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New insights into BMP-7 mediated osteoblastic differentiation of primary human mesenchymal stem cells.

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Abstract

Bone Morphogenetic Proteins (BMPs) are members of the TGF-beta superfamily of growth factors. Several BMPs exhibit osteoinductive bioactivities, and are critical for bone formation in both developing and mature skeletal systems. BMP-7 (OP-1) is currently used clinically in revision of posterolateral spine fusions and long bone non-unions. The current study characterizes BMP-7 induced gene expression during early osteoblastic differentiation of human mesenchymal stem cells (hMSC). Primary hMSC were treated with BMP-7 for 24 or 120 h and gene expression across the entire human genome was evaluated using Affymetrix HG-U133 Plus 2.0 Arrays. 955 probe sets representing 655 genes and 95 ESTs were identified as differentially expressed and were organized into three major expression profiles (Profiles A, B and C) by hierarchical clustering. Genes from each profile were classified according to biochemical pathway analyses. Profile A, representing genes upregulated by BMP-7, revealed strong enrichment for established osteogenic marker genes, as well as several genes with undefined roles in osteoblast function, including MFI2, HAS3, ADAMTS9, HEY1, DIO2 and FGFR3. A functional screen using siRNA suggested roles for MFI2, HEY1 and DIO2 in osteoblastic differentiation of hMSC. Profile B contained genes transiently downregulated by BMP-7, including numerous genes associated with cell cycle regulation. Follow-up studies confirmed that BMP-7 attenuates cell cycle progression and cell proliferation during early osteoblastic differentiation. Profile C, comprised of genes continuously downregulated by BMP-7, exhibited strong enrichment for genes associated with chemokine/cytokine activity. Inhibitory effects of BMP-7 on cytokine secretion were verified by analysis of enriched culture media. Potent downregulation of CHI3L1, a potential biomarker for numerous joint diseases, was also observed in Profile C. A focused evaluation of BMP, GDF and BMP inhibitor expression elucidated feedback loops modulating BMP-7 bioactivity. BMP-7 was found to induce BMP-2 and downregulate GDF5 expression. Transient knockdown of BMP-2 using siRNA demonstrated that osteoinductive properties associated with BMP-7 are independent of endogenous BMP-2 expression. Noggin was identified as the predominant inhibitor induced by BMP-7 treatment. Overall, this study provides new insight into key bioactivities characterizing early BMP-7 mediated osteoblastic differentiation.

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