The Role of Vitamin D Receptor in Osteoblasts and Bone Mineralisation

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ABSTRACT

Age-related bone loss is associated with a change in bone remodelling characterised by decreased bone formation relative to bone resorption. It is well described that age-related bone loss is accelerated as a consequence of vitamin D deficiency, a process which can be replicated in rodent studies. While vitamin D has been shown to play important roles for adequate bone mineralisation and the prevention of osteoporosis, the exact mechanisms remain controversial. It is clear that vitamin D is necessary for the stimulation of intestinal calcium and phosphate absorption, maintenance of calcium homeostasis and supply of calcium and phosphate for bone mineralisation. However, vitamin D has also been shown to directly act on bone cells to promote mineralisation as well as regulate bone resorption. The question of the essential nature of the in vivo role for the direct actions of vitamin D on bone has proven to be difficult to resolve. The only published mouse model which addresses the direct actions of vitamin D in osteoblasts is the osteoblast-specific vitamin D receptor transgenic mouse, or OSVDR mouse. Using this transgenic mouse model, it has been reported that the enhanced vitamin D activity in osteoblasts promotes bone formation and mediates reduction in bone resorption most likely through reduced RANKL signalling of osteoclastogenesis. The reported overall bone phenotype of the OSVDR was increased vertebral trabecular bone as well as increased cortical bone volume leading to increased bone strength. In contrast to the findings in OSVDR mice, global VDR knockout mice can mineralise osteoid in the presence of high levels of dietary calcium and phosphate, therefore many have concluded that the role for direct vitamin D activity in bone cells is redundant. This view however, does not take into account the fact that vitamin D activity in bone cells may play a permissive role to optimise bone health by modulating mineralisation and bone resorption.

Thus, the studies conducted in this thesis are aimed to further address the role of osteoblastic VDR in bone remodelling and bone architecture. Specifically, these studies aimed to further
establish the phenotype of the OSVDR mouse model utilising 3D micro-CT analyses as well as establish the role of vitamin D activity in osteoblasts during vitamin D deficiency and dietary calcium depletion. The effects of these physiological interventions on OSVDR mice are described in terms of bone structure, cellular activities, biochemical parameters, and gene expression profiles of bone and other organs involved in calcium and phosphate homeostasis. The overall hypothesis is that VDR activity in mature osteoblast lineage is important to regulate processes of bone remodelling and maintenance of an optimal skeletal structure.

The data presented within these chapters showed that the phenotype of increased bone mineral volume is present in more regions of bone, which was not previously recognised. Furthermore, during vitamin D deficiency, while bone loss occurs in wild-type mice, OSVDR mice maintain both cortical and trabecular bone volume, indicating that bone loss due to vitamin D deficiency is due, at least in part, to reduced vitamin D activity in osteoblasts. In contrast to vitamin D deficiency, the effects of low calcium stress in OSVDR mice results in bone loss comparable to wild-type mice, which is likely to be due to a disruption of bone remodelling, since we observed lowered osteoblast, osteoclast and osteocytes activities.

Intriguingly, low calcium fed OSVDR mice demonstrate a marked increase in serum fibroblast growth factor 23 (FGF23) levels, resulting in suppressed renal 1,25-dihydroxyvitamin D (1,25D) synthesis, and reduced expression of intestinal calcium absorption genes. Thus, the inappropriately low 1,25D-mediated intestinal calcium absorption in OSVDR mice, fed low calcium, may further contribute to the reduction in bone mineralisation and bone volume. These data suggest that in addition to the reported direct action of vitamin D activity in osteoblasts to regulate bone turnover, VDR-mediated activity in osteoblast also plays a role in the endocrine feed-back mechanism of renal 1,25D synthesis, which may contribute to the maintenance of bone mineral and the resulting bone phenotype.

In summary, the findings from this thesis implicate the essential role of vitamin D and VDR in osteoblasts either directly or indirectly impacts on bone homeostasis, including osteoclast
activity, osteoblast differentiation, osteocyte activity, bone FGF23 production and renal feed-
back signalling.
DECLARATION

“This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Nga Ngoc Lam and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text”

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INTERNATIONAL AND NATIONAL SCIENTIFIC MEETINGS AND AWARDS ARISING FROM WORK PRESENTED IN THIS THESIS

PRESENTATIONS

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National

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• Australian Society for Medical Research: Best Poster Award in Healthy Aging, 2009

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