Susanne Grässel · Attila Aszódi *Editors*

Cartilage

Volume 3: Repair Strategies and Regeneration

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Preface

The closing, third volume of the Cartilage book series is dedicated to provide an overview about the current procedures of articular cartilage repair. The text is designed to be of use to multiple medical and basic science disciplines as orthopedics, rheumatology, and trauma surgery and all basic and clinical investigators working in the field of cartilage regeneration. This volume covers various cartilage repair strategies including cell-based, biomolecule-modulated, gene transfer, and tissue engineering approaches.

Chapter 1 provides an overview of the current status and future perspectives of cartilage repair strategies. The authors, after giving a short introduction to the clinical relevance and pathology of cartilage injuries, summarize the principles of currently practiced cartilage repair modalities including palliative approaches, strategies based on bone marrow stimulation, whole-tissue transplantation, and tissue engineering strategy. Recent advances of stem cell-based therapies and biomaterial scaffold designs in cartilage repair strategies are also presented. The chapter opens a discussion of the remaining scientific and clinical challenges in cartilage repair, specifically highlighting the need of enhancement of tissue integration, maintenance of cell phenotype, prevention of OA progress, and simplification of surgical and rehabilitation procedures.

The next four chapters give details for cell-based cartilage regeneration strategies. Chapter 2 focuses on adult *mesenchymal stem cells* (MSCs) and their growth factor-modulated surface marker expression. The authors clarify the characteristics and the embryonic origin of cartilage progenitor cells and summarize the contribution of MSCs from different origins to cartilage repair. Finally, a few examples of promoting articular cartilage phenotype by growth factor administration, in relation to the modulation of surface marker expression, are given. Chapter 3 introduces the *chondrogenic progenitor cell* (CPC), a specific cell type bearing stem cell characteristics such as migratory activity, clonogenicity, and multi-potency. These cells, which are present in osteoarthritic cartilage tissue and involved in regeneration processes, provide a promising alternative approach for cartilage repair. Various factors modulating the chondrogenic potential of CPCs including transcription factors, cytokines, growth factors, extracellular matrix molecules, and calcium homeostasis are presented. Chapter 4 demonstrates the attractiveness of *induced pluripotent stem* (iPS) cells for cartilage regeneration, which originates from their immense expandability and their intrinsic ability to give rise to stable hyaline cartilage. The

application of iPS cells can overcome most problems of classical cell-based regeneration strategies such as the extremely limited supply of human articular chondrocytes and the restricted differentiation capacity of mesenchymal stem cells from bone marrow or adipose tissue. Beyond being a potential alternative cell source for articular chondrocyte implantation, iPS cells are particularly promising for in vitro modeling of genetic diseases and for drug testing. Reprogramming patient-specific cells with a genetic predisposition and engineering disease-specific genetic variations into healthy control iPS cells promise to recapitulate "diseases in a dish" more realistically than immortalized human cell lines and will be an invaluable complementation for animal models. Whether iPS cells will satisfy these tremendous expectations will depend on our ability to upscale iPS cell culture, to derive sufficient amounts of relevant cell types like chondrocytes from iPS cells with acceptable efforts, and to find clinically safe reprogramming techniques for iPS cell-based therapies. Chapter 5 provides a short overview about current procedures for cell-based treatment strategies like bone marrow stimulation techniques, osteochondral transplantation, and *autologous chondrocyte transplantation*. Requirements and outcome parameters for a successful treatment and future directions in cartilage regeneration are discussed. Finally treatment recommendations according to cartilage defect size and depth are given.

