IBMS BoneKEy. 2010 May;7(5):187-189
http://www.bonekey-ibms.org/cgi/content/full/ibmske;7/5/187
doi: 10.1138/20100445

MEETING REPORTS

Systemic and Local Regulation of Skeletal Metabolism – Meeting Report from the IBMS Davos Workshop: Bone Biology & Therapeutics

March 14-19, 2010 in Davos, Switzerland

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At the IBMS Davos Workshop: Bone Biology & Therapeutics, a number of subjects concerning the systemic and local regulation of skeletal metabolism were covered, including osteocytes (osteocyte remodeling, sclerostin, LRP4 and periostin); central regulation of bone; and vascular calcification. This *Meeting Report* summarizes the most interesting presentations given at the meeting.

Osteocytes

Osteocyte Remodeling

Osteocytes play an essential role in bone turnover and appear to regulate the activation of bone remodeling, exerting both positive and negative regulation on osteoclasts and osteoblasts (1). As described by Lynda Bonewald (University of Missouri at Kansas City, Kansas City, Missouri, USA), osteocytes can also remodel their perilacunar and canalicular matrix and this regulation is under both hormonal and mechanical control (abstract 7). During pregnancy and lactation osteocytes directly mobilize mineral from their perilacunar and pericanalicular matrix, thus contributing to maternal bone loss. This is thought to be due to the elevation of parathyroid hormone-related protein (PTHrP) during pregnancy and lactation that leads to an increase in osteocyte lacunar size by approximately 20% while returning to normal size within one week of forced weaning. Osteocytes can express markers of osteoclasts and can selectively remodel the perilacunar matrices in response to calcium demand. In comparison, non-calcium demanding conditions, such as immobilization, do not cause perilacunar matrix loss.

Sclerostin

Osteocytes express *SOST* and *PTH1R* and the two major bone anabolic pathways, inhibition of sclerostin and induction by PTH, partially overlap as PTH bone anabolism is blunted in both *SOST*-overexpressing and *SOST*-deficient mice (2). In addition, it has been shown that PTH suppresses MEF2-stimulated *SOST* bone enhancer activity and thus sclerostin levels (3). Interestingly, in the genome-wide association studies (GWAS) in osteoporosis reported by Matt Brown (Diamantina Institute, Brisbane, Australia), MEF2C was strongly associated with BMD (abstract 10). Similar to PTH treatment, mechanical loading decreases sclerostin levels, and this is partly mediated by *periostin*. Conversely, *SOST* is upregulated by skeletal unloading.

Sclerostin passes through the osteocytic canalicular network to osteoblasts on the bone surface where it binds to the Wnt co-receptors LRP5 and LRP6 and interestingly, as described by Michaela Kneissel (Novartis Institutes for BioMedical Research, Basel, Switzerland), sclerostin has now also been shown to bind to LRP4, also mediating the inhibitory function on Wnt/β-catenin signaling and bone formation (abstract 8). It has also been shown in studies of *SOST* and *LRP5* double knockout mice that *SOST* requires, at least in part, LRP-dependent pathways. Recent work indicates that sclerostin not only acts in a paracrine

fashion but is also likely to act in an autocrine manner affecting osteocyte function, as loss of *SOST* action in mice results in decreased osteocyte apoptosis.

LRP4

The interaction between sclerostin and LRP4 is required to mediate the sclerostin inhibitory function on bone formation and this was shown by LRP4 missense mutations that lead to high bone mass and sclerosis. As reported by Elke Piters (University Antwerp, Edegem, Belgium) *et al*., these mutations led to impaired sclerostin action and reduced sclerostin binding, and these results imply that LRP4 is indeed involved in bone regulation (abstract 126). Interestingly, in the GWAS studies reported by Matt Brown (abstract 10), LRP4 and *SOST* were found to be strongly associated with high fat bone mass studies.

Periostin

Periostin is an extracellular matrix protein and its expression is increased in periosteal osteoblasts and osteocytes upon mechanical stimulation. Periostin has been shown to regulate SOST and the periostin-deficient mouse does not have this SOST response to loading (4). According to Nicolas Bonnet (Geneva University Hospital, Geneva, Switzerland) *et al*., increases in cortical bone, but not trabecular bone, are mediated by periostin and mice lacking periostin are resistant to cortical bone loss induced by hindlimb suspension in mice (abstract 164).

