International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 10, No. 3, 2025

The Preparation of Silk Protein/Copper Sulfide Composite System and its Application in Tumor Treatment

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Abstract: Nanobiotechnology provides opportunities for targeted therapy of tumor drugs, and simple and effective methods for constructing nanotherapeutic agents has emerged as a research hotspot.Silk protein (SF) has biocompatibility, and copper sulfide (CuS) has unique optical properties that have attracted the attention of researchers. This article mainly elaborates on the biological characteristics of silk protein and copper sulfide, studies the preparation method of SF/CuS nanocomposite system and its application in tumor treatment. It is found that there is relatively little research on this nanocomposite system, which will be a new direction for future research.

Keywords: Tumor Treatment; Silk Protein; Copper Sulfide.

1. Introduction

Cancer is a major disease that poses a threat to human health. The Global Cancer Report shows that in the past two years; the incidence and mortality of cancer worldwide have been continuously increasing. In 2022, an estimated 4.82 million new cancer patients cases **were diagnosed** in China and the death toll reached as high as 2.57 million· China has the highest number of new cancer cases in the world. Faced with such a severe national situation, China, following the United States, has also proposed a strategic plan for "Precision Medicine", hoping that researchers from different backgrounds such as medicine, chemistry, biology, and materials will lead and implement this major system engineering based on interdisciplinary scientific research, such as genome sequencing, new tumor diagnostic technologies, new therapies, personalized treatments, etc., to achieve significant breakthroughs in anti-cancer research and work together to ensure human life, health, and safety. At present, chemotherapy is still the main means of treating cancer, but the non-specific nature of chemotherapy drugs and the multidrug resistance of tumors can easily lead to tumor recurrence. Therefore, developing advanced tumor targeted therapy technologies is a cutting-edge scientific issue with important practical significance and clinical value.

With the development of emerging nanobiotec photothermal therapy *(PTT)* hnology, nanotechnology has been applied in multiple disciplines such as imaging diagnosis and treatment, comprehensive chemotherapy, radiotherapy, and gene therapy, providing new research opportunities for targeted therapy of tumor drugs. However, challenges such as complex preparation, poor hydrophilicity, and residual chemical toxicity still hinder the therapeutic process of these nano agents, and the use of simple and effective methods to construct nano therapeutic agents has aroused great interest among researchers. Silk is mainly composed of silk fibroin protein (*SF*) and sericin protein (*SS*), and is an important natural fiber. Silk fibroin, as a type of natural polymer, has been reported to be used in drug delivery nanosystems. It has the characteristics of designable structure and function, diverse drug monomers, excellent stability, and biocompatibility, which can effectively solve the problems of low drug loading, poor water solubility, and low bioavailability in the process of drug molecule delivery. It has become an ideal drug delivery carrier and tissue engineering scaffold, and its rich functional groups (-OH, -COOH, $-NH_2$) provide a molecular basis for chemical modification and functional integration [2]. At the same time, inorganic nanomaterial copper sulfide (*CuS*) has received widespread attention due to its unique optical and catalytic properties: it has strong absorption and efficient photothermal conversion ability (photothermal therapy, *PTT*) in the near-infrared region (NIR-I, 750-900 nm), and can mediate local high-temperature ablation of tumors; The Cu^{2+} released in the tumor microenvironment can catalyze Fenton like reactions, converting overexpressed hydrogen peroxide (H_2O_2) into highly cytotoxic hydroxyl radicals (·OH), achieving chemodynamic therapy (*CDT*).Constructing an SF/CuS multifunctional nanocomposite system to achieve synergistic enhancement and synchronous diagnosis and treatment of PTT/CDT/chemotherapy/immunotherapy, improving the colloidal stability and biological distribution of CuS through SF encapsulation, and enhancing tumor specific killing efficiency through stimulus responsive release mechanisms (eg. *pH, GSH, NIR* light) [3,4].

2. Material Foundation and Characteristics

2.1. Silk Fibroin (SF)

1. Basic information

Silk protein is composed of two parts: silk fibroin protein (*SF*) and sericin protein (SS).Among them, silk fibroin is the main component of silk, accounting for 70% to 80% of the weight of silk, while sericin protein is wrapped around the outer layer of silk fibroin, accounting for 20% to 30%.Silk fibroin is composed of a heavy chain (H chain) and a light chain (L chain) connected by a disulfide bond, forming an H-L complex. The H-chain is mainly composed of glycine (Gly), alanine (Ala), and serine (Ser), with highly repetitive amino acid sequences, forming a β - folded structure, endowing silk with excellent mechanical strength and toughness. Sericin fibroin (*SS*) is a water-soluble glycoprotein mainly composed of serine, aspartic acid, etc. It wraps around the outer layer of silk fibroin and plays a role in adhesion. [5-7]

2. Characteristics of Biomaterials

Silk protein has good biocompatibility, biodegradability, mechanical strength, and flexibility, making it widely used in biomedical fields such as drug delivery, tissue engineering, and wound dressings.

