J Musculoskelet Neuronal Interact 2005; 5(4):333-334

Hylonome

Summary

Summary - Osteocytes and Mechanotransduction

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Discussion at this workshop was lively, probably due to the still mysterious nature of the osteocyte. One of the most intensive discussions was whether the osteocyte can modify its microenvironment. **Nancy Lane** showed convincing evidence of a "halo" surrounding osteocyte lacunae in mice treated with glucocorticoids. The halo contained hypomineralized bone suggesting that the osteocyte can "leach" mineral from its microenvironment. Increased lacunar size was observed similar to that observed with various pathologic conditions, such as hyperparathyroidism and in non-pathological conditions such as in hibernating bears. The controversial term "osteocytic osteolysis" was raised. It was suggested that the term "osteocyte modification of its microenvironment" be used to avoid any misunderstanding concerning the mechanism whereby the osteocyte can either remove or lay down new matrix. Another reason for this change in terminology was because the term "osteocytic osteolysis" fell out of favor for almost 3 decades due to assumptions that the osteocyte could resorb in a similar fashion to the osteoclast and that several investigators were describing artifact due to tissue processing.

While generally accepted that PTH can increase lacunar size in disease states of hyperparathyroidism, it is not clear how the carboxy-terminal fragments of PTH affect osteocytes. **Paola Divieti-Pajevic** showed convincing data of receptors for these fragments in osteocyte-like cells. It was not clear why higher expression would exist on the osteocyte compared to the osteoblast, especially as these fragments appear to be inducing apoptosis in the cells expressing this receptor. It was not clear if the PTHtype 1 receptor and the C-PTH receptors may have opposing functions required for a balance between viability and osteocyte death.

It has also been assumed that as the osteocyte is embedded in osteoid, the cytoplasm shrinks, leaving behind dendritic processes. Assumptions have been made that the osteocyte becomes a passive cell with little to do with initiation of modeling and remodeling that takes place on the bone surface. **Lynda Bonewald** presented data suggesting that perhaps the osteocyte can generate new processes, not only at the time of embedding but also when the osteocyte is embedded in mineralized matrix. The molecule E11/gp38 was shown to be responsible for elongation of dendritic processes in MLO-Y4 cells in response to fluid flow shear stress. As E11 gene and protein expression are increased *in vivo* in response to load, not only in osteocytes near the bone surface, but also in deeply embedded osteocytes, osteocytes may be able to either generate or elongate processes while embedded in bone. Whether osteocytes can do this only in unmineralized osteoid or might "regenerate" processes in mineralized bone is unknown.

Abnormal lacuno-canalicular networks have been suggested to be the cause or the result of disease conditions. **Jian Feng** showed that the lacuno-canalicular system in Dentin Matrix Protein1 null mice was extremely abnormal compared to wild-type mice. The walls of the lacunae and canaliculi are rough and not smooth, and no lamina limitans is observed. Collagen fibers fill the space where the glycocalyx normally is located. In the Dmp1 knockouts, the dendritic membranes appear wavy, giving the impression that the dendrite is compressing or buckling. This abnormal morphology is most likely due to defects in mineralization in these Dmp1 null mice as patches of osteoid are present between mineralized matrix. Fluorochrome labeling is punctate and diffuse. Numerous calcospherulites are present in the osteoid suggesting defects in mineral propagation. It was proposed that osteocytes in these mice might be "hyperstressed" as they are surrounded by a poorly mineralized matrix, therefore continuously sending signals of bone formation which only result in more poorly mineralized bone.

Numerous mechanosensors have been proposed for osteocytes and none is more controversial than cilia. **Darryl Quarles** proposed that PKD1 and PKD2 may play a role in mechanosensing on the osteocyte. Two seasoned investigators in the room, Howard Winet and Mitch Schaffler, stated that they had been looking for cilia on osteocytes for years and had not been successful. Darryl responded that he did not know if

The author has no conflict of interest.

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Accepted 4 August 2005

traditional cilia were present in osteocytes or not, but PKD1 and PKD2 are expressed in both osteoblasts and osteocytes and that a consitutively active form of PKD1 did regulate gene expression in these cells, specifically Runx2. This suggests that these two proteins, normally mechanosensory components of cilia in the kidney, do have a function in bone cells, whether they are components of traditional cilia or not.

During the final discussion, the role of osteocytes in maintaining "optimal" bone mineralization was discussed. Particularly, the discussion focused on whether Frost's old data on micropetrosis and loss of osteocytes in aging bone reflect a true change in bone matrix mineralization due to the absence of osteocytes, or reflect an apparent increase in volume mineral content due to infilling of the lacunar-canalicular space with mineralized material. In addition, it was also noted that we still do not have proof of osteocyte function, whether it be mechanical or metabolic in nature. John Curry brought up that teleosts do not have osteocytes and survive quite well. It was also noted by Scott Miller that fish actually maintain calcium metabolism through their scales. Logically it followed that as vertebrates do not have scales, perhaps osteocytes have assumed this function. In summary, osteocyte biology remains a controversial and relatively unexplored area.