protective effect in metabolic bone diseases (Figure 2).

These results reveal a new role of vaspin in regulating BMSC function and provide new ideas for exploring its application in tissue repair, regeneration, and treatment of metabolic diseases. Therefore, in-depth research on the mechanism of vaspin in regulating the osteogenic and chondrogenic differentiation of BMSCs will help develop new therapeutic strategies to address bone metabolism-related diseases. Vaspin provides a new strategy for cell therapy of metabolic and degenerative diseases by regulating BMSC function through multiple targets. In the future, gene editing and biomaterial technology can be combined to optimize the spatiotemporal specific delivery of vaspin and explore its dynamic role in the pathological microenvironment.

THE REGULATORY EFFECT OF APN ON BMSCs

APN is a protein hormone mainly secreted by adipose tissue. It plays a key role in the pathogenesis and pathophysiological process of obesity, type 2 DM, cardiovascular disease, metabolic syndrome and other metabolic diseases[69-71]. APN is a protein with a molecular weight of approximately 30 kDa, consisting of 244 amino acids and a monomeric glycoprotein. It has an N-terminal signal sequence, a non-homologous or hypervariable region, a collagen domain, and a C-terminal globular domain[72]. Its gene is located on human chromosome 3q27, encoding a relatively large molecular weight protein. Despite its complex structure, it has extremely strong biological activity[73,74]. The role of APN in metabolic syndrome has been widely studied by activating downstream signaling pathways such as AMPK, p38 MAPK, and PI3K/AKT through the combination of Adiponectin receptor 1/2 receptors[75,76]. However, its regulation of stem cell function has gradually become a new area of research interest.

Previous reports have found that APN can enhance endothelial progenitor cell migration through the PI3K signaling pathway and promote cell regeneration in bone injury areas through blood flow migration[77,78]. In contrast, further research has found that APN depletion accelerates BMSC migration under low oxygen conditions. Compared to the wild type mouse group, the BMSCs in APN-KO mice were more abundant, and the colony forming ability and proliferation rate of APN-KO BMSCs were significantly increased. Interestingly, markers of pluripotency and self-renewability (SRY-box transcription factor 9, Nanog, and octamer-binding transcription factor 4) were significantly upregulated in BMSCs with APN deficiency. Mechanistically, APN deficiency may inactivate GSK3β through AKT activation, leading to high activation of stem cell factor/signal transducer and activator of transcription 3/hypoxia inducible factor 1α and increased migration ability of APN-KO BMSCs[6]. However, another study suggested that APN promotes BMSC migration and bone regeneration by regulating the stromal cell-derived factor 1 (SDF-1)/CXC receptor 4 axis in a mouse bone defect model, by increasing circulating SDF-1 concentration and decreasing SDF-1 expression in the bone marrow after injury to regulate the SDF-1 chemotaxis gradient of BMSCs migration from bone marrow to circulation[78]. The differences require further research to confirm. Supplementing with APN can effectively protect BMSCs from the effects of fluid shear stress, promote BMSC viability in fluid shear stress cultured rats, and reduce cell apoptosis. Specifically, APN pretreatment further increased the phosphorylation levels of AMPK and acetyl-CoA carboxylase, upregulated the expression of B cell lymphoma-2, and decreased the expression of B cell lymphoma-2-associated X[79].

