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Controlled delivery systems for tissue repair and regeneration

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ABSTRACT

Tissue repair and regeneration is one of the major challenges of these years, aimed to restore functional and anatomical properties after traumatic, infective or degenerative diseases. New therapeutic approaches include the use of controlled delivery systems and advanced medical devices for the targeting and delivery of bioactive molecules, mesenchymal stem cells and/or growth factors, providing both the structural integrity and the biochemical information to cells when they are growing into a specific kind of tissue.

The review will focus on the repair and regeneration techniques for epithelial and musculoskeletal tissues with the aim to introduce and discuss innovative approaches such as cell and/or growth factors delivery, and newly designed polymeric scaffolds for tissue engineering. After a brief introduction explaining the state of the art referred to the specific tissues (skin, cartilage, bone), repair and regeneration techniques the authors own experience on the topic will be presented and deeply discussed through their experimental works.

1. Introduction

Tissue *repair* and *regeneration* are different natural processes that spontaneously initiate the healing process of cells and tissues after injury. In healthy tissues, healing, in the form of regeneration or repair, occurs after practically any insult that causes tissue destruction, and is essential for the survival of the organism. Regeneration refers to the proliferation of cells and tissues to replace lost structures, such as the growth of an amputated limb in amphibians. In mammals, whole organs and complex tissues rarely regenerate after injury, and the term is usually applied to processes such as liver growth after partial resection or necrosis, but these processes consist of compensatory growth rather than true regeneration [1]. Tissues with high proliferative capacity, such as the hematopoietic system and the epithelia of the skin and gastrointestinal (GI) tract, renew themselves continuously and can regenerate after injury, as long as the stem cells of these tissues are not destroyed [2].

Repair most often consists of a combination of *regeneration* and *scar formation* by the deposition of collagen. The relative contribution of regeneration and scarring in tissue repair depends on the ability of the tissue to regenerate and the extent of the injury. For instance, a superficial skin wound heals through the regeneration of the surface epithelium. Fibrosis is the typical result of extensive deposition of collagen that occurs under chronic inflammation, i.e. when scar formation is highly stimulated by the local production of growth factors and cytokines promoting fibroblast proliferation and collagen synthesis, that is accompanied by extra cellular matrix (ECM) damage. Regeneration and repair mechanisms involve the control of cell proliferation and signal transduction pathways, and the many functions of ECM components. Moreover, cells in the ECM, such as fibroblasts, macrophages, and other cell types, produce growth factors, cytokines, and chemokines that are critical for regeneration and repair.

Regenerative medicine is a new way of treating injuries and diseases and it uses three different approaches: *i)* cells, *ii)* bioartificial tissues and *iii)* specifically growth tissues [3,4]. Independently from the approach used, the main goal of the regenerative medicine is to replace or to regenerate human cells, tissues and organs and to restore or establish the normal and original function of the damaged or compromised tissue [5]. In this context, the term

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"tissue engineering" refers to methods and techniques used to improve the regeneration of human cells and tissues, including the manipulation of natural and synthetic materials which provide both the structural integrity and the biochemical information to young cells when they are growing into a specific kind of tissue (Fig. 1) [6]. Tissue engineering typically involves three main elements which provide the essential factors for the physiological regeneration process. The first component is a substrate (membranes, foams, meshes, gels and 3D-scaffolds) for the tissue-conduction properties. These properties are defined as the ability to support the cell migration into the defect site from the host tissue and to promote the cell proliferation and growth. The second element is represented by chemical signals, as growth factors (VEGF, BMPs, TGF-βs and IGFs), that provide the tissue-inductive properties, the ability to induce the proliferation of a specific kind of cells and to drive them to produce the new tissue. The last component are the cells: they can be differentiated cells or undifferentiated cells, such as adult (somatic) stem cells, embryonic, and induced pluripotent stem cells.

The review wishes to provide an overview on the tissue regeneration approaches developed by the authors. It will focus on the repair and regeneration techniques for epithelial and musculoskeletal tissues with the aim to introduce and discuss innovative approaches such as cell and/or growth factors delivery, and newly designed polymeric scaffolds for tissue engineering.

