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Review

Effect of TNFα on osteoblastogenesis from mesenchymal stem cells

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ABSTRACT

Background: Bone destruction and osteoporosis are accelerated in chronic inflammatory diseases, such as rheumatoid arthritis (RA) and periodontitis, in which many studies have shown the proinflammatory cytokines, especially TNFα, play an important role; TNFα causes osteoclast-induced bone destruction as well as the inhibition of osteoblastogenesis.
Scope of review: Here we review our current understanding of the mechanism of the effect of TNFα on osteoblastogenesis from mesenchymal stem cells (MSCs). We also highlight the function of MSC in the pathogenesis of autoimmune diseases.
Major conclusions: Many studies have revealed that TNFα inhibits osteoblastogenesis through several mechanisms. On the other hand, it has been also reported that TNFα promotes osteoblastogenesis. These discrepancies may depend on the cellular types, the model animals, and the timing and duration of TNFα administration.
General significance: A full understanding of the role and function of TNFα on osteoblastogenesis from MSC may lead to targeted new therapies for chronic inflammation diseases, such as RA and periodontitis.

1. Introduction

Bone mineral density and bone strength are mainly determined by the balance between bone formation by osteoblasts and bone resorption by osteoclasts. Interestingly, osteoblasts are derived from mesenchymal stem cells, whereas osteoclasts are derived from monocytes or macrophages of hematopoietic lineage. Osteoclastogenesis is under the strict control of osteoblasts producing macrophage colony-forming units (M-CSF), receptor activator of NFκB ligand (RANKL), and osteoprotegerin (OPG) [1]. However, recent studies have shown that osteoblasts regulate osteoclastogenesis through mechanisms independent of M-CSF, RANKL, and OPG [2].

Bone destruction and osteoporosis are accelerated in chronic inflammatory diseases, such as rheumatoid arthritis (RA) and periodontitis, in which many studies have shown the proinflammatory cytokines, especially TNFα, play an important role [3–5]; TNFα causes osteoclast-induced bone destruction [6–8] as well as the inhibition of osteoblastogenesis. In the current review article, we focused on the mechanism of the effect of TNFα on osteoblastogenesis from mesenchymal stem cells.

2. Mesenchymal stem cells

In 1976, Friedenstein et al. first identified bone marrow (BM) stromal cells, describing an adherent fibroblast-like population able to differentiate into the bone that they referred to as osteogenic precursor cells [9]. BM-derived mesenchymal stem cells (MSCs) reside in BM stroma, providing the supporting feeder cells necessary for hematopoietic progenitor cell growth but they may also differentiate into connective tissue cells, such as osteoblasts, osteocytes, chondrocytes, adipocytes and smooth muscle cells [10,11]. MSCs exist in almost all tissues; they can be easily isolated from the bone marrow, adipose tissue, umbilical cord, fetal liver, muscle, and lung, and can be successfully expanded in vitro [12]. In addition, in 2011, Kurth et al. reported the existence of resident MSCs in the knee joint synovium that undergo proliferation and chondrogenic differentiation following injury in vivo [13].

BMMSCs are thought to be derived from the bone marrow stromal compartment, initially appearing as adherent, single colony clusters (colony-forming unit-fibroblasts [CFU-Fs]), and subsequently proliferating on culture dishes [14]. To date, the CFU-F assay has been considered one of the gold standards for determining the incidence of clonogenic BMMSC [14]. In addition, a good correlation between CFU-F and MSC frequencies was obtained by flow cytometry using a previously published immunophenotype [15].

In 2006, the Tissue Stem Cell Committee of the International Society for Cellular Therapy proposed a set of minimum criteria that defined human MSC in the position paper [16] as follows. The cell must adhere to plastic when cultured under standard conditions and express the surface marker cluster of differentiation (CD) 73, CD90, and CD105, and not express CD45, CD34, CD14, CD11b, CD79, or CD19. Additionally, human MSC must be capable of in vitro differentiation into osteoblasts, adipocytes, and chondrocytes, i.e. “trilineage differentiation”.

Platelet-derived growth factor receptor-α (PDGFR-α) + stem cell antigen-1 (Sca-1) + dual-positive (PαS) cells have been isolated and characterized in mice [17]. The PαS cells fulfill the basic requirements

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for the definition of MSC in mice. These cells are capable of unlimited self-renewal and can differentiate into osteoblasts, chondrocytes, and adipocytes under appropriate conditions in vitro [18]. On the other hand, CD146, a cell adhesion molecule of the immunoglobulin superfamily expressed in a restricted range of normal cells, is one such marker that has helped discern the in vivo localization and function of human MSC [19].

Due to the limitation of using embryonic stem (ES) and induced pluripotent stem (iPS) cells in the clinic, great interest has developed in MSC, which are free of both ethical concerns and teratome. MSCs have been shown to be effective in the treatment of many disorders, including both immune diseases and non-immune diseases. Osiris' Prochymal, the world's first stem cell drug approved in Canada on May 12, 2012, was successful in phase III clinical trials in treating graft versus host disease (GVHD) and Crohn's disease and has become the only stem cell-based drug approved by the FDA [12].

However, in 2011, MacDonald et al. highlighted that the findings from animal models of autoimmune rheumatic diseases may not be predictive of outcomes in clinical studies [20]. In addition, preclinical experimentation is a scientific and regulatory requirement, and therefore proper screening and selection of clinically relevant animal models that specifically reproduce the biologic features of the disease under study will be critical [20].

