# Differentiation of Bone Marrow Mesenchymal Stem Cells in Osteoblasts and Adipocytes and its Role in Treatment of Osteoporosis

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Osteoporosis is a systemic metabolic bone disorder characterized by a decrease in bone mass and degradation of the bone microstructure, leaving bones that are fragile and prone to fracture. Most osteoporosis treatments improve symptoms, but to date there is no quick and effective therapy. Bone marrow mesenchymal stem cells (BMMSCs) have pluripotent potential. In adults, BMMSCs differentiate mainly into osteoblasts and adipocytes in the skeleton. However, if this differentiation is unbalanced, it may lead to a decrease in bone mass. If the number of adipocyte cells increases and that of osteoblast cells decreases, osteoporosis can result. A variety of hormones and cytokines play an important role in the regulation of BMMSCs bidirectional differentiation. Therefore, a greater understanding of the regulation mechanism of BMMSC differentiation may provide new methods to prevent and treat osteoporosis. In addition, autologous, allogeneic BMMSCs or genetically modified BMMSC transplantation can effectively increase bone mass and density, increase bone mechanical strength, correct the imbalance in bone metabolism, and increase bone formation, and is expected to provide a new strategy and method for the treatment of osteoporosis.

MeSH Keywords: **Adipocytes • Cell Transplantation • Osteoblasts • Osteoporosis • Stem Cell Research**

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## Background

Osteoporosis is a common metabolic bone disease characterized by decreases in bone mass and density and degradation of the bone microstructure, resulting in fragile bones that are prone to fracture. This process is the same for primary and secondary osteoporosis [1]. With an aging population, the incidence of osteoporosis is increasing each year. The latest statistics show that the number of osteoporosis patients in China has reached 90 million, and in women older than 50 years the incidence is greater than 20% [2]. Osteoporosis causes a higher incidence of fractures, mortality, and morbidity, and is a serious threat to the quality of life of aging individuals [3].

Changes in the internal environment of the human body as it ages result in changes in bone metabolism. The amount of organic matter decreases, with a relative increase in the proportion of inorganic matter, eventually leading to osteoporosis. An increase in the fragility of the trabecular bone and a decrease in the elastic modulus cause a reduction in mechanical strength and a decrease in the load-bearing capacity of bone. Therefore, the trabecular bone is prone to microfracture, further reducing its strength and leading to the occurrence of osteoporotic fractures [4]. Osteoporosis and osteoporotic fractures create a heavy burden on society and families and has become an important public health issue worldwide.

At present, the drug treatment for primary osteoporosis mainly targets the symptoms and complications. Therapeutic mechanisms include the acceleration of bone formation, the inhibition of bone resorption, and agents that promote bone mineralization. Correcting abnormal bone turnover can improve bone mass and reduce the incidence of fractures. However, pharmacotherapy can be prohibitive in cost, take a long time to be effective, and lead to adverse reactions. Long-term use of hormone replacement therapy may increase the risk of breast cancer, stroke, and cerebral infarction [5]. Bisphosphonate therapy may lead to severe suppression of bone turnover and even osteonecrosis of the mandible [6]. Therefore, it is essential to develop improved therapies.

The fundamental mechanism of osteoporosis is an imbalance of bone resorption and formation. Excessive bone resorption leads to reduced bone mass and destruction of the bone structure [7,8]. Bergman et al. [9] indicated that osteogenesis decreased and adipogenic differentiation increased with aging in animals, and that these are the main causes of senile osteoporosis. Therefore, according to the pathogenesis of the disease, a treatment that increases the number of osteoblasts and decreases the number of adipose cells, in theory, will lead to a cure for osteoporosis.

## Bone Marrow Mesenchymal Stem Cells (BMMSCs)

The rapid development of regenerative medicine and technology for stem cell transplantation is bringing new hope to patients with osteoporosis. BMMSCs have the ability to self-renew and differentiate into a mesodermal cell line, initially derived from bone marrow stromal cells. Therefore, BMMSCs could offer a potential source of cell and gene therapy. Rodan et al. [10] demonstrated that BMMSCs have multiple differentiation potentials. Different transcription factors can regulate BMMSC differentiation into osteoblasts and adipocytes. Both of these types of cells play an important role in the maintenance of normal bone stability states.

