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Perspective Article

Hylonome

Summary - Bone Matrix

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In skeletal tissues (bone, cartilage, tendon and ligament), extracellular matrix (ECM) comprises the overwhelming majority of the tissue, while the cellular components that synthesize and maintain that matrix occupy only a small fraction of the tissue volume. A large number of skeletal biologists consider the matrix and its constituent parts (collagen polymers, non-collagenous proteins, proteoglycans, microfibrils, mineral) primarily in terms of their biomechanical contributions to tissue function. However, the extracellular matrix is also a major source of biological information that skeletal cells can receive and act upon. For example, ECM glycoproteins and proteoglycans in bone bind a variety of growth factors and cytokines, and serve as a repository of stored signals that act on osteoblasts and osteoclasts; well-known examples of matrix-bound growth factors and cytokines include BMPs and TGFβs. There is also an emerging understanding that extracellular matrix molecules themselves can serve regulatory roles, providing both direct biological effects on cells as well as key spatial and contextual information. These concepts, focusing on the skeletal extracellular matrix as a dynamic, informative environment, formed the core theme explored in the **Bone Matrix** session.

Marian Young (NIDCR-NIH) discussed the roles of Small Leucine Rich Proteoglycans (SLRPs) in skeletal regulation and aging. Recent studies from her laboratory revealed that the SLRPs biglycan and decorin each modulate osteoblast differentiation, function and life span, and that their absence leads to osteopenia. In addition, biglycan can modulate osteoclast function. Among the key discussion points/unresolved questions raised were 1) whether all SLRPs modulate bone cell functions, and 2) whether the extracellular matrix produced in the aging skeleton contains the same array of signaling molecules as in young skeletal tissue.

Lynn Sakai (Shriner's Hospital, Portland, OR) discussed the fibrillins, their roles in connective tissue development and disease, and their recently identified role as mediators of growth factor signaling. Fibrillins are extracellular matrix proteins that form the core structure of microfibrils, and are ubiquitous in their presence and distribution in connective tissues. Fibrillins 1 and 2 are involved in skeletal development and function; mutations of these proteins lead to skeletal malformations in Marfan's syndrome and congenital contractural arachnodactyly (CCA), respectively. Recent studies show that several Latent TGFb Binding Proteins (LTBPs) as well as BMP-7 can associate directly with fibrillin microfibrils, providing a means by which microfibrils can control the sequestration and spatial presentation of these molecules to skeletal cells. A key discussion point concerned the extent to which fibrillin effects on bone development result from mechanically-driven processes (i.e., loss of tissue elasticity of the perichondrial ring allowing too much longitudinal growth in Marfan's disease; too much stiffness restricting the growth plate in CCA) or from biologically-driven processes such as alterations in the concentration and presentation of growth factors.

Kurt Hankenson (University of Pennsylvania) discussed the function of the thrombospondin proteins in bone development, remodeling and repair. Thrombospondins (TSPs) belong to the family of matricellular proteins that includes osteopontin, bone sialoprotein and osteonectin, among other molecules. TSPs can modulate skeletal cell function by interacting directly with cells or by modulating the activity of other matrix molecules or cytokines. Studies to date reveal that the skeletons of TSP-deficient mice develop normally, but show defects in their responses to physiological and pathological challenges. The most extensive skeletal data are available for TSP-1 null mice; however, an unresolved question that produced considerable discussion concerned TSP-2 deficiency, which appears to exert envelope-specific effects in bone, such that different effects are seen on endocortical and periosteal surfaces.

Sarah Dallas (University of Missouri) added a unique and novel perspective to the discussion of bone matrix, showing time-lapse videos of early bone matrix assembly by osteoblasts *in vitro*. These videos demonstrated that the

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assembly of fibronectin in bone matrix by osteoblasts is a highly dynamic process, characterized by large cell movements, stretching and contracting of matrix fibrils, and the movement of entire packets of matrix material from one location to another. These data generated extensive discussion of several issues, including 1) whether the highly dynamic assembly process seen with the early fibronectin component of bone matrix also occurs during assembly of the collagen matrix and 2) how these matrix assembly processes differ between woven and lamellar bone formation. Additional data were presented showing that early osteocytes move about extensively within their lacunae, and may also dynamically insert and remove their processes from among different canaliculi.

Finally, **Charles Sfeir** (University of Pittsburgh) discussed the SIBLING proteins, with particular emphasis on Phosphophorin (PP), a cleavage product of Dentin Sialophosphoprotein (DSPP) that is implicated in regulation of matrix mineralization in dentin. Recent studies suggest a complex role for PP that includes cell-signaling activity as well as and a direct role in regulating biomineralization processes. Studies also suggest that post-translational modification of PP can alter its function. The importance of PP and other potential multifunctional matrix molecules was discussed. Finally, examples were also presented for how matrix-resident signals could be employed in tissue engineering to provide biological, spatial and contextual information to cells. These novel ideas about building biological signals into engineered tissues and materials provided the focus for lengthy discussions.