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Role of Cannabinoid Receptors CB1 & CB2 during Osteoblast Differentiation of Human Mesenchymal Stem Cells

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Abstract

Regenerative medicine is an emerging new medical discipline that aims at treating chronic, age related degenerative diseases e.g. diabetes, Parkinson's disease, osteoporosis, osteoarthritis, using stem cells. Complicated and non healed fractures represent a major health care problem that not only affecting elderly patients with osteoporosis but also young person's exposed to traumatic injuries due to accidents and in patients with cancers e.g. osteosarcoma or metastatic cancers resulting in bone destruction. Regenerative medicine can provide a novel approach for enhancing bone regeneration. It is known that disturbances of the balance between osteogenesis and adipogenesis lead to metabolic diseases such as osteoporosis. Cannabinoid receptors and their ligands have been involved in the regulation of various physiological processes and have become the focus of cell therapy and a potential method therapy for significant health concern like osteoporosis. Thus, their role aimed at altering the differentiation direction of Mesenchymal Stem Cells (MSCs) to promote osteoblast differentiation and inhibit adipocyte differentiation. Cannabinoid receptor type 2 signaling using selective receptor compounds encourages the expression of osteogenic genes and enhances mineralization.

Introduction

Osteoporosis, a progressive bone disease involving the appearance of porous bone, characterized by reduced bone mass and strength and increased volume of marrow adipose tissue that leads to fragility of micro architecture and a consequent increase in fracture risk [1]. Its prevalence increases with age making it a significant clinical problem as human life span increased [2]. Bone marrow contains pluripotent mesenchymal progenitor cells that can self-renew and are, meaning they are capable of differentiating into various types of specialized cells including osteoblasts, chondrocytes, and adipocytes [3]. Healthy bone mass and shape are determined and regulated by multiple mechanisms involving a balanced remodeling action of bone destruction and formation. Osteoporosis results from the disturbance of this balance due to the reduced rate of MSCs to produce bone forming osteoblast rather than adipocyte to compensate the osteoblasts bone resorption action; in other words, an inadequate formation response to increased resorption during bone remodeling [1,4].

Cannabinoid Receptors CB1 & CB2 role, during Osteoblast Differentiation of Human Mesenchymal Stem Cells (MSCs)

It is generally accepted that the Endocannabinoid System (ECS) key components have been reported in the skeleton. Osteoblasts and other cells of the osteoblastic lineage, as well as osteoclasts, and their precursors [5]. They are consisting of at least two types of cannabinoid receptor, CB1, and CB2, G-coupled protein which works mainly by inhibiting c-AMP [6,7].

Some studies found that activation of CB2 was found to be involved in the regulation of osteoblast differentiation and bone formation it using to recent CB1, CB2 receptor agonist and CB2 selective agonist has shown stimulation of the early differentiation of bone marrow-derived osteoblast precursors and enhanced bone nodule formation in osteoblast cultures *in vitro* [8,9].

Sun et al. [10] suggested that activation of CB2 receptor plays an essential role in osteogenic differentiation of hBMSCs given the Lack of CB2 receptor expression of samples collected from osteoporotic patients compared to healthy donors. *Lentivirus*-mediated overexpression succeeded

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in restoring CB2 osteogenic differentiation of bone marrow MSCs isolated from osteoporotic patients. This finding may provide an innovative strategy for a treatment approach for osteoporosis [11].

Several studies reported that endocannabinoid and their metabolizing enzymes are present in the skeleton [12]. Also, CB2 receptors are highly expressed on peripheral blood mononucleated cells and immune cells including macrophage, monocytes, B and T lymphocytes and a significantly high level of CB2 receptors are expressed in Osteoblasts, osteoclasts and osteocytes compared to CB1 expression [9,13-15].

Endocannabinoids and their receptors role gained lots of attention in the regulation of bone metabolism field [12,16]. Regarding bone mass regulation and bone turnover, activation of CB2 receptors increases bone formation by inducing BMMSCs differentiation and the lack of CB2 receptor is associated with osteoporosis [10]. Mice deficient in CB2 had higher peak bone mass than wild-type but developed lower bone mass on aging, due to reduced bone formation. And observations of combined deficiency in CB1, and CB2 showed enhanced bone buildup [17]. CB2 receptor modulation had expanded therapeutic potentials which encouraged the increased of CB2 receptor selective ligands, either as agonists or as antagonists/inverse agonists development. ALP is essential for bone mineralization as it increases the local concentration of phosphate ions and aids in the construction of hydroxyapatite crystals and the mineralized matrix [16].

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