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The impact of leptin on stem cell differentiation towards osteoblasts: Assessed by an osteo/chondro microRNA signature

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Abstract

Leptin has been shown to exert dual effects on bone mass. A reduction in net bone mass is obtained through a CNS (hypothalamic) mediated effect, while leptin (from adipose tissue) directly may enhance bone mass via its impact on osteoblasts. It has also been shown that osteoblasts produce their own leptin, which may act as an autocrine factor in preserving bone homeostasis. The present investigation focuses on the contribution of leptin on stem cell differentiation towards osteoblasts, as estimated by an osteochondral microRNA signature (hsa-mir-149, -328, and -339). Experimental conditions were as follows in terms of permutations of variable:

1) Mineralizing medium + Dex (low level) , PTH, Calcitriol, BMP2, TGFβ1 or Leptin

Chosen for further assessment: Dex + BMP2 and Dex + Leptin

2) Dex + Leptin or BMP2 ± scaffolds (film on ”plate”) ± intermittent mechano-stimulation

Chosen for further assessment: Cell in scaffolds subjected to intermittent mechano-stimulation

3) Condition under #2) with cells transfected every 5 days with siRNA against Leptin + Ob-Rb or Jak2 + Stat3, or all four

4) Condition under #2) with cells transfected with pre-miRNAs 149, 328 or 339, or both

5) Final experiment: Applied condition according to #3) and #4) and assessed all end-point parameters (like gene expression of leptin, OB-Rb, Jak2, Stat3, Runx2, Coll1α1, Osteocalcin, mineralization surface, OPG/RANKL-ratio, induced osteoclast resorption surface, levels of miRNA species 149, 328 and 339.

In Summary: The estimated contribution of leptin to osteoblastic differentiation of stem cells (hMSCs) appeared to be: a) Average impact on osteoblastic gene expression: 32%

• Average impact on mineralization and remodeling potential: 45%

• Average impact on osteochondral microRNAs: 22%.

• Similar results obtained with cells transfected with pre-miRNAs 328 and 339.

• The impact of leptin on osteoblast differentiation was confirmed by knocking down the expression of LEPR (OB-Rb), Jak2, and Stat3, respectively by manipulating with the intrinsic level of the miRNA species 320 and 338.

Biography

Jan O. Gordeladze, PhD (born 25th of April, 1950), holds a triple professor competence (medical biochemistry, physiology, and pharmacology), and is presently working as a professor at the Department of Biochemistry, Institute of Basic Medical Science, University of Oslo, Norway. He has previously been employed as the medical director of MSD, Norway, serving two years as a Fulbright scholar at the NIH, Bethesda, Maryland, USA, and from 2006-2009 being employed as associate professor at the University of Montpellier, France. He has published more than 100 scientific articles, reviews/book chapters and presented more than 250 abstracts/posters/talks at conferences world wide.