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Foxc2 over-expression in bone marrow mesenchymal stem cells stimulates osteogenic differentiation and inhibits adipogenic differentiation

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Abstract The forkhead box C2 (Foxc2) protein, a member of the forkhead/winged helix transcription factor family, is strongly expressed in developing embryo and is required in various developmental processes. However, the precise function of Foxc2 in osteoblast differentiation remains largely unknown. The present study investigated the role of Foxc2 overexpression on osteogenic and adipogenic differentiations. In our experiment, rabbit bone marrow mesenchymal stem cells (BMSCs) were transduced with lentiviral vectors containing Foxc2 or green fluorescent protein (GFP), and the gene expression and biological activity of Foxc2 were examined in vitro. The results showed that the mRNA and protein expressions of Foxc2 were stable and high in cells transduced with Foxc2 compared with those transduced with GFP. The overexpression of Foxc2 increased the mRNA and protein levels of COLI, OCN, and OPN; enhanced the activity of ALP after osteogenic induction; and decreased the expression of PPARγ-2 and the total droplet number after adipogenic induction. In addition, Foxc2 enhanced the expression of β-catenin, an important modulator of osteoblastogenesis. XAV939, a small molecule inhibitor of the Wnt-β-catenin pathway, suppressed Foxc2-mediated regulation of BMSC differentiation. These findings demonstrate that the overexpression of Foxc2 gene in BMSCs may promote osteogenic differentiation and inhibit adipogenic differentiation, and this effect can be mediated via activating the canonical Wnt-β-catenin signaling pathway.

Keywords Foxc2 · Bone marrow mesenchymal stem cells · Osteogenic differentiation · Adipogenesis · Wnt-β-catenin

Introduction

Loss of bone mass poses a challenge in orthopedic surgery and requires the application of bone grafts or substitutes. The limitations associated with bone loss requiring massive bone grafts for reconstruction are well documented [1, 2]. Bone tissue engineering is an attractive approach for treating bone loss in various shapes and amounts. Bone marrow mesenchymal stem cells (BMSCs) have the potential to be used in bone tissue engineering owing to their general availability, self-renew ability, and osteogenic potential [3]. Now, there is sound evidence that osteoblasts are among the cell types derived from BMSCs, which are therefore excellent candidates for bone repair.

BMSCs contain a subset of multipotent cells that give rise to osteoblasts, adipocytes, chondrocytes, and myocytes [4]. Osteoblasts and adipocytes share a common progenitor, both derived from stromal cells in bone marrow, and bone loss is associated with an expansion of adipose tissue in bone marrow [5]. An increased fat content in bone correlates negatively with bone mass during aging and bone acquisition during growth [6, 7]. In addition, there is an inverse relationship between the amount of trabecular bone and that of adipose tissue in bone marrow [8]. Therefore, the enhancement of osteoblastogenesis with a concomitant decrease in adipogenesis may provide a therapeutic target for treating bone loss.

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