Susanne Grässel · Attila Aszódi *Editors*

Cartilage

Volume 1: Physiology and Development

Springer

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Preface

Volume one of a book series comprised of three volumes is dedicated to provide an overview about physiology and biology of permanent cartilage tissue and its role as a template in development and skeletal growth.

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 and joint physiology and development.

Three types of cartilage (hyaline, elastic, and fibrous) have been characterized on the basis of histological criteria and mechanical properties. The most prevalent type is hyaline cartilage which is a visually uniform, translucent tissue found in the skeleton of all vertebrates. Articular cartilage, the most familiar hyaline permanent cartilage, forms the smooth gliding surface of joints, such as the knee and hip that permits locomotion in humans and animals. Injuries to this tissue and degradative diseases as osteoarthritis impair joint mobility and are a great challenge of modern regenerative medicine. Hyaline cartilage also comprises the growth plate, the transient and temporary template required for endochondral bone formation in fetal development, skeletal growth, and repair processes, i.e., after fracture. In addition, hyaline cartilage occurs as a permanent structural tissue in costal cartilage and tracheal reinforcing rings.

Cartilage is a matrix-dominated tissue, and with regard to its abundance, the matrix is mainly composed of collagens and proteoglycans. These two main components form suprastructures interconnected by plenty of proteins that way forming a kind of alloy. Cartilage fibrils vary in their molecular organization, their width, and their orientation in the tissue in order to resist forces generated by external load. Proteoglycans, especially the lectican family, provide the required tissue elasticity and resilience by dissipating load. The interconnecting molecules, sometimes also referred to as adaptor proteins, are from a biochemical point of view mainly non-collagenous glycoproteins and small leucine-rich repeat proteoglycans which closely regulate the assembly and connection of the fibrillar and extrafibrillar matrices. Chapters 1, 2, and 3 of this volume summarize information about the impact of proteoglycans, forming the extrafibrillar matrix, on cartilage physiology and integrity; the role of the different collagens in cartilage matrix homeostasis and formation of fibrillar suprastructures; and the role of non-collagenous matrix adaptor proteins in growth factor binding, mediation of inflammatory and immune responses, and their use as biomarkers in cartilage-associated diseases.

In long bones, a specialized structure called the growth plate is responsible for the linear growth and forms just below the epiphysis at both ends of the cartilaginous mold. The growth plate is organized into zones which reflect the sequential differentiation stages of chondrocyte proliferation, maturation, and hypertrophy. The differentiation process is accompanied by the establishment of cellular anisotropy and planar polarity that generates the unique spatial structure of the tissue. Chondrocyte differentiation and polarity are essential and mutually interacting foundations of the normal growth plate function, and their disturbance results in chondrodysplasias with impaired longitudinal growth. Chapter 4 will focus on the mechanisms responsible for the establishment and maintenance of the structural polarity of the cartilaginous growth plate.

The cell fate of hypertrophic growth plate chondrocytes at the chondro-osseous junction has been a subject of discussion for several decades: on the one hand, there is ample evidence for programmed cell death by apoptosis or other mechanisms in the lower hypertrophic zone; on the other hand, several studies have indicated that some hypertrophic chondrocytes may not be "terminally differentiated" but are able to further differentiate into osteoblasts. Comprehensive insight into this novel concept of the fate of hypertrophic chondrocytes is provided by Chap. 5. Hypoxia-driven pathways, governed by the hypoxia-inducible factors (HIFs), are absolutely essential for the survival and functioning of chondrocytes in these challenging conditions. HIF-mediated signaling has also been implicated in joint formation and the integrity of the adult articular cartilage. Thus, the oxygen-regulated genetic program mediated by HIFs is key to the controlled development, growth, health, and disease of endochondral bone summarized in Chap. 6.

Chapter 7 focuses on our current understanding at the cellular and molecular levels, from creation to maturation of a synovial joint. Morphologically, we know there is the formation of interzone regions at the presumptive sites of the future joint. Molecularly, we have some insights into signals that direct the initiation and progression of interzone regions toward a joint. And through innovative technologies in mouse genetics and genomics, we are beginning to understand the developmental processes, with the identification of progenitor cell pools, and to trace origin of cells and track the fate of descendent cells from initiation to formation of the complete joint.

Chapter 8 provides an overview about signaling factors which control cartilage formation, development, and the differentiation and maturation of chondrocytes during embryonic skeletal development. The orchestrated formation, differentiation, and degradation of cartilage and bone are regulated by a multitude of signaling systems and transcription factors. The identified signaling molecules include Ihh, PTHrP, FGF, BMP, Wnt, IGF, CNP, and CCN proteins. One essential group of regulators of chondrogenesis comprises members of the Hedgehog (Hh) morphogen family. Hedgehogs act as long-range morphogens during chondrocyte development and endochondral ossification. Mutations in Hh effectors, receptors, and co-receptors, as well as in ciliary proteins that act as modulators of Hh reception, result in skeletal and craniofacial deformities. Chapter 9 summarizes the current understanding of Hh production and signaling in chondrocytes in development and disease. Wnt signals play important regulatory roles in those processes. In the vertebrate genome,

a total of 19 different Wnt ligands are encoded which can utilize diverse signaling pathways acting either positively or negatively on chondrogenesis and during cartilage development, forming a highly interactive system addressed by Chap. 10.

