Review Article

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Natural Fibrous Polymers for Tissue Engineering

Thais Sayuri Iguma[1], Sonia Maria Malmonge[2] and Arnaldo R. Santos Jr[1*]

[1]Centro de Ciências Naturais e Humanas (CCNH), Universidade Federal do ABC, Brazil.

[2]Centro de Engenharias, Modelagem e Ciências Sociais Aplicadas, Universidade Federal do ABC, Brazil.

[*]Correspondence:
Arnaldo R Santos Jr, Centro de Ciências Naturais e Humanas, Universidade Federal do ABC, Brazil, E-mail: arnaldo.santos@ufabc.edu.br.

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ABSTRACT

As life expectancy grows, many age-related diseases are becoming increasingly evident such as osteoporosis, diabetes or cardiovascular disorders. Not only that, some studies are also pointing up an increase of road accidents and trauma injuries boosting the implants market. Many techniques have been developed in order to repair damaged organs, and Tissue Engineering (TE) is a promising one. In order to reduce the dependence on transplanted tissues and organs, TE combines the field of life science with engineering by developing a 3D template (scaffold) which temporarily mimics an extracellular matrix (ECM) and provides a support for cells to grow and proliferate with the right stimuli (signals). Not only may the source of the cells and signals vary, but also the scaffold itself. Depending on the purpose, there are many possibilities in which the scaffold can be designed: ceramic materials, synthetic or natural polymers with a vast range of architecture. Creating a system as similar as possible to ECM is advantageous for the cells, for this reason fibrous structures and natural polymers, such as collagen and gelatin, are outstanding regarding TE.

Keywords

Tissue engineering, Disease study, Organs, Polymers, Implants.

Introduction

Over the years, life expectancy has been growing considerably. According to the Global Burden of Disease Study 2017, People are living approximately 23 years longer in 2017 than they were in 1950 [1]. On the other hand, many age-related diseases are becoming increasingly evident, for example, osteoporosis, diabetes or cardiovascular disorders [2], and researchers have been striving to improve the quality of life of those in need. In the same way, not only the elderly citizens are under the spotlight of medical researches, but also people of all ages who have suffered tissue lesions from mechanical trauma or degenerative diseases. Some studies are also pointing up an increase of road accidents and trauma injuries [3,4], boosting the implants market [5]. Many techniques have been developed in order to repair damaged organs, such as the replacement of the injured tissue or regeneration stimulus of the patient's own tissue [6].

Two main procedures used for repairing lesions can be mentioned: transplant and implant [6]. In the first one, organs or tissues are provided from living donors, cadavers or even from other species (xenotransplantation), and it is commonly associated with rejection and microbial contamination, which requires immunosuppressive medications. Moreover, transplant techniques have some obstacles concerning religion and ethical issues [6,7]. Implants, on the other hand, have many advantages comparing to transplants. For instance, an implant (or bioimplant) does not necessarily need a donor, since it is an engineering device designed specifically for replacing or assisting natural tissues [5]. The prostheses can be made with a huge variety of biomaterials among the three major classes: metallic, ceramic, and polymeric materials [8].

Biomaterials can be described as "Any substance (other than a drug) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ or function of the body" [9,10], and it can be classified into three groups: bioinert, bioactive or bioresorbable. The essential characteristic of bioinert materials is the almost nonexistent interaction between material-tissue interface, providing to the tissue a minimum response, frequently resulting in the formation of a fibrous capsule around the implant. Bioactive materials have the ability to supply with considerable interaction between the tissue and the device, as a consequence of strong chemical bonds. Finally, bioresorbable materials do not have to be surgically removed from the body, i.e., they can be absorbed and eliminated by the organism itself without harmful responses. Bioinert materials are frequently associated with metals, bioactive with ceramics and bioresorbable with polymers, but those materials are often found associated as a composite [8,12,13].

Nowadays, polymers are widely used in biomedical field, because they are versatile and have several advantages comparing to metals and ceramics. Polymeric materials usually exhibit low density, and low resistance to temperature. Nonetheless, they can be easily tailored with an extensive range of desirable properties. There are many particular ways to classify polymers. One of them is related to their origin: natural or synthetic. Natural biopolymers are derived from renewable or biological sources whereas synthetic are chemically synthesized. Polymer biological applicability is ample: from medical supplies (blood bags and surgical tools), to therapeutic treatment (implants) and recently reaching regenerative medicine and tissue engineering [14,15].