BMMSCs do not require matching in transplantation, and do not lead to immunological rejection. Therefore, BMMSCs transplantation can be a new therapeutic method of treating osteoporosis. BMMSCs can stably express CD29, CD44, CD73, CD105, and HLA. However, some research indicated that mesenchymal stem cells do not express major histocompatibility complex (MHC) class II and do not express or have low expression levels of MHC class I. Human MHC class I is the main antigen-induced allogeneic immune rejection, resulting in mesenchymal stem cells with low immunogenicity. In addition, BMMSCs do not express T cell costimulatory molecules such as B7-1 and B7-2, and do not express or stimulate apoptosis molecules such as CD40, CD80, CD86, and FasL. Thus it lacks the second signal, which is necessary for T cell activation.

Osteoporosis is characterized by bone loss accompanied by fat tissue increase, which is an important indicator of poor hematopoietic function. In recent years, some scholars have raised the point that blood disease is one of the pathogeneses of osteoporosis. They considered that the emergence of osteoporosis is associated with chronic blood loss. Osteoporosis exists in patients with some hematological system diseases such as sickle cells anemia, chronic hemolytic anemia, and pernicious anemia [11]. There may be a relationship between osteoporosis and bone marrow hematopoietic function.

## The Mechanisms of BMMSC-Mediated Bone Regeneration

BMMSCs are separated easily, can be induced to proliferate, have multipotent differentiation potential, and retain the "homing" feature, thus rendering them the first choice in bone tissue repair and treatment of related diseases. BMMSCs can differentiate into osteocytes, osteoblasts, adipocytes, and chondrocytes, which are widely present in bone marrow and cancellous bone and play an important role in bone metabolism [12]. Many studies have confirmed that BMMSCs can differentiate

into osteoblasts and secrete a variety of osteogenic activity factors under certain induced conditions after being isolated and cultured *in vitro*. They demonstrate good prospects in repairing bone and soft tissue injury *in vivo* [13]. Animal experiments have demonstrated that systemic or local injection of autologous BMMSCs is rarely rejected during transplantation. However, it has been reported that the capacity of BMMSCs from osteoporosis patients to differentiate into osteoblasts is lower than that in healthy individuals [14]. Rodriguez et al. [15] compared the BMMSCs from postmenopausal women with osteoporosis to those from healthy volunteers. They found that the BMMSCs from osteoporosis patients have less sensitivity to insulin-like growth factor (IGF) and a weaker ability to differentiate into osteoblasts. Zhang et al. [16] reported that there was less calcified nodule formation in the osteogenic differentiation medium, confirming the decreased osteogenic differentiation capability of BMMSCs from osteoporosis patients.

In recent years, researchers have realized the important role of bone marrow stem cells in anabolic processes in bone and have begun to fundamentally study the mechanism of abnormal BMMSCs leading to osteoporosis. Although osteoporosis is caused by a variety of mechanisms, its most basic and direct mechanism is osteoblast generation. Many other research groups have suggested other supplementary opinions. Nuttal et al. [17] considered that osteoporosis could be prevented and cured by inhibiting BMMSC differentiation into adipocytes, creating more osteoblasts. The balance of differentiation between osteoblasts and adipocytes maintains the balance of bone and adipose tissue [18]. When a large number of BMMSCs differentiate into adipocytes, the number of osteoblasts will be reduced accordingly. It is also possible that the osteoblasts and adipocytes each differentiate into the other. Even terminally differentiated cells can return to the non-stereotypical BMMSC state and then re-differentiate [19]. Therefore, the inhibition of adipogenic differentiation and promotion of osteogenic differentiation of BMMSCs have become an important method for treating osteoporosis.

## Differentiation of BMMSCs and the Treatment of Osteoporosis

### Promotion of the osteogenic differentiation of BMMSCs

A differentiation pathway of BMMSCs involves the progression from osteogenic cells into preosteoblasts and finally into osteoblasts. Once the osteoblast has formed, it can secrete several extracellular matrix proteins to control the mineralization of bone matrix. Therefore, the occurrence, proliferation, differentiation, and maturation of osteoblasts are closely related to the normal growth and development of bones, and if any one of these processes is inhibited, a bone growth

disorder results. The occurrence of osteoporosis has a direct relationship with an increase in bone resorption and a decrease in bone formation [20]. In osteoporosis treatment programs, the top priority is to improve the condition by improving osteoblast proliferation. The differentiation of BMMSCs is affected by many factors, such as hormones, cytokines, and physiotherapy. Therefore, we can treat osteoporosis by inducing BMMSCs to differentiate into osteoblasts and by promoting the number of osteoblasts.

