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Development of Silk Scaffolds for Newer Areas of Applications in Tissue Engineering

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ABSTRACT

A number of innovative concepts in tissue engineering have been evolved over the past few years. The focus has been towards repair, sustenance and restoration of the biomechanical functions of the musculoskeletal system. Silk fibroins are considered as natural polymers having many merits in their characteristics like acceptable level of biocompatibility, very good mechanical strength and have slow rate of degradation. Hence, they merit consideration as a suitable scaffolding material in end uses relating to mulculoskeletal tissue engineering. The current trends in research have been studied herein during the past few years. A considerable literature review has been taken into account and covered. The area of tissue engineering provides an appropriate means for repair and replacement of damaged tissues and organs using artificial materials. The objective has been to show the status quo of the recent research relating to silk-based scaffolds being used in the musculoskeletal system. Also, a comprehensive guideline has been provided for silk biomaterial from bench to bedside.

Keywords: Silk; Scaffold; Musculoskeletal System; Tissue Engineering; Regeneration

Introduction

Musculoskeletal tissues, which include bone, cartilage, ligament/tendon, skeletal muscle, and intervertebral disc, are highly susceptible to injury or damage arising from degenerative changes, external force impingement, or sports-related activities. Within the clinic, growing concerns over the complications of autografting (e.g., donor site morbidity, infection increased surgery time) and allografting (e.g., graft rejection, limited quantity) as well as the limited availability and efficacy of these tissue repair options have prompted the development of various tissue engineering (TE) strategies [1-3]. TE is an interdisciplinary field that combines the principles of engineering and biomedical sciences for the development of biological substitutes that restore, maintain, or improve tissue function. Through the effective integration of biological scaffold materials, cells, and bioactive factors, the goal of replacing or supporting the function of defective or injured body parts is expected to be realized [4]. Silk fibroin (SF), a natural protein material that has been clinically used as a suture for decades, is now widely lucubrated and utilized in a variety of new biomedical applications including TE [5].

Silk fibers possess advantageous properties over most synthetic and natural fibers with a unique combination of toughness, biocompatibility, biodegradability, low immunogenicity, and thermal stability, which may better meet the requirements of musculoskeletal TE [6]. Silk from silkworms can be broadly categorized into mulberry and non-mulberry silk, depending on the food source of the worm [7]. The domesticated mulberry silk worm Bombyxmori is commonly cultivated through large-scale sericulture [8]. The non-mulberry silkworms, including Antheraeamylitta (A. mylitta), muga silkworm Antheraeaassamensis (A. assamensis), oak silkworm Antheraeapernyi (A. pernyi), Philosamiaricini (P. ricini), and Samiacynthia ricini (S. cynthia ricini), produce silk that have a particular peptide recognition sequence: Arg-Gly-Asp (RGD) [8,9]. This is a cell attachment domain in extracellular matrix proteins recognized by integrins, which promote cell adhesion of various different cell types. Hence, non-mulberry silk biomaterials are superior over mulberry silks in TE applications [10].

Silk fibers with a triangular cross section are primarily composed of two proteins: The central protein known as silk fibroin is covered by a glue-like coating composed of another protein called sericin [11]. The earliest use of silk for suture materials was found to have significant biocompatibility issues, which provoke immunological reactions ranging from delayed hypersensitivity to acute and chronic inflammatory processes [12]. However, sericin-free fiber was later found to exhibit only a weak immunoreactivity, which greatly increases its application potential in the medical field [13,14]. In the past few years, SF materials and their derivatives have been the target of intensive research in the biomedical field. Silk materials have numerous advantages in TE applications that are unmatched by other materials, including

(1) Increased biocompatibility suitable for cell adhesion and proliferation with less inflammatory responses in vivo;

(2) Enhanceable and modifiable mechanical properties with different silk fibroin solution concentrations and porosities to better meet target tissue requirements;

(3) Nontoxic degradation products and controllable biodegradability achieved through modification of the β-sheet structure;

(4) Excellent structural adjustability enabling the fabrication of a scaffold with desirable features for specific applications [15].

At present, the most widely used biodegradable implantable polymer materials include poly (lactic acid) (PLA), polyglycolic acid (PGA), and their copolymers, which can basically meet the application of scaffold materials in terms of degradability but are not as good as silk fibroin materials in terms of biocompatibility and cell adhesion [16]. In addition, silk materials also have unique advantages over other biopolymer materials. Collagens exhibit a variety of characteristics making them highly biocompatible and nontoxic, but their poor mechanical properties (Young's modulus: 0.0018–0.046 GPa) make them play a minor role in the process of musculoskeletal regeneration [17]. Chitosan exhibits structural similarity to the extracellular matrix and has a hydrophilic surface that promotes cell adhesion, proliferation, and differentiation [18]. Chitosan alone lacks sufficient mechanical strength, which limits its application as a three-dimensional scaffold in musculoskeletal tissue engineering (MTE). Natural biopolymers have shown superiority in biomedical applications since they have proven to be most compatible with the native extracellular matrix (ECM). Despite the great compatibility with native ECM, all biopolymers were insufficient in delivering the desired performances in one or more aspects [19]. Relatively speaking, silk material is more balanced in properties and more suitable for MTE. By modifying the molecular structure and morphology of silk proteins through the use of certain organic solvents for processing or surface modification, we can further improve various aspects of the scaffold properties and function, thus expanding their applications in drug delivery and TE.

