Cartilage

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Editors

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Volume 2: Pathophysiology

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Preface

Volume two of this book series comprised of three volumes is dedicated to provide an overview about the pathophysiology of cartilage, joint tissue, and intervertebral disks.

The text is designed to be of use to multiple medical and basic science disciplines as orthopedics, rheumatology, and trauma surgery and all basic investigators working in the field of cartilage, joint, and intervertebral disk pathophysiology.

This volume focuses on the major cartilage pathophysiologies which include osteoarthritis and rheumatoid arthritis, degeneration of intervertebral disks, and genetic skeletal diseases as cartilage collagenopathies and other hereditary chondrodysplasias resulting from mutations in structural cartilage proteins.

Chapter 1 provides an overview about *osteoarthritis (OA)* which is the most common joint disorder and known as a leading cause of disability in the adult population. It is now appreciated that all components of the joint, including the cartilage, calcified cartilage, synovial joint lining, and periarticular bone, undergo pathological changes during the initiation and progression of OA. Some of these alterations can be attributed to direct injury and mechanical disruption of the tissues, but in general the mechanisms are dependent on active cell-mediated processes that occur during the long time course of the disease. A deeper understanding of the specific and unique roles of complex signaling networks and their downstream targets involving biochemical crosstalk among the cartilage, synovium, bone, and other joint tissues will provide mechanistic insights into the pathologic processes that affect the cartilage and other joint tissues in OA, but also may identify potential therapeutic targets for treatment of this debilitating disease. Chapter 2 provides insight into mechanical stress as an obligatory etiological factor in the development of OA. Understanding how tissues of the joint respond to mechanical injury is likely to inform our understanding of pathogenesis. Articular cartilage is avascular yet responds rapidly and strongly to a range of mechanical stresses. It does so by activating a number of mechanosensitive pathways mediated by release of molecules trapped within the pericellular matrix as well as by triggering mechanoreceptors at the cell surface. These pathways appear to be relevant to the in vivo response to mechanical disruption and affect the course of experimental OA.

The gradual loss of articular cartilage from the surface of articulating joints is a feature of OA. It is marked by degradation of the cartilage matrix, including the large aggregating proteoglycan aggrecan, the small leucine-rich proteoglycans

known as SLRPs, and the fibrillar type II collagen. Chapter 3 discusses the major families of cartilage-degrading enzymes, the matrix metalloproteinases (MMPs), and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) families. Factors that regulate MMP and ADAMTS activity, with a focus on MMP-13, ADAMTS-4, and ADAMTS-5 as the major protagonists of cartilage degradation, are discussed. The important role of degraded matrix fragments in regulating inflammation in osteoarthritis, via Toll-like receptor signaling, is highlighted. Chapter 4 puts emphasis on the functions of proteoglycans as one of the main components of the articular cartilage ECM. Proteoglycans bind water and provide the basis for absorbing high compressive loads. Additionally, they bind cytokines, chemokines, growth factors, and morphogens, thereby protecting these factors against proteolysis and/or acting as a depot of regulatory factors when matrix degradation occurs. They also modulate signaling pathways and create morphogen gradients by immobilization of ligands in the ECM and regulation of the turnover of ligands. Given these important roles of proteoglycans in regulating cell functions, it is well understandable that the loss of ECM and degradation of proteoglycans during OA induce severe changes in cartilage homeostasis.

The presence and production of soluble factors in the osteoarthritic joint have always been a focus of research, as they are assumed to play a role in the initiation and/or progression of the disease. Chapter 5 reviews research data which assign an important role to chemokines, growth factors, and adipokines in OA; however it also emphasizes on a traditionally studied subset of inflammatory, anti-inflammatory, and modulatory cytokines. Differential profiles of these factors compared to healthy joints were found in the knee and other OA affected joints, whereby joint damage itself induces a specific change in the secretory pattern of diverse soluble factors.

Genetic skeletal diseases are a diverse and complex group of over 450 rare diseases that affect the development and homeostasis of the skeleton. Although individually rare, as a group of related genetic skeletal diseases, they have an overall prevalence of at least 1 per 4,000 children, which extrapolates to a minimum of 225,000 people in the European Union, and this extensive burden in pain and disability leads to poor quality of life and high healthcare costs. Dominant-negative (qualitative) defects in numerous cartilage structural proteins result in a broad range of genetic skeletal diseases. Chapter 6 will focus on mutations in fibrillar and fibril-associated collagen genes which cause a wide range of chondrodysplasias, ranging from premature arthritis to severe early lethal disorders. Mutations of cartilage-specific collagens can cause cartilage tissue dysfunction by reducing synthesis of structurally normal protein or through protein misfolding which leads to intracellular retention and degradation and consequent secretion of reduced amounts of structurally abnormal protein. In addition, collagen misfolding mutations can induce a cellular unfolded protein response which ultimately promote apoptosis and thus contribute to the pathology. Chapter 7 will focus on a disease spectrum resulting from mutations in the glycoproteins, cartilage oligomeric matrix protein (COMP), type IX collagen, and matrilin-3, which together cause a continuum of phenotypes that are among the most common of the autosomal dominant genetic skeletal diseases. Pseudoachondroplasia (PSACH) and autosomal dominant multiple

