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Comparison of the Effects of PTH (1-34), PTHrP (1-36) and Abaloparatide (ABL) on the Murine Osteoblast Transcriptome

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Osteoporosis is a prevalent disease with substantial morbidity/mortality among the aging population. Due to gaps in knowledge, current therapeutics are limited in their ability to prevent degeneration of bone while also stimulating formation of new bone. Teriparatide (PTH (1-34)) and its analogs PTHrP (1-36) and abaloparatide (ABL), have been utilized for treatment of osteoporosis but have significant limitations in efficacy over long-term use. Research from our laboratory has shown PTH (1-34), PTHrP (1-36), and ABL exert time and dose-dependent differential responses in the osteoblast, leading us to hypothesize they may also differentially modulate the osteoblast transcriptome. In this study we show that treatment of mouse calvarial osteoblasts with 1 nM of these peptides for 4 h results in differing effects on the osteoblast transcriptome by performing gene enrichment analysis of RNA-Seq data. Genes were selected with a Log2 fold change >1 and a false discovery rate <0.05. These data were analyzed and compiled into heat maps for each peptide and smear/volcano plots. RNA-Sequencing revealed that PTH (1-34) regulated 367 genes, 194 were unique; PTHrP (1-36) regulated 117 genes, 15 were unique; ABL regulated 179 genes, 20 were unique. There were 74 genes shared only among PTH(1-34) and ABL; 16 genes shared only among PTH (1-34) and PTHrP; and 83 genes shared among all three peptides. Data collected show pathway-specific differences including, 1) cAMP/PKA, 2) Wnt/β-catenin, 3) Transcriptional regulation 4) Inflammatory response 5) Transmembrane transport, 6) Metabolism, and 7) NF-kB. Further analysis of the data illuminated that the three peptides increased Vitamin D receptor (VDR) and Cbp/p300-interacting transactivator 1 (CITED1) mRNAs similar to RankL expression. These findings were confirmed via qRT-PCR of additional cultured samples of mouse calvarial osteoblasts, treated with 1 nM of PTH (1-34), PTHrP (1-36), and ABL for 4 h prior to harvest. RankL mRNA, VDR mRNA, and CITED1 mRNA were measured for each sample and statistical differences were analyzed via Kruskal Wallis $p<0.05$. Additionally, we analyzed mRNA levels of several genes of interest, including WNT7b, WNT11, TCF7, SFRP4, FZD5, PP2R2A, and DVL3 mRNA. Pathway analysis and subsequent qRT-PCR confirmation has shown that PTH (1-34) and ABL lead to a significant increase in Wnt11 mRNA, while PTHrP (1-36) does not. Our findings highlight the complexity of the genetic and functional events triggered by PTH (1-34) and its analogs. Many studies have examined PTH signaling in the osteoblast/osteocyte; ours is the first to examine global effects of these peptides on the osteoblast transcriptome. Further delineation of which signaling events are attributable to PTH (1-34), PTHrP (1-36), and ABL exclusively and which are shared among all three will further our understanding of the effects these peptides have on the osteoblast and lead to refinement of PTH-derived treatments for osteoporosis.

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