Since the substrate plays important roles as framework supporting the migration of cells from the surrounding tissue into the damaged tissue and as delivery system for the controlled or prolonged release of cells, genes, and growth factors, the first part of the review (Section 2) is dedicated to materials used to make scaffolds. They can be polymers and especially biodegradable, biocompatible polymers, also biomaterials provided with ligands for cell receptor (integrines) or that may selectively adsorb adhesion proteins which cells can bind. Moreover, the scaffold can be a reinforced structure which maintains the shape of the defect site preventing any distortion of host tissues and also it can be a barrier to prevent the infiltration of tissues that are not involved in the reconstruction process and that may limit the regeneration process [7–9].

The approaches of regenerative medicine can be different depending on the tissue to be repaired/regenerated, on the type of injury and on the pathologic or healthy tissue condition. Polymer scaffolds combined with, drugs, growth factors or cells, can be used for different final applications such as the regeneration of coronary arteries, bone, articular cartilage, for the reconstruction of human mandible, ear and blood vessels, and for the therapeutic treatment of diabetic foot ulcers or intractable diseases. A brief chapter (Section 3) of the review is dedicated to antimicrobial drugs that are often added to the scaffold/substrate for tissue regeneration since infections are the main pathologies that can arise in an injury process, or that can be caused by human intervention during a surgery.

Taking into account that mesenchymal/stromal stem cells (MSCs) are presently acquired as Active Pharmaceutical Ingredient in terms of identification criterion, sources as well as activity and formulation aspects, the review's Section 4 provides a detailed

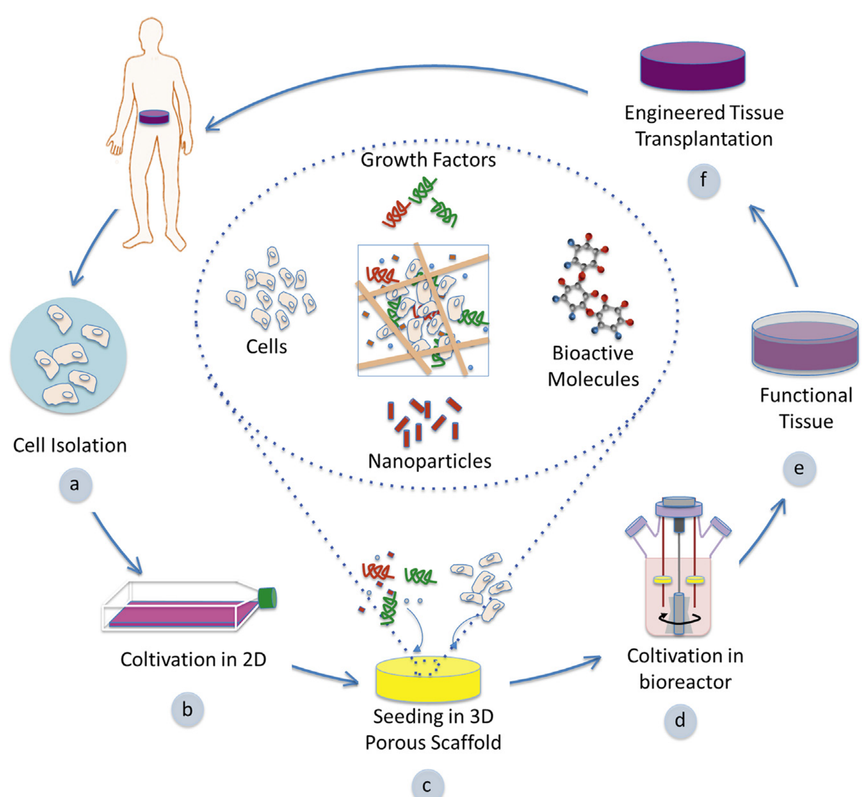

Fig. 1. Cells are isolated from donor patients (a), and expanded *in vitro* on two-dimensional surfaces (b), the cells are seeded onto three-dimensional biodegradable porous scaffolds combined with growth factors, bioactive molecules, and micro- and/or nanoparticles (c), and cultured in bioreactor. The scaffolds are able to mimic the three-dimensional microenvironment of the physiological and dynamic extracellular matrix, which naturally provides mechanical and biochemical support to the cells. The cell constructs are further cultured in bioreactors (d) to provide optimal conditions (with regard to the composition of the medium, the oxygenation, the temperature, and the pH value) for obtaining a three-dimensional functional tissue (e). Once a functioning tissue has been successfully engineered, the construct is transplanted into the patient defect to replace the damaged tissues (f). (Freely adapted with permission from Dvir et al., 2011 [6]).