Meanwhile, APN can also affect BMSC differentiation towards osteogenesis, adipogenesis, and chondrogenesis by regulating the activity of related transcription factors. APN can activate the Wnt/β-catenin pathway, which is a classic pathway for osteogenesis[80]. When the pathway is activated, GSK3β is inhibited, and excessive β-catenin enters the nucleus, activating the expression of downstream gene cyclinD1 and promoting osteogenic differentiation[81-84]. According to reports, transfection of BMSCs with recombinant adenovirus carrying the *APN* gene increased the expression of Wnt/β-catenin pathway related molecules in cells, and increased the expression of osteogenic factors such as bone morphogenetic protein 2, Runx2, and OCN[85]. APN can also upregulate the levels of osteogenic related genes and promote osteogenic differentiation of BMSCs and C3H10T1/2 cells by activating the APN-activating adaptor protein, phosphotyrosine interaction, PH domain and leucine zipper containing 1-p38 MAPK pathway in a cyclooxygenase-2 dependent manner[86,87]. Wang *et al*[88] found that human amnion-derived mesenchymal stem cells promoted APN secretion by activating adaptor protein, phosphotyrosine interaction, PH domain and leucine zipper containing 1-ERK1/2, thus inducing the osteogenesis of human amnion-derived mesenchymal stem cells[88]. In addition, APN is the key molecule of multi-directional BMSC differentiation in ovariectomized mice, which has the characteristics of promoting bone formation and anti-fat, which is closely related to the Sirt1 and Wnt signaling pathways[89].

However, studies have shown that APN reduces ALP activity and vitamin D receptor expression in the late stage of osteogenic differentiation, thereby weakening osteogenic ability. In contrast to osteogenic differentiation, APN inhibits PPAR-γ activity through AMPK/mammalian target of rapamycin signaling, reduces adipocyte generation, and suppresses adipocyte differentiation[90,91]. The osteogenic and adipogenic differentiation balance of BMSCs is regulated by multiple factors, and APN mainly reduces the proportion of adipogenic differentiation by promoting osteogenic differentiation. The effect of APN on chondrogenic differentiation of BMSCs has been less studied, but some studies have shown that it can increase chondrocyte proliferation, proteoglycan synthesis, and matrix mineralization, upregulate the

expression of collagen type II alpha 1 chain, aggrecan, Runx2, ALP, and type X collagen[92,93]. In addition, studies on cartilage induced scaffolds have shown that the combination of exogenous factors such as insulin-like growth factor 1 receptor and transforming growth factor-beta 1 can significantly promote the transformation of stem cells into cartilage differentiation[94]. APN receptors 1 and 2 (AR1 and AR2) are important mediators of APN biological functions[95]. The circulating level and local expression of APN in bone marrow of old mice were significantly higher than those of young mice. The activation of AdipoRon plays an important role in promoting bone differentiation of BMSCs from young mice, while the old mice show impaired bone repair and migration and decreased osteogenic differentiation, which may be attributed to increased AR2 expression and enhanced cell aging driven by subsequent activation of downstream mammalian target of rapamycin pathway. AdipoRon significantly enhanced BMSC migration ability, the number of ALP-positive cells and the expression of osteogenic markers (including ALP, osterix, RUNX2, type I collagen, OCN and OPN) in young mice[96,97], which indicated that the osteogenic differentiation of BMSCs in young mice was enhanced, but it showed the opposite effect on BMSCs from old mice[96]. The above differential reactions may be due to the different distribution of AR1 and AR2 in young and old BMSCs (Figure 2).

To sum up, APN has potential therapeutic value in bone metabolism diseases and tissue repair by regulating the proliferation, migration, apoptosis, and differentiation of BMSCs through multiple targets. Future research can further explore the specific effects of different subtypes of APN on BMSCs, and develop clinical translation strategies based on the APN-BMSCs axis, such as combined biomaterial applications.

