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Dual effects of heparin on BMP-2-induced osteogenic activity in MC3T3-E1 cells

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Abstract:
Heparin displays several types of biological activities by binding to various extracellular molecules, including pivotal roles in bone metabolism. We have previously reported that heparin competitively inhibits the binding activity of bone morphogenic protein-2 (BMP-2) to BMP and the BMP receptor (BMPR) and suppresses BMP-2 osteogenic activity. In the present study, we examined whether heparin affects osteoblast differentiation induced by BMP-2 at various time points *in vitro*. We found that 72 h of treatment with heparin inhibited alkaline phosphatase (ALP) activity. However, 144 h of treatment enhanced the ALP activity in BMP-2-stimulated MC3T3-E1 cells. Although heparin decreased the phosphorylation of Smad1/5/8 after 0.5 h of culture, prolonged periods of culture with heparin enhanced the Smad phosphorylation. In addition, 72 h of treatment with heparin enhanced the mRNA expression of runx2 and osterix in BMP-2-stimulated MC3T3-E1 cells. Furthermore, the mRNA expression of BMP antagonists and inhibitory Smads induced by BMP-2 was preferentially blocked by heparin at the 24 and 48 h time points. These findings indicate biphasic effects of heparin on BMP-2 activity and suggest that heparin has complex effects on the BMP-2 osteogenic bioactivities. Prolonged culture with heparin stimulated BMP-2-induced osteogenic activity *via* down-regulation of BMP-2 antagonists and inhibitory Smads.

Key words:
osteoblast, heparin, BMP-2, Smad, Runx2, osterix