Susanne Grässel · Attila Aszódi *Editors*

Cartilage

Volume 2: Pathophysiology

Springer

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Editors
Susanne Grässel
Orthopädische Klinik für die Universität Regensburg
Universitätsklinikum Regensburg
Regensburg
Germany

Attila Aszódi
Department of General, Trauma, and Reconstruction Surgery
Ludwig-Maximilians-University
Munich
Germany

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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
Munich, Germany — Attila Aszódi

Contents

Contributors

Attila Aszódi, PhD Laboratory of Experimental Surgery and Regenerative Medicine, Clinic for General, Trauma and Reconstruction Surgery, Ludwig-Maximilians-University, Munich, Germany

Yvonne Bastiaansen-Jenniskens, PhD University Medical Center Utrecht, Department of Orthopaedics, Utrecht, The Netherlands

John F. Bateman, PhD Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, Australia

Biochemistry and Molecular Biology, University of Melbourne, Parkville, Australia

Peter Bell, PhD Institute of Genetic Medicine, Newcastle University, International Centre for Life, Newcastle upon Tyne, UK

Jessica Bertrand, PhD Otto-von-Guericke University Magdeburg, Department of Orthopaedic Surgery, Magdeburg, Germany

Michael D. Briggs, PhD Institute of Genetic Medicine, Newcastle University, International Centre for Life, Newcastle upon Tyne, UK

Trevor L. Cameron, PhD Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, Australia

Danny Chan, PhD School of Biomedical Sciences, The University of Hong Kong, Pokfulam, Hong Kong

Wilson C.W. Chan, PhD School of Biomedical Sciences, The University of Hong Kong, Pokfulam, Hong Kong

Laura B. Creemers, PhD University Medical Center Utrecht, Department of Orthopaedics, Utrecht, The Netherlands

Kirsty L. Culley, PhD Hospital for Special Surgery Research Institute and Weill Cornell Medical College, New York, NY, USA

Amanda J. Fosang, PhD University of Melbourne Department of Paediatrics and Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, VIC, Australia

Stephanie J. Gauci, PhD University of Melbourne Department of Paediatrics and Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, VIC, Australia

Mary B. Goldring, PhD Hospital for Special Surgery Research Institute and Weill Cornell Medical College, New York, NY, USA

Susanne Grässel, PhD Experimental Orthopaedics, Department of Orthopaedic Surgery, ZMB/BioPark 1, University of Regensburg, Regensburg, Germany

Annelena Held, PhD Otto-von-Guericke University Magdeburg, Department of Orthopaedic Surgery, Magdeburg, Germany

Heba M. Ismail, PhD Arthritis Research UK Centre for OA Pathogenesis, Kennedy Institute of Rheumatology, NDORMS, University of Oxford, Oxford, UK

Zsuzsa Jenei-Lanzl, PhD Experimental Orthopaedics, Department of Orthopaedic Surgery and Laboratory of Experimental Rheumatology and Neuroendocrine Immunology, Department of Internal Medicine I, University of Regensburg, Regensburg, Germany

Sarah Yoon Ji Kwon, PhD School of Biomedical Sciences, The University of Hong Kong, Pokfulam, Hong Kong

Shireen R. Lamandé, PhD Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, Australia

Departments of Paediatrics, University of Melbourne, Parkville, Australia

Christopher B. Little, PhD Raymond Purves Bone and Joint Research Laboratories, Kolling Institute, Institute of Bone and Joint Research, Sydney Medical School Northern, University of Sydney, St. Leonards, NSW, Australia

Miguel Otero, PhD Hospital for Special Surgery Research Institute and Weill Cornell Medical College, New York, NY, USA

Katarzyna A. Piróg, PhD Institute of Genetic Medicine, Newcastle University, International Centre for Life, Newcastle upon Tyne, UK

Daniel Saris, PhD University Medical Center Utrecht, Department of Orthopaedics, Utrecht, The Netherlands

Ravi Savarirayan, PhD Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, Australia

Departments of Paediatrics, University of Melbourne, Parkville, Australia

Victorian Clinical Genetics Service, Parkville, Australia

Akansha M. Shah, PhD School of Biomedical Sciences, The University of Hong Kong, Pokfulam, Hong Kong

Heather Stanton, PhD University of Melbourne Department of Paediatrics and Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, VIC, Australia

Rainer H. Straub, MD Laboratory of Experimental Rheumatology and Neuroendocrine Immunology, Department of Internal Medicine I, University of Regensburg, Regensburg, Germany

Tonia L. Vincent, FRCP, PhD Arthritis Research UK Centre for OA Pathogenesis, Kennedy Institute of Rheumatology, NDORMS, University of Oxford, Oxford, UK

Pathogenesis of Osteoarthritis in General

1

Mary B. Goldring, Kirsty L. Culley, and Miguel Otero

Abstract

Osteoarthritis (OA) is the most common joint disorder and is 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. Based on clinical observations and experimental studies, it is now recognized that it is possible for individual patients to exhibit common sets of symptoms and structural abnormalities due to distinct pathophysiological pathways that act independently or in combination. Recent research focusing on the underlying pathological mechanisms has identified complex signaling networks involving biochemical cross talk among the cartilage, synovium, bone, and other joint tissues. These complex networks involve interplay among anabolic, catabolic, and inflammatory signals within a background of poorly characterized genetic factors. A deeper understanding of the specific and unique roles of these mediators and their downstream targets 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.

