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Roger Melick Young Investigator Award 2009

Winner: Nicola Lee

Poster Abstract:

Osteoblast specific Y1 deletion enhances bone formation

N. J. Lee[1] , R. F. Enriquez[2] , A. D. Nguyen[1] , K. L. Doyle[1] , A. Sainsbury[1] , P. A. Baldock[2] , H. Herzog[1]

[1] *Neuroscience Program, Garvan Institute of Medical Research, Sydney, NSW, Australia*

[2] *Bone & Mineral Research Program, Garvan Institute of Medical Research, Sydney, Australia*

Neuropeptide Y (NPY) has been shown to play a critical role in the regulation of bone metabolism by signaling via Y1 and Y2 receptors. Centrally, hypothalamic Y2 but not Y1 receptors have been shown to be important for the action of NPY on bone formation and osteoblast activity. However, the peripheral mechanism remains unknown. In-situ hybridisation on femur sections reveals the presence of Y1 but not Y2 receptor mRNA in osteoblasts, consistent with a direct role for the Y1 receptor on bone cells.

To investigate the role of the Y1 receptor on osteoblastic cells, we generated mice with selective deletion of the Y1 receptor in osteoblasts by crossing $Y1^{lox/lox}$ mice with 2.3ColCre and 3.6ColCre mice expressing Cre specifically in osteoblasts utilising different regions of the α_1(I)-collagen promotor. The 3.6ColCre line expresses Cre early during osteogenic differentiation whilst in the 2.3ColCre line, Cre expression is restricted to maturing osteoblasts. In 16 week old male mice body weight was unaltered in both lines of ColCre;$Y1^{lox/lox}$ mice when compared to their $Y1^{lox/lox}$ littermates. Importantly, whole body bone mineral density was increased in both 2.3ColCre;$Y1^{lox/lox}$ ($p=0.05$) and 3.6ColCre;$Y1^{lox/lox}$ mice ($p=0.05$).

Osteoblast-specific Y1 receptor deletion also resulted in a marked increase in femoral cancellous bone volume (2.3ColCre;$Y1^{lox/lox}$ 16.2 ± 1.6, 3.6ColCre;$Y1^{lox/lox}$ 16.6 ± 1.2, compared to $Y1^{lox/lox}$ 12.0 ± 1.1 %; $p=0.05$ and $p=0.05$ respectively). This increase in bone volume was associated with an increase in mineral apposition rate (2.3ColCre;$Y1^{lox/lox}$ 2.31 ± 0.06, 3.6ColCre;$Y1^{lox/lox}$ 2.31 ± 0.06, compared to $Y1^{lox/lox}$ 2.01 ± 0.07 mm/day; $p=0.004$ and $p=0.005$ respectively). No significant differences were observed in osteoclast number or osteoclast surface area between groups suggesting that bone resorption has not been affected.

Together these data demonstrate a direct role for the Y1 receptor on osteoblasts in the regulation of osteoblast activity and bone formation in vivo. Understanding the action of NPY on osteoblasts to regulate bone metabolism will have powerful therapeutic implications in diseases such as osteoporosis.