Tissue Engineering

Tissue engineering (TE), as the name suggests, combines the field of life science with engineering in order to reduce the dependence on transplanted tissues and organs from a donor (allogeneic) or the same patient (autogenic). The essence of TE is to provide a solution promoting repair, replacement or even regeneration of damaged tissues caused by diseases or injuries instead of replacing them. TE is founded on the combination of three pillars: cells, signaling mechanism and a three-dimensional template (scaffold) [16]. To summarize, it involves the production of a 3D template which temporarily mimics an extracellular matrix (ECM), providing a support for cells to grow and proliferate with the right stimuli (signals). The system can be firstly cultured in vitro and subsequently implanted in the patient, or directly applied in vivo [16,17].

The cellular sources in TE may vary: cells can be provided from a different individual, other species (both can cause immunological rejection) or stem cells from the patient himself [17]. To assist the cells proliferations, many techniques can be adopted, such as chemical stimuli substances (growth factors and adhesion molecules) or mechanical stimuli (bioreactors). The TE success also depends on the implantable matrices: scaffolds must guarantee an environment for cells to adhere and proliferate. In order to provide that, the device must have biocompatibility and a propitious architecture with interconnected pores to assist cell incorporation and allow movement of fluids as nutrient delivery and waste removal [16,17].

Khademhosseini & Langer (2016) have put forward several advances concerning TE over the last decade. Not only novel methods regarding cellular sources and stimuli (iPSCs and CRISPR-Cas9), but also state-of-the-art technologies creating efficient scaffolds (programmed modular self-assembly and bioprinters). Furthermore, besides the well-known applications for organs such as skin, bone, cartilage, liver and intestine [18], they pointed up a few potential applications of TE designed to assist, for example, neuronal connections, vascular tissue or lateral collateral ligaments. Additionally, the authors mentioned applications beyond medical purpose, such as biological actuators, robotic and food industry [19].

Depending on the purpose, there are many possibilities in which the scaffold can be designed. Firstly, the biomaterial is usually ceramic or polymer (natural or synthetic), or even both combined as a composite. Ceramics are brittle, with low elasticity and hardly molded, which may be an obstacle for implantation. However, its high mechanical stiffness shows similarities to bone tissue [16]. On the other hand, for soft tissue applications, polymers might present better results. As such, one of the advantages of polymers in TE is the different fabrication techniques resulting in unique scaffold architectures as similar as possible to the original tissue. Polymer fibrous structures, for instance, have shown to have promising potential in TE due to its morphological resemblance to ECM [20].

Fibrous Materials

Regarding fibrous scaffolds, not only the nature of the material is important, but also the morphology and fiber pattern play a pivotal role to guarantee success in TE. Several tissues and organs have their own particular pattern of fiber organization, and the topographic and mechanical feature is crucial for cells to survive and proliferate in order to become functional tissues. Thus, it is necessary to understand the interaction between cell and ECM. Depending on the chosen technique, it allows to organize the fiber orientation pattern, fiber dimensions, pore size, and so forth. Also, there are several methods available on the market with a different range of cost, availability, processability and results [20].

So far, electrospinning is probably the most common technique to design fibrous scaffolds [20]. The method uses electrostatic interaction to produce fibers with solution or melted polymer. Even though it can reach finer diameters, it has several disadvantages comparing to others, e.g., smaller pore sizes, hindering cell infiltration, and inefficiency in building 3D structures [21-23]. Centrifugal spinning is a different technique which uses a centrifugal force provided from a rotating spinning head to produce fibers. The fluid is ejected when the centrifugal force exceeds its surface tension, and the liquid is deposited on the collector, solidifying. The method is safer, and it has higher production rate comparing to electrospinning [24]. Considerable novel techniques have been developed as an alternative to both methods described previously. Solution blow spinning (SBS) is a versatile and accessible method consisting in spraying a polymer solution jet accelerated by compressed gas. The injection rate and pressure can be regulated and, once the fibers are extruded and deposited on the collector, the solvent evaporates. Airbrushing is another accessible technique (similar to airbrushing for painting), which uses compressed nitrogen stream to push the polymer onto the collector. This method is easier to handle, even though the solution rate cannot be controlled. Comparing to electrospinning, SBS and airbrushing are safer, more versatile and portable [25-27].

