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Perspective Article

Hylonome

Summary – Aging of osteoblast biology session

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The original focus of this session was to discuss aging in bone. Presenters covered many aspects of bone biology and including effects of new prostanoid receptor agonists. Key questions on how well rat and mouse skeletons may replicate changes in aging human skeletons, given the differences between species in number of turnover cycles, duration of active endochondral osteogenesis and age of onset of growth plate maturation and closure, were not discussed. While telomere shortening and exposure to environments that modify and injure DNA are significant regulators of aging in human cells, these may not be as relevant to mice and rats. **Dr. R. Jilka** discussed regulation of progenitor cells and their plasticity. A recently published study of an activating mutation of p53 showed reduced longevity, increased resistance to tumors and a paucity of stem cells in all organs. In bone, stem cell estimates are made through surrogate CFU-f assays, and these clearly show decreases with aging. Plasticity that leads to changes in cell fate, such as preference for differentiation into adipocytes rather than osteoblasts, and the association of such changes with the rate of bone turnover and hematopoietic or fatty marrow need more in-depth investigation. Many of our current ideas are based on associations and correlations of outcomes. We need to leverage the new functional genomic and proteomic technologies to construct new models of cell networks and then manipulate environmental controls of those networks and cell fate. Bone regulating hormones and drugs, such as bisphosphonates, regulate apoptosis but appear to do so through quite different biochemical pathways and with different requirements for transcription. The longevity of a BMU is significantly longer than the cells that comprise the BMU. What regulates the number of cells at any one point in time, and what determines the time of death over the life of a BMU? If the environment is manipulated to prolong life and delay death, what are the consequences for function? Because interactions between bone cells and their matrices are so important for function, are there some functions that are more relevant at different times in aging?

Dr. N. Fedarko began to address some of these questions as he focused on the spectrum of proteins synthesized by bone cells isolated from young and old humans. His data showed significant differences in the proportion and nature of proteins synthesized by primary osteoblasts from donors of different ages. He speculated that there are subsets of osteoblasts, each of which synthesize a unique profile of extracellular matrix proteins that in turn feed the cells with signals for proliferation and apoptosis specific for different stages of aging. He pointed out that proliferation of bone cells decrease with time when cultured on plastic, but remain relatively stable over time when extracellular matrix proteins are used. Mix-and-match combinations of primary osteoblasts from bones of young and old humans showed cells from young donors to be plastic and able to adapt their attachments to matrices from donors of varying age. In contrast, cells from aged donors were unable to adapt to signals from young extracellular matrices in terms of integrin profiles. Some discussion focused on what would constitute a representative sample size when studying human donors, and how to standardize exclusion and inclusion criteria for aging in humans. The mechanisms that regulate which subset of osteoblasts dominates and which subsets are eliminated at any given age and why, are unknown. Is there an extracellular matrix composition that is more desirable than another for any given age? Could the agents that inhibit apoptosis do so by modifying the spectrum of extracellular matrix proteins to maintain function? Current rat and mouse protocols for *in vivo* and *in vitro* protocols have failed to take these significant changes in the extracellular matrix protein composition in aging into account. New models are needed to better understand regulation of changes in the proteins comprising the matrix and their significance. The changes in protein composition of bone extracellular matrix during aging and in different species, also needs more understanding, perhaps through applications of proteomics technologies.

The final talk by **Dr. H.Z. Ke** focused on two new non-prostanoid agonists that bind selectively to EP2 and EP4, and induce anabolic responses in a number of different protocols, using such as fracture and ovariectomy of young and old rats. EP2 agonists appear to induce local anabolic effects (in part, because of their limited availability), while EP4

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receptor agonists induced systemic responses. Both of the new agents require injection, rather than the oral delivery of the prostaglandins. It is long past time for a definition of "anabolic" to encompass functionality and geometric shape changes that significantly impact biomechanical properties of bone strength. The current use of "anabolic" includes brute increases in bone mass, often in the form of woven bone, that may have little or no effect on bone strength. Prostaglandins and their receptor agonists and the bone morphogenetic proteins are especially challenging in this regard, because they appear to induce bone in the marrow at sites in which bone is not usually present. Much of the discussion centered on the discrepancy between an increase in bone mass induced by anabolic agents and correlations with biomechanical properties of strength. In the case of the EP2 receptor agonist, the increment in bone mass gain was not accompanied by changes in bone shape conducive to strengthening bone or by an equivalent increment in biomechanical properties of bone. There was also discussion on the need for investigators to include more details on side effects profiles, especially in studies of prostanoid receptor agonists, and what side effects were most relevant in rat and mouse models.

This session made clear the need for more research on aging, new models that replicate the human diversity in bone extracellular protein matrices with age, and criteria to select bone cells and matrix combinations for improved interpretations of outcomes. We need a more precise definition of gerontological aging, which includes changes in the frail elderly and very old, to better define the animal and cell models needed to study aging phenomena. Factors protecting BMU longevity; the significance of specific age changes on progenitor cell proliferation and implications of pharmacological regulation of apoptosis in bone from different age donors all need further investigation. There is a need for new animal protocols and more sophisticated cell models to give us much better understanding of aging human bone and its interplay with changes due to chronic disease, as current generations of humans extend their longevity to more than 100 years.