M.B. Goldring (✉) • K.L. Culley • M. Otero
Hospital for Special Surgery Research Institute and Weill Cornell Medical College, New York, NY 10021, USA
e-mail: goldringm@hss.edu; culleyk@hss.edu; oterom@hss.edu

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1.1 Introduction

Osteoarthritis (OA) is the most common joint disorder and the major cause of disability in the adult population. The pathophysiology of the disease is characterized by progressive loss of articular cartilage, cartilage calcification, osteophyte formation, subchondral bone remodeling, and mild to moderate inflammation of the synovial lining. Although cartilage destruction is the hallmark of OA disease, the involvement of changes in the periarticular tissues, including the subchondral bone, ligaments, tendons, menisci, and synovial membrane, is now well recognized (Loeser et al. 2012a; Goldring and Goldring 2007). For example, ligaments and menisci are important for maintaining biomechanical stability in the joint, and their injury can lead eventually to cartilage loss. In addition, multiple factors are involved in the pathogenesis of OA, including genetic susceptibility, biomechanics of the affected joint, and the presence and extent of inflammation. It has been difficult, therefore, to identify specific targets for therapy.

Investigations in various in vitro models and preclinical in vivo models during the past decades have focused primarily on cartilage degradation or repair as a therapeutic target and more recently on how biomechanical and cellular responses in chondrocytes are modified by interactions with other joint tissues, in particular, the synovium and bone (Goldring et al. 2011; Goldring and Otero 2011; Goldring and Berenbaum 2015). This chapter focuses on the role of the chondrocyte in maintaining cartilage homeostasis and responding to adverse events in the whole joint that modify cartilage integrity and result in the initiation and progress of the osteoarthritis disease program.

1.2 Disease Etiologies and Therapeutic Prospects

Studies in patients that undergo operative procedures indicate that there are different etiologies and time courses that result in the initiation and development of OA. These subsets represent a continuum of early, progressive, and end-stage OA and include (1) anterior cruciate ligament (ACL) injury (<35 years of age), (2) acute meniscal injury (26–40 years of age), (3) degenerative meniscus (40–65 years of age), and (4) total joint replacement (>50 years of age). Epidemiologic studies have established that there is a strong relationship between ACL disruption and the risk for subsequent development of OA (Segawa et al. 2001; Buckwalter and Brown 2004; Roos 2005; Lohmander et al. 2007; Meunier et al. 2007). Studies of populations with meniscal injury have also been useful for identifying OA risk factors (Englund and Lohmander 2004). Meniscal injuries are commonly seen in association with ACL injury (Jones et al. 2003; Louboutin et al. 2009).

Current understanding indicates that the aberrant distribution of forces in cartilage leads to altered mechanotransduction in the chondrocytes and subsequent activation of catabolic and inflammatory genes, deregulated matrix synthesis, and decreased repair capacity (Lotz and Kraus 2010; de Lange-Brokaar et al. 2012) (see also Chap. 2). The development of posttraumatic cartilage pathology may in turn

adversely impact the structural and functional properties of periarticular bone. The damaged meniscus is an additional source of inflammatory cytokines, chemokines, and reactive oxygen species that could promote expression and activation of proteolytic enzymes and adversely affect cell survival and synthetic activity of chondrocytes and cells of other joint tissues (Englund et al. 2009; Rai et al. 2013).

In addition to trauma or injury, there are other factors that influence the disease process, including aging, genetic predisposition, abnormal biomechanics, obesity, and comorbidities such as cardiovascular disease, metabolic syndrome, and diabetes. However, OA clinical trial designs have not accounted for these multifactorial aspects in disease subsets, but rather have selected subjects based on joint location or diagnosis as primary OA or secondary to other types of arthritis (Punzi et al. 2010; Kloppenburg 2014; Stiebel et al. 2014; Detert et al. 2014). There is a need, therefore, for optimization of cohort selection based on classifying OA patients according to disease phenotypes related to distinct pathophysiological pathways (Bijlsma et al. 2011; Blanco and Ruiz-Romero 2012; Conaghan 2013; Henrotin 2014).

Given the complexity of OA, it is not surprising that there is no structure-modifying agent for OA and the available pain therapies have limited efficacy and associated toxicities (Matthews and Hunter 2011). However, it is unlikely that a single therapy will be effective against both symptoms and structural changes in the entire spectrum of OA patients (Mobasheri 2013a, b; Pulsatelli et al. 2013; Thakur et al. 2014). Most trials have addressed function and pain at later stages of disease when there is already radiographic evidence of disease progression such as joint space narrowing and osteophytes. The development of validated diagnostic and prognostic molecular biomarkers (Lafeber and van Spil 2013; Hsueh et al. 2014; Lotz et al. 2013; Tonge et al. 2014), as well as novel imaging biomarkers (Hunter et al. 2013), that could be used for evaluating pre-symptomatic early-stage disease, may permit therapeutic interventions to halt or slow OA progression prior to irreversible joint damage. There is therefore a need for deeper understanding of the structure and function of articular cartilage and other joint tissues and how they interact and respond to adverse environmental insults in ways that disrupt normal joint homeostasis.

