Advances in Cancer Research through Functionalized Silk Fibroin Nanomaterial Drug Delivery Systems

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Abstract. With the continuous development of medical and materials science technologies, drug delivery materials have started transitioning from synthetic to natural materials. Silk fibroin, known for its excellent biocompatibility and drug-loading capabilities, has shown immense potential and broad prospects in enhancing cellular drug uptake rates and tumor tissue aggregation through the construction of nanomaterial drug delivery systems, thereby improving drug resistance issues and increasing the efficiency of cancer treatment. This paper summarizes and prospects the application of functionalized silk fibroin nanomaterials in the field of drug delivery, based on relevant domestic and international research. It aims to provide a reference for further in-depth research in this area.

Keywords: Functionalized Silk Fibroin, Nanomaterial Drug Delivery, Cancer Research.

1. Introduction

Silk fibroin (SF) is a hydrophilic glycoprotein extracted from silkworm silk, characterized by its ease of modification, excellent biocompatibility, adjustable biodegradability, hemostatic performance, low inflammatory response, good gas permeability, and high safety. The application development of silk fibroin as a drug carrier in the biomedical field has become a hot topic of research both domestically and internationally [1]. Based on domestic and international research results, this paper reviews the functionalized SF nanomaterial drug delivery systems and their applications in cancer treatment, demonstrating their broad application prospects in clinical cancer treatment [2].

2. Functionalization of Silk Fibroin

Silk fibroin, with its excellent biocompatibility, tunable degradation rate, appropriate mechanical strength, and drug-loading characteristics, has gradually become a hot topic in the field of biomedical materials [3]. When silk fibroin materials undergo reprocessing and require improved mechanical properties or specific biological functionalities, further treatments are necessary, such as enhancing physical and mechanical properties, loading drugs, or integrating multiple functional materials [4]. Various forms of multifunctional composite materials developed from silk fibroin have been extensively studied, including nanospheres and hydrogels [5].

2.1. Silk Fibroin Nanospheres

Controlled drug release is achieved through the preparation of nanoparticles by combining silk fibroin with polymers of varying degradation rates. Drug delivery systems can include nanoparticles, microspheres, and more [6]. Zhang Zifan [7] and others reviewed the progress in research on drug-loaded silk fibroin nanoparticles, discussing their controlled release effects under various conditions and summarizing multiple methods to enhance the preparation efficiency of nanoparticles. They anticipate that future drug-loaded nanoparticles will evolve towards controllable release, harmlessness to humans, and high therapeutic efficiency. Zhou Jiabao et al. [8] mixed silk fibroin with formic acid and added polyaniline microspheres in different proportions, then obtained a composite nanofiber membrane through ultrasonication. This membrane was treated with anhydrous ethanol for 10 minutes, then placed in a 10% sodium hypochlorite solution for 15 minutes; it was subsequently washed with 70% ethanol and dried to obtain a halogenated composite nanofiber membrane. Experimental results showed that when the mass fraction of polyaniline was 5%, the

inhibition rates against Staphylococcus aureus and Escherichia coli reached 78.73% and 80.96%, respectively; after halogenation, the inhibition rates against both bacteria could reach 100%. This composite membrane has good physicochemical properties and antimicrobial performance, indicating a certain application prospect in antimicrobial biomaterials [9-11].

Li Ying et al. [12] developed silk fibroin microspheres of varying sizes using an enzymatic hydrolysis-drying-dissolution method, which demonstrated excellent water insolubility and stable dispersity. The characterization of the microspheres' morphology and structure revealed that the method produced nanospheres, with the smallest average diameter of (32±11) nm achieved when the enzyme concentration was 2% and the self-assembly time for the protein was 4 hours. By controlling the self-assembly process of silk fibroin, it was possible to produce nanoscale silk fibroin microspheres without introducing any solvents, making the process environmentally friendly and ensuring the safety and non-toxicity of the silk fibroin microspheres. These nanoscale silk fibroin microspheres show great potential for applications in the medical field due to their environmentally friendly production process and their excellent properties. Yan Yu and others employed a desolvation method to prepare silk fibroin nanoparticles (SF-NPs) and evaluated the physicochemical properties and biocompatibility of the resulting nanoparticles. The results indicated that the SF-NPs produced by this method had uniform particle size and good biocompatibility, suggesting a promising application prospect in the field of drug delivery.

