ISSN: 13434292
Volume 139, Issue 01, July, 2021

The future prospects of functional biomaterials −Tissue reconstruction achieved by materials alone−

Haishima, Y.[1], Kishida, A.[1]

Hoshi University, School of Pharmacy, Department of Analytical Chemistry, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan[1]

ABSTRACT— Tissue repair and regeneration is an interdisciplinary field focusing on developing bioactive substitutes aimed at restoring pristine functions of damaged, diseased tissues. Biomaterials, intended as those materials compatible with living tissues after in vivo administration, play a pivotal role in this area and they have been successfully studied and developed for several years. Namely, the researches focus on improving bio-inert biomaterials that well integrate in living tissues with no or minimal tissue response, or bioactive materials that influence biological response, stimulating new tissue re-growth. This review aims to gather and introduce, in the context of Italian scientific community, cutting-edge advancements in biomaterial science applied to tissue repair and regeneration. After introducing tissue repair and regeneration, the review focuses on biodegradable and biocompatible biomaterials such as collagen, polysaccharides, silk proteins, polyesters and their derivatives, characterized by the most promising outputs in biomedical science. Attention is pointed out also to those biomaterials exerting peculiar activities, e.g., antibacterial. The regulatory frame applied to pre-clinical and early clinical studies is also outlined by distinguishing between Advanced Therapy Medicinal Products and Medical Devices.

KEYWORDS: tissue engineering; biomaterials; silk proteins; collagen; polysaccharides; glycosaminoglycan's; aliphatic polyesthers

1. INTRODUCTION

Regenerative medicine is the branch of medicine that aims to restore, repair or replace damaged or diseased cells, organs and tissues. It includes the generation and use of therapeutic cells, stem cells, engineered tissues and the production of artificial organs together with polymer scaffolds. Therefore, it can be defined a multidisciplinary approach that includes biology, engineering and materials science with the main goal to guarantee an adequate, functional and permanent therapy in patients with damaged organs or tissues. The approaches may include, but are not limited to, the use of soluble molecules, gene therapy, stem cell transplantation, tissue engineering and the reprogramming of cell and tissue types. In particular, the aim of tissue engineering is the fabrication of three-dimensional (3D) scaffolds that can be used for the reconstruction and regeneration of damaged tissues. They have a crucial role because they represent an alternative to conventional implantation or replacement of organs and tissues. The scaffolds can act as acellular material, or they can be combined with cells. Another possibility is loading scaffolds with soluble molecules such as antibiotics, chemotherapeutic agents and growth factors that are transported into the surrounding environment, providing the therapeutic or regenerative effect [1].

In order to have an application in the field of tissue engineering, the scaffolds must meet some fundamental requirements, which can be summarized as follows: biocompatibility, biodegradability, process ability, sterilizability, mechanical properties, porosity. All these properties are mainly related to biomaterial properties, with the exception of porosity that refers to scaffold architecture. Biocompatibility is an essential property for the biomaterials intended to be used in tissue engineering, and according to this property the biomaterials can be divided into four categories, as schematized in Figure 1.

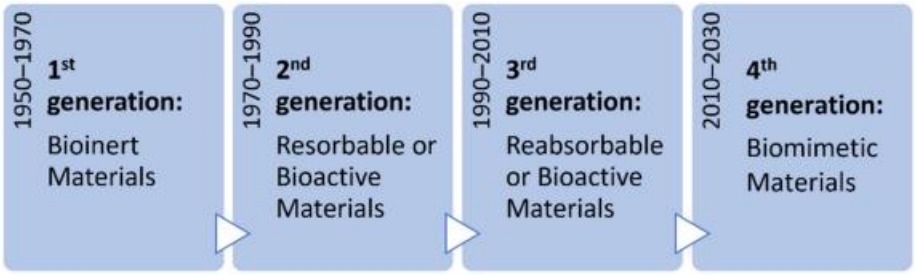

Figure 1. Schematic representation of scaffold categories divided in four generations.