The following two chapters deal with the role of biologic agents for the regenerative process of cartilage injury. Chapter 6 describes the *growth factors* with the most promising in vitro and in vivo data in cartilage repair, namely, bone morphogenetic protein-7, transforming growth factor-β, fibroblast growth factor-18, connective tissue growth factor, insulin-like growth factor-1, and recent advancements with autologous solutions of growth factors, such as platelet-rich plasma. Each section provides a background on mechanism of action, summarizes pivotal basic science research, and describes the results of clinical application in animal and human models of chondral disease. In chapter 7, *platelet-rich plasma* (PRP), an autologous blood-derived concentrate rich in growth factors, is introduced. Currently PRP is the most exploited biological approach for conservative management (simple intra-articular injections) and as an augmentation during surgical procedures. It has been applied both to treat osteoarthritis and chondral/osteochondral lesions in different joints, with the primary aim of providing symptomatic relief and functional recovery, and to induce a positive modulation of the entire articular microenvironment. The authors summarize the clinical evidence available on the role of PRP to treat cartilage pathology, focusing in particular on the data coming from randomized controlled trials.

Subchondral sclerosis is one of the hallmark findings of osteoarthritis (OA) and has long been discussed as one of its causes. Chapter 7 focuses on the changes in the *subchondral bone*, which often precede cartilage destruction in the development of the disease. Integration of the so far published data including in vitro, in vivo, and mathematical work suggests a critical role for this tissue in nutrition and oxygen supply to the articular cartilage, which may become even more critical in energy-demanding processes of healing and regeneration. Indeed, the success of current predictive diagnostics like specialized MRI techniques and scintigraphy as well as

successful regenerative clinical therapies like microfracturing, AMIC, or NAMIC can be better explained if the subchondral bone is taken into account as a supply route for the cartilage. Consequently the subchondral bone has to be included into the diagnostic and therapeutic concepts aiming to regenerate lost or damaged cartilage for advanced diagnosis and treatment of OA.

The next two chapters provide the concepts of *gene therapy* and *tissue engineering* for cartilage repair. Gene therapy protocols are well suited to deliver genes coding for therapeutic factors over time in a spatially defined manner within sites of cartilage injury resulting from acute trauma or during osteoarthritis. The focus of Chapter 9 is to examine the benefits of gene therapy to improve cartilage repair in such lesions, based on promising experimental and clinical evidence in relevant models in vivo using growth, transcription, and signaling factors capable of stimulating the chondrogenic and chondro-reparative processes locally. A continuous, combined effort between scientists and orthopedic surgeons may allow to bring gene therapy from encouraging data at the bench to a successful, safe translation in the broadly affected human population. Chapter 10 summarizes several promising options to engineer articular cartilage-like constructs, ranging from applying biological factors to mechanical, magnetic, or even electrical stimuli. The paradigm of cartilage tissue engineering classically comprises three pillars: cells, scaffolds, and signals. As cell sources for cartilage repair are addressed by other chapters in this volume, the author focuses on the two remaining pillars. First, due to their importance for the subsequent tissue engineering path, scaffold-free and scaffold-based applications are distinguished. Although most classical techniques in the field are scaffold-based, relatively more attention is now paid to emerging scaffold-free methods as articular cartilage repair constructs. Only proper tissue organization will permit long-term functional durability, and mimicking tissue growth without artificial support structures holds a lot of potential. While the extracellular matrix is an integral aspect of the tissue properties, it also impedes the integration of the repair construct into the surrounding host tissue. Several approaches to tackle this dilemma are depicted. The importance to develop bioreactors is also emphasized as they are inevitable for the reproducible application of sophisticated mechanobiological stimulation regimes. In this context, the contribution of selected growth factors is described. At the end of the chapter, the importance of integrating multiple of these parameters into multimodal concepts for achieving phenotypic stability of the engineered cartilage-like constructs is addressed.

Finally, Chapter 11 focuses on different *animal models* which play an important role to test novel experimental strategies and reconstructive surgical treatments of focal articular cartilage defects. Such animal models need to reflect the different appearances and etiologies of cartilage defects, e.g., caused by trauma or osteoarthritis. Depth of articular cartilage defects plays an important role. Full-thickness chondral defects do not extend into the subchondral bone, while osteochondral defects penetrate the cement line and extend to the subchondral bone, thereby changing its structural integrity. Mice, rats, rabbits, goat, sheep, minipigs, and horses are representing good models, bridging the gap between in vitro studies and clinical experiments in human. Each of them has benefits and limitations. Evaluation

of cartilage repair may be performed using a large variety of methods, among which nondestructive evaluations and histological scoring, the latter being considered as the gold standard. As the available reconstructive surgical approaches for articular cartilage repair become increasingly complex, precise animal models to test and to translate new surgical techniques into appropriate clinical treatments are required.