The chosen material is crucial when it comes to designing an efficient scaffold for TE. Fibrous materials can be made by synthetic and natural polymers or even both combined. Among synthetic fibers, poly (vinyl alcohol) (PVA), poly (vinylpyrrolidone) (PVP), poly (ethylene glycol) (PEG), polylactic acid (PLA), poly (lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) are frequent in the literature [20]. Polysaccharides, such as alginate and cellulose, and also polymers derived from collage are natural materials commonly used to produce fibers. Their lack of parameters control (mechanical properties and processability) is disadvantageous comparing to synthetic fiber. However, natural polymer, in general, still has higher biocompatibility and bioactivity, with better resemblance to the ECM and an intrinsic capacity to promote recognition to the cells [20,27-30]. Frequently, synthetic and natural polymers are used together in order to benefit from the best properties of each material, for example, Gelatin/PCL composites [29].

Collagen and Gelatin

Collagen is a high molecular weight protein described as a natural biopolymer predominant protein in the ECM, providing strength and structural stability to soft and hard connective tissues [16,30]. For that reason, it also has a significant potential regarding biomaterial, and it is widely used in pharmaceutical and biomedical fields, for instance. The collagen source is ample: it is possible to obtain this material from tissues of many animals, such as mouse, rat, rabbit, cow, pig and chicken. However, most commercial collagen for biomedical application is primally provided from skin and tendon of animals such as cows and pigs [31]. Concerning TE, collagen plays an important role by promoting biological and structural support for the ECM. In fact, collagen fibrils can be associated as a natural 3D scaffold, contributing to the maintenance of most connective tissues. In order to increase some mechanics properties, (e.g., higher tensile strength and stability), crosslinking and self-assembly mechanisms may be necessary [31]. Collagen and its derivative, gelatin, due to their stiffness and elasticity properties, can be applied as a cardiac scaffold, for example [32]. Moreover, collagen and gelatin can also be found combined as a composite: collagen, because of its resemblance to ECM, being more receptive and hosting the cells, and gelatin acting as a carrier and release system for chemical stimuli substances [33].

Gelatin is a colorless substance extracted from animal sources, such as cattle bones, pig skin and fish [15]. It is described as a biocompatible and biodegradable polymer, which, for life science applications, can be used as wound dressing material, drug delivery carriers and scaffolds in tissue engineering. Depending on the purpose, a gelatin can occur in different structures, such as coating [34], films [35], porous sponge [36] or fibrous arrangement, commonly associated with other materials (e.g., Gelatin/PCL) [29]. However, in virtue of its weak mechanical properties and easy dissolution (due to its high solubility in water), gelatin depends on crosslinking mechanisms to stabilize it [36]. Crosslinking gelatin not only increases mechanical properties, but also enhances stability and provides insolubility. The three main routes to crosslinking gelatin are through chemical, physical or enzymatic methods. Crosslinking gelatin using glutaraldehyde (GTA) is a chemical method, and one of the most common mechanism in the biomedical field literature, essentially because of its efficiency. GTA, however, is cytotoxic and, without proper removal, the residue can be harmful to the cells [36]. There are two main methods of crosslinking by GTA: solution or vapor phase. The GTA solution makes it harder to remove residues after the process, even though it is faster and efficient. Vapor phase, on the other hand, it is a time-consuming method and, whether the structure of the scaffold is a thick/bulk material (e.g., sponge), it is difficult to reach the core, resulting in worse crosslinking degree. However, when it comes to fibrous gelatin structures, the contact surface area of the material is usually wider, and the pores, larger. Thus, vapor GTA might have greater potential [36,37].

Fibrous scaffolds made with pure gelatin are not common in TE literature. As previously mentioned, they are usually combined with other materials, improving mechanical properties and stability. Plus, the predominant scaffold manufacturing technique is still electrospinning, which might even allow crosslinking during the process (in situ) in order to control the degradation rate and final morphology, instead of using GTA solution or vapor [38]. Gelatin fibrous scaffolds may have significant potential for soft tissue injuries, such as skin regeneration [39] and others.

