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VIEWPOINT

Skeletal Regulatory Mechanisms Translate to Therapeutics

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There was a time, not so very long ago, when regulatory mechanisms that mediate bone cell growth and differentiation were pursued within the context of gaining insight into fundamental parameters of biological control. Diagnostics and therapeutics for skeletal disorders were, to a large extent, developed by independent approaches which relied primarily on chemistry, pharmacology, and pharmacokinetics.

Over the past several years much of this has changed. Parochially defined barriers have been overcome and there is a broad-based appreciation of the concept that the cellular and molecular parameters of bone cell proliferation and differentiation offer valuable insight into the basis of skeletal pathologies and, equally important, into development of targeted treatments. It is readily acknowledged that insight into developmental regulatory mechanisms, particularly definition of gene regulatory mechanisms supporting the structural and functional properties of osteoblasts and osteoclasts, can translate directly to clinical management of bone diseases (e.g., osteoporosis and osteosarcoma) that affect a large segment of our population.

Translational research is far more than a trendy cliché. It is an effective approach that has evolved (emerged) from the systematic characterization of stages in development and remodeling of skeletal tissue. This has been complemented by an understanding of gene regulatory parameters that support the development and maturation of bone as a structural and functional tissue. Together with increased awareness of integrated responsiveness by bone to a spectrum of physiological mediators that include but are not restricted to growth factors and steroid hormones, mechanisms have been defined that can be selectively and specifically modulated to alter the course of skeletal dysfunction.

This Prospect Series provides insights into approaches that are being taken to exploit the biological properties of skeletal tissue that have the potential for application to treatment of bone pathology.

The prospect by Bruder et al. (page 283, this issue) offers valuable insight into the manner in which the search for mesenchymal stem cells has provided a foundation for lineage mapping of osteoblastic and chondrocytic pathways. At the same time one can appreciate the potential applications of mesenchymal stem cells to bone fracture repair and skeletal regeneration treatment by both direct cell implantation and through gene therapy.

The prospect by Delany et al. (page 295, this issue) highlights the involvement of glucocorticoids as physiological mediators of bone formation and resorption. At the cell and tissue levels they address glucocorticoid stimulation of osteoblasts and the paradoxical downregulation of genes associated with extracellular matrix biosynthesis. At the molecular level these authors describe encounters of glucocorticoid with signaling pathways for both transcriptional and post-transcriptional control that are central to the bone cell repertoire of growth and differentiation gene expression.

The prospect by Baran (page 303, this issue) complements the well-established vitamin D mediated transcriptional control by vitamin D, highlighting compelling findings which indicate that membrane-mediated nongenomic pathways interface with those influencing transcriptional control by the hormone.

Fulfillment of the promise for application of skeletal molecular mediators to the diagnosis and treatment of bone pathologies is a realistic expectation. White et al. (page 307, this issue) describe the strength of exploiting sequences residing within the vitamin D receptor gene to uncover subtleties in vitamin D receptor regulation. At the same time, they present the implications of specific vitamin D receptor alleles for

development of degenerative skeletal disease. Cielinski and Marks (page 315, this issue) utilize this prospect as a vehicle to explain how rodent mutants functionally associated with osteopetrosis offer clues to the activities of the osteoclast which is the culprit cell in bone resorption. Dresner-Pollak and Rosenblatt (page 323, this issue) explore how recently acquired knowledge of integrins as biological signaling molecules that access and export regulatory information across the plasma membrane may be exploited to block osteoclast adhesion at bone surfaces. Here the interactions between cell structure, the extracellular matrix and cytoskeleton are apparent that may further offer opportunities for targeting gene regulatory pathways associated with bone resorption by modulating activities of integrin-mediated phosphorylation signaling pathways.

A crystal ball is unnecessary to have confidence that the marriage of biology and biotechnology will yield therapeutically relevant approaches to the diagnosis and treatment of skeletal disease.