Chapter 8
Generation of Scaffold Free 3-D Cartilage-Like Microtissues from Human Chondrocytes

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ABSTRACT

Since our society is characterized by an increasing age of its people on the one hand and a high number of persons dealing with sports on the other hand, the number of patients suffering from traumatic defects or osteoarthritis is growing. In combination with the articular cartilage specific limited capacity to regenerate, a need for suitable therapies is obvious. Thereby, cell-based therapies are of major interest. This type of clinical intervention was introduced to patients at the beginning of the 1990s. During the last years, a technological shift from simple cell suspensions to more complex 3D structures was performed. In order to optimize the scaffold free generation of cartilage, such as microtissues from human chondrocytes, the authors examine the influence of a static or spinner flask culture with respect to differentiation and architecture of the engineered microtissues. Additionally, the impact of the soluble factors TGF-β_2 and ascorbic acid on this process are investigated. The results demonstrate a positive impact of TGF-β_2 and ascorbic acid supplementation with respect to general Type II Collagen and proteoglycan expression for both the static and spinner flask culture.

INTRODUCTION

In our society, more and more people get the chance to reach an old age and therefore diseases are increasing which are linked to age-related degeneration of various tissues and organs, e.g. cardiovascular diseases, or reduced ability to move the joints. A 2005 study demonstrated that every second person at an age above 60 years has osteoarthritically modified joints (Schneider, 2005). Concomitant with these aging problems the number of active living people doing all

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kinds of sports including sports with high risk of injuries, such as downhill skiing, skateboarding, or even playing football is increasing. This frequency of traumatic injuries, especially in the musculoskeletal system and aged tissues or organs with reduced or changed functionalities, made it necessary to develop and improve procedures to repair or even better regenerate diseased or damaged tissues. A well-known example for an approach to repair diseased and/or lost tissue is the implantation of a joint prosthesis in the knee, or the hip in patients with osteoarthritis. Osteoarthritis (OA) is sometimes also called degenerative arthritis because it is a "wearing out" condition involving the breakdown of cartilage in the joints. Here, "repair" means the replacement of lost or destroyed tissue with a joint made of a synthetic material (e.g. metal, ceramic, polyethylene) which is suitable to regain the lost function and which does not harm the body anyhow, e.g. triggering cellular toxicity, carcinogenicity, and/or hypersensitivity (Wolford, 2006; Callaghan, 2008). In contrast, the regeneration process has the aim to re-establish the original tissue with respect to morphology and physiology. To reach this goal appropriate cells and/or tissue structures, also called scaffolds, have to be arranged inside (*in vivo*) or outside (*in vitro*) the body and should fit ideally into the tissue defect. These attempts to design and grow tissues in the laboratory lead to the term "Tissue Engineering" appearing the first time in 1987 at a meeting of the National Science Foundation in the U.S.A. and the therapeutic application of these *in vitro* grown tissues made of cells and/or biomaterials forwarded the discipline "Regenerative Medicine." Final aim is a regenerated tissue with perfect fittings which does not differ from the original one with respect to morphology, histology, function and durability.

The objective of this chapter is to introduce the engineering of cartilage-like microtissues, which could be used to regenerate cartilage defects originating from traumatic events, or even degenerative diseases. Furthermore, these microtissues could also be useful tools in research and pharmacological test systems. The distinctive feature is to go this developmental path without using any biomaterials as scaffold basis to design these *in vitro* tissues. Without using any scaffolds, the development of cartilage-like microtissues built by human chondrocytes themselves has been achieved, and therefore, it could be used as a strictly autologous transplant. This special attribute reaches the second aim of the project. The *in vitro* tissues should not induce any immune response in the patient, such as allergies or transplant rejection. To optimize cell and tissue differentiation, bioactive molecules as well as special culture conditions were applied.

BACKGROUND

Articular Cartilage

One of the most important prerequisites of fully functional joints in the human body is an intact articular cartilage and their functionality is strongly influenced by the load bearing and gliding abilities of the cartilage tissue (Wright, 1976). In a normal healthy situation, articular cartilage displays superior biomechanical properties, such as high resiliency combined with a well-lubricated surface. The remarkable mechanical properties of hyaline cartilage are strongly influenced by its tissue architecture, composed of a fluid and solid phase and their interactions. The main constituent of the liquid phase is water with additional ionic and non-ionic solutes. The latter represents almost 75-70% of the wet weight of hyaline cartilage (Maroudas, 1979). In contrast, the solid phase consists of nearly 10% chondrocytes, 10-30% Collagen, 3-10% proteoglycans, 10% lipids, and small amounts of glycoproteins (Muir, 1979). The central metabolic component of the cartilage is the chondrocyte, the cartilage cell, which is responsible for the matrix synthesis, secretion, and arrangement (Mow, 1992). The main components

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