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Effects of nanomechanical bone tissue properties on bone tissue strain: Implications for osteocyte mechanotransduction

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Bone is a dynamically adaptable material that, under normal circumstances, will respond to changes to its functional requirements by altering its micro- and macro-structural organization. The cells in bone thought to be the primary mechano-sensors that orchestrate this remarkable process by transducing musculoskeletally derived mechanical input signals into biological output[1], is the osteocyte, the most abundant bone cell[1]. These cells are thought to coordinate the actions of osteoblasts building new bone and osteoclasts removing bone to maintain or alter bone structure[2]. This process is not wholly understood and key issues regarding how skeletal mechanical loading is ultimately sensed by osteocytes, the translation of the mechanical input into biochemical signals (mechanotransduction), and how these signals are conveyed to other non-sensing bone cells remain. The complex hierarchical structure of bone influences how forces applied or encountered at the whole bone organ level (macroscopic) are distilled or modified before transmission to individual bone cells (cellular level)[3,4] is unclear. A more detailed understanding of the structure of bone tissue should lead to a better understanding of the osteocyte mechanotransduction process.

Here we show, using a variety of characterization techniques including atomic force microscopy, micro-Raman imaging, nanoindentation based elastic modulus mapping, and electron microscopy, that the bone tissue directly surrounding osteocyte lacunae forms a unique microenvironment that is distinctly different compared to bone tissue not associated with osteocyte lacunae. This approximately 2 microns to 8 microns wide peri-lacunar region consists of bone tissue that is typically less mineralized with a distinctly different collagen fibril organization. In young healthy bone, the peri-lacunar tissue also exhibits a lower elastic modulus compared to bone tissue at some distance from the lacuna. We have previously shown that the lacuna acts as a strain concentrator effectively amplifying the macroscopic strain applied to the whole bone[4,5] and this amplification factor is a function of the local peri-lacuna bone tissue material properties[6]. There is increasing evidence that the osteocyte has the ability to alter its microenvironment[7-10], which in turn will result in altered tissue properties and ultimately may lead to changes in the local lacuna strain field influencing the osteocyte[6]. For instance, if the peri-lacunar tissue properties are the same as the far field tissue (away from the lacuna), the presence of a lacuna in the bone tissue results in a strain concentration of about 1.5-1.8 depending upon the geometry of the lacuna[5]. If the local tissue around the osteocyte is 38% softer that the surrounding bone tissue, the strain amplification factor actually increases, resulting in 15% increase in bone tissue strain at the lacuna[6]. Thus, by altering the local osteocyte lacuna bone tissue microenvironment, the ratio of the global bone strain to the local osteocyte lacuna tissue strain can be altered to maintain, to some degree, a consistent osteocyte mechanical stimulation given an alteration in globally applied loads. For example, this would imply that in skeletal unloading situations (e.g., bed rest, reduced gravity), the peri-lacunar tissue should exhibit a lower peri-lacunar tissue modulus than normally loaded tissue so that the available skeletal loads are converted to higher tissue strains at the lacuna. Conversely, in higher loaded bone (e.g., weightlifting, gym-

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nastics), the difference in peri-lacuna tissue modulus and the surrounding bone tissue should be less, resulting in reduced lacunar bone tissue strains. More importantly, if the peri-lacunar tissue region becomes more mineralized due to the age-related increase in tissue mineralization[11], the strain signal to the osteocyte may be reduced under normal loading conditions potentially contributing to the progression of osteoporosis. In related work, we investigated the peri-lacunar bone matrix elastic modulus associated with osteocytes within trabecular bone from 20-month-old OVXed rats (110 days post-OVX) and sham-operated controls. Peri-lacunar bone tissue elastic modulus in OVXed rats 2-3 microns from the osteocyte lacuna was increased by 35% compared to matrix more than 10 microns from the lacunae. There was no increase in the peri-lacunar bone tissue stiffness in sham-operated animals. Based on our previous work, this suggests that this stiff peri-lacunar bone tissue may attenuate the strain signal acting on embedded osteocytes. Thus, given equal skeletal forces, embedded osteocytes in the OVXed animals would experience less mechanical strain.

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