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## **Sclerostin : a key regulator of bone metabolism**

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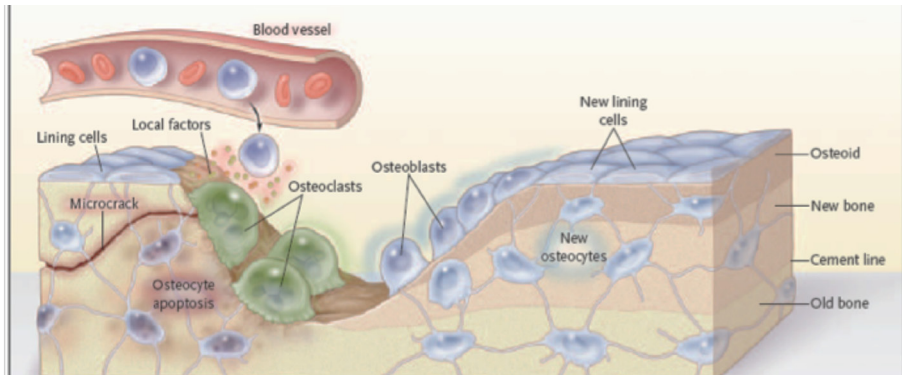
# Preface



## **Preface**

Bone is a living tissue. Throughout life the skeleton constantly maintains its structural integrity by replacing old or damaged bone with newly laid down bone by a process called remodelling. This process of bone remodelling is accomplished by a tight collaboration between bone resorbing osteoclasts and bone forming osteoblasts, working together as a basic multicellular unit (BMU) (Figure 1). Bone remodelling commences by attraction of osteoclast precursors to bone sites, where they further differentiate into mature multinucleated osteoclasts, which start to resorb bone, leaving behind a resorption cavity. Osteoblasts are subsequently attracted to this resorption pit by signals derived from the osteoclasts and stimulatory factors embedded in the bone matrix, released by resorption (1). Over a period of 3 to 4 months the resorption cavity is refilled with new layers of bone matrix, layed down by the osteoblasts, which subsequently mineralizes. In healthy adults, the amount of bone formed equals that initially resorbed. The activity of osteoclasts and osteoblasts are tightly regulated, by each other, but also by a third type of bone cell, the osteocyte (2,3). Osteocytes are terminally differentiated osteoblasts embedded in the bone. During the process of bone formation, about 10-20% of the osteoblasts are buried in the bone matrix by the advancing osteoblasts. These cells differentiate into osteocytes, developing long dendritic processes through which they keep contact with the osteoblasts on the bone surface. This way osteocytes can be found regularly scattered throughout the bone, making up for more the 90% of all bone cells, and forming a dense network with their dendritic pseudopods, through which they can communicate with each other and cells on the bone surface (4).

For many years osteocytes were thought to be involved in the regulation of bone remodelling, but due to their embedment in bone, these cells were difficult to study, and their exact function remained an enigma. However, recent studies illustrated that osteocytes are indeed the main orchestrators of bone remodelling. Osteocytes produce RANKL, a major stimulatory signal for osteoclast differentiation and activity, by which they can regulate bone resorption (6,7). Similarly osteocytes can control the rate of bone formation by synthesizing sclerostin, a key inhibitory signal for osteoblast activity and lifespan (8).



**Figure 1.** A schematic overview of the bone remodelling cycle. Lining cells and osteocytes release local factors that attract cells from blood and marrow into the remodeling compartment in which osteoclastogenesis occurs. Osteoclasts resorb matrix, then successive teams of osteoblasts deposit new lamellar bone. Osteoblasts that are trapped in the matrix become osteocytes; others die or form new, flattened osteoblast lining cells. Reproduced with permission from the New England Journal of Medicine (5), Copyright Massachusetts Medical Society

Disturbances in the balance between bone resorption and bone formation form the pathophysiological basis of many bone diseases. The most prevalent bone disease is osteoporosis, in which an increased bone resorption is not sufficiently compensated by bone formation, leading to gradual bone loss and deterioration of its microstructure leading to increased bone fragility (9). Conversely, there are several, less prevalent, bone disorders in which there is an imbalance in favour of bone formation, leading to increased accumulation of bone and thick bones. These sclerosing bone disorders can be caused either by impaired production or activity of osteoclasts (osteopetroses), or by increased production of osteoblasts (hyperostoses or osteoscleroses) (10). Sclerostin was discovered a decade ago by studies of two such bone sclerosing dysplasias namely, sclerosteosis and van Buchem disease (11-14). Both these disorders are the result of impaired sclerostin synthesis, leading to an imbalance of bone remodelling in favour of bone formation.

The aim of this Thesis is the investigation of the role of sclerostin in bone metabolism in humans. In Chapter 1 we review current knowledge of sclerostin, and the sclerostin-deficient disorders sclerosteosis and van Buchem disease. In Chapter 2, we describe the characteristics and performance of the assay we used to measure sclerostin levels

in blood. In Chapters 3 and 4 we report studies of patients and disease carriers of sclerosteosis and van Buchem disease, respectively. In Chapter 5 we present the results of treatment of van Buchem disease with glucocorticoids. In the subsequent Chapters we report studies of the regulation of sclerostin synthesis by systemic factors, such as glucocorticoids (Chapter 6) and PTH (Chapter 7) and the role of sclerostin in type 2 diabetes mellitus (Chapter 8), Paget's disease of bone and prostate cancer metastatic to the skeleton (Chapter 9).

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