### *Therapies that promote osteogenic differentiation*

#### Estrogen

The incidence of osteoporosis is significantly increased among postmenopausal women by a decrease in estrogen levels after menopause [21]. The estrogen receptor is one type of nuclear hormone receptor that has an extremely important role in maintaining the equilibrium between bone resorption and formation [22]. Gray [23] and Komm [24] indicated that the estrogen receptor is expressed in the osteoblast, and that estrogen has a regulating effect. Other studies also confirmed that estrogen has an important effect in regulating differentiation of osteoblasts [25,26]. A certain concentration of estradiol (1–10 nmol/L) can promote BMMSC proliferation, osteogenic differentiation, and chondrogenic differentiation [27]. Estrogen can also promote osteoblast proliferation, and maturation, and the expression and secretion of BMP2 [28]. Li et al. [29] indicated that estrogen enhanced the osteogenic potential and the activation of β-catenin in MSCs from ovariectomized rats *in vitro*. Gopalakrishnan [30] showed that estradiol has a positive effect on BMMSC-derived osteoblast proliferation and function. However, long-term hormone replacement therapy (HRT) can have adverse effects. The incidences of coronary heart disease, stroke, and breast cancer have been shown to be increased in postmenopausal women treated with estrogen.

In addition, estrogen has also been proven to inhibit adipocyte progression into fat [31]. Estrogen can act on osteoblasts or BMMSCs of the target site and inhibit the transcript levels of lipoprotein lipase, influencing the distribution of body fat. Okazaki et al. [32] indicated that estrogen not only promoted osteogenic differentiation of the BMMSCs, but also inhibited adipogenic differentiation.

### *Physiotherapy that promote osteogenic differentiation*

#### Pulsed electromagnetic fields (PEMFs)

Electromagnetic technology in orthopedic therapy has had more than a century of exploration. PEMFs were initially used clinically in the 1970s. In recent years, with the development

of electromagnetic technology, PEMFs have been used to promote BMMSC proliferation and differentiation [33]. Studies have shown that low-frequency PEMFs can promote osteoblast proliferation [34,35]. Simmons et al. [36] found that after stimulation with PEMFs (12 Hz, 1.1 mT), MSC proliferation was accelerated, with morphological and biological characteristics consistent with osteoblast formation. Fu et al. [37] and Sun et al. [38] indicated that PEMFs can accelerate osteogenic differentiation of cultured human BMMSCs and enhance bone repair.

Research has indicated the potential of PEMFs as a new bone treatment. It has attracted more and more interest in the field of osteoporosis [39,40]. An osteoporosis study by Takayama et al. [41] showed that PEMFs (15 Hz) can significantly increase bone mass in ovariectomized rat bone. After measuring the contents of calcium and other bone minerals, they concluded that PEMFs can significantly reduce bone loss.

Researchers have confirmed that PEMFs can promote BMMSC differentiation and proliferation by altering signaling pathways and promoting the secretion of growth factors. Through a greater understanding of PEMF mechanisms, their clinical application value will become more significant. Garland et al. [42] treated one of the knee joints of patients with chronic spinal cord injury using PEMFs for 6 months and used the other knee as the control. In the second month, the bone mineral density (BMD) of the treatment group increased by 5.1%. By the sixth month, the BMD had increased to nearly normal levels. In a study by Tabrah et al. [43] 20 patients with osteoporosis were treated with PEMFs. They found that the BMD of the radius had significantly improved, and long-term observation showed no significant changes.

Low-intensity and low-frequency PEMFs have a greater effect on osteoblast proliferation, which can accelerate cell proliferation, cell differentiation, and bone-like tissue formation. Its stimulating effect on osteoblasts occurs during the early stages of cell maturation. This may be because of the electromagnetic field acting on charged particles within the cells, especially in the small mass of the electron-ion, which then produces centripetal force, called Lords force. This force can regulate bone metabolism and promote BMMSC differentiation into osteoblasts, leading to increased bone formation and density. PEMFs have great potential for maintaining bone structure and increasing bone density, thereby preventing and treating osteoporosis. They show a broad range of clinical applications.

### Inhibition of the adipose differentiation of BMMSCs

Osteoblasts, fat cells, and other cell lines derive from a common precursor cell – bone marrow cells. BMMSCs differentiate into osteoblasts and adipocytes with an inverse relationship.