Conclusion

It is not possible to define the best technique to use in all TE applications. The chosen method and material always depend on the purpose, since every choice has its own advantages and disadvantages. It is crucial to understand the structure and function of the original tissue, designing the apparatus with great potential to mimic the tissue, e.g., fibrous materials with structural similarities to ECM. For soft tissue, for example, polymers can do a greater job than ceramics, but still, there is a vast range of options among them. Usually, natural polymers, such as collagen and gelatin, are preferable than synthetic due to their better biodegradability and biocompatibility. However, their lack of mechanical properties and uneven characteristics can be disadvantageous. To solve that problem, crosslinking may be applied. Several techniques are described in literature to produce fibrous materials, and electrospinning is the most used method. Nonetheless, it would be appealing to attempt other techniques such as SBS and airbrushing, because of all the advantages listed on this work.

References

1. http://www.healthdata.org/policy-report/findings-global-burden-disease-study-2017
2. Jaul E, Barron J. Age-related diseases and clinical and public health implications for the 85 years old and over population. Frontiers in Public Health. 2017; 5: 335.
3. Morgado MA, Jalles F, Lobo S, et al. Road traffic injuries and road safety measures: can we do any better. Pediatr Therapeut. 2017; 7: 319.

4. Etehad H, Yousefzadeh-Chabok S, Davoudi-Kiakalaye A, et al. Impact of road traffic accidents on the elderly. Arch Gerontol Geriatr. 2015; 61: 489-493.
5. Prakasam M, Locs J, Salma-Ancane K, et al. Biodegradable materials and metallic implants - a review. J Funct Biomater. 2017; 8: 44.
6. Santos Jr AR. Bioresorbable Polymers for Tissue Engineering, In: Eberli D, Editor, Tissue Engineering, Rijeka: In-Tech. 2010; 225-246.
7. Cohen LR. Increasing the supply of transplant organs: the virtues of a futures market. George Washington Law Rev.1989; 58:1-51.
8. Patel NR, Gohil PP. A review on biomaterials: scope, applications & human anatomy significance. Int J Emerging Tech Adv Eng. 2012; 2: 91-101.
9. Williams DF. Definitions in biomaterials: progress in biomedical engineering. Biomaterials. 1987; 10: 216-238.
10. Park JB, Bronzino JD. Biomaterials: principles and applications. CRC Press. 2002; 250.
11. Vladescu A, Surmeneva MA, Cotrut CM, et al. Bioceramic coatings for metallic implants. In: Antomiac IV, Handbook of Bioceramics and Biocomposites, Switzerland: Springer. 2014; 1-31.
12. Ratner BD, Hoffman AS, Schoen FJ, et al. Biomaterials Science - An Introduction to Materials in Medicine, 3th ed. Elsevier. 2012; 1573.
13. Meyers SR, Khoo X, Huang X, et al. The development of peptide-based interfacial biomaterials for generating biological functionality on the surface of bioinert materials. Biomaterials. 2009; 30: 277-286.
14. He W, Benson R. Polymeric biomaterials. In: Kutz M, Applied Plastics Engineering Handbook, 2nd ed. William Andrew Publishing. 2017; 145-164.
15. Balaji AB, Pakalapati H, Khalid M, et al. Natural and synthetic biocompatible and biodegradable polymers. In: Shimpi NG, Biodegradable and Biocompatible Polymer Composites: Processing, Properties and Applications. Duxford: Woodhead Publishing, 2017; 3-32.
16. O'brien FJ. Biomaterials and scaffolds for tissue engineering. Materials Today. 2011; 14: 88-95.
17. Santos Jr AR, Zavaglia CAC. Tissue Engineering Concepts. In: Saleem Hashmi, Editor, Reference Module in Materials Science and Materials Engineering. Oxford: Elsevier. 2016; 1-5.
18. Langer R, Vacanti JP, Vacanti CA, et al. Tissue engineering: biomedical applications. Tis Eng. 1995; 1: 151-161.