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 the authors of this volume who managed to complete their chapters on time and who dedicated their spare time to writing their reviews.

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Overview: State of the Art and Future Prospectives for Cartilage Repair

1

Yangzi Jiang, Hang Lin, and Rocky S. Tuan

Abstract

Articular cartilage degeneration, for example, resulting from joint injury and trauma, has remained a major clinical challenge as cartilage does not have self-healing capability, and osteoarthritis (OA) often ensues. OA affects over 15% of the population, including 65% of those above 65 years of age, and is a major cause of physical disabilities. There is thus a need to develop treatment strategies that can effectively target prevention and/or blockage of early stage disease progress, rather than prosthetic replacement of the joint at the end stage. This chapter provides an overview of the state of the art and future prospectives of cartilage repair strategies. The clinical relevance and tissue pathology of cartilage injury are first introduced, covering the structure and function of cartilage tissue and evaluation and clinical management of cartilage injuries. Next, the principles and strategies of currently practiced cartilage repair are summarized, including palliative approaches (e.g., arthroscopic debridement/lavage), intrinsic repair (e.g., bone marrow stimulation technique—abrasion, drilling, and microfracture), whole tissue transplantation (e.g., osteochondral graft transplantation), and tissue engineering strategy (e.g., autologous chondrocyte implantation/transplantation). An overview of recent advances in cartilage repair strategies is presented, particularly the progress made in stem cell-based therapies and biomaterial scaffold designs. The chapter concludes with a discussion of the remaining scientific and clinical challenges in cartilage repair, specifically highlighting the need of enhancement of tissue integration, maintenance of cell phenotype, prevention of OA progress, and simplification of surgical and rehabilitation procedures.

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1.1 Introduction

1.1.1 Clinical Relevance and Needs of Cartilage Repair

Cartilage is the load-bearing surface of the synovial joint, or diarthrosis, which is generally considered a tissue with simple structure, as it is avascular and hypocellular and consists primarily of extracellular matrix (ECM) and a small amount of chondrocytes. The principal function of cartilage is to provide weight-bearing and mechanical support. However, cartilage has limited self-repair ability. Injury in cartilage often represents the initiation of joint degeneration and eventually leads to degenerative joint diseases, such as osteoarthritis (OA). OA is the most common cause of loss of mobility in elderly adults, and it has profound social, physical, psychological, and economical consequences (Callaghan 2003). Taking the United States as an example, OA affects 27 million adult Americans, including 65% of those above 65 years of age (Goldring 2006; Lethbridge-Cejku et al. 2003), and directly contributes to 9–10% of the disabilities (Felson 2004). There is no cure for OA, and osteoarthritic patients suffer from chronic pain and limited joint movement, distress and depression, and lost productivity. With the increasing aging demographics, OA is thus recognized as a significant global burden with clearly unmet clinical needs (World Health Organization 2002).

OA of the knee and hip joints are major causes of mobility impairment. The risk factors of OA include both intrinsic or progressive systemic factors, as well as factors that affect joint local mechanical environments (Fig. 1.1). Gender, family history, developmental joint growth, and shape abnormality are considered the intrinsic systemic factors, while progressive systemic factors, such as aging, hormonal status, nutrition, and lifestyle, vary among individuals. These systemic risk factors are related to the susceptibility to OA, but insults to the joint local mechanical environment, caused by overload (e.g., as a result of obesity), repetitive joint loading (e.g., in elite athletes), injury and trauma (e.g., from accident), or instability (e.g., resulting from joint surgeries), directly harm articular cartilage.