Chondrogenesis, e.g., the formation of cartilage from precursor cells, is characterized by drastic changes in cell shape and size. This involves major reorganization of the cytoskeleton, in particular, the actin network. Recent years have provided new insights into both the regulation of actin organization during chondrogenesis and into the downstream mechanisms connecting actin dynamics to chondrocyte gene expression which is addressed by Chap. 11.

Bringing together international experts from diverse fields of musculoskeletal research was a demanding task requiring patience and persistence. For that we are very grateful to our authors of this volume who managed to complete their chapters on time and who dedicated their spare free time to writing their reviews.

Regensburg, Germany — Susanne Grässel
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Cartilage Proteoglycans

1

Anders Aspberg

Abstract

Proteoglycans are key components of the cartilage extracellular matrix and essential for normal tissue function. The core protein and the glycosaminoglycan chains both contribute to function and provide different properties of the individual proteoglycans. This review is focused on the two main families of cartilage proteoglycans.

The first of these is the lectican family, including aggrecan, versican, and the cartilage link protein. The aggregating proteoglycan network formed by aggrecan, link protein, and hyaluronan provides biomechanical properties that give the tissue its ability to withstand and distribute load.

The second group discussed is the small leucine-rich repeat proteoglycan family, which includes decorin, biglycan, asporin, fibromodulin, lumican, keratocan, osteoadherin, proline-/arginine-rich end leucine-rich repeat protein, epiphycan, mimecan, opticin, chondroadherin, and chondroadherin-like. These proteoglycans bind collagens and are important regulators of cartilage extracellular matrix assembly. In addition, some of these proteoglycans bind and regulate growth factors and their receptors and regulate innate immunity through interactions with Toll-like receptors or the complement system.

This review will give an overview of the structure and function of the different aggregating proteoglycans and small leucine-rich repeat proteoglycans in normal cartilage extracellular matrix.

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1.1 Introduction

Articular cartilage function depends on the molecular composition and organization of its extracellular matrix (ECM). This complex protein network fills the space between the cells and provides a structural scaffold, giving the tissue its unique biomechanical properties.

Disturbed cartilage ECM composition or organization, either by failure to produce and assemble the ECM building blocks or dysregulated ECM degradation, is a key factor in the development of joint disease such as osteoarthritis.

The components of cartilage ECM are usually grouped into proteoglycans, collagens, and non-collagenous proteins, each providing specific functionalities to the composite ECM material. This chapter will give an overview of cartilage proteoglycans, while the latter molecular classes will be discussed in Chaps. 2 and 3, respectively.

1.2 Proteoglycans

A proteoglycan is a protein posttranslationally modified with one or several glycosaminoglycan (GAG) chains, a type of linear carbohydrate polymers. The GAG chains are composed of repeating disaccharide units, with different specific disaccharides used in the different types of GAGs: hyaluronan, chondroitin/dermatan sulfate (CS/DS), heparan sulfate (HS)/heparin, and keratan sulfate (KS). The proteoglycan-forming GAGs CS/DS and HS are attached to the core protein by linkage to serine residues in Ser-Gly sequence motifs through a specific tetrasaccharide linker. Keratan sulfate is either O-linked (KS type II) to serine or threonine residues or N-linked (KS type I). Unlike other GAGs, hyaluronan is not attached to a protein core but is extruded into the extracellular environment by transmembrane hyaluronan synthases. Further variation and specificity in GAG structure are achieved through sulfation at different positions of the individual disaccharide units and through epimerization of uronic acid residues in DS and HS. The cellular synthesis of GAGs is complex and not yet entirely understood, with a large number of different enzymes involved in producing and modifying the GAG chains. The details of structural variation and synthesis of GAGs are beyond the scope of this chapter and have been the subject of many excellent recent reviews; see, for example, (Mikami and Kitagawa 2013).

In cartilage, a key function of proteoglycan is to provide swelling pressure, allowing the tissue to take up and distribute mechanical load. This is achieved by the aggrecan-hyaluronan matrix (see below). Other cartilage proteoglycans play vital roles in guiding the ECM assembly, functioning as tissue reservoirs for soluble factors or as cell surface receptors. Additional functions of proteoglycans include regulating the innate immune system through interaction with complement components and Toll-like receptors (TLRs), which may lead to an inflammatory response and contribute to osteoarthritis pathogenesis (Orlowsky and Kraus 2015).