

cAMP enhances the bone morphogenetic protein-2 (BMP-2)-dependent differentiation of osteoprogenitor cells.

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INTRODUCTION: Bone morphogenetic proteins (BMPs), members of the transforming growth factor- β (TGF- β) superfamily, regulate proliferation, differentiation, and apoptosis of various types of cells. Recent studies suggest that the elevation of intracellular cyclic adenosine monophosphate (cAMP) regulate BMP2-induced osteogenesis (1). However, the precise mechanisms underlying the enhancing effect of cAMP on BMP2 signaling have not been completely revealed. In this study we investigated the effect of the elevated cAMP level and PKA activation on the BMP2-induced osteoblast differentiation of C2C12 cells.

METHODS: BMP2 induced osteoblast differentiation in C2C12 cells was investigated with or without forskolin, a cAMP generating agent. Osteoblast differentiation was assayed using alkaline phosphatase activity, RT-PCR, western blot analysis, cell proliferation, as well as specific MAP kinase inhibitors.

RESULTS: Alkaline phosphatase activity and its mRNA were consistently induced by BMP2 treatment. The pretreatment of C2C12 cells with Forskolin, a cAMP generating agent (Fig.1), dbcAMP, an analogue of cAMP, or IBMX (3-isobutyl 1-methyl xanthine), a nonspecific inhibitor of phosphodiesterases elicited further activation of alkaline phosphatase (ALP). Furthermore, elevated intracellular cAMP level increases the phosphorylation of p38 and prolongs Samd1/5/8 phosphorylation. However, BMP2-induced Erk 1/2 phosphorylation and cell proliferation were suppressed in the presence of cAMP.

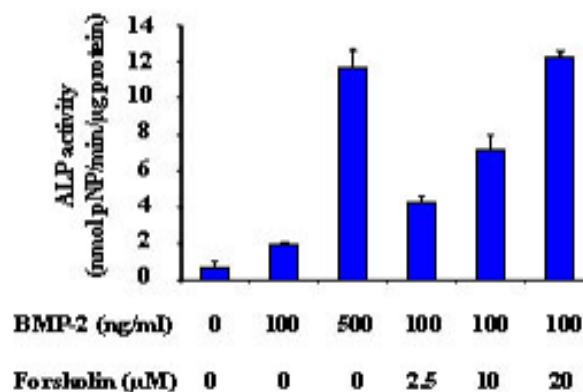


Fig.1: cAMP intensified BMP2-induced ALP activity. C2C12 Cells were pretreated 4 hours with forskolin, and then stimulated with BMP-2 (100 or 500 ng/ml). After 6 days, ALP activity was measured.

DISCUSSION & CONCLUSIONS:

In this study we aimed to determine the effect of cAMP levels on the BMP2-induced differentiation of osteoblast precursor cells to more mature osteoblastic cells. Our results indicate that the elevation of intracellular cyclic adenosine monophosphate (cAMP) and the activation of protein kinase A may be key BMP2-activated signaling events that lead to differentiation of osteoblast precursor cells into more mature osteoblast-like cells.

REFERENCES: ¹ L. Zhao, S. Yang, G.Q. Zhou, J. Yang, D. Ji, G. Sabatakos and T. Zhu (2006) The International Journal of Biochemistry & Cell Biology Volume 38, Issue 12, 2006, Pages 2064-2073.

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