Current clinical OA management is mainly concerned with symptom reduction, e.g., pain, swelling, and stiffness, with oral nonsteroidal anti-inflammatory drugs (NSAIDs) being the most commonly used pharmacological treatment at mid-stage of the disease, and arthroplasty, an irreversible procedure, as the final solution to maintain joint function (Fig. 1.2). Consequently, it is highly desirable to develop treatment strategies that target the prevention and/or blockage of the progress of diseases in the early stage, rather than replacement of the joint at the end stage. Therefore, treatments that aim to repair cartilage defects have been under active investigation and are expected to provide more treatment choices to OA patients.

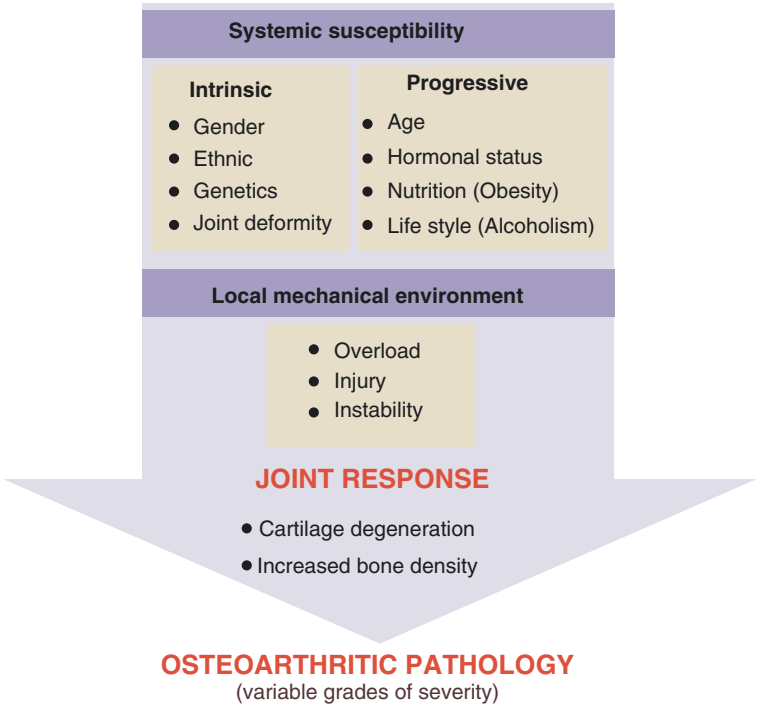

Fig. 1.1 Risk factors of osteoarthritis (OA) and the relationship between cartilage injury and OA

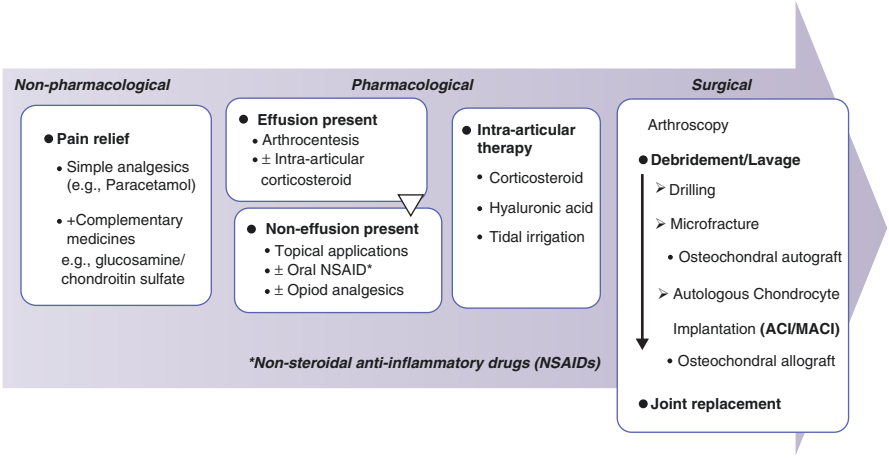

Fig. 1.2 Current OA clinical management and cartilage repair interventions. *ACI* autologous chondrocyte implantation, *MACI* matrix-associated autologous chondrocyte implantation