2006 IOF+ANZBMS Combined Meeting

Combined Meeting of the
3rd IOF Asia-Pacific Regional Conference on Osteoporosis *and the*
16th Annual Meeting of the ANZ Bone & Mineral Society
~ 22-26 October 2006, Port Douglas, Australia ~

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Invited Plenary Abstract

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Bone remodelling and the roles of nuclear receptor

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Nuclear receptors (NRs) are ligand-dependent transcription factors, and form a gene superfamily. Their fat soluble ligands like steroid hormones and vitamin D are well known to support bone formation and bone remodeling through gene regulations mediated through NRs. However, the physiological roles of NRs in bone tissues still remain unclear.

To investigate the physiological roles of VDR, we had generated VDR deficient mice by a conventional gene targeting, and found that $VDR^{-/-}$ knockout (VDRKO) mice showed features typical of vitamin D-dependent type II rickets like bone loss by impaired mineralization (Yoshizawa T. *et al.*, *Nat. Genet.*, 16, 391, 1997). Likewise, the male-specific significance of AR in bone remodeling has been demonstrated by ARKO mice (Kawano H. *et al.*, *PNAS*, 100, 9416, 2003).

However, primary target cells of such NR functions in bones have not yet been defined. To directly examine physiological impact of AR in osteoclasts, we used a Cre/*lox*P system to disrupt AR gene in osteoclasts. The osteoclast-specific ARKO (Oc-ARKO) mice had normal appearance, but exhibited clear loss of bone mass with enhanced bone remodeling. Osteoblast-specific VDRKO (Ob-VDRKO) mice unexpectedly exhibited clear increases in bone mass as well as bone mineral density with less bone remodeling. Thus, the present study reveals the physiological impact of AR and VDR function in bone.