2. Silk Proteins

Silk is a natural material produced by many arthropods, such as silkworms and spiders [6]. Silk proteins used in the biomedical field are principally extracted by Bombyx mori cocoons composed of two proteins, silk fibroin (SF) and silk sericin (SS), characterized by different structures and properties. Silk fibroin is a fibrous and hydrophobic protein that represents about 65–85% *w*/*w* of cocoon and is widely used in the textile industry for thousands of years. During the last two decades, SF was studied mainly for biomedical applications and it was approved by the Food and Drug Administration (FDA) as a suture thread (Surusil®, Suru; Sofsilk™, Covidien) and as a scaffold (Seri® Surgical Scaffold, Allergan, Medford, MA, USA) [7], [8]. Silk sericin is a globular hydrophilic protein that covers the SF filaments and maintains the structural integrity of cocoon. It was routinely discarded by the textile industry through a degumming process; however, during the last decades, it has been demonstrated that SS is a bioactive compound with antioxidant, anti-tyrosinase, anti-elastase and anti-bacterial properties [9], [10], other than showing anticoagulant, anticarcinogenic characteristics, it is biocompatible, UV resistant and able to absorb moisture [11- 13].

3. Future Perspectives

All the discussed biomaterials are promising in the field of tissue regeneration. Generally speaking, recent trends are towards tissue engineered scaffolds, i.e., hybrid systems combining cells with polymer materials with particular focus on tissue restoring ability of mesenchymal stem cells (MSC). Moreover, different biologic molecules such as growth factors and cytokines can usefully improve regeneration activity. As long as silk and silk derivatives is concerned, during the last two decades, both in vitro and in vivo results underlined the high therapeutic potential of SF and SS based materials for tissue engineering applications. Despite the intense interest of the scientific community, the clinical applications of these two proteins are still far. The routinely clinical use of silk protein-based scaffolds was strictly correlated to their large-scale production, maintaining both high-quality level and batch-to-batch consistency. All production steps need to be performed according to the Good Manufacturing Practices and overcoming some problems such as low production yield, high costs and lack of infrastructure and expertise. Silk proteins were produced by living organisms and not synthesized in a laboratory; this aspect complicates the validation of all production steps. A full defined characterization of raw materials and final products must be conducted to obtain reproducible, safe and effective constructs for tissue engineering applications. As long as PLA, PLGA and PCL are concerned future trends are towards to derivatize these polymers in order to modulate their properties (such as the mechanical ones) depending on their applications.

4. Conclusions

The review highlights how wide is the area of biomaterials for application in tissue engineering, and which tremendous impact biomaterials are having and will have for future clinical applications. Continued growth of this field depends both on the development of new materials, improved scaffold processing techniques and improved cell manipulation techniques. The three factors are interdependent and should be optimized in

order to further improve tissue regeneration opportunities. Despite the wide research carried on tissue regenerative approaches and biomaterials, only few products reached clinical market. The gap is due to different reasons such as poor identification of clinical critical adoption criteria, lack of translation from early research process and its clinical application, fail of clinical trials, lack of compliance to regulatory constraints. Hopefully, this gap will be reduced in the near future, due to optimized research in cell therapy combined to tbiopolymers.

5. REFERENCES

[1] Institute of Food Research. The Codex Recommendation by the CODEX Alimentarius Commission Committee on Food Labelling. 2000. http://www.foodallergens.info/Legal/CO- DEX.html. Accessed on April 1, 2021.

[2] Ebisawa M, Ikematsu K, Imai T, Tachimoto H. Food allergy in Japan. J. World Allergy Org. 2003; 15: 214–217.

[3] Akiyama H, Imai T, Ebisawa M. Japan food allergen labeling regulation--history and evaluation. Adv Food Nutr Res. 2011; 62: 139–171. PMID:21504823, doi:10.1016/B978-0-12- 385989-1.00004-1

[4] Consumer Affairs Agency, Government of Japan. Appendix, Labeling of foods containing allergens. 2015. https://www. caa.go.jp/policies/policy/food_labeling/food_labeling_act/ pdf/food_labeling_cms101_200720_01. Accessed on April 1, 2021.