When the BMMSCs differentiate into osteoblasts, the adipogenic differentiation is weakened; when the BMMSCs differentiate into adipocytes, the osteogenic differentiation is weakened [44,45]. Thompson et al. [46] indicated that BMMSCs can differentiate into osteoblasts and fat cells under natural conditions without any intervention, both of which maintain a dynamic equilibrium. If the balance is disrupted, a metabolic bone disease such as osteoporosis will occur. The relationship between bone formation and adipogenesis is complex in the bone marrow microenvironment. Osteoblasts and adipocytes are both derived from BMMSCs, which have pluripotent potential. There is a mutual reversal relationship and a large degree of plasticity between osteoblastic and adipogenic differentiation [47]. Clabaut et al. [48] co-cultured these 2 kinds of cells, but without direct contact. Investigation of gene expression showed that the osteoblasts tended to turn into adipocytes (lipoprotein lipase and leptin) with a decrease in the expression of osteocalcin. They concluded that the presence of adipogenic cells can contribute to osteoblast differentiation into cells with a fat cell phenotype, leading to an increase in the number of lipoblasts. This differentiation process may be triggered by the lipoblasts themselves. Therefore, for the treatment of the osteoporosis, it is essential to inhibit the proliferation of adipocytes and to promote their apoptosis. Research has shown that the number of adipocytes in the bone marrow of senile patients or postmenopausal women with osteoporosis is greater than that in healthy people, and that BMMSCs tend to differentiate into adipocytes rather than osteoblasts. For some patients with diabetes, research found that with increasing age and the administration of many hypoglycemic agents such as thiazide drugs, BMMSCs more easily differentiate into adipocytes. The number of osteoblasts decreases and that of adipocytes increases, leading to osteoporosis.

Therefore, it is very important to identify the key factors in the process of BMMSC differentiation into adipocytes. Inhibition of this process will prevent osteoporosis. This understanding will provide new targets and perspectives, generating new therapeutics. Zhao et al. ([49] indicated that estrogen not only promotes BMMSC differentiation into osteoblasts but also inhibits their differentiation into adipocytes. This research provided a new theory that estrogen deficiency leads to osteoporosis. However, other groups have demonstrated that long-term estrogen replacement therapy increases the incidence of breast cancer [50,51].

The numbers of osteoblasts and adipocytes are very important for bone formation. Research has shown that glucocorticoids also have a regulatory effect on the differentiation of BMMSCs. Long-term, high-dose glucocorticoids promoted adipogenic differentiation and inhibited osteoblast differentiation, leading to osteoporosis [52]. However, in the physiological range, glucocorticoids promote BMMSC differentiation into

not only adipocytes but also osteoblasts. Low glucocorticoid concentrations favor BMMSC proliferation. However, high glucocorticoid concentrations promote lipogenesis and BMMSC proliferation, decreasing the expression of peroxisome proliferator-activated receptor gamma (PPARγ) and inhibiting bone formation [53]. Kelly et al. [54] indicated that 1,25 dihydroxy vitamin D3 [1,25(OH)2D3] blocks adipogenic differentiation and inhibits lipogenesis, both induced by glucocorticoid-mediated decreased RNA expression of the late adipocyte gene markers aP2 and adipsin. Duque et al. [55] showed that 1,25(OH)2D3 also inhibits the expression of PPARγ2 in senescence-accelerated mice. PPARγ2 can accelerate adipogenic differentiation, which can have an important positive regulatory role during the early stage of adipogenic differentiation. Considering all of this research together, we suggest that identification of an effective method to promote osteoblast differentiation and to inhibit adipogenic differentiation will create a bright future for the treatment of osteoporosis.

## Stem Cell Transplantation and Osteoporosis

Current osteoporosis treatments target osteoclasts and osteoblasts. Although this strategy has some benefits, it does lead to long-term adverse effects. Stem cell transplantation is a new type of treatment with a unique advantage. The pathology of osteoporosis is related to a decline in the number and function of osteoblasts. We can treat osteoporosis through stem cell transplantation and promote stem cells to differentiate into osteoblasts [56]. BMMSCs are commonly used in the cell transplantation therapy field. Human BMMSCs in the body have strong potential for osteoblast differentiation and bone formation, and their transplantation into critical areas can increase bone mass, improve bone density, rebalance the internal bone tissue environment, promote osteoporotic fracture healing, and control the progress of early-stage osteoporosis. Therapeutic methods include autologous or allogeneic stem cell transplantation and gene-modified stem cell transplantation.

