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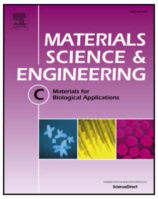

Review

Silk fibroin-based biomaterials for musculoskeletal tissue engineering

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ABSTRACT

Tissue engineering (TE) is an emerging and promising strategy to heal tissue failure by integrating science and technology of materials, cells and growth factors. With the increasing of aging population, restoring musculoskeletal tissue has become the focus of TE. Among various materials tested in TE, silk fibroin (SF) is increasingly being recognized as a promising material. SF, a natural protein polymer with excellent physiochemical characteristics, has established a good reputation in terms of musculoskeletal tissue engineering (MTE). The present article provides an overview of SF and introduces various approaches of fabricating SF-based biomaterial followed by their applications in MTE.

1. Introduction

The damage or function failure of tissues impairing human health is a big problem, of which millions of patients die every year. Musculoskeletal tissues including bone, cartilage, tendon, ligament, and skeletal muscle, play great roles in protecting internal organs and maintaining motions of body, and are easily impaired by many diseases and injuries, like osteoarthritis, suboptimal osteogenesis, trauma, etc., which consequently decrease the quality of life [1]. Although musculoskeletal tissues own naturally self-healing capacity, it is inefficient and they can't be healed by traditional clinical treatments sometimes [2]. Clinically, the replacement of damaged parts with autografts is an ideal approach, however limited by many factors, such as the shortage of donor supply, which has spurred the development of TE, especially MTE facing imperious demands [3–5].

For regenerating musculoskeletal tissues, MTE has become a promising alternative strategy and resulted impressive outcomes [6,7]. TE is a multidisciplinary field aiming at restoring tissues by combining science and technology of cells, materials and biochemical cues [8,9]. Tissue repair is a complicated cascade of biological events controlled by numerous biological signals at local injury sites allowing progenitors and inflammatory cells to migrate and trigger healing processes [10]. Thereafter for the sake of regenerating tissue, a biomaterial with appropriate surface and 3D structure is critical, because cell attachment, growth, and differentiation require sufficient nutrition and oxygen to perform a desired tissue function [11,12]. Besides, appropriate mechanical properties and biodegradability matching the repaired tissue growth are also necessary [13,14]. With these optimal properties, the bio-matrix could provide better release kinetics of loaded growth factors and (or) incorporated stem cells, which could accelerate the repairation process. Both natural and synthetic polymers have been processed via kinds of technologies into different forms biomaterials, including porous scaffold, nanofibrous membrane, microparticle, and hydrogel utilized widely in MTE [15]. However, both of them two have advantages and disadvantages respectively. For example, synthetic materials such as polylactic acid (PLA), polyurethane (PU), poly(lactide-*co*-glycolide) (PLGA), and polycaprolactones (PCL) are very impressive due to their unique properties (e.g. degradation rate, plasticity, and mechanical characteristics) and can be easily customized for some specific applications. Nevertheless, these advantages are eclipsed by their acidic degradation products harmful to the body, which limits their potential use [14,16–19]. Comparing to synthetic polymers, although natural biopolymers (e.g. collagen, elastin, albumin, and hyaluronan) offer better cyto-compatibility, they have limitations such as difficulty in processing and often poor mechanical property [20].

Over last several decades, researchers have paid extensive attentions to naturally protein-based polymers which are promising candidates for MTE owning to their desirable properties, such as controllable structure, excellent biocompatibility and processability [21–23]. SF is a natural protein-based polymer attracting increased attention nowadays for its potentiality in TE. SF possesses high biocompatibility, controllable biodegradability, low immunogenicity and limited pathogen transmission [24–26]; it also owns excellent mechanical property and structural integrity, which is desirable in TE, especially in MTE (Fig. 1 and Table 1) [27–29]. So far many studies have explored potentials of SF-based biomaterials in MTE both in vitro and vivo [30,31]. This

