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The Effects of Bisphosphonates on Osteonecrosis of Jaw Bone: A Stem Cell Perspective

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Abstract : Mesenchymal stem cells (MSCs) are crucial cell types for bone maintenance and growth along with resident bone progenitor cells providing bone tissue integrity during osteogenesis and skeletal growth. Any deficiency in this regulation would result in vital bone diseases. Of those, osteoporosis, characterized by a reduction in bone mass and mineral density, is a critical skeletal disease for especially elderly people. The commonly used drugs for the osteoporosis treatment are bisphosphonates (BPs). The most prominent role of BPs is to prevent bone resorption arisen from high osteoclast activity. However, administrations of bisphosphonates may also cause bisphosphonate-induced osteonecrosis of the jaw (BIONJ). Up to the present, the researchers have proposed several circumstances for BIONJ. However, effects of long-term and/or high dose usage of BPs on stem cell's proliferation, survival, differentiation or maintenance capacity have not been evaluated yet. The present study will be held to; figure out BPs' effects on MSCs in vitro in the aspect of cell proliferation and toxicity, migration, angiogenic activity, lineage specific gene and protein expression levels, mesenchymal stem cell properties and potential signaling pathways affected by BP treatment. Firstly, mesenchymal stem cell characteristics of Dental Pulp Stem Cells (DPSCs) and Periodontal Ligament Stem Cells (PDLSCs) were proved using flow cytometry analysis. Cell viability analysis was completed to determine the cytotoxic effects of BPs (Zoledronate (Zol), Alendronate (Ale) and Risedronate (Ris)) on DPSCs and PDLSCs by the 3-(4,5-di-methyl-thiazol-2-yl)-5-(3-carboxymethoxy-phenyl)-2-(4-sulfo-phenyl)-2H-tetrazolium (MTS) assay. Non-toxic concentrations of BPs were determined at 24 h under growth condition, and at 21 days under osteogenic differentiation condition for both cells. The scratch assay was performed to evaluate their migration capacity under the usage of determined of BPs concentrations at 24 h. The results revealed that while the scratch closure is 70% in the control group for DPSCs, it was 57%, 66% and 66% in Zol, Ale and Ris groups, respectively. For PDLSs, while wound closure is 71% in control group, it was 65%, 66% and 66% in Zol, Ale and Ris groups, respectively. As future experiments, tube formation assay and aortic ring assay will be done to determinate angiogenesis abilities of DPSCs and PDLSCs treated with BPs. Expression levels of osteogenic differentiation marker genes involved in bone development will be determined using real time-polymerase change reaction (RT-PCR) assay and expression profiles of important proteins involved in osteogenesis will be evaluated using western blotting assay for osteogenically differentiated MSCs treated with or without BPs. In addition to these, von Kossa staining will be performed to measure calcium mineralization status of MSCs.

Keywords : bisphosphonates, bisphosphonate-induced osteonecrosis of the jaw, mesenchymal stem cells, osteogenesis
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