

## **Novel phosphorylated players in osteoblastic differentiation of mesenchymal stem cells revealed by mass spectrometry.**

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Since bone fractures and loss represent huge costs for the public health system and often affect the patient's quality of life, understanding the molecular basis for bone regeneration is essential. Cytokines, such as IL-6, IL-10 and TNF $\alpha$ , secreted by inflammatory cells at the lesion site, in the very beginning of the repair process, act as chemotactic factors for mesenchymal stem cells, which proliferate and differentiate into osteoblasts through the paracrine action of bone morphogenetic proteins (BMPs), mainly BMP-2. Although it is known that BMP-2 binds to ActRI/BMPRI and activates the SMAD 1/5/8 downstream effectors, little is known about the intracellular mechanisms participating in osteoblastic differentiation. In this study, we assessed differences in the phosphorylation status of different cellular proteins upon addition of BMP-2 to the culture medium of isolated human mesenchymal stem cells (MSCs) using Triplex Stable Isotope Dimethyl Labeling coupled with HILIC-RP-nLC/MS. From 150  $\mu$ g of starting material, more than 1,100 proteins containing two or more peptides were identified and quantified at five different time points, 60 of which are differentially phosphorylated (peptide p value <0.05). Proteins related with cytoskeleton rearrangement, Ubiquitin-Proteasome pathway and nuclear RNA processing suggest novel aspects of MSCs osteoblastic differentiation. Support: FAPESP, CNPq, FINEP, MCT, DECIT-MS, BNDES.

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