3. MSC in inflammatory-related bone diseases

Recently, a growing body of evidence has indicated that BMMSCs produce a variety of cytokines and display profound immunomodulatory properties, perhaps by inhibiting the proliferation and function of several major immune cells, such as natural killer cells, dendritic cells, and T and B lymphocytes [21].

3.1. Rheumatoid arthritis (RA)

RA is a chronic and systemic inflammatory disease, characterized by the destruction of the articular cartilage and bone in its chronic phase. Although histologic analyses of the periarticular trabecular bone have demonstrated that osteoclastic bone resorption is greatly stimulated in RA patients, the mechanism of the joint destruction in RA patients remains to be determined.

We have demonstrated that the number of CFU-F increases in the joints adjacent to the inflamed joints and correlates with the number of CFU-GM; the number of CFU-GM correlated with the level of IL-1β in the synovial fluid of the adjacent joint [22]. In addition, we have demonstrated the effect of bone marrow grafting on a titanium porous-coated implant in bilateral total knee arthroplasty [23], after we examined the characteristics of CFU-F of BM from patients with autologous bone grafting or rheumatoid arthritis (RA) [24,25]. The final fluoroscopically-guided radiographs revealed a decrease in the number of knees with radiolucent lines after marrow grafting compared to those without grafting, suggesting that the iliac bone marrow is useful as a bone grafting material to enhance biological fixation in porous-coated implants [23].

BMMSC may be primarily involved in joint damage in RA [26]. In addition, studies have demonstrated that increased local production of TNFα may injure the BM microenvironment and may affect the reserves of BM hematopoietic progenitor cells [27]. MSC from RA patients impaired clonogenic and proliferative potential in association with premature telomere length loss [28]. On the other hand, in patients with advanced osteoarthritis, chondrogenic and adipogenic activity of MSC were reduced [29].

3.2. Systemic lupus erythematosus (SLE)

SLE is a disease of unknown etiology in which tissues and cells are damaged by pathogenic autoantibodies and immune complexes. In 2007, Sun et al. reported that BMMSC derived from patients or mice with SLE showed impairment of osteogenic differentiation following successive cell passage in vitro [30]. On the basis of the promising clinical outcomes in SLE mice, Sun et al. treated four cyclophosphamide/glucocorticoid treatment-refractory SLE patients using allogenic bone marrow MSC transplantation (MSCT) and showed stable 12–18 months of disease remission in all treated patients [31]. The patients benefited from the amelioration of disease activity, and improvement in serologic markers and renal function, suggesting that allogenic MSCT may be a feasible and safe salvage therapy for refractory SLE patients [31]. In addition, because allogenic BMMSC from a patient's family member without human leukocyte antigen match is an easily accessible stem cell resource, MSCT may offer another effective cell therapy with fewer side effects [31].

3.3. Systemic sclerosis (SSc)

SSc is a chronic multisystem disorder of unknown etiology characterized clinically by thickening of the skin caused by accumulation of connective tissue and by involvement of visceral organ. Larghero et al. explored the phenotypical and functional characteristics of in vitro expanded bone marrow mesenchymal stem cells from patients with systemic sclerosis [32]. Their findings show that BM-derived MSCs from patients with SSc under the described culture conditions exhibit the same phenotypic, proliferative, differentiation potential and immunosuppressive properties as their healthy counterparts.

4. Mechanisms of osteoblast differentiation

4.1. Role of Wnt in osteoblastogenesis

Osteoblasts are derived from mesenchymal progenitor cells in the bone marrow or pericytes. Their maturation process includes consecutive stages of proliferation, matrix production and matrix mineralization [39]. Osteoblasts can ultimately become osteocytes. Activation of the Wingless-type MMTV integration site (Wnt) pathways facilitates osteoblast specification from mesenchymal progenitors and enhances bone mass and strength. Thus, the Wnt pathway has emerged as a crucial regulator of bone formation and regeneration (Fig. 1). For more details of Wnt signaling, we recommend the review article of Kuhl et al. [40].

4.2. Effect of GSK3β on osteogenesis

Glycogen synthase kinase 3β (GSK3β) is known to modulate cell apoptosis and differentiation through multiple intracellular signaling pathways [41]. GSK3 is now known to target multiple cell regulatory proteins and to be controlled by both Wnt signaling and the PI3K/Akt

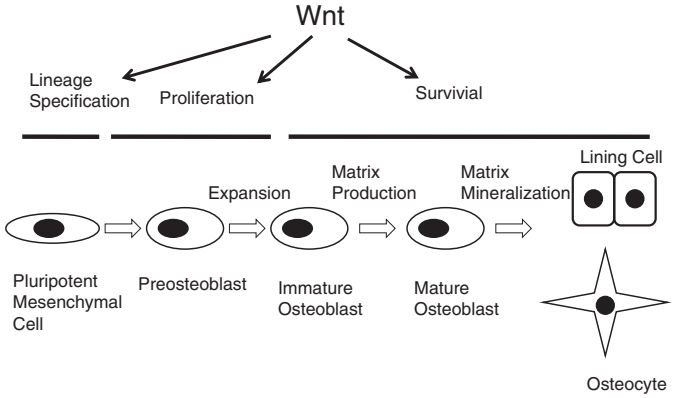

Fig. 1. Wnts affect multiple stages of osteoblast-lineage maturation. Modified from ref. [39].