### Autologous or allogeneic stem cell transplantation

Studies have reported that BMMSCs can migrate to the site of an injury, creating a favorable microenvironment for tissue repair through specific differentiation processes [57]. Animal studies have shown that autologous or allogeneic stem cell transplantation enhanced bone mass in mice with osteoporosis and that stem cells can be injected directly into the trabecular bone surface [58]. BMMSCs can participate in the repair of damaged or diseased tissue, especially in an environment in which a large number of unique cells is required. Some animal studies suggest that administering stem cells intravenously can also promote bone formation [59]. In a study by Ocarino Nde [60], 0.75 million BMMSCs isolated from healthy

rats were injected into the femurs of osteoporotic rats, and the results showed that the trabecular bone percentage in the femurs was similar to that in the femurs from healthy rats, indicating that osteoporosis may be treated by BMMSC injection. Wang et al. [61] injected BMMSCs mixed with calcium alginate gelatin into the distal femur in rabbits with osteoporosis. After 8 weeks, they showed that, compared with the injection of calcium alginate gelatin, the MSC-alginate gelatin injection group had more new bone formation, increased trabecular bone density, improved bone mechanical strength, and a strengthening effect on local bone. Okamoto et al. [62] showed that when BMMSCs were injected into the femurs of post-oophorectomy mice with osteoporosis, the bone mineral density increased significantly.

These studies represent the beginning of a new era in which autologous stem cell transplantation is becoming a potential therapeutic strategy used to treat metabolic and genetic bone diseases, including osteoporosis.

### Cytokine improves the repair of BMMSCs

Growth and development of the tissues is a process of mutual conciliation between the cells and cytokines. Cytokines can regulate cell division, matrix synthesis, and tissue differentiation. Because of the importance of promoting tissue repair and regeneration, cytokine is considered an important element in bone tissue engineering.

The prerequisite of differentiating into osteoblasts is the proliferation of bone marrow stem cells when repairing bone injury. It is necessary to reasonable regulate the contradictions of cell proliferation and differentiation if we want to achieve an effective bone repair. Various growth factors are involved in the regulation of stem cell proliferation and differentiation, rational use of which can promote bone repair. Studies showed that bone morphogenetic protein 2 (BMP-2) is one of the strongest bone growth factors, which can induce bone formation *in vivo* and has an important role in bone tissue injury and repair [63,64]. It is also suggested that BMP-2 has a strong effect in quickly inducing BMMSCs to differentiate into osteoblasts [65]. Stromal cell-derived factor-1 (SDF-1) is the main chemokine mediating the migration of stem cells, which plays a key role in mobilization and homing of hematopoietic stem cells and progenitor cells in the outer peripheral circulation. It also can promote osteogenic differentiation of BMMSCs and stimulate angiogenesis. A series of studies showed that SDF-1 can induce BMMSCs to migrate to the damaged parts, promote osteogenic differentiation, and improve repairing efficiency (66-69). Fibroblast growth factor 2 (FGF-2) is a bone growth factor and a potent mitogenic original, which can increase proliferative capacity of BMMSCs and produce more cell quantity, and this effect is more evident at low cell density. At

the same time, it promotes BMMSCs to differentiate into os-teoblasts, promote collagen synthesis and angiogenesis, and obviously promotes osteogenesis and shortens bone tissue healing time [70,71]. In addition, FGF-2 can maintain multi-differentiation potential of MSCs [72].

### Genetically modified stem cell transplantation

Although stem cell transplantation can improve the symp-toms of osteoporosis, actual treatment is limited because it is easily impeded by a variety of factors. Therefore, to improve the proliferative capacity, increase the number of transplan-tations, and enhance the osteogenic differentiation ability of BMMSCs, researchers hope to use genetically modified stem cells to improve therapeutic efficacy [73]. Currently, gene ther-apy is widely used in clinical research because of its good tar-geting properties. BMMSCs have become ideal carrier cells for transplantation due to their pluripotent and continuous ampli-fication capabilities [74]. Genetically modified stem cells with altered phenotypes can change the direction of cell differen-tiation to inhibit adipogenic differentiation or promote osteo-genic differentiation, facilitating osteogenic differentiation for the treatment of osteoporosis.