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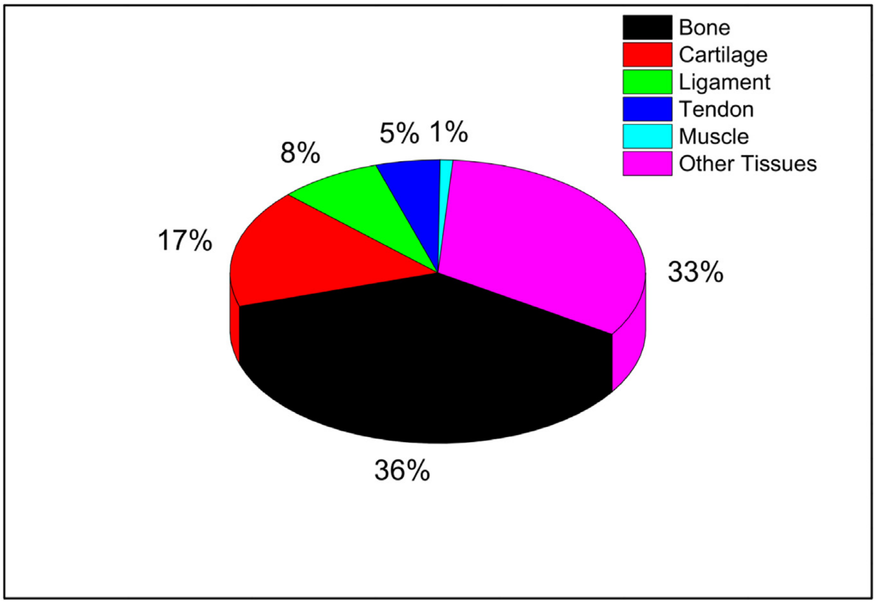

Fig. 1. Relative percentage on silk-based in vitro engineering of various tissues based on detailed analysis of the number of publications and citations on the use of SF as scaffold for TE.

Table 1
List of other tissues apart from musculoskeletal tissue engineered using different formats of SF-based biomaterials.

Tissue types	Pure silk biomaterials		Composited biomaterials		Chemically modified	
Blood vessel	Non-woven SF net	[32]	SF/collagen tube	[41]	Sulfated silk nanofibrous scaffold	[44]
	Silk fiber mesh	[33]	SF/PLA tube	[42]		
	Silk tube	[34–39]	SF/PHBHH$_x$ scaffold	[43]		
	Silk thread	[40]				
Nerve	Silk fiber	[45–48]	SF/hyaluronic acid scaffold	[52]		
	Electrospun silk mat	[49]	PLGA/SF hybrid film	[53]		
	SF nerve conduit loaded with NGF/GPNF	[50]	SF/PLA-collagen electrospun scaffold	[54–56]		
	SF nanofiber tube	[51]	*B. mori* SF/Tussah SF nanofiber	[57]		
Skin	Slik nonwoven/woven nanofiber	[58–60]	SF/alginate blended sponge	[62]		
	3-D nonwoven scaffold	[61]	Chitin/SF nanofibrous scaffold	[63]		
			Collagen/SF electrospun scaffold	[64]		
Bladder	Silk film	[65,66]				
	Knitted silk sling	[67]				
	Gel-spun SF matrix	[68,69]				
Cornea	Silk film	[70–73]	SF coated with collagen	[74]		
	Porous silk film	[4]				
Liver			SF/collagen film	[75,76]	Silk modified with lactose coating	[84]
			SF/collagen 3D scaffold	[77,78]	Silk modified with lactose 3D sponge	[85]
			SF/chitoan scaffold	[79–81]		
			PLA/SF microparticles scaffold	[82,83]		
Spinal cord	SF nanofibrious scaffold	[86,87]				
Trachea	Silk as a biomaterial coating	[88]	SF/chitosan blended scaffold	[89]		
Inter-vertebral disc tissue	Silk scaffold	[90]			Silk scaffold modified with RGD	[91]
Eardrum	Silk membrane	[92–95]				
Tooth					Silk scaffold modified with RGD	[96,97]

review creates an overview of silk fibroin and introduces various approaches to fabricate SF-based biomaterial. Besides, this article is focused on applications of SF in MTE and prospects for further development.

2. Characteristics of silk fibroin

2.1. Silk fibroin for biomedical applications

Silk proteins are spun into fibers from glands of silk producing arthropods (e.g. silkworms, spiders and scorpions) during their metamorphosis [98,99]. Silk, one of the oldest natural polymers, has an evolutionary history spanning over 380 million years. It has been widely recognized that silk functions as an attractive polymer for different biomedical applications [100–105]. SF-based biomaterials are mainly prepared from silkworm silk produced by *Bombyx mori*. *B. mori* silk is also known as mulberry silk and has several major advantages over other natural polymers derived from tissues of allogeneic or xenogeneic origins (Table 2). For instance, regarding to those materials, the risk of infection is high and processing such materials is also expensive because of complex isolation and purification procedures. In contrast, silk fiber purification is routinely carried out using a simple alkali or enzyme based degumming procedure, which yields fibrin without sericin. Additionally, In biomedical applications, SF offers economic advantages due to the large-scale processing infrastructure already in place for traditional silk textile industries [98].