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VIEWPOINT

Bone Molecular Biology and Pathology

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For many years bone was viewed as refractory to elucidation of regulatory mechanisms that are operative at the cellular and molecular levels. Despite the well defined contributions to skeletal integrity and calcium-mediated metabolic control, the tissue was considered unapproachable by traditional protocols utilized for isolating distinct populations of cells, subcellular fractionation, and isolation of regulatory macromolecules. These impediments are no longer obstacles to addressing specific questions related to metabolic and developmental control in bone.

The roots of our current understanding of bone biology and pathology reside in a systematic characterization of bone matrix proteins and bone cells which was pursued simultaneously with histological and ultrastructural analyses. Although descriptive, these approaches provided a viable basis for initial insights into structural and functional properties of bone formation and remodelling. More recently, molecular approaches have supported quantitation of gene expression at multiple levels in bone and yielded profiles of gene expression that chart a course of skeletal development and characterize skeletal pathologies. Concepts that emerged include but are not restricted to: 1) integration of regulatory signals and macromolecules between osteoblasts and osteoclasts; 2) proliferation-differentiation interrelationships that support progressive development and maintenance of the osteoblast phenotype; 3) developmental, stage-specific responsiveness to growth factors and steroid hormone mediators of osteoblast proliferation and differentiation as well as maintenance of bone cell phenotypic properties; and 4) cell structure-function interrelationships that integrate, amplify or dampen regulatory signals which control gene expression at the transcriptional and post-transcriptional levels.

The clinical issues are not separate from the fundamental biological regulatory questions. The combined development and application of molecular, cellular and biochemical approaches have provided a developmental sequence of gene expression that reflects stages of skeletal proliferation and differentiation. Particularly relevant have been in situ methods where gene expression can be evaluated within the context of bone tissue organization. The prospect series in this issue captures several of the key concepts and experimental approaches that support current research initiatives in bone molecular biology and pathology.

The Parfitt (page 273, this issue) Prospect presents an overview of cellular, biochemical and physiological parameters of skeletal remodeling incorporating the manner in which bone replacement supports calcium homeostasis and the load-bearing responsibilities of the tissue. Fundamental mechanisms are supported by an insightful presentation of both concepts, experimental approaches and key findings. The Prospects by Aarden et al. (page 287, this issue), Robinson and Einhorn (page 300, this issue), Partridge et al. (page 321, this issue), Collin-Osdoby (page 304, this issue), and Siddhanti and Quarles (page 310, this issue) encapsulate current knowledge of the principal cells involved with bone formation and bone resorption. Valuable insight is provided into strengths and limitations of several model systems which effectively support strategies that are being actively pursued to elucidate parameters of skeletal regulation. Particularly significant is the information being provided for direct translation of fundamental understandings of bone cell regulation to clinical applications. There is an exciting potential for rectification of skeletal disorders which involve aberrations in expression of cell growth and phenotypic genes.

How do physiological mediators of bone cell structure and function modulate expression of genes that are essential to development and maintenance of the physiological integrity of skeletal tissue? Without a doubt the intercellu-

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lar and intracellular signalling pathways considered in the Partridge et al. and Siddhanti and Quarles Prospects are worthy of consideration. Over the past several years our knowledge of factors which contribute to bone cell growth and differentiation within the context of both normal biological parameters and pathology have been a primary focus for many investigators. The search for a skeletal morphogen has not yielded a single macromolecule. Rather a repertoire of cytokines and growth factors have emerged which act in a developmental stage-specific manner to exert positive and negative control on cell growth and bone phenotypic genes. Contributions to bone growth as well as resorption by several such factors increases our awareness of the complexities of regulatory mechanisms involved in skeletal homeostasis and remodeling. At the same time, it is apparent that our growing appreciation of regulatory complexity provides multiple opportunities for the requisite diversity necessary for responsiveness to skeletal cell and tissue requirements. These involve short term changes associated with metabolic homeostatic control and long term commitments to bone tissue activity. Several skeletal regulatory factors are covered in the prospects by Partridge et al. (parathyroid hormone), Delany et al. (page 328, this issue) (insulin-like growth factor 1), Rosen and Bar-Shavit (page 334, this issue) (proenkephalin-derived peptides), Felix et al. (page 340, this issue) (colony-stimulating factor-1), Bonewald and Dallas (page 350, this issue) (TGFβ), and Bab and Einhorn (page 358, this issue) (OGP).

How can a series of genes with promoters constructed of modularly organized regulatory elements resembling an endocrinology textbook respond to an integrated series of developmental and homeostatic regulatory signals mediated by a broad spectrum of physiological factors to orchestrate growth, differentiation and establishment as well as maintenance of the structural and functional properties of bone tissue? The complexity of the sentence posing this highly relevant question reflects the challenge we face. There is a valid basis for optimism. We are rapidly contributing to the database of bone structural and regulatory parameters. It is justifiable to anticipate that tissue targeting of skeletal regulatory factors will permit selective modulation of bone cell proliferation and differentiation. Together with the applications of molecular approaches for diagnosis of skeletal diseases future therapeutic approaches will be increasingly selective and effective.