

Preface

Bone biology and skeletal health are topics of great interest and extensive scientific activity. It therefore seems logical to initiate a series of review volumes that describe current developments in bone biology and the treatment of bone diseases. New knowledge as reported in a wide array of primary publications is evaluated, summarized and its significance explored. To accomplish this effectively requires topical focus and expertise. This first volume in the series *Topics in Bone Biology* is focused on *Bone Formation*, the cells that initiate this process, its regulation and its disorders. Subsequent volumes will focus on *Bone Resorption* and *Engineering of Functional Skeletal Tissues*. We hope that our readers will find this first volume both useful and exciting, as we have in putting it together.

The first chapter in this volume, authored by Bukka, McKee and Karaplis, deals in molecular terms with the differentiation of the bone-forming cells. It describes how undifferentiated mesenchymal cells condense to assume the shape of skeletal elements and then follow one of two paths to form the two types of bone, trabecular and membranous. Until recently, knowledge of pertinent gene expression and the mechanisms of osteoblast differentiation was fairly limited, but now a number of factors regulating bone cell differentiation have been identified and characterized. The authors describe specific genes that alter a precursor cell's commitment to a particular lineage, and then discuss specific transcription factors that determine the fate of each cell type. Proteins specific to osteoblasts, such as osteocalcin, and regulation of their expression, are topics discussed in the remainder of the chapter.

Karin and Farach-Carson, in the second chapter, deal with a topic of special interest to experimentalists, namely osteoblast culture *in vitro*. Bone cell culture is essential to understanding what these cells can do, how they respond to regulatory molecules, to stress, and under what conditions they thrive or fail to thrive. At the same time, the authors emphasize that an event observed *in vitro* must be demonstrated to occur *in vivo* in order to assign it functional significance, a lesson that in the excitement of discovery may be forgotten. Experimentalists will appreciate the large amount of cell culture and cell line information that is made available by the authors in the form of extensive tables not readily available elsewhere.

The regulators of bone formation and remodeling are many, both systemic and local. Hurley and Lorenzo, in the third chapter, discuss how growth hormone and the insulin-like growth factor 1 modulate bone formation, as do thyroid hormone, the gonadal hormones, glucocorticoids, and vitamin D, which, its name notwithstanding, effectively acts like a steroid hormone. Parathyroid hormone, PTH, as is well known, is a major regulator of both rapid and long-term bone cell responses, mediated by the PTH receptor of the osteoblast. The more recently discovered parathyroid-related protein,

PTHrP, which binds to the same receptors as PTH, plays a critical role in both intramembranous and endochondral bone formation and development. Local regulators that are discussed include prostaglandins, transforming growth factor-beta, platelet-derived and fibroblast growth factors, as well as a series of newer factors, such as the core-binding factor, osterix, and RANK, RANK-ligand, and osteoprotegerin. Because bone formation and resorption are so closely linked, especially in bone remodeling, the authors discuss the role many of these systemic and local factors play in osteoclast formation and bone resorption.

The skeleton contains virtually all of the body's calcium. Initiating the deposition of the bone mineral, principally calcium phosphate, is a major function of the osteoblasts. Calcium is deposited into cartilage, thus leading to the formation of trabecular or endochondral bone. It is also directly deposited in membrane (or intramembranous) bone, yet the mechanisms of calcification are still not fully understood. Puzas, in the fourth chapter, discusses in detail mineralization and the signals that circulate between osteoblasts and osteoclasts, thus assuring mineralization, on the one hand, and mineral dissolution, on the other. Matrix vesicles, spatial localization of matrix formation, and cellular recognition, as by osteoblasts of the osteoclast lysosomal enzyme, are among the topics that are discussed.

The skeleton fulfills two major functions, metabolic and mechanical, with the mechanical or support function clearly an evolutionary goal. Turner, in Chapter 5, discusses the interrelationship between mechanical usage and metabolic response. For instance, weight bearing or, in engineering language, mechanical loading, causes stress, with maximum stress in a given bone site leading to enhanced bone formation. Stress also causes trabeculae and collagen fibers to align in the direction of the stress. Static loading, however, does not lead to enhanced bone formation. It may be evident that bone cells are the sensors that transduce stress, but the precise way this occurs has only recently been explored and is discussed in detail by Turner. The chapter is enriched by a large number of illustrations.

Martin and Seeman, in Chapter 6, discuss in detail the role played by reduced bone formation in the pathogenesis of bone disease. They thus move in their discussion from the cell to the organ and illustrate how current concepts of bone formation have been developed from *in vitro* studies of cell and organ culture and from *in vivo* studies of mutant mice. They emphasize that the reduction in bone mass associated with aging is related to a reduction in bone formation and further that the increase in bone remodeling that occurs as a result of the decrease in estrogen at the menopause leads to a negative bone balance. This in turn contributes to trabecular and cortical thinning, and increased cortical porosity. Thus research aimed at treating bone fragility should focus on understanding and modulating bone formation, as well as on minimizing bone resorption.

In recent years significant progress has been made in identifying the genetic bases of many diseases affecting bone. In Chapter 7, McLean and Olsen describe in detail diseases involving excess bone formation, many of which are rare. In a number of instances the genetic basis of the disease has been elucidated, although the mechanism by which the genetic defect is translated into the specific disease remains unknown. One example discussed by McLean and Olsen is endosteal hyperostosis (van Buchem type). This disease begins at puberty and affects a large number of bones. The genetic region that has been linked to the disease also may be linked to sclerosis and involves a large (52 kb) deletion flanked by two genes whose dysregulated expression may cause van Buchem disease. McLean and Olsen list many of

these diseases in table form, thereby enabling the reader to understand similarities and differences more readily.

In Chapter 8, Peterlik reviews the means by which osteoblast function is impaired in certain bone diseases (growth retardation, osteomalacia, rickets, metabolic bone diseases, and osteoporosis) and then analyzes a variety of therapeutic and preventative approaches that can minimize or cause the disease to regress. For example, physical exercise, through its strengthening of muscle, also strengthens bone. Peterlik describes the cellular mechanisms by which this occurs. At the same time he calls attention to the observation that estrogens facilitate transduction of mechanical stimuli into skeletal responses. This therefore adds to the more widely appreciated effects of estrogen on bone health, discussed in detail in an earlier section of the chapter. Throughout Peterlik provides insight into the molecular pharmacology of the various agents and drugs that can modulate osteoblast function and thus be used to treat bone diseases selectively.

As editors, we want to thank our author colleagues for the wealth of information contained in their contributions, their willingness to adapt their chapters to make this volume into a meaningful beginning of the series, and their readiness critically to incorporate recent findings in their final texts. We thank Springer UK for sharing our enthusiasm for this volume and the series as a whole.

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