Stem cell transplantation research is opening up a new field for the treatment of bone diseases [75]. Gene therapy is also an effective and practical emerging technology. However, both have shortcomings. Cell transplantation has the limitation of prosoplasia, while gene therapy also has unavoidable disad-vantages, such as immune response and expression instability. These 2 methods can complement each other, and their com-bination can expand the ability of stem cells to treat a great-er number of diseases, but it also creates a safe, stable, and efficient expression system that does not elicit an immune response. Kumar et al. [76] transfected BMMSCs with an ad-enovirus carrying BMP-2 and then transplanted these cells into post-oophorectomy mice with osteoporosis. They found that osteogenic differentiation of the BMMSCs was promot-ed. Baltzer et al. [77] showed an impressive reduction in bone loss following the intramedullary transfer of IL-1Ra genes into ovariectomized mice. This proof of concept encouraged further development of gene therapy approaches to treat osteoporo-sis. In a study by Lien et al. [78], CXCR4 was transfected into mouse MSCs by adenoviral infection, yielding high expression of CXCR4. After a single intravenous infusion, they showed full recovery of bone mass and a partial restoration of bone forma-tion in glucocorticoid-induced osteoporotic mice. Their study showed that the systemic transplantation of genetically ma-nipulated MSCs can ameliorate osteoporosis.

In recent years, genetically modified stem cell transplantation has undergone rapid development. By combining stem cell transplantation and its associated gene expression with the ability to promote osteogenic differentiation of BMMSCs, this method will have broad prospects for treating osteoporosis.

### Shortcomings of BMMSCs as a therapeutic agent for treating osteoporosis

It is generally accepted that BMMSCs can be cultured *in vitro*, and the chance of malignant transformation is less. However, some studies have shown that BMMSCs transplantation can promote the proliferation of tumors in some experimental mod-els. Therefore, security and long-term adverse effects should be thoroughly investigated and verified.

There are still many issues that need to be resolved in using BMMSC transplantation to treat osteoporosis. The first issue is how to ensure the security. Tumorigenesis, immunological rejection, and the spread of pathogens are potential problems for BMMSCs transplantation [79]. Stem cells and tumor cells have many similar features, such as unlimited proliferation and strong anti-apoptotic ability [80]. Kang [81] reported that cell transplantation will contribute bone mineral metabolism dis-order in the short term, and then lead to bone formation dis-order and increased bone resorption. The second issue is how to maintain the potential of osteogenetic differentiation and the efficiency of bone tissue formation. However, some stud-ies indicated that these abilities will disappear gradually over time with cell expansion *in vitro* and there will be fewer cells after implanting *in vivo* [82,83]. Multiple infusions of BMMSCs are required to improve and maintain bone density. The third issue is that the timing and environment of gene modification of stem cells must be suitable, and the level of target gene ex-pression must be maintained *in vivo*. The fourth issue is how to choose a suitable cell scaffold material and how to pro-mote the material compatibility and enhance the osteogenic ability of BMMSCs *in vivo*. In addition, stem cell transplanta-tion also involves ethical issues. In a word, the microenviron-ment in bone marrow is complex and contains monocytes, fi-broblasts, and HSCs, in addition to adipocytes and osteoblasts; these cells all play roles in aging and adipogenetic differenti-ation. Thus, although BMMSCs transplantation for the treat-ment of osteoporosis has a bright future, further research and exploration are needed.

## Conclusions

Osteoporosis is a bone disease requiring long-term treatment. With the advent of an aging society, the incidence of fractures caused by osteoporosis will significantly increase. Although the available clinically applied drugs have some effect on the treat-ment of osteoporosis, they are associated with adverse reac-tions, limiting their use. Although osteoporosis has a variety of causes, the most basic and direct mechanism is decreased

osteogenic differentiation and increased adipogenic differentiation in the bone marrow. With age, the microenvironment in the bone marrow cavity changes, increasing the number of fat cells and inhibiting bone formation. During this process, adipose tissue gradually replaces bone tissue, leading to osteoporosis. Therefore, no matter which therapeutic method is used for treating osteoporosis, it is essential to directly or indirectly promote osteogenic differentiation, increase the number of osteoblasts, inhibit fat differentiation, and improve bone metabolism, thereby treating the underlying causes of osteoporosis.

The elucidation of the mechanism of osteoporosis and research focused on BMMSC transplantation in the treatment of osteoporosis provide a line of attack. If we can find an effective way to regulate BMMSC differentiation into osteoblasts without harming fat cells, BMMSCs have to potential to prevent and treat osteoporosis in the near future.

## Disclosure of conflict of interest

None.

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