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Bone and Osteoarthritis

Springer

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British Library Cataloguing in Publication Data
Bone and osteoarthritis. - (Topics in bone biology ; v. 4)
1. Osteoarthritis - Pathogenesis 2. Bone
I. Bronner, Felix II. Farach-Carson, Mary C., 1958-616.7'223071
ISBN-13: 978-1-84628-513-4 e-ISBN-13: 978-1-84628-701-5

Library of Congress Control Number: 2007930210

Printed on acid-free paper

9 8 7 6 5 4 3 2 1

Springer Science+Business Media
springer.com

Preface

Osteoarthritis (OA) is a progressive and debilitating disease that affects some two thirds of people older than 65 years. Yet how the disease arises and what cellular and molecular changes the cartilage cells undergo in the course of the disease is not well understood. In recent years, bone and bone changes have been invoked as causing or contributing to cartilage destruction. Moreover, clinical care of osteoarthritic patients often falls on orthopaedic surgeons, as when an arthritic hip needs replacement. It therefore seemed logical for the series *Topics in Bone Biology* to devote a volume to this disease and its relationship to bone and bone metabolism, particularly because many matrix molecules and signaling pathways are common to both cartilage and bone.

In Chapter 1, Roach and Tilley discuss the pathobiology of OA, list the risk factors (aging, loading, genetics) and describe the clinical features (pain being the most prominent), the diagnostic procedures, and the changes in cartilage that occur during the disease process. They also refer to the role of subchondral bone, a topic more prominently discussed in Chapter 2. Roach and Tilley illustrate the microscopic changes that articular cartilage undergoes, including the Mankin scale for evaluating these changes, discuss apoptosis and necrosis of the cartilage cells, and then outline what can be done about the disease (risk factors, medication, surgical intervention). This chapter, like all the others, has an extensive list of references and full color illustrations.

In Chapter 2, Lajeunesse and Reboul discuss the role of bone in the development of OA. They point out that chondrocytes function under largely hypoxic conditions and that the response to severe hypoxia initiates angiogenesis, with the vessels that penetrate cartilage deriving from subchondral bone. Disease initiation and progression is characterized by dedifferentiation of the cartilage cells and changes in bone tissue that involve both osteoclasts and osteoblasts. Osseous outgrowths, termed osteophytes, occur at the margin of cartilage and bone, and may contribute to joint dysfunction and immobility. The authors hypothesize that some macrophages from the inflamed synovial membrane release growth factors that ultimately lead to osteophyte formation. Lajeunesse and Reboul then proceed to discuss risk factors, relating them to bone metabolism, review possible interaction and crosstalk between bone and cartilage, and conclude that "changes in subchondral bone and . . . [in] osteoblast metabolism are key in the initiation and progression of OA."

In Chapter 3, Goldring discusses the anabolic and catabolic roles of cytokines, growth factors, and bone-derived molecules that modulate cartilage cell behavior. When adult chondrocytes, which maintain cartilage structure and function, undergo phenotypic change to

become "abnormal," dysregulated signaling contributes to further disease progression. Topics discussed by Goldring include matrix destruction and synthesis in OA, mouse models of the disease, and detailed analyses of the role of such factors as the inflammatory cytokines, such as interleukins, and the chemokines. Growth and differentiation in OA are affected by the insulin-like growth factor, the transforming growth factors, the bone morphogenetic factors, and the fibroblast growth factors, which are discussed in detail, as are their interaction and influence on cartilage homeostasis and expression of matrix genes. The chapter concludes with a discussion of subchondral bone factors that may bring about abnormal chondrocyte responses.

In Chapter 4, Blom and van den Berg analyze the role of the synovium in OA, a tissue that has only recently been identified as having a role in the osteoarthritic process. Normally the synovium controls the environment within the joint by acting as gateway for substances that enter or leave the joint and by synthesizing hyaluronan and lubricin, two compounds that give the joint fluid its mechanical properties. Synovial macrophages, overexpressed in inflammation, induce osteophytes and thus contribute to joint dysfunction. Synovial macrophages also appear to induce cartilage changes. These changes are discussed in detail. Blom and van den Berg then proceed to analyze the catabolic and anabolic roles of cytokines in the osteoarthritic synovium and discuss possible gene therapy, inasmuch as OA is often local, expressed in only one or two sites in the body. Targeting and silencing the synovial macrophage may become one approach to treating some types of OA.

A characteristic aspect of osteoarthritis is the degradation of the normal cartilage resulting from a change in matrix composition involving collagen and other matrix molecules. As described in detail by Heinegård in Chapter 5, the matrix is indeed a network, with collagen molecules serving as cross-bridges, and when these are broken, different molecular domains are exposed, leading to different, often abnormal, binding, and providing sites that may now be accessible to degradative enzymes. To be sure, degradation is followed by increased synthesis of the degraded constituents, but this repair may be inadequate, leading to a decrease in joint strength and ultimately to the pathologic changes that characterize osteoarthritis. Heinegard discusses the major molecules involved, the various collagens, aggrecans, thrombospondins, biglycan, and decorin, and has included figures that indicate the spatial relationships and interactions of the various molecules.

