2009 ANZBMS-IBMS Joint Meeting

2nd Joint Meeting of the International Bone & Mineral Society and the Australian and New Zealand Bone and Mineral Society

21-25 March 2009, Sydney, Australia

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Christopher & Margie Nordin Young Investigator Poster Award

Winner: Ee-Cheng Khor

Poster Abstract:

The regulation of Protein Kinase C δ in bone homeostasis

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Bone homeostasis is maintained by the bone remodelling process which involves bone resorption by osteoclasts and bone formation by osteoblasts. Disruption of this balanced process is associated with bone diseases. Osteoclasts are formed from the fusion of macrophage precursor cells stimulated with the receptor activator of NF-κB ligand (RANKL). The signalling pathways that regulate osteoclast formation are not fully understood. Protein kinase C (PKC) has been implicated in regulating RANKL signalling pathways and osteoclastogenesis. To further investigate specific the role of PKC isoforms in osteoclast biology, we have compared the gene expression profile of PKC isoforms in RAW cell and primary bone marrow monocyte (BMM) derived osteoclasts and found that PKCδ is highly expressed in osteoclasts. Further studies using isoform-specific agonists and antagonists of PKC activity support a role for PKCδ in osteoclasts. Inhibition of PKCδ by Rottlerin inhibited osteoclastogenesis and bone resorption, whereas activation of PKCδ by Bryostatin 1, enhanced osteoclastogenesis and osteoclast size. RT-PCR showed that the expression of osteoclast fusion gene DC-STAMP is up-regulated in Bryostatin 1 treated cells. Using luciferase reporter gene assays, we showed that the expression of constitutively active and dominant negative PKCδ mutants regulate NFATc1 and NF-κB transcriptional activity, which are essential for osteoclastogenesis. Interestingly, mCT and histology analysis demonstrates that PKCδ deficient (PKCδ-/-) mice exhibit an osteopetrotic (increased bone mass) phenotype. Alcian blue staining showed the presence of cartilaginous bars in the trabecular bone of PKCδ-/- mice consistent with an osteopetrotic phenotype. These findings suggest PKCδ mediates bone homeostasis via the regulation of osteoclast differentiation.