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Effect of Zoledronic Acid on Osteoblastic Differentiation of Mesenchymal Stem Cells and Epigenetic Changes

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Zoledronic acid (ZA) is a bisphosphonate that is used to prevent skeletal fractures in patients with cancer, as well as for treating osteoporosis. Complete mechanism of action of ZA is not understood, and their actions on the osteoblasts are confusing. Epigenetic changes such as DNA methylation are regulatory mechanisms that control stem cell differentiation. In this situation, ZA induces osteoblastic differentiation in MSC, but regulatory mechanisms are unknown. Gene specific methylation of RUNX2, OSX, DLX5 and BSP genes and global methylation status were evaluated by methylation specific PCR (MSP) and specific antibody, respectively. Also, the effect of ZA on the BSP gene expression was evaluated by RT-PCR.

MSP present 3 different methylation patterns. Global methylation assay present hypomethylation in osteoblastic differentiation period. RT-PCR present BSP gene expression in differentiated MSCs but not in undifferentiated MSC.

ZA didn't change RUNX2, DLX5 methylation status in differentiated than undifferentiated MSCs. Therefore, MSCs are heterogeneous populations because they were methylated and unmethylated in same time. But, OSX promoter methylation status hypomethylated during osteoblastic differentiation. This finding shows that OSX gene regulation followed from epigenetic changes such as promoter hypomethylation. BSP methylation status shows that its expression independent from epigenetic modifications. Also, expression of RUNX2, DLX5 and BSP may be influenced from other epigenetic changes such as histone modifications. This confirm new epigenetic hypothesis that says epigenetic changes in the human methylome is dynamic changes during differentiation.