Interestingly, chondrocytes that reside in diseased cartilage are metabolically hyperactive. In discussing anabolic mediators that may play a role in raising cartilage metabolism, Fukui and Sandell, in Chapter 6, point out that increased anabolism of cartilage cells may prevent disease progress, but, by inducing "abnormal" proteins, may also accelerate the progress of the disease. The authors describe and discuss the various anabolic molecules, for example, aggrecan and collagens II, IX, and XI. They then analyze the significance of hyperanabolism in terms of possible degradative and repair mechanisms, calling attention to the fact that enhanced metabolism simply may constitute a reparative response to matrix damage. There follows a discussion of various factors that may be involved in the hyperanabolic response, calling attention to, among others, leptin, a hormone that only recently has been identified as also involved in bone metabolism. The authors conclude by raising the question, crucial to an understanding of the disease, at what time point the normal repair

process involving removal of damaged tissue and its replacement changes to the hyperanabolic state, that is, overproduction of proteins such as aggrecan or the matrix metalloproteinases.

In Chapter 7, Shapiro, Adams, Srinivas, and Freeman discuss the hypertrophy of the cartilage cell—a feature characteristic of OA—and its ultimate death. They point out that cell volume increases in response to changes in the extracellular matrix and that changes in cell volume lead to changes in the osmotic pressure of the cartilage territorial matrix fluid. In turn, the membrane of the cartilage cell changes in response sensitivity, and the cell hypertrophies and ultimately dies. After a detailed description of the events involved in cell hypertrophy and death, the authors advance two hypotheses, one of which relates to hypertrophy, stating that the late-stage cells are maintained in a catabolic state they term *autophagy,* with cell death following. The number of cells is thus reduced. Autophagy and related processes are thought to be regulated by a signaling molecule, mTOR. The second hypothesis is that initiation of the phenotypic changes of the cartilage cell that lead to the disease is the result of a variant of ischemia reperfusion, that is, a pathologic increase in joint vascularity.

All diseases seem to have a genetic basis, sometimes the result of a single mutation, more often involving several genes, with even that gene combination accounting for only a portion of disease susceptibility and incidence. In the case of OA, Chapman and Roach, in Chapter 8, first discuss the predisposing genes, reviewing family and twin studies. They then proceed to analyze the various candidate genes, for bone density and mass and for effects on the extracellular matrix, and describe the results of linkage scans, focused in particular on chromosome 2. The second portion of the chapter deals with epigenetic changes, that is, heritable changes that do not alter the DNA sequence. These arise when genes, not normally expressed by a given cell, are "unsilenced," as by demethylation, leading to the expression of "abnormal" proteins, for example, aggrecan or the matrix metalloproteins. Epigenetic changes are increasingly recognized as of importance for development and as involved in many chronic diseases, and their role in OA may also have significance for therapy.

Animal models are important for the study of human disease, with OA no exception. Whether the disease occurs in an animal species spontaneously or is induced, its progress, because it is so much faster than in the longer living human, can be studied more effectively and more readily subjected to therapeutic trials. Bendele, in Chapter 9, discusses the various animal models that have been utilized to study OA, the use of partial meniscectomy and transection of the anterior crucial ligament in dogs, unilateral medial meniscal tear in older rats, intraarticular injection of iodoacetate in rats, as well as spontaneous and induced arthritis in mice. Throughout, the text emphasizes the need to match expectation of what may be achieved with the model or lesion that has been selected before testing pharmacologic agents. Guinea pig and rabbit models of OA are discussed in detail. The chapter closes with a discussion on the differences between animal models and the human disease and, as also stressed throughout the chapter, by emphasizing both the limitations and advantages of animal models in the search for therapeutic approaches.

How the mechanical aspects of joint function are modulated by molecular signals emitted by the articular cartilage and subchondral bone, and how joint injury and OA affect these mechanical functions is discussed by Chai, Stevens, and Grodzinsky in Chapter 10. After briefly discussing how the structure of the extracellular matrix of cartilage is designed to

withstand dynamic forces, the authors describe the clinical features of the disease and then proceed to elaborate on the various types of loads applied to the joint and how these can be tested in vitro. They discuss confined and unconfined loading, and point out the need for clearly defining the rate of loading, the peak stress, and final strain, as these define the threshold of tissue damage. The chapter then discusses the effect of mechanical loading and injury on chondrocyte apoptosis and necrosis, on gene expression, and how mechanoresponsiveness is compromised by mechanical injury. The authors conclude by pointing to new research and therapeutic directions that may emerge from proteomic analysis of tissue inflammation and matrix degradation.

In Chapter 11, Bingham discusses medications used to treat the signs of symptoms of OA, with emphasis on the diminution of pain. Because the efficacy of analgesics is limited and arthroplasty has high cost and not insignificant mortality and morbidity, it is important to have and develop drugs that slow disease progression. Bisphosphonates are one class of drugs that are coming into use with OA, largely because they have proved effective in osteoporosis and in Paget's disease and because these compounds act on subchondral bone. Bingham then discusses other inhibitors of osteoclasts such as interleukin-1, diacerein, as well as inhibitors of interleukin-1. The chapter concludes with an analysis of the role matrix metalloproteinase and cathepsin inhibitors can play in treatment of the disease.

Developing this book entailed bringing together bone and rheumatology specialists and encouraging a common language. We thank the authors for making this book possible and for their informative and timely contributions. Special thanks go to Dr. H.I. Roach, not only for making available information on the most current research on OA and thus guiding the editors, but also for her willingness to coauthor two chapters. Springer-UK, the publishers of this series, have, as in the past, produced a handsome book, and, by making it possible to publish color illustrations, have markedly enhanced the usefulness of this volume.

M.C.F.-C. wishes to dedicate this volume to her friend and childhood mentor, Mrs. Kathryn W. Moore, who passed away in 2005 after decades of enduring the constant pain of osteoarthritis with her characteristic cheer and dignity.

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April 2007

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