(1) Biocompatibility and Degradability of Silk Protein

Silk fibroin (*SF*) is a common natural biopolymer with excellent biocompatibility, biodegradability, and mechanical properties due to its structure and chemical composition. Its decomposition products (mainly peptides and amino acids) lack cytotoxicity and can be absorbed, metabolized, and excreted normally by the human body, making SF a promising material for therapeutic applications. [8-9]

(2) Structure modifiability of silk protein

Silk protein provides functional groups including hydroxyl and carboxyl groups, which can form covalent and non covalent bonds with other reagents. The functionalization modification methods mainly include introducing different functional groups to change its chemical properties and biological functions. The introduction of these functional groups can be achieved through various chemical reactions, such as acylation, esterification, covalent modification, etc. Zheng Jinping et al. studied the color modification of silk fibroin protein by aromatic amine dye/formaldehyde, forming stable covalent bonds that have a certain impact on the mechanical properties of silk. [10]

(3) Loading and release mechanism of silk protein drugs

Silk protein has high mechanical strength and toughness, which can increase drug stability in vitro, deliver peptide or protein drugs in the form of microspheres, nanoparticles, hydrogels, microneedles, and control drug release through enzymatic decomposition in vivo to achieve different functions. Degradation products can be absorbed and metabolized in vivo without inflammation. [11] Wang X et al. proposed a water-based preparation method based on silk/PVA film. [12]

2.2. Copper Sulfide Nanomaterials (CuS)

1. Basic information

Copper sulfide (*CuS*) nanomaterials have become an important inorganic functional component in the field of tumor therapy due to their unique optical, catalytic, and diagnostic properties. Its core advantage lies in **the synergy of near-infrared light responsiveness** and **multi enzyme mimetic activity**, providing a material basis for the construction of multifunctional anti-tumor platforms.

2.3. Biological Functional Characteristics

(1) Photothermal Therapy (*PTT*)

CuS exhibits strong localized surface plasmon resonance (*LSPR*) effects in the near-infrared first region and second region. Under the action of 808 nm laser, the photothermal conversion efficiency (η) can reach 56-63% [13]. The mechanism is derived from the 3d orbital transition of valence band electrons to Cu^{2+}, which generates thermal energy through non radiative relaxation at temperatures greater than 50℃, achieving local high-temperature ablation of tumors [14].Zhang et al. loaded copper sulfide (*CuS*) into hyaluronic acid nanoparticles (*HANP*) and developed an activatable Cy5.5-HANP/CuS (*HANPC*) nanocomposite material. After laser irradiation of tumors, the tumor inhibition rate reached 89.74% on the 5th day [15].

(2) Photodynamic therapy (*PDT*)

CuS can generate reactive oxygen species (*ROS*) through type I (electron transfer) and type II (energy transfer) pathways under near-infrared light excitation, possessing photodynamic therapy capabilities. Near infrared light excites the release of Cu^{2+}, which produces reactive oxygen species (·OH, O_2^-) through the Haber Weiss reaction [16]. Zou Tao et al. prepared hollow copper sulfide nano drug carriers（CuS@Pt (IV)@PEG）, It has photodynamic therapy effect and can more effectively promote tumor cell death. [17]

(3) Chemodynamic Therapy (*CDT*)

Overexpressed H_2O_2 in the tumor microenvironment (*TME*) can be activated by Cu^+/Cu^{2+} released by CuS, and converted into **highly toxic hydroxyl radicals (· OH) through a** Fenton like reaction, achieving selective oxidative damage. Z. Qin et al. synthesized silver doped copper sulfide nanoparticles (BSA Ag: CuS) using bovine serum albumin (BSA) as a template and stabilizer, which showed synergistic therapeutic effects with CDT. [18]

3. Preparation of SF/CuS Composite System and its Role in Tumors

The abundant - COOH and - NH_2 groups in SF molecular chains can form metal ligand complexes with Cu^{2+}, forming multiple intermolecular forces, mainly through in-situ synthesis and surface coating methods.

(1) In-situ synthesis method

Cai et al. used silk fibroin as a biological template to prepare silk fibroin copper sulfide nanoparticles (*SF/CuS NPs*) with excellent photothermal response properties in situ, and used electrospinning technology to prepare photothermal nanofiber membranes (*PVA SF/CuS*). The synthesized SF/CuS NPs endow the nanofiber membrane with excellent photothermal bactericidal properties. [19]

(2) Surface covering method

Biofilm encapsulation of inorganic nanoparticles is an effective method in tumor treatment. [21] Wang et al. used electrostatic interactions to coat silk protein nanoparticles (SFNPs) with four different cationic polymers (ethylene glycol chitosan, N, N, N-trimethyl chitosan, polyethyleneimine, and PEGylated polyethyleneimine), and prepared SFNP composite materials with core-shell structure (CS SFNPs). These SFNPs exhibit good colloidal stability in biological media and can be used as drug carriers for anti-cancer drug delivery systems. [20]

(3) Other methods

Wang H. et al. synthesized copper sulfide nanoparticles with strong near-infrared absorption that can be dispersed in regenerated silk protein solution in situ using silk protein molecules as biological templates. [22]

(4) The role in tumor treatment

The SF/CuS composite system synergizes the biocompatibility of SF with the multimodal therapeutic capabilities of CuS, enabling targeted drug delivery and controlled release. Through photothermal (*PTT*), photodynamic (*PDT*), and chemodynamic (*CDT*) effects, this platform induces localized hyperthermia, reactive oxygen species (ROS) generation, and Fenton-like reactions, achieving synergistic tumor cell ablation. Moreover, SF encapsulation mitigates CuS-associated toxicity and facilitates biodegradation into non-toxic amino acids, enhancing biosafety.

4. Future and Prospects

There have been many studies on copper sulfide based in vivo synergistic tumor therapy photothermal therapy nano systems, which use biological encapsulation to construct nano systems. However, research on SF/CuS composite systems is relatively scarce and will be a future research direction.

Acknowledgments

Supported by the Chongqing Changshou District Science and Technology Plan Project (CSKJ2024015), Chongqing Municipal Natural Science Foundation (CSTB2024NSCQ-MSX0075), Science and Technology Research Program of Chongqing Education Commission (KJZD-202304501).

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