[5] Shoji M, Adachi R, Akiyama H. Japanese food allergen labeling regulation: an update. J AOAC Int. 2018; 101(1): 8–13. PMID:29202908, doi:10.5740/jaoacint.17-0389

[6] Matsuda R, Yoshioka Y, Akiyama H, et al. Inter-laboratory evaluation of two kinds of ELISA kits for the detection of egg, milk, wheat, buckwheat, and peanut in foods. J. AOAC Int. 2006; 89: 1600–1608. PMID:17225608, doi:10.1093/ jaoac/89.6.1600

[7] Watanabe Y, Aburatani K, Mizumura T, et al. Novel ELISA for the detection of raw and processed egg using extraction buffer containing a surfactant and a reducing agent. J Im- munol Methods. 2005; 300(1-2): 115–123. PMID:15907925, doi:10.1016/j.jim.2005.02.014

[8] Shibahara Y, Oka M, Tominaga K, et al. Determination of crustacean allergen in food products by sandwich ELISA [in Japanese]. Nippon Shokuhin Kagaku Kogaku Kaishi. 2007; 54(6): 280–286. doi:10.3136/nskkk.54.280

[9] Seiki K, Oda H, Yoshioka H, et al. A reliable and sensitive immunoassay for the determination of crustacean protein in processed foods. J Agric Food Chem. 2007; 55(23): 9345– 9350. PMID:17929889, doi:10.1021/jf0715471

[10] Sakai S, Matsuda R, Adachi R, et al. Interlaboratory evaluation of two enzyme-linked immunosorbent assay kits for the determination of crustacean protein in processed foods. J AOAC Int. 2008; 91(1): 123–129. PMID:18376594, doi:10.1093/jaoac/91.1.123

[11] Abbott M, Hayward S, Ross W, et al. Validation procedures for quantitative food allergen ELISA methods: community guidance and best practices. J AOAC Int. 2010; 93(2): 442– 450. PMID:20480889,

doi:10.1093/jaoac/93.2.442

[12] Sakai S, Adachi R, Akiyama H, Teshima R. Validation of quantitative and qualitative methods for detecting allergenic ingredients in processed foods in Japan. J Agric Food Chem. 2013; 61(24): 5675–5680. PMID:23039046, doi:10.1021/ jf3033396

[13] Yamakawa H, Akiyama H, Endo Y, et al. Specific detection of wheat residues in processed foods by polymerase chain reaction. Biosci Biotechnol Biochem. 2007; 71(10): 2561–2564. PMID:17928695, doi:10.1271/bbb.70251

[14] Yamakawa H, Akiyama H, Endo Y, et al. Specific detection of buckwheat residues in processed foods by polymerase chain reaction. Biosci Biotechnol Biochem. 2008; 72(8): 2228–2231. PMID:18685187, doi:10.1271/bbb.80237

[15] Watanabe T, Akiyama H, Maleki S, et al. A specific qualitative detection method for peanut (Arachis hypogaea) in foods using polymerase chain reaction. Journal of Food Biochemistry. 2006; 30(2): 215–233. doi:10.1111/j.1745-4514.2006.00056.x

[16] Taguchi H, Watanabe S, Temmei Y, et al. Differential detection of shrimp and crab for food labeling using polymerase chain reaction. J Agric Food Chem. 2011; 59(8): 3510–3519. PMID:21395255, doi:10.1021/jf103878h

[17] Yamakawa H, Akiyama H, Endo Y, et al. Specific detection of soybean residues in processed foods by the polymerase chain reaction. Biosci Biotechnol Biochem. 2007; 71(1): 269–272. PMID:17213648, doi:10.1271/bbb.60485

[18] Yano T, Sakai Y, Uchida K, et al. Detection of walnut residues in processed foods by polymerase chain reaction. Biosci Bio- technol Biochem. 2007; 71(7): 1793–1796. PMID:17617706, doi:10.1271/bbb.70118

[19] Taguchi H, Watanabe S, Hirao T, et al. Specific detection of potentially allergenic kiwifruit in foods using polymerase chain reaction. J Agric Food Chem. 2007; 55(5): 1649–1655. PMID:17288438, doi:10.1021/jf0624446