19. Khademhosseini A, Langer R. A decade of progress in tissue engineering. Nature Protocols. 2016; 11; 1775-1781.
20. Simbara MMO, Santos Jr AR, Andrade AJP, et al. Comparative study of aligned and nonaligned poly(ε-caprolactone) fibrous scaffolds prepared by solution blow spinning. J Biomed Mater Res Part B. 2019; 107B:1462-1470.
21. Repanas A, Andriopoulou S, Glasmacher B. The significance of electrospinning as a method to create fibrous scaffolds for biomedical engineering and drug delivery applications. J Drug Deliver Sci Technol. 2016; 31: 137-146.
22. Szentivanyi AL, Zernetsch H, Menzel H, et al. A review of developments in electrospinning technology: new opportunities for the design of artificial tissue structures. Int J Artif Organs. 2011; 34: 986-997.
23. Wu Y, Wang Z, Fuh JYH, et al. Direct E-jet printing of threedimensional fibrous scaffold for tendon tissue engineering. J Biomed Mater Res Part B. 2017; 105: 616-627.
24. Zhang X, Lu Y. Centrifugal spinning: an alternative approach to fabricate nanofibers at high speed and low cost. Polymer Reviews. 2014; 54: 677-701.
25. Hell AF, Simbara MMO, Rodrigues P, et al. Production of fibrous polymer scaffolds for tissue engineering using an automated solution blow spinning system. Res Biomed Eng. 2018; 34: 273-278.
26. Daristotle JL, Behrens AM, Sandler AD, et al. A review of the fundamental principles and applications of solution blow spinning. ACS Appl Mater Interfaces. 2016; 8: 34951-34963.
27. Tutak W, Sarkar S, Lin-Gibson S, et al. The support of bone marrow stromal cell differentiation by airbrushed nanofiber scaffolds. Biomaterials. 2013; 34: 2389-2398.
28. Ma PX, Zhang R. Synthetic nano-scale fibrous extracellular matrix. J Biomed Mater Res. 1999; 46: 60-72.
29. Zhang Y, Ouyang H, Lim CT, et al. Electrospinning of gelatin fibers and gelatin/PCL composite fibrous scaffolds. J Biomed Mater Res Part B Appl Biomat. 2005; 72: 156-165.
30. Chen FM, Liu X. Advancing biomaterials of human origin for tissue engineering. Progr Pol Sci. 2016; 53: 86-168.
31. Chattopadhyay S, Raines RT. Review collagen-based biomaterials for wound healing. Biopolymers. 2014; 101: 821-833.
32. Chimenti I, Rizzitelli G, Gaetani R, et al. Human cardiosphere-seeded gelatin and collagen scaffolds as cardiogenic engineered bioconstructs. Biomaterials. 2011; 32: 9271-9281.
33. Hiwatashi N, Hirano S, Mizuta M, et al. Biocompatibility and efficacy of collagen/gelatin sponge scaffold with sustained release of basic fibroblast growth factor on vocal fold fibroblasts in 3-dimensional culture. Annals of Otology, Rhinology & Laryngology. 2015; 124: 116-125.
34. Jafari M, Paknejad Z, Rad MR, et al. Polymeric scaffolds in tissue engineering: a literature review. J Biomed Mater Res Part B Appl Biomat. 2017; 105: 431-459.
35. Aldana AA, Abraham GA. Current advances in electrospun gelatin-based scaffolds for tissue engineering applications. Int J Pharm. 2017; 523: 441-453.
36. Yang G, Xiao Z, Long H, et al. Assessment of the characteristics and biocompatibility of gelatin sponge scaffolds prepared by various crosslinking methods. Sci Rep. 2018; 8: 1616.
37. Nagarajan S, Soussan L, Bechelany M, et al. Novel biocompatible electrospun gelatin fiber mats with antibiotic drug delivery properties. J Mater Chem B. 2016; 4: 1134-1141.
38. Kishan AP, Nezarati RM, Radzicki CM, et al. In situ crosslinking of electrospun gelatin for improved fiber morphology retention and tunable degradation. J Mater Chem B. 2015; 3: 7930-7938.
39. Dias JR, Baptista-Silva S, de Oliveira CMT, et al. In situ crosslinked electrospun gelatin nanofibers for skin regeneration. Eur Pol J. 2017; 95: 161-173.