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## Review

## Silk as an innovative biomaterial for cancer therapy



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## ABSTRACT

Silk has been used for centuries in the textile industry and as surgical sutures. In addition to its unique mechanical properties, silk possesses other properties, such as biocompatibility, biodegradability and ability to self-assemble, which make it an interesting material for biomedical applications. Although silk forms only fibers in nature, synthetic techniques can be used to control the processing of silk into different morphologies, such as scaffolds, films, hydrogels, microcapsules, and micro- and nanospheres. Moreover, the biotechnological production of silk proteins broadens the potential applications of silk. Synthetic silk genes have been designed. Genetic engineering enables modification of silk properties or the construction of a hybrid silk. Bioengineered hybrid silks consist of a silk sequence that self-assembles into the desired morphological structure and the sequence of a polypeptide that confers a function to the silk biomaterial. The functional domains can comprise binding sites for receptors, enzymes, drugs, metals or sugars, among others. Here, we review the current status of potential applications of silk biomaterials in the field of oncology with a focus on the generation of implantable, injectable and targeted drug delivery systems and the three-dimensional cancer models based on silk scaffolds for cancer research. However, the systems described could be applied in many biomedical fields.

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## 1. Introduction

Silks are fibrous proteins produced by a variety of insects and spiders (Fig. 1). They provide structural roles in cocoon and web formation, nest building, and egg coating as lifelines.<sup>1</sup> The

most extensively characterized silks are from the domesticated silkworm, *Bombyx mori*, and from spiders, *Nephila clavipes* and *Araneus diadematus*.<sup>2</sup>

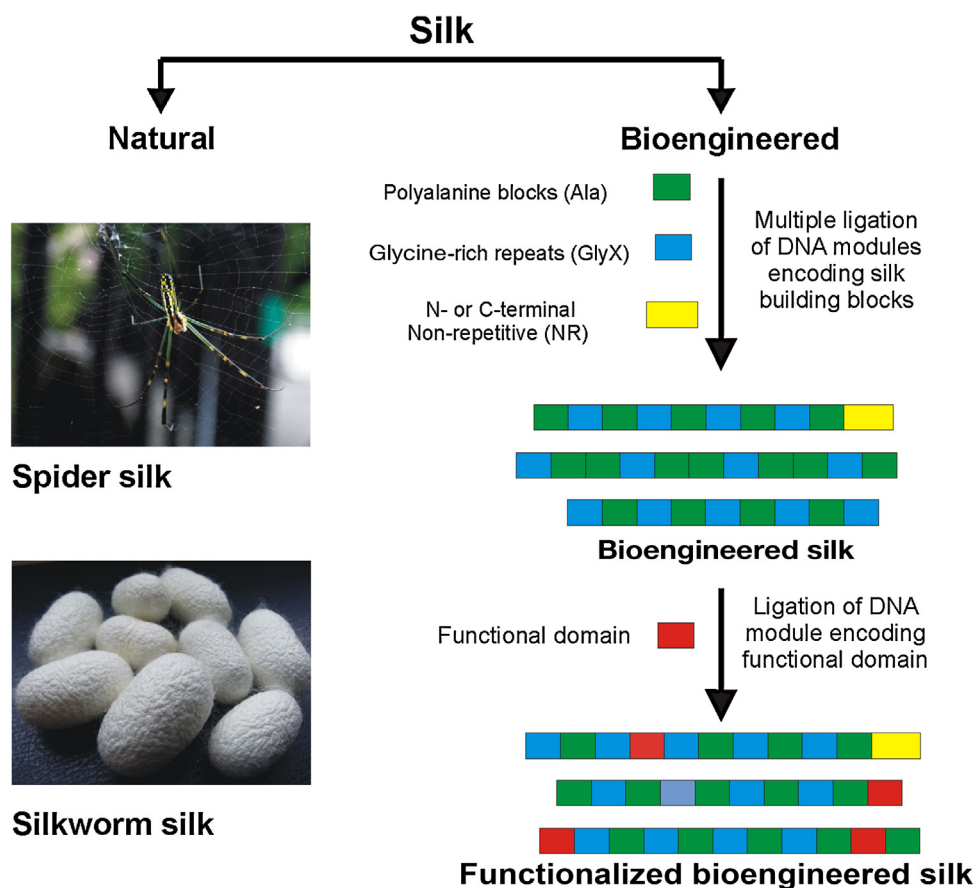
The silkworm silk obtained from the cocoon of *B. mori* consists of two major fibroin proteins: light chain (~26 kDa) and heavy chain (~390 kDa). These core chains

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**Fig. 1 – The origin of silk for biomedical application. The most intensively studied silks are silkworm silk and spider silks. Silks can be collected from nature or biotechnologically produced. Genetic engineering allows to design synthetic silk genes. Moreover, bioengineered silk can be modified by adding a sequence encoding peptide that confers a function to the silk biomaterial.**

are coated with proteins called sericins that hold the fibroin fibers together and form the complex fibers of the cocoon case. Silk proteins have a modular structure containing large internal repetitive sequences flanked by shorter terminal domains (N- and C-terminals).<sup>3</sup> The repetitive motif is mainly composed of sequence of six amino acid residues (Gly–Ala–Gly–Ala–Gly–Ser)<sub>n</sub>. It has amphiphilic characteristics, comprising hydrophilic, amorphous regions and hydrophobic, crystalline domains that form a beta-sheet secondary structure. The alanine-rich regions are responsible for the silk self-assembly properties and the mechanical stability of the biopolymer. Sericins are the source of immunogenic reaction; therefore, they are removed from the silk fibroin during the de-gumming process, in which silk cocoons are boiled in an alkaline solution. Numerous *in vitro* studies have shown that fibroins support attachment and proliferation of different cell types after prior sericin extraction.<sup>3</sup> Silk fibroin is a versatile biomaterial that can be formed into various structures, shapes, and dimensions.<sup>4,5</sup>

Spiders produce seven types of silk with various applications and properties.<sup>6</sup> Among them, dragline silk is the most extensively studied and the best characterized.<sup>7</sup> It is one of the strongest known natural materials. In silk from the *N. clavipes* spider, the dragline silk is made of two proteins:

major ampullate spidroin 1 and 2, MaSp1 and MaSp2 (ADF3 and ADF4 for *A. diadematus*). Similar to silkworm silk, three regions can be distinguished in spidroins: (1) a non-repetitive N-terminal domain (of approximately 130 amino acids), (2) a dominant fragment consisting of repetitive motifs and (3) a non-repetitive C-terminal domain (of approximately 110 amino acids).<sup>8</sup> The N- and C-terminal domains are involved in the assembly and processing of silk fibers.<sup>9,10</sup> The amino acid composition of the repetitive peptide blocks consists mainly of glycine and alanine with a significant contribution of glutamic acid, proline and arginine to form four groups: (1) GPGXX, GPGGX and (2) GGX, which are responsible for elasticity of silk, (3) alanine (A) or glycine–alanine (GA) chains, which create beta-sheet structures and are responsible for the strength of silk, and (4) a spacer sequence of unknown structural role.<sup>7,11</sup>

Silks are derived from nature or are produced in an expression system (Fig. 1). Silkworm silk is obtained from cocoons of domesticated silkworms. However, breeding spiders on a large scale is limited due to their cannibalistic nature. Moreover, they produce different types of silk simultaneously. Therefore, numerous studies have focused on the identification of the spidroin genes, recognition of the spidroin structures, and exploration of the process of silk assembly, which could finally result in the production of an artificial silk fiber. However, the

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