Central Regulation of Bone

Evidence during recent years has demonstrated that bone remodeling is not only regulated by endocrine/paracrine/autocrine factors but also by neuronal ones, specifically by sympathetic nerves (5;6). Afferent hypothalamic signals inhibit bone formation and favor bone resorption via the activation of sympathetic neurons stimulating the beta2-adrenergic receptor (β2AR) expressed by osteoblasts. β2AR signaling in osteoblasts is now shown to be a major regulatory pathway, not only through effects on osteoblast proliferation but also for trafficking of bone marrow hematopoietic cells and, unexpectedly, for glucose homeostasis. Therefore, as described by Florent Elefteriou (Vanderbilt University, Nashville, Tennessee, USA), it is reasoned that pathologies or drugs that have the ability to modulate sympathetic tone and β2AR signaling are likely to affect bone homeostasis and bone mass (abstract 6). Indeed, depression and different classes of antidepressant drugs are linked to this neuronal pathway and the regulation of bone homeostasis. As described by Paul Baldock (Garvan Institute of Medical Research, Sydney, New South Wales, Australia) *et al*. (abstract 161), endogenous opioids are known to exert powerful negative effects on bone mass, and hypothalamic signaling is important for this mechanism. The dynorphins are a component of the endogenous opioid system and are expressed within the central nervous system during pain, addiction and depression. The bone phenotype of the dynorphin knockout mouse was examined. The dynorphin receptor is a kappa opioid receptor (KOR) and neither dynorphin nor its receptor is present in osteoblasts. Consequently, there are no local bone effects of dynorphin. The KOR-deficient mouse has no bone phenotype; however the dynorphin-deficient mouse has a bone phenotype similar to that of the neuropeptide Y-deficient mouse. These results show that the endogenous opioid system is required for normal bone homeostasis. The dynorphin system acting via neuropeptide Y may represent a pathway by which higher processes such as stress and depression influence skeletal metabolism.

Vascular Calcification

Vascular calcification is similar to skeletal mineralization and involves the deposition of hydroxyapatite crystals. As reported by Vicky MacRae (University of Edinburgh, Midlothian, UK) *et al*. (abstract 180), the differentiation and calcification of osteoblasts was compared to that of vascular smooth muscle cells in their expression patterns of osteocytic marker

genes. Calcium deposition expression of osteoblast markers and mineralization regulators were significantly elevated in mineralizing osteoblasts and there were significant increases in osteocytic markers after 28 days of culture of murine calvarial osteoblasts. Similarly, calcium deposition and expression of chondrocytic markers, osteoblast markers and regulators of mineralization were significantly elevated in aortic vascular smooth muscle cell cultures, confirming the chondro-osseous phenotype associated with vascular calcification. In addition, in the vascular smooth muscle cells, significant increases were seen in the osteocytic markers sclerostin, Dmp1, Phex, Mepe and E11. FGF3 expression was also significantly changed, together with FGF23-specific signaling involving Klotho and FgfR1.

In another study by Anna Idelevich (The Hebrew University of Jerusalem, Rehovot, Israel) *et al.* (abstract 172), chondrogenic-like differentiation of vascular smooth muscle cells was demonstrated in a vascular smooth muscle cell line overexpressing osteocalcin. Another presentation by Catherine Shanahan (Kings College London, London, UK) focused on the earliest events of calcification in vascular smooth muscle cells (abstract 15). Calcification is initiated in matrix vesicles derived from apoptotic and stressed vascular smooth muscle cells. Normally these vesicles are loaded with inhibitors of mineralization to keep in check the amount of calcification, however, if these inhibitors are dysfunctional, calcification pathologies develop such as in chronic kidney disease. Recent work has focused on how the vesicles calcify and has identified initiators of mineralization such as annexins. Finally, as reported by Ian Reid (University of Auckland, Auckland, New Zealand) the similarities of calcium deposition in osteoblasts and vascular smooth muscle cells are interesting in light of evidence that calcium supplementation caused vascular events (abstract 20).

Conflict of Interest: None reported.

Note: Abstracts from the meeting have been published as a supplement to *Bone*. 2010 Mar;46(Suppl 1):S1-S90.

References

1. Henriksen K, Neutzsky-Wulff AV, Bonewald LF, Karsdal MA. Local communication on and within bone controls bone remodeling. *Bone*. 2009 Jun;44(6):1026-33.

2. Kramer I, Loots G, Studer A, Keller H, Kneissel M. Parathyroid hormone (PTH) induced bone gain is blunted in SOST overexpressing and deficient mice. *J Bone Miner Res*. 2009 Jul 13. [Epub ahead of print]

3. Leupin O, Kramer I, Collette NM, Loots GG, Natt F, Kneissel M, Keller H. Control of the SOST bone enhancer by PTH using MEF2 transcription factors. *J Bone Miner Res*. 2007 Dec; 22(12):1957-67.

4. Bonnet N, Standley KN, Bianchi EN, Stadelmann V, Foti M, Conway SJ, Ferrari SL. The matricellular protein periostin is required for sost inhibition and the anabolic response to mechanical loading and physical activity. *J Biol Chem*. 2009 Dec 18;284 (51):35939-50.

5. Elefteriou F, Ahn JD, Takeda S, Starbuck M, Yang X, Liu X, Kondo H, Richards WG, Bannon TW, Noda M, Clement K, Vaisse C, Karsenty G. Leptin regulation of bone resorption by the sympathetic nervous system and CART. *Nature*. 2005 Mar 24;434(7032):514-20.

6. Wong IP, Zengin A, Herzog H, Baldock PA. Central regulation of bone mass. *Semin Cell Dev Biol*. 2008 Oct;19(5):452-8.