Senile Osteoporosis by BMSCs

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Senile osteoporosis has become a worldwide bone disease with the aging of the world population. Unlike postmenopausal osteoporosis which is linked to menopause in women, senile osteoporosis is due to aging, hence, affecting both men and women. Evidence has shown that with age increase, bone marrow stromal cells (BMSCs) differentiate into more adipocytes rather than osteoblasts and undergo senescence, which leads to decreased bone formation and contributes to senile osteoporosis. Therefore, modulating BMSCs to stimulate them either differentiate into more osteoblasts than adipocytes or eliminate their senescence will be wonderful strategies for treating senile osteoporosis. Here, the treatment of senile osteoporosis by aiming at BMSCs is introduced.

senile osteoporosis bone marrow stromal cells treatment

1. Introduction

In old ages, bone marrow stromal cells (BMSCs) either differentiate into more adipocytes than osteoblasts or assume senescence, which ultimately results in senile osteoporosis. Therefore, in order to treat senile osteoporosis, it is required to use the strategies in what BMSCs can be stimulated either to differentiate into more osteoblasts than adipocytes or be eliminated their senescence. To date, numerous molecules including parathyroid hormone (PTH 1–84) or only its N-terminal fragment teriparatide (PTH 1–34), bisphosphonates, tetracycline, cationic peptides and antibodies like denosumab and romosozumab have been used in the treatment of senile osteoporosis [1][2][3][4][5]. However, most of them are limited either, due to their severe side effects or inhibition of just bone resorption without decreasing bone regeneration. Therefore, in order to reduce such limitations, there is the need of using cell-based therapy strategy, for which BMSCs can act as an ideal cell source, due to their self-renewing and differentiation ability into various types of cells. In addition, easy isolation with high yields from different tissues, and immunosuppressive and immunoprivileged properties of BMSCs also make them the preferable cell source in cell-based therapies [6].

2. Treatment of Senile Osteoporosis by Aiming at BMSCs

In order to treat senile osteoporosis, several researchers have reported the successful transplantation of BMSCs using animal models. Transplanted BMSCs serve in bone formation either by allocating damaged areas to differentiate into osteoblasts or assume paracrine mode, due to which they secrete specific growth factors to make a favorable environment for the nearby cells to repair the degenerative tissue [7]. Ichioka et al. injected normal allogeneic BMSCs intra bone marrow into the senescence accelerated mouse prone 6 (SAMP6) mice, which naturally prone to senile osteoporosis in their early lives. They demonstrated that the injected normal BMSCs were

able to prevent the senile osteoporosis in SAMP6 mice with an increase in trabecular bone mass and decline in bone mineral density (BMD) loss [8]. Takada et al. also treated osteoporosis after it occurred in aged SAMP6 mice by injecting normal allogeneic BMSCs locally into their bone marrow. After the clinical examinations, no signs of senile osteoporosis were found, hence, succeeded in proving their hypothesis [9]. In another experimental procedure, when BMSCs isolated from healthy rats were injected into the bone marrow of femurs of osteoporotic female ovariectomized rats, a quite increase in the bone mass of femur was observed after examination [10]. Similarly, Kiernan et al. also found an increase in bone formation when they injected systemically normal allogeneic BMSCs into the bone marrow of senile osteoporotic mouse model, giving a clue towards their applications against human senile osteoporosis [11].

Certain factors, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have also been recognized to play significant roles in treating senile osteoporosis by stimulating BMSCs to differentiate into more osteoblasts than adipocytes. Suppression of ectopic viral integration site-1 (Evi1) gene through RNA interference in rat BMSCs resulted in increased osteogenesis and decreased adipogenesis, suggesting Evi1 as a potent target for treating osteoporosis [12]. Jing et al. have reported enhancer of zeste homology 2 (EZH2) factor as a competent therapeutic target for enhancing bone formation during osteoporosis as its suppression led to increased osteogenesis rather than adipogenesis [13]. Recently, Zhou et al. uncovered the role of orcinol glucoside (OG), a constituent of traditional Chinese medicine, in promoting bone formation. They reported that OG was able to revert the BMSCs differentiation fashion of more into adipocytes than osteoblasts in old ages through Wnt/β-catenin signaling pathway, thus, may act as a novel therapeutic agent against senile osteoporosis [14]. Li et al. found the increased bone formation and decreased fat accumulation after injecting aptamer-antagomiR-188 into the bone marrow of osteoporotic aged mice. The aptamer-antagomiR-188 actually inhibited miR-188, whose overexpression is actually responsible for reducing osteogenesis and increasing adipogenesis [15]. Let-7, a miRNA family, has also been distinguished to promote osteogenesis and decline adipogenesis in BMSCs [16]. Very recently, Zhao et al. have demonstrated that miR-21 possesses the ability to stimulate the osteogenic differentiation of BMSCs by finding the role of miR-21 inhibitor in inhibiting BMSCs differentiation into osteoblasts [17]. Recently, lncRNA Bmncr was found as key regulator in promoting osteogenesis and inhibiting adipogenesis in mice during aging, suggesting it to be a therapeutic target against senile osteoporosis in future [18]. Chen et al. reported that overexpression of lncRNA XIST led to the inhibition of osteogenic differentiation of BMSCs in 3-week-old Sprague Dawley rats [19], thus, its inhibition through specific inhibitor can revert the phenomenon and can treat the senile osteoporosis. Most recently, Zhu et al. have identified lncRNA HOXA-AS2 as a key positive regulator in causing osteogenesis in BMSCs through NF-κB signaling inactivation [20], which may act as a new therapeutic target against senile osteoporosis.

Different approaches have also been used to eliminate the senescence of BMSCs, and thus, treat senile osteoporosis. Elimination of senescent cells is of much importance regarding bone mass and strength. In order to uncover such importance, Farr et al. used some genetic and pharmacological procedures to eliminate the senescent cells. They found that activating INK-ATTAC caspase 8 in senescent cells or treating senescent cells with JAK inhibitor or senolytics increased bone mass and bone strength in mice with the bone loss [21]. A senolytic drug, ABT263 can also reduce senescence associated factors, hence, can act as a good therapeutic drug against senile osteoporosis [22]. Gao et al. delivered tetramethylpyrazine (TMP) locally into the bone marrow of aging mice

with established senescent BMSCs microenvironment and a significant reduction was found in senescent phenotype via modulating Ezh2-H3k27me3, suggesting TMP as a potent local eliminator of senescent BMSCs in age-related bone loss [23]. Sun et al. suppressed the expression of NADPH oxidase, which is mainly involved in ROS formation in BMSCs. They found a significant increase in osteoblasts differentiation of BMSCs. Moreover, they also found an increase in bone formation after treating SAMP6 mice with apocynin for three months, hence, declared apocynin as a competent therapeutic agent against age-related bone loss [24]. More recently, Zhou et al. demonstrated that resveratrol was able to attenuate senescence and promote osteogenic differentiation of BMSCs by inhibiting AMPK activation/ROS inhibition signaling pathway in aged mouse, suggesting resveratrol as a novel therapy against senile osteoporosis, due to its inhibiting effects on ROS formation in BMSCs [25].

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