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MEETING REPORT

Update on Osteocytes (Sun Valley 2012)

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Meeting Report from the 42nd International Sun Valley Workshop: Musculoskeletal Biology, Sun Valley, ID, USA, 5–8 August 2012

This session began with a review of the 'first-ever' session to focus on osteocytes that was held in Sun Valley in the August of 2001. At that time, osteocytes were proposed to be multifunctional cells, but there was limited data to support this hypothesis.[1] In the last 11 years, this has changed and osteocytes are recognized as multifunctional cells.[2] Some of the functions of osteocytes, in addition to being mechanosensory cells, include acting as orchestrators of bone remodeling, and regulators of both calcium and phosphate mineral homeostasis. This session focused on three main areas: receptor activator of nuclear factor kappa-B ligand (RANKL) production by osteocytes, the role of parathyroid hormone (PTH)/PTH-related peptide in regulating osteocyte function, and recent investigations into crosstalk between osteocytes and muscle.

Osteocytes appear to act as endocrine glands targeting other organs such as the kidney, the immune system, and so on. While dogma assumes that the muscle–bone relationship is driven purely by mechanical factors, bone can act, in effect, as an 'endocrine organ' to control muscle physiology and disease. The traditional view of skeletal muscle and bone interaction is that skeletal muscle loads bone and bone provides an attachment site for muscle. This mechanical perspective implies that as muscle function declines, this would result in decreased loading of the skeleton and therefore would result in a decrease in bone mass. Conversely, muscle has been shown to secrete 'myokines', therefore leading to the hypothesis that muscle may produce factors that target bone, specifically the osteocyte. Dr Bonewald in collaboration with Drs Marco Brotto and Mark Johnson at the University of Missouri-Kansas City have begun to examine the molecular and cellular mechanisms that contribute to the coordinated development of bone and muscle conditions. It has been discovered that muscle produces a factor(s) that maintains osteocyte viability in the presence of glucocorticoid.[3] This factor is most highly produced by myotubes, but not myoblasts, and by contracted extensor digitorium longus, a fast-twitch muscle as compared with soleus, a slow twitch muscle. The protective mechanism of this factor is mediated through β-catenin. With age, this factor is no longer present. Identification of this factor is in process.

Osteocytes are thought to orchestrate bone homeostasis by regulating both bone-forming osteoblasts and bone-resorbing osteoclasts. It is well known that osteoclast differentiation and function is regulated by receptor activator nuclear factor-κB ligand, RANKL. Previously it was assumed that RANKL was mainly expressed by osteoblasts or stromal cells in bone marrow. Hiroshi Takayanagi of Tokyo Medical and Dental University presented data on osteocyte regulation of osteoclastic bone resorption through RANK/OPG expression.[4] RANKL is a key cytokine for osteoclast differentation and function, but accumulating evidence indicates the diverse roles of RANKL in many biological systems including the immune system. RANKL is expressed by mesenchymal cells, including osteoblastic cells, as well as hematopoietic cells such as Tcells; thus it has been difficult to precisely characterize RANKL-expressing cells under physiological and pathological settings. Using *in vitro* isolation and culture of primary osteocytes, Takayanagi's laboratory identified RANKL to be among the mechanically responsive genes in osteocytes. They also analyzed RANKL expression in osteocytes by sorting enhanced green fluorescent protein (EGFP)-positive cells from calvarial cells derived from CAG-CAT EGFP transgenic mice crossed with DMP-1 Cre mice. RANKL expression in osteocytes was about ten times higher than that in osteoblasts. Osteocyte-specific RANKL knockout mice revealed the crucial role of osteocytes in supporting osteoclastogenesis in adult bone remodeling. This was similar to the findings of Charles O-Brien's laboratory.[5] In addition, Dr Takayangi presented data on osteoblast-to-osteocyte differentiation and the discovery of semaphorin genes, specifically semaphorin A expressed in both osteoblasts and osteocytes that functions similarly as OPG functions to inhibit osteoclast activity.

It has recently been shown that the PTH receptor functions in osteocytes to regulate bone remodeling[6] and calcium homeostasis.[7] Dr Teresito Bellido of Indiana University gave an update on recent work and new observations regarding how PTH, a central regulator of bone homeostasis, regulates osteocytes. PTH downregulates sclerostin, an osteocyte inhibitor of bone formation, and stimulates increased expression of RANKL. Mechanical stimulation reduces sclerostin expression,[8] suggesting that osteocytes might coordinate the osteogenic response to mechanical loading and therefore sclerostin downregulation may be a pre-requisite for load-induced bone formation. Dr Bellido's laboratory compared the anabolic response to loading in transgenic mice engineered to maintain high levels of human sclerostin in osteocytes while

expressing the constitutively active PTH receptor. Sclerostin expression remained high in these transgenic mice after loading, which is most likely responsible for the maintenance of periosteal bone formation in these transgenic mice as compared to controls. However, load-induced bone formation was reduced by 70–85% in transgenic mice, most likely due to the lack of induction of Wnt target genes as induced by loading in control mice. Thus, downregulation of Sost/sclerostin in osteocytes is essential for anabolic response to loading. Dr Bellido also presented some preliminary data showing PTH also increases fibroblast growth factor (FGF)23 expression in osteocytes. FGF23 is an osteocyte factor that inhibits phosphate re-absorption by the kidney.[9] Dr Bellido presented data showing the presence of FGF1 receptor in both osteoblasts and osteocytes. However, the autocrine and paracrine effects of FGF23 on osteocytes and osteoblasts remain to be determined.

Two award-winning young investigators also presented their data during this session. Dr Vaibhav Saini, an Alice L Jee Award winner and a postdoctoral fellow in Dr Paola Divieti's laboratory at Harvard Medical School, presented data on mice lacking the PTH type 1 receptor in osteocytes, again validating the importance of sclerostin and RANKL in osteocyte function. Julia Hum, a student in Dr Fred Pavalko's laboratory at Indiana University and also the winner of the Charles H Turner award, presented live imaging of Src activation in osteoctyes in response to mechanotransduction. Her images captivated the audience and raised questions regarding the sensitivity of dendrites as compared to the cell body and the function of Src in osteocytes. The session ended with speculation on if and when the next update on osteocytes will be held and if there are still unknown functions of the osteocyte to be discovered.

Note: Abstracts from the 42nd International Sun Valley Workshop: Musculoskeletal Biology can be accessed at: http://www.ibmsonline.org/p/cm/ld/fid=156.

Conflict of Interest

The author declares no conflict of interest.

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