The following aspects have been considered

a) Improved mechanical properties

b) Increased biocompatibility

c) Controllable biocompatibility

d) Excellent structural processability

Categorization on Morphological Basis

In recent years, many reports have been published on the application of silk materials in tissue engineering and drug delivery. Among them, the degummed silk fiber is usually reconstructed into different morphological types for increasing use in various applications. The mechanical properties as well as various primary features of silk can be modified through different processing methods. In general, varying conditions, such as silk concentration, methanol/salt treatment, pore size and porosity, processing temperature, etc., are capable of modulating the properties of the silk scaffold. Additionally, silk fibroin can also be physically blended or chemically cross-linked with various other complementary materials for the reinforcement of scaffolds and enhance their mechanical properties. The control of different morphological types of scaffolds therefore delivers the control of their specific characteristics, providing a pathway for the regeneration application in MTE. To obtain different types of scaffolds, degummed silk is dissolved into fresh SF solution, which can be used to fabricate into films, knitted scaffold, cords, 3D porous/sponge, hydrogels, electrospunfibers, particles, and composite scaffolds (Figure 1). The different characteristics of various morphological types of silk scaffolds are thus individually discussed.

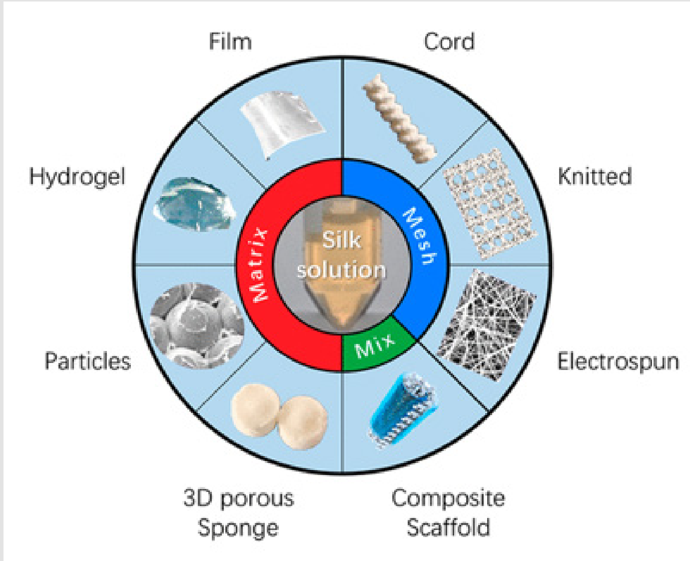

Figure 1.

The following types have been considered

a) Films [20,21]

b) Knitted scaffold [22]

c) 3D porous or spongs [23]

d) Hydrogel [24]

e) Electrospinning [25]

f) Composite scaffolds [26]

Areas of applications

a) Silk scaffolds in muscoskeletal tissue engineering [27]

The following aspects have been considered

i) Progress in the Utilization of Silk Scaffolds in Musculoskeletal TE over the Years

ii) Classification of Studies

b) Silk scaffolds in bone tissue engineering [28]

The following have been considered

i) Silk source

ii) Morphological Type of Scaffolds

iii) Cells

iv) Animal Models

v) Mechanical Stimuli

vi) Bioactive Factors

c) Silk Scaffolds in Ligament/Tendon Tissue Engineering [29]

The following have been considered

i) Silk Source

ii) Morphological Type of Scaffolds

iii) Cells

iv) Animal Models

v) Mechanical Stimuli

vi) Biological Factors

d) Silk Scaffolds in Cartilage Tissue Engineering [30]

The following aspects have been considered

i) Silk Source

ii) Morphological Type of Scaffolds

iii) Cells

iv) Animal Models

v) Mechanical Stimuli

vi) Biological Factors

e) Silk Scaffolds in Osteochondral Tissue Engineering [31]

f) Silk Scaffolds in Skeletal Muscle Tissue Engineering [32]

g) Silk Scaffolds in IVD Tissue Engineering [33]

Future Perspectives

The following aspects have been considered [34]

a) Controllable Parameters in Musculoskeletal Tissue Engineering

b) Limitations of Silk Scaffolds in Clinical Applications

c) How to Promote the Clinical Applications of Silk Scaffold

Conclusion

The human health can get adversely affected by damage caused to musculoskeletal tissues, comprising bone, cartilage, tendon, ligament, and skeletal muscles. The repair and replacement of damaged tissues using synthetic material can be made possible by means of tissue engineering. The demerits and issues associated with conventional surgical techniques have strongly prompted the evolution and progress of tissue engineering. The objective has been to show the present position of research on silk-based scaffolds to be used in the musculoskeletal system over the past few years. The effective use of silk scaffolds in the musculoskeletal system shows the worth of silk fibroin in tissue engineering, thereby offering strong evidence to enable the design of silk scaffolds having better performance and integrated designs. Also, a comprehensive guide is offered for silk biomaterials from bench to bedside herein, enabling a feasible route for researchers inclined to proceed further for clinical conversion of their research studies.

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