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Review

Stem cells and biomimetic materials strategies for tissue engineering

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ABSTRACT

Stem cells have been recognized as a promising alternative to somatic cells in the application of cell therapy owing to their potential to renew themselves through cell division and to differentiate into a wide range of specialized cell types. In order to maintain the phenotype expression and differentiated functions of stem cells, the simulated natural environment of the biomimetic material support has to provide the appropriate signals to the attached cells. Scaffolds with biomimetic components and nanotexture can provide chemical, physical as well as spatial cues that are essential to mimic natural tissue growth. Moreover, the plasticity of stem cells provides the basic possibility for multiple-tissue engineering using a certain type of stem cells. Progress in the understanding of self-renewal and directed differentiation of stem cells on biomimetic materials will lead scientists to propose the possibility of cell-based therapies to treat diseases, including the use of stem cells in tissue engineering. In this review paper, we will discuss the current state of the art and future perspectives on stem cells and biomimetic materials strategies for tissue engineering.

Contents

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1. Current tissue engineering

Since the initiation of tissue engineering 15 years ago, the development is still far from achieving its long-term goal: to control and regulate the potential of natural tissue regeneration for defect repair or even organ regeneration. Although a series of technological advancements have been achieved thus far, new strategies are needed to further develop tissue engineering for wider clinical applications.

The so-called triad in tissue engineering encompasses three basic components: scaffolds, cells and signaling biomolecules (or growth factors). The principal components of extracellular matrix (ECM) are collagen biopolymers, mainly in the form of fibers and fibrils. One specific design objective of a porous scaffold for tissue engineering is to fabricate a porous scaffold out of absorbable polymer that mimic the extracellular matrix in supporting cell proliferation and organization. Other forms of polymer organization like gels, foams, and membranes have also been used as scaffolds for tissue engineering. The various forms can be combined in the laboratory to create imitations of biopolymer organization for specific tissue type [1]. Scaffolds can be enriched with signaling biomolecules, which may be surface bound or blended. Those developmental signals provided by the scaffolds will induce the cells to secret extracellular matrix and/or tissue/organ regeneration.

1.1. Scaffold development

1.1.1. Synthetic and natural materials for scaffolds

In general, to promote cellular functions, scaffolds used for tissue engineering should have the following characteristics: biocompatibility, biodegradability, reproducibility, high porosity with interconnected pores, and no potential of serious immunological or foreign body reactions. In addition it is also highly desirable that the scaffold has the ability to promote ECM secretion, and to carry biomolecular signals [2–5]. Owing to their functional properties and design flexibility, polymers are the primary choice of materials for making scaffolds. Polymers used for making scaffolds are classified as either naturally derived polymers or synthetic polymers [6]. The former includes collagen, gelatin, chitosan, chitin, cellulose, and starch. The later includes frequently used biodegradable synthetic polymers such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone)(PCL) and poly(lactic-co-caprolactone) (PLA-CL). These are all approved by the US Food and Drug Administration (FDA) for certain biomedical applications. In Table 1, we highlight the degradation characteristics of various synthetic polymers. The biodegradation rate is one of most important considerations and it is highly desirable to ensure that the degradation rate matches with the speed of new tissue regeneration at the defect site. If the degradation is more rapid than the tissue regeneration, the scaffold will lose its carrier function for cell growth; on the other hand, if the degradation is too slow compared to the tissue regeneration, the scaffold will impede tissue regeneration.

Table 1
Biodegradable synthetic polymers and their degradation rates

Biodegradable polymer	Typical applications	Polymer degradation rate (months)
Polyorthoester	Bone ingrowth applications, drug delivery	Half life of 4 h
Poly(DL-lactic acid) (PDLA)	Drug delivery, tissue regeneration	12–16
Poly(L-lactic acid) (PLLA)	Sutures, orthopedic devices, tissue regeneration	>24
Poly(glycolic acid) (PGA)	Drug delivery, sutures.	6–12
Poly(lactide-co-glycolide) (PLGA) (50:50)	Sutures, films for retinal pigment epithelium transplantation and guided tissue regeneration, fracture fixation, oral implant, drug delivery.	Half life of 1.5 months
Polycaprolactone (PCL)	Long-term implantable drug delivery system, tissue regeneration.	>24
Polyanhydrides	Orthopedic prosthesis, drug delivery.	Half life of 1 h
Tyrosine-derived polycarbonates	Orthopedic applications.	Very slow degradation

Table 2
Traditional technologies for tissue scaffold fabrication

Technology		Advantages	Disadvantages
Thermally induced phase separation (TIPS)		Simple and fast, with wide ranges of shapes and sizes.	Low level of pore size control.
Porogen leaching		Inexpensive, able to form pores with defined shapes.	Time-consuming, undesirable porogen residue.
Gas foaming		Permits solvent free formation of porous scaffold.	Low interconnectivity, low pore size.
Solid free-form (SFF)	Stereolithography	Relatively good resolution.	Limited photopolymer materials available, expensive.
	Selective laser sintering	Plastic or plastic composite using fiber or others as filler.	Reduced resolution and poor surface finish
	3D-pinting	Laser is not needed, less expensive.	Adhesive liquid may reduce biocompatibility of scaffold.
	Wax printing	Laser is not needed, less expensive.	Ceramic materials are used, not suitable for polymer
	Fused deposition modeling	Controllable fiber pattern.	Limited to thermoplastic materials with good viscosity property, cannot encapsulate cells or other biological agents.
	Bioplotter	Direct incorporation of cells into the scaffold	Limited 3D size.

Collagen, the primary structural protein of the native ECM, is the most widely used natural polymer for making scaffolds. Furthermore, it has desirable functional properties, making it favorable for cellular growth. Since collagen extracted from natural sources is known to elicit immunogenic responses upon implantation, the direct use of natural collagen has become limited. Instead, purified collagen or reconstituted collagen, which causes relatively low immunogenic responses, can be produced by biochemical processing and is commercially available. The main disadvantage of using collagen in scaffold is the rapid degradation rate and weak mechanical property. To overcome this deficiency, collagen fibers have been cross-linked to retard the degradation rate.

Due to its favorable biocompatibility and biodegradability, PLA is one of the most frequently used synthetic polymers for scaffold materials [7]. The left-handed (L-lactide) and right-handed (D-lactide) are the two enantiomeric forms of PLA, with PDLA having a much higher degradation rate than PLLA. PLLA is better than PDLA for its higher biocompatibility. Its high mechanical strength makes it suitable for many medical applications, such as biodegradable suture, bone fixation pins etc. PGA is a hydrophilic polymer with a higher biodegradation rate than PLA both *in vivo* and *in vitro*. As for PLGA, the copolymer of PLA and PGA, the biodegradation rate and mechanical strength can be manipulated by changing the ratio of LA and GA units. In order to ameliorate the acidic byproducts of biodegradation, a copolymer of PLA and PCL is used. The copolymer ratio of PLA and PCL can be adjusted for a longer degradation period and other properties such as hydrophilicity and mechanical properties can be adjusted as well [8]. Using the above mentioned polymers, various types of porous scaffold can be made and the surface can also be functionalized to achieve higher biocompatibility for enhanced performance [9–11].

1.1.2. Technologies for scaffold fabrication

Although a number of fabrication technologies have been applied to process biodegradable and bioresorbable materials into 3D polymeric scaffolds with high porosity and surface area, most of these methods focus on fabrication at the micro or macro level. In Table 2 we