1.3 Articular Cartilage Physiology

Adult articular cartilage is composed of a specialized matrix of type II collagen and the large aggregating proteoglycan, aggrecan, along with several “minor” collagens and small proteoglycans. Its unique structural organization provides tensile strength via the collagen network and compressive resistance via the proteoglycans, which contribute to the capacity of the matrix to accommodate more than 70 % water (Heinegard and Saxne 2011; Onnerfjord et al. 2012; Hunziker et al. 2014) (for further details, see Chaps. 3 and 4). Cartilage is relatively hypocellular compared with other tissues, with the chondrocytes constituting only 1–2 % of the total cartilage volume, and it lacks a vascular supply and innervation. In normal adult articular

cartilage, the chondrocyte has limited proliferative capacity and its ability to perform low-turnover repair declines with age. Since the half-life of type II collagen within the cartilage collagen network is more than 100 years, whereas the proteoglycan components have half-lives of weeks to years, the chondrocyte is involved mostly in replacing the glycosaminoglycans on the aggrecan and other small proteoglycan core proteins. The importance of these matrix proteins in determining the structural and functional properties of the articular cartilage can be observed in chondrodysplasias and other heritable disorders where mutations or deficiencies in cartilage matrix genes result in altered skeletal development often associated with the premature development of OA (Sandell 2012) (see also Chap. 6) (Fig. 1.1).

Chondrocytes in articular cartilage exist in lacunae as single cells encased in a pericellular matrix (PCM) consisting of collagen VI microfibrils, hyaluronan, perlecan, biglycan, aggrecan as monomers or small aggregates, and type IX collagen but virtually no type II collagen (Wilusz et al. 2014). The PCM helps to maintain the

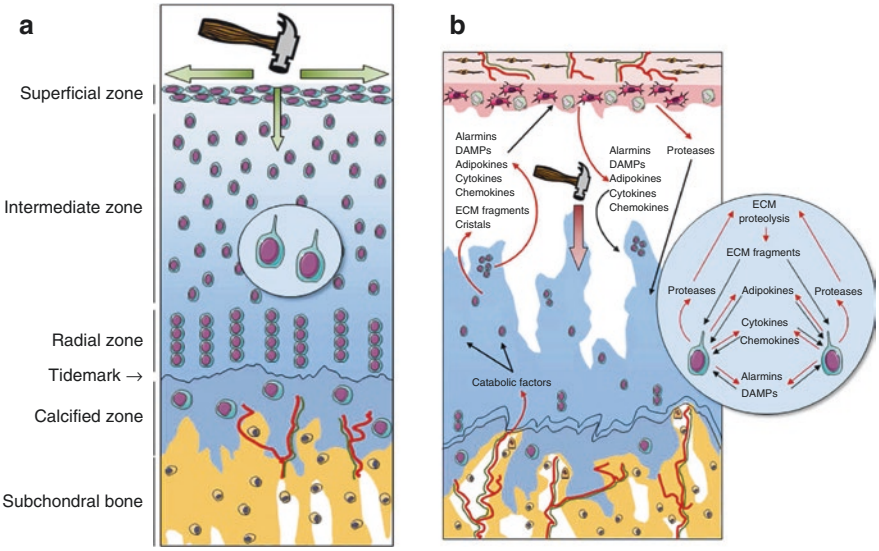

Fig. 1.1 Schematic representation of cartilage organization in the healthy joint and in osteoarthritis. (**a**) Each of the four different zones of healthy articular cartilage, the superficial, intermediate, radial, and calcified zones, is characterized by distinct chondrocyte morphology and extracellular matrix organization and composition. The calcified zone differs from the three other zones by the mineralization of its extracellular matrix, by the presence of vessels (*red*), and by nerve fibers (*green*) that originate from the subchondral bone. The calcified zone interfaces with the non-mineralized cartilage, from which it is separated by the tidemark, and the subchondral bone. (**b**) In OA, there is progressive loss of cartilage matrix from the superficial zone associated with chondrocyte phenotypic modifications, including the formation of clusters, catabolic activation, and hypertrophic differentiation. Cytokines, chemokines, alarmins, DAMPs, adipokines, and other mediators released into the synovial fluid from the cartilage, synovium, and other joint tissues amplify a vicious circle of cartilage damage. In addition to cartilage damage, remodeling of the subchondral bone occurs with the development of vessels (*red*) located in vascular channels, which also contain osteoblasts, osteoclasts, and sensory nerves (*green*) (From Houard et al. (2013) with permission)