epiphyseal dysplasia (MED) define a disease spectrum typified by varying degrees of short-limbed dwarfism, joint pain with stiffness, and early-onset OA. New insight into disease-related musculoskeletal complications such as myopathy, ligamentous laxity, and tendinopathy has been gained through the analysis of mouse models of the PSACH and MED disease spectrum.

Chapter 8 will summarize and discuss the role of integrins in the physiology and pathophysiology of the growth plate and articular cartilage. Integrins are membrane receptors responsible for bidirectional communication between the cells and the surrounding by transmitting physicochemical signals through adhesion complexes. In addition, integrins are involved in sensing mechanical stress signals generated by the extracellular matrix and transduce them into the cell interior converting physical stimuli to biochemical signaling. Chondrocyte integrins have thus indispensable roles in cartilage development, skeletal growth, and articular cartilage function.

Chapter 9 will focus on the peripheral nervous system which is critically involved in the metabolism of joint tissue and intervertebral disks (IVD). Nerve fibers of sympathetic and sensory origin innervate synovial tissue and subchondral bone of diarthrodial joints. During endochondral ossification in embryonic limb development, sensory and sympathetic neurotransmitters modulate osteo-chondrogenic differentiation of mesenchymal progenitor cells, vascularization, and matrix differentiation indicating a distinct role in skeletal growth and possible limb regeneration processes. In adults, sensory and sympathetic neurotransmitters are involved in the pathology of inflammatory diseases as rheumatoid arthritis which manifests mainly in joints. In addition, they might play a role in the pathogenesis of a priori degenerative joint disorders, as OA and intervertebral disk degeneration.

Tissues of intervertebral disks share similarities to those of diarthrodial joints, such as a thin layer of cartilage that lines the interface between the joint and the bony elements and a central space rich in extracellular matrix molecules that promotes lubrication and maintains osmotic pressure. Like the pathophysiology of other cartilaginous joints, intervertebral disks undergo biomechanical and structural changes as a result of aging and mechanical insults. Due to higher mechanical loading, lumbar disks are more susceptible to degeneration, which can lead to symptomatic outcomes such as low back pain, sciatica, and other physical disabilities. These affect the quality of life as we age and present a significant burden to the healthcare system globally. Chapter 10 will provide an overview of the intervertebral disk in health and disease.

Bringing together international experts from diverse fields of musculoskeletal research was a demanding task requiring patience and persistence not only for volume one of this book series but also for this volume. For that we are very grateful to our authors of this volume who managed to complete their chapters and who dedicated their spare free time to writing their reviews.

Regensburg, Germany — Susanne Grässel
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Contents

1 Pathogenesis of Osteoarthritis in General 1
Mary B. Goldring, Kirsty L. Culley, and Miguel Otero

2 Cartilage Injury and Osteoarthritis 27
Heba M. Ismail and Tonia L. Vincent

3 Proteoglycan and Collagen Degradation in Osteoarthritis 41
Stephanie J. Gauci, Heather Stanton, Christopher B. Little, and Amanda J. Fosang

4 Role of Proteoglycans in Osteoarthritis 63
Jessica Bertrand and Annelena Held

5 Pro- and Anti-inflammatory Cytokine Profiles in Osteoarthritis 81
Yvonne Bastiaansen-Jenniskens, Daniel Saris, and Laura B. Creemers

6 Molecular Genetics of the Cartilage Collagenopathies 99
Shireen R. Lamandé, Trevor L. Cameron, Ravi Savarirayan, and John F. Bateman

7 Pseudoachondroplasia and Multiple Epiphyseal Dysplasia: Molecular Genetics, Disease Mechanisms and Therapeutic Targets 135
Michael D. Briggs, Peter Bell, and Katarzyna A. Piróg

8 Integrin-Mediated Interactions in Cartilage Physiology and Pathophysiology 155
Attila Aszódi

9 The Sensory and Sympathetic Nervous System in Cartilage Physiology and Pathophysiology 191
Susanne Grässel, Rainer H. Straub, and Zsuzsa Jenei-Lanzl

10 Intervertebral Disc Degeneration 229
Akansha M. Shah, Sarah Yoon Ji Kwon, Wilson C.W. Chan, and Danny Chan

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