CONCLUSION

Adipokines, including visfatin, chemerin, vaspin, and APN, are a group of biologically active peptides and proteins secreted by adipose tissue. These factors play important roles in regulating metabolic processes, inflammation, and angiogenesis, and regulate the proliferation, differentiation, migration, and immune regulatory functions of BMSCs through complex signaling pathways (Table 1). They have potential value in tissue repair and regenerative medicine. For example, visfatin enhances osteogenic differentiation by upregulating Runx2 expression, regulates adipogenic differentiation, and plays a role in stem cell aging. Chemerin regulates BMSC chemotactic migration through the CMKLR1 receptor, while vaspin protects BMSC function by reducing oxidative stress levels and may regulate cartilage differentiation through the ERK1/2 pathway. APN activates the PPARγ pathway through Adiponectin receptor 1 to promote BMSC osteogenic differentiation, but its bidirectional regulatory effect on osteogenic differentiation still needs further exploration. These adipokines can promote BMSC differentiation into adipocytes, while others may inhibit their differentiation into osteoblasts. The regulation of this differentiation direction depends not only on the type of adipokines, but also on the microenvironment in which BMSCs are located. In addition, the concentration-dependent effects of adipokines, heterogeneity of receptor expression and functional differences under pathological conditions (such as obesity and type 2 DM) have not been clarified. It is worth noting that current research primarily focuses on the *in vitro* effects of a single adipokine, lacking analysis of the dynamic balance of adipokine networks and the complex interactions in the *in vivo* microenvironment. The synergistic or antagonistic effects, signaling pathway interactions, and differences in *in vivo* and *in vitro* studies between different adipokines still need further clarification.

Despite these advances, further in-depth exploration is needed to understand the specific mechanisms by which adipokines affect BMSC function. A particularly exciting area of research is how adipokines work synergistically to regulate BMSC function, and the role of these regulators in disease occurrence and development. Future research directions can focus on the following aspects: (1) Combination of single cell sequencing and gene editing: Using single cell sequencing technology to reveal the differences in BMSCs subsets' responses to specific adipokines, and further verifying the functional specificity of key receptors (such as AR1/AR2) by *CRISPR/Cas9* gene editing technology. For example, we can design a *CRISPR/Cas9* gene editing system for AR1/AR2. By KO or mutation of these receptors, we can observe the functional changes of BMSCs under the action of fat factors so as to deeply explore the interaction mechanism between fat factors and BMSCs; (2) 3D co-culture model and disease simulation: Establish a 3D co-culture model to simulate the interaction between adipose tissue and BMSCs in obesity or diabetes. In this model, specific fat factors and inflammatory factors (such as tumor necrosis factor-α and interleukin-6) can be introduced to observe their synergistic/antagonistic effects on BMSCs. This not only helps to reveal the mechanism of adipokines in the disease state, but also provides an important basis for developing new therapeutic strategies for metabolic diseases and bone health problems; (3) Development and application of adipokine sustained-release hydrogel scaffold: Develop fat factor sustained-release hydrogel scaffold, such as combining an adipokine with biological materials such as β-tricalcium phosphate to form composite materials. The efficacy of these composites in bone defect repair was evaluated by animal experiments, and then whether they promoted BMSC proliferation, differentiation and bone formation was tested. This will provide new ideas and methods for the application of adipokine in bone tissue engineering; and (4) Design and implementation of targeted regulation strategy of adipokines: Aiming at the abnormal function of BMSCs in patients with metabolic diseases, design targeted regulation strategy of adipokines. For example, we can develop a nano-delivery system of vaspin, which can accurately deliver fat factors to target tissues or cells through nanotechnology, so as to achieve precise regulation of BMSC function. This targeted delivery system not only has the advantages of high efficiency and low toxicity, but also provides a new method for the treatment of metabolic diseases and bone health problems. To sum up, future research should continue to explore the specific mechanisms of the influence of fat factors on BMSC function, and use advanced biotechnology and model systems to verify these mechanisms. Through concrete examples and illustrative descriptions, we can more clearly see the clinical relevance and operability of these research directions, thus providing an important basis for developing new treatment strategies for metabolic diseases and bone health problems.

