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Mini Review

Regenerative Medicine: A Multidisciplinary Approach to a Complex Problem

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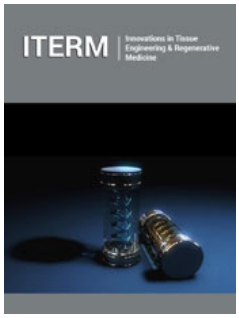

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Introduction

Despite the successful progresses in organ transplant, the organs shortage and the long waiting lists make it of the most challenging issues of our times. In fact, just a small percentage of patients receive transplants [1,2]. while every day around 18 people die waiting for them [3]. The possibility to create de novo tissues and organs and/or to promote their regeneration is of prominent interest in the research community. In the last years, many innovative approaches have been introduced and new technological advancements are undergoing. Currently, the most diffused methodologies rely on regenerative medicine, that combines the use of stem cells, stimulated with specific factors, and scaffolds, where cells can grow to substitute damaged tissues, inducing their repair and improving their functions [4]. Scaffolds possess a defined structure, with precise pore size and distribution [5,6], and determined mechanical properties which can tackle stress ensuring biological interconnections [7]. Regenerative medicine combines different disciplines, such as chemistry, physics, biology and tissue engineering to obtain functional materials. In this minireview, we will focus on the materials and fabrication methods that are used to prepare the scaffolds, the type of cells that are commonly used for regeneration, and finally the current advances in clinical approval.

The Scaffold: Materials and Fabrication Procedures

Three-dimensional Nano scaffolds are usually composed biodegradable, biocompatible and non-immunogenic polymers. Natural polymers extracted from Extracellular Matrix Components (ECM), such as collagen, fibrin and hyaluronic acid [8-10], alginate [11] and agarose [12], present the advantage of being easily biodegraded through enzymatic degradation or other natural chemical processes, and they often contain already the necessary components for cellular adhesion [13]. Synthetic polymers, on the other hand, can be easily engineered to obtain the desired mechanical properties and they can also be functionalized with proteins or peptides to improve cell adhesion and growth [13]. Among the most used synthetic polymers we can find Polyethylene glycol (PEG), Poly (2-Hydroxy Ethyl Methacrylate) (PHEMA) [14], Polyacrylamide [15], Poly(N-isopropyl Acrylamide) (PNIPAAm) [16], Poly(Lactic-co-Glycolic Acid) (PLGA), Poly(L-Lactic Acid) (PLLA), poly(Caprolactone) (PCL), poly(ethylene oxide) (PEO), poly(vinyl alcohol) (PVA) [17].

The morphology, the structure, the porosity and the mechanical properties of the scaffolds must be controlled during the fabrication procedure to obtain the desired performances. Usually, there are composed of hydrogels or nanofibers. Hydrogels can be prepared via natural gelation processes induced by temperature, pH, ionic strength or enzymatic cross-linking [13]. Other fabrication techniques include solvent casting or particles leaching, freeze drying, gas foaming, 3D bioprinting, photolithography. 3D bioprinting is one of the most innovative fabrication techniques, allowing to prepare biocompatible scaffolds suitable for cell growth [18,19] that are able to reproduce extracellular matrix, vascular and nervous systems properties [20-22].

Regarding the preparation of nanofibers, the most common techniques are electrospinning, self-assembly, and phase separation. Electrospinning uses an electric field to draw charged polymer solutions into fibers with diameter in the order of few nanometer [23]; however,

the production is limited to thin two-dimensional (2D) sheets. Self-assembly, on the other hand, exploits noncovalent bonds to fabricate 3D scaffolds [24]. Thermally Induced Phase Separation (TIPS) is a new technique based on the polymer dissolution in a good solvent, with subsequent phase separation and gelation, solvent removal and freeze-drying. The advantage of this technique is that it can be used in combination with the other techniques mentioned before to increase the complexity and functionality of the final structure [23,24].

The Cells

Cells seeded on the scaffolds can be derived from the patient itself (autologous), a different individual (allogeneic) or can be originated from animals (xenogeneic). Commonly, stem cells, chondrocytes and fibroblasts have been exploited in regenerative medicine [25-28]. In parallel, administration of factors stimulating body's healing process has been also successfully used. While some human tissues, such as liver and lungs show high regeneration capacities, others are very limited, as cornea and cartilages [29]. Materials mimicking the extracellular matrix have been applied both as substrates and as means for providing factors and molecules necessary for promoting cellular differentiation and regeneration [30-32]we test the hypothesis that tissue-specific ECM influences the differentiation of murine ESCs. We induced murine ESCs to differentiate by embryoid body formation, followed by dissociation and culture on ECM prepared by decellularisation of either osteogenic cell (MC3T3-E1.

Advances in Clinical Translation

Currently, four clinical trials are ongoing exploiting specifically scaffolds for treating different kinds of disease conditions and three have been already completed [33]. Several of these technologies and some developed medical devices are being evaluated in clinical trials or have been approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA). It has to be noted that the vast majority of them are based on cell-free instruments, due to a series of limitations related to high costs of production and time-consuming procedures required before approval on the market [34,35].

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