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UNDERSTANDING THE ROLE OF INTERLEUKIN-17 IN BONE REMODELLING MECHANISM OF STEM CELLS OF HUMAN EXFOLIATED DECIDUOUS TEETH (SHED)-DERIVED OSTEOBLAST CELLS

PENYELIDIK

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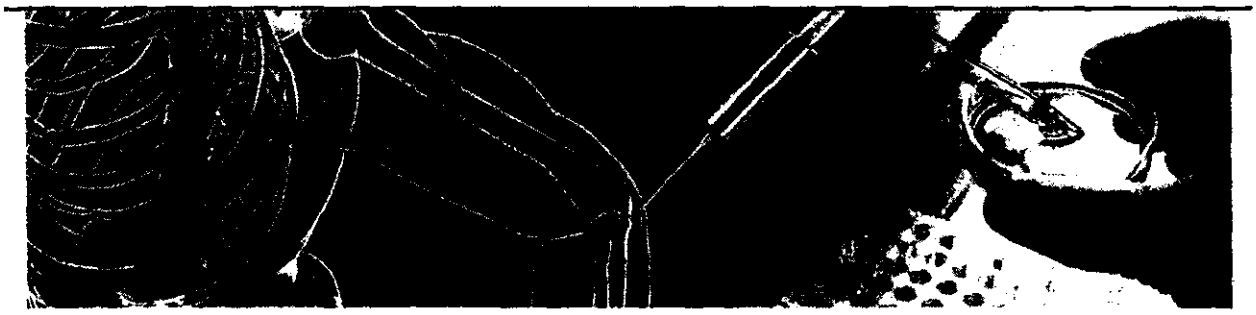

Understanding the role of interleukin-17A in bone remodelling mechanism of stem cells of human exfoliated deciduous teeth-derived osteoblast cells

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ABSTRACT (120 words)

Interleukin-17A (IL-17A) enhances the osteogenic differentiation and increases osteoprotegerin (OPG)/receptor activator of NF-κB ligand (RANKL) expression of the stem cells from human deciduous teeth (SHED). The OPG/RANKL system is essential in bone metabolism where RANKL augments bone resorption whereas OPG favours osteogenesis. This study investigates the effects of IL-17A on the osteogenic differentiation and its effect on the RANKL/OPG signalling pathway. IL-17A enhanced proliferation and alkaline phosphatase activity in SHED in a dose-dependent manner. IL-17A also increased calcium deposition which indicated mineralization activity. Moreover, the expressions of ALP, COL1A1, RUNX2, OCN, OPN and OPG were significantly up-regulated when treated with IL-17A. In contrast, IL-17A down-regulated RANKL expression in SHED. Interestingly, the OPG/RANKL ratio was significantly higher in IL-17A-treated groups. We also demonstrated that IL-17A activated MAPK signalling pathway by significant up-regulation of upstream activators and downstream targets of ERK, P38 and JNK pathway. We conclude that IL-17A demonstrates osteo-stimulating effects; thus suggests the use of IL-17A in bone substitutes to promote bone regeneration.

1. INTRODUCTION

Bone regeneration is a complex mechanism where various cells, intracellular and extracellular molecular-signalling pathways are involved in a continuous process. Osteoprotegerin (OPG), receptor activator of nuclear factor κB (RANK), and RANK ligand (RANKL) were first reported to involve in the bone remodelling process by Simonet et al. (1997). RANKL is essential for osteoclast differentiation via its receptor RANK, which is located on the osteoclast membrane, whereas OPG is a soluble decoy receptor that inhibits osteoclast differentiation through its binding to RANKL (Walsh and Choi, 2014). Thus, the RANK/RANKL/OPG signalling pathway is important to regulate the bone homeostasis process.

Dental pulp stem cells (DPSCs) are the promising cell source for cell-based hard tissue engineering. Stem cells from human exfoliated deciduous teeth (SHED) are highly proliferative clonogenic cells capable of differentiating into various cell types. This multipotency, in addition to the relative accessibility, made SHED an appealing source of cells for application in regenerative medicine. They can differentiate odontogenically, osteogenically, adipogenically, chondrogenically, or neurally both *in vitro* and *in vivo* (Miura et al., 2003). SHED were similar to bone marrow mesenchymal stem cells (BMMSCs) in their osteogenic differentiation capacity (Yamaza et al., 2010). SHED exhibited superior osteoblastic differentiation capability in comparison with DPSCs (Govindasamy et al., 2010; Govindasamy et al., 2011; Wang et al., 2012). SHED also presented abundance of extracellular matrix (ECM) and growth factors compared with DPSCs and BMMSCs (Nakamura et al., 2009). A recent study by Nakajima et al. (2018) demonstrated that the degree of bone regeneration with SHED was comparable with DPSCs and BMMSCs 12 weeks after transplantation. Thus, SHED exhibit bone regeneration ability and is one of the best candidate for cell-based therapy.

Several growth factors and signalling molecules may influence the growth and differentiation of human MSCs. In the bone replacement therapy, the synergistic action of both