Table 1 Function and molecular mechanism of common adipokines regulating bone marrow-derived mesenchymal stem cells

Adipokines	Models	Molecular mechanism	Function	Ref.
Visfatin	BMSCs	NAD-Sirt1	Promoting osteogenic differentiation	[22]
Visfatin	C3H10T1/2 cells	Sirt1 pathways	Promoting osteogenic differentiation, inhibiting adipogenic differentiation	[23]
Visfatin	Senile MSCs	NAD^+-Sirt1	Delay aging	[26]
Visfatin	BMSCs	NAD^+-Sirt1-p53	Delay aging	[27]
Chemerin	OVX mices	-	Inhibiting angiogenesis and osteogenic differentiation	[40]
Chemerin	MC3T3-E1 cells	Wnt-β-catenin	Inhibiting osteoblast differentiation and proliferation	[41]
Chemerin	Raw264.7 cell lines	RANK signal transduction	Enhancing osteoclast differentiation	[41]
Chemerin	C3H10T1/2 cells	Akt-GSK3β-β-catenin	Osteogenic differentiation	[42,43]
Chemerin	BMSCs	G2/M phase cyclin	Inhibiting adipogenic differentiation, clone amplification and proliferation	[45,46]
Chemerin	BMSCs	PPARγ-chemerin-CMKLR1	Inhibiting lipogenesis	[35]
Vaspin	BMSCs	PI3K-AKT and ERK1/2	Enhancing cell survival and proliferation	[62]
Vaspin	BMSCs	NF-κB pathways	Anti-inflammatory effect	[63]
Vaspin	BMSCs	MAPK-p38, MAPK-ERK	Anti-apoptosis effect	[64]
Vaspin	BMSCs	ERK1/2 pathways	Osteogenic differentiation	[67]
Vaspin	BMSCs	Akt pathways	Differentiation into chondrocytes	[68]
APN	EPCs	PI3K pathways	Promoting cell regeneration	[77,78]
APN	BMSCs	SCF-STAT3-HIF1α	Promoting cell migration	[6]
APN	BMSCs	SDF-1-CXCR4	Promoting cell migration and bone regeneration	[78]
APN	BMSCs	AMPK pathways	Promoting cell viability and reduce apoptosis	[79]
APN	BMSCs	Wnt-β-catenin-GSK3β	Osteogenic differentiation	[81-84]
APN	BMSCs	Wnt-β-catenin	Osteogenic differentiation	[85]
APN	BMSCs and C3H10T1/2 cells	APN-APPL1-p38 MAPK	Osteogenic differentiation	[86,87]
APN	HASCs	APPL1-ERK1/2	Osteogenic differentiation	[88]
APN	BMSCs	Sirt1, Wnt pathways	Promoting bone formation and anti-fat formation	[89]
APN	BMSCs	AMPK-mTOR	Inhibiting osteogenic differentiation	[90,91]
APN	Chondrocytes	-	Promoting proliferation, proteoglycan synthesis and matrix mineralization	[92,93]
APN	BMSCs	-	Enhancing migration ability and osteogenic differentiation ability	[96,97]

BMSCs: Bone marrow mesenchymal stromal cells; NAD: Nicotinamide adenine dinucleotide; Sirt1: Sirtuin 1; OVX: Ovariectomized; MSC: Mesenchymal stromal cell; RANK: Receptor activator of nuclear factor-kappa B; AKT: Protein kinase B; GSK3β: Glycogen synthase kinase 3 beta; PPARγ: Peroxisome proliferator-activated receptor γ; CMKLR1: Chemokine-like receptor 1; APN: Adiponectin; EPC: Endothelial progenitor cell; PI3K: Phosphoinositide-3 kinase; ERK1/2: Extracellular regulated protein kinases 1/2; NF-κB: Nuclear factor kappa B; MAPK: Mitogen-activated protein kinase; SCF: Stem cell factor; STAT3: Signal transducer and activator of transcription 3; HIF1α: Hypoxia inducible factor 1α; SDF-1: Stromal cell-derived factor 1; CXCR4: CXC receptor 4; AMPK: Adenosine 5'-monophosphate-activated protein kinase; APPL1: Adaptor protein containing a PH domain, PTB domain and leucine zipper motif 1; HASCs: Human amnion-derived mesenchymal stem cells; mTOR: Mammalian target of rapamycin.

FOOTNOTES

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Country of origin: China

ORCID number: Rui-Ming Wen 0009-0004-1636-106X; Hai-Xia Wang 0000-0001-9789-997X.

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