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Silk fibroin biomaterials for tissue regenerations[☆]

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ABSTRACT

Regeneration of tissues using cells, scaffolds and appropriate growth factors is a key approach in the treatments of tissue or organ failure. Silk protein fibroin can be effectively used as a scaffolding material in these treatments. Silk fibers are obtained from diverse sources such as spiders, silkworms, scorpions, mites and flies. Among them, silk of silkworms is a good source for the development of biomedical device. It possesses good biocompatibility, suitable mechanical properties and is produced in bulk in the textile sector. The unique combination of elasticity and strength along with mammalian cell compatibility makes silk fibroin an attractive material for tissue engineering. The present article discusses the processing of silk fibroin into different forms of biomaterials followed by their uses in regeneration of different tissues. Applications of silk for engineering of bone, vascular, neural, skin, cartilage, ligaments, tendons, cardiac, ocular, and bladder tissues are discussed. The advantages and limitations of silk systems as scaffolding materials in the context of biocompatibility, biodegradability and tissue specific requirements are also critically reviewed.

Contents

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1. Introduction

The limited supply of donors and increasing morbidity have put new demands on tissue engineering (TE) as a treatment of organ failures [1]. The TE approach involves regenerating tissue within suitable scaffold with the goal of implanting the constructed tissue at the target site. The regeneration of functional tissue requires a suitable microenvironment that closely mimics the host site for desired cellular responses [1]. Such an environment is typically provided by 3-D tissue engineering scaffold that acts as an architectural template [2]. Apart from biocompatibility, which is the essential prerequisite for any biomaterial, matching the degradation time with that of the tissue regeneration is also a critical requirement for a cell scaffolding material. Such a match can maintain the mechanical properties and structural integrity of the engineered tissue in all stages of its regeneration process. In addition, degraded products of the biomaterial should be safely metabolized and cleared from the host body.

Materials like polymers, metals and ceramics are widely used as cell scaffolds for tissue engineering. Both synthetic and natural polymers have been trialed, though each has its own limitations. While the former allows easy processing and modifications, the later offers better cyto- and bio-compatibility [3]. There is no universal biomaterial that meets the scaffolding requirements for all the tissues. Different issue constructs require biomaterials with specific physical, mechanical and degradation properties. Hence there is on-going search for universal biomaterial for regeneration therapy.

Protein, being a component of natural tissues, is a rational choice for applications in tissue engineering. Structural proteins such as collagen, elastin, elastin-like-peptides, albumin and fibrin are used as sutures, tissue scaffolds, haemostatic and drug delivery agents [4]. Silk fibroin of silkworms is a commonly available natural biopolymer with a long history of applications in the human body as sutures. Currently silk sutures are used in lips, eyes, oral surgeries and in the treatment of skin wounds [5]. Increasingly, silk fibroin is exploited in other areas of biomedical science, as a result of new knowledge of its processing and properties like mechanical strength, elasticity, biocompatibility, and controllable biodegradability [5]. These properties of silk fibroin are particularly useful for tissue engineering.

Furthermore, recent studies evaluates silk as a part of flexible electronic devices for real-time physiological and functional recording and optical systems for diagnosis and treatments [6,7]. Silk possesses excellent (ca. 95%) optical transparency throughout the visible range with remarkable surface smoothness and aqueous processing, all of which facilitates its application in optics and photonics biosensor [7,8]. Such silk based systems are implantable and have necessary functionality and sensitivity required for advanced applications. Several reviews are published on the fabrication, structure, and the application of silk based biomaterials [2,5,9,10]. In view of growing applications of silk in new areas of tissue engineering and knowledge on characteristics of silk constructs, a further and more detailed review is now warranted.

This review article is focused on recent research based on silk fibroin in the field of tissue regeneration and evaluates its prospects for further development in therapeutic related applications. The review starts with a brief overview of silk protein. The silk protein fibroin structure and morphologies are included as these aspects are highly relevant to the applications of silk biomaterials in tissue engineering. The different silk based platforms are discussed, followed by an account of their applications in tissue regeneration.

2. Silks of silkworms: source, chemistry and structure

Silk proteins are present in glands of silk producing arthropods (such as silkworms, spiders, scorpions, mites and bees) and spun into fibers during their metamorphosis. Silkworm's silk is an established fiber extensively used in the textile industry. On the other hand, the cannibalistic nature of spiders restricts the commercial production of spider silk [5]. Additionally, the yield of fiber from a single silk cocoon is 600–1500 m, compared to only ~137 m from the ampullate gland of a spider and ~12 m from the spider web [11]. Spider silks are also heterogeneous in nature. Therefore, silk based biomaterials are commonly prepared from silkworm silk. Of note is the silk produced by *Bombyx mori*, a member of the *Bombycidae* family. *B. mori* silk is also known as mulberry silk. Another silk producing family is *Saturniidae* and the silk is known as non-mulberry silk.

Silk has several major advantages over other protein based biomaterials, which are derived from tissues of allogeneic or xenogeneic origins. As such, the risk of infection is high for those materials. Processing of such materials is also expensive due to the stringent protein isolation and purification protocols. In contrast, silk is an established textile fiber and nearly 1000 metric tons of silk are produced and processed annually. Silk fiber purification is routinely carried out using a simple alkali or enzyme based degumming procedure, which yields the starting material for sericin free silk based biomaterials. It is also economically advantageous to use silk for biomedical applications, because of available large scale processing infrastructure of traditional silk textile industries.

Silk possesses large molecular weight (200–350 kDa or more) with bulky repetitive modular hydrophobic domains, which are interrupted by small hydrophilic groups [12]. The N and C termini of silk fibroin are highly reserved [5]. Silk fibroin of *B. mori* is composed of a heavy (H), and a light (L) chain linked together by a disulfide bond [13]. A 25 kDa glycoprotein, named P25, is also non-covalently linked to these chains [14]. The hydrophobic domains of H chains contain Gly-X (X being Ala, Ser, Thr, Val) repeats and can form anti-parallel β-sheets. The L-chain is hydrophilic in nature and relatively elastic. P25 protein is believed to play significant role in maintaining the integrity of the complex [15,16]. H-fibroin, L-fibroin, and P25 are assembled in the ratio of 6:6:1 in mulberry silk [17]. Non-mulberry silks lack light (L) chain and P25 [2,16]. Instead, they contain heavy (H) chain homo-dimers with a molecular weight of ~330 kDa formed by individual proteins (~160 kDa) [18]. Non-mulberry *Saturniidae* silks exhibit a