2.2. Silk Fibroin Hydrogels

Hydrogels are a type of 3D network structure made from natural or synthetic polymers. Silk fibroin hydrogels are well-known for their excellent biocompatibility and adjustable degradation properties. Chen Runzhi [14] and others summarized methods for modifying silk fibroin hydrogels used in bone tissue engineering, including enhancing the mechanical properties of hydrogels, boosting their bioinductive effects, and adjusting their biodegradation capabilities.

Hydrogels, with their relatively uniform particle size, can convert sliding friction at the contact surface into rolling friction and have good hydration properties, serving as lubricating materials between joints. The team led by He Xiangming [15] utilized microfluidic technology to prepare silk fibroin-based magnesium oxide-loaded hydrogel microspheres (MgO@Silk-MA) from natural silkworm cocoons. Their lubrication in aqueous environments reduced joint friction and thus cartilage wear. In vivo injection experiments in mice with osteoarthritis showed that the optimal lubrication performance was achieved when the mass fraction of MgO@Silk-MA was 3%, reducing the average friction coefficient by about 25%. The width of wear marks decreased by 84.17%, maintaining stable lubrication performance over nearly two weeks. The silk fibroin-based magnesium oxide-loaded hydrogel microspheres exhibited excellent lubrication effects, slowing down heterotopic ossification and skeletal mineralization. Silk fibroin/sodium alginate hydrogels, with their porous structure, are more suitable as drug carriers compared to pure sodium alginate hydrogels [16-18].

2.3. Silk Fibroin Films

The team led by Wang Pengwei [19] developed silk fibroin films with enhanced water stability and ductility by preparing a silk fibroin (SF) aqueous solution containing 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC). The films were characterized in terms of dissolution rate and mechanical properties. The results showed that EDC could act not only as a crosslinker but also as a plasticizer in interaction with SF, providing a new method for constructing flexible SF films [20]. The hydrophilicity of EDC imparts improved surface hydrophilicity, reducing the brittleness of silk films and serving as a reference for the application of flexible wound dressings.

3. Nanomaterial Drug Delivery Systems

Drug delivery systems are designed to efficiently transport drugs to target organs by controlling aspects such as space, time, and dosage, thereby increasing drug utilization, enhancing therapeutic

effects, reducing costs, and minimizing side effects. These systems are primarily used for treating diseases like inflammation and cancer. Nanomaterial drug delivery systems involve combining nanocarrier materials with therapeutic drugs to form nanocomplexes, which then accumulate chemotherapeutic drugs at specific lesion sites. Effective drug delivery is crucial for treating diseases. Thanks to the unique size and performance advantages of silk fibroin nanomaterials, they can significantly enhance the efficiency of drug delivery to target sites and reduce off-target rates. The goal of drug delivery is not only to transport and release drugs at target locations but also to maximize the reduction of off-target effects, thereby improving therapeutic outcomes [21]. Because nanomaterial drug delivery systems can increase drug solubility, enhance targeting, and boost therapeutic effects, they have become a hot topic in research for targeted cancer treatment.

Nanomaterial systems loaded with anti-tuberculosis drugs can target these drugs to infected cells or lesion sites, offering controlled drug release, reducing dosing frequency, and minimizing dose-dependent adverse reactions [22]. In the clinical treatment of rheumatoid arthritis, nanocarrier-based drug delivery systems have been implemented to deliver therapeutic drugs to inflamed joints for disease control [23]. Recent research has also explored the application of these systems for drug delivery to eyes, blood vessels, heart, and other tissues and organs, with the aim of advancing the application of microneedle technology [24]. The team led by Yuan Tingxun [25] analyzed the development of anti-tuberculosis drug nanomaterial delivery systems, confirming that these systems can directly deliver anti-tuberculosis drugs to infected cells, with high drug loading, enhanced targeting, improved drug bioavailability, and reduced dosing frequency. As research and application of nanotechnology in disease diagnosis and treatment continue to deepen, researchers have designed various functional nanomaterial delivery systems for the efficient diagnosis and treatment of thrombosis [26]. New nanomaterial drug delivery systems have become an important technological platform for the research of thrombosis diagnosis and treatment, showing significant potential for transformation. These systems are designed to be safer, more effective, and more economical for the precise diagnosis and clinical treatment of thrombosis.

4. Cancer Treatment Applications

To date, cancer remains one of the most challenging health issues facing humanity. Nanomaterial drug delivery systems have the ability to accumulate anticancer drugs in large quantities at tumor sites, while their physicochemical properties can reduce toxic side effects, thereby enhancing the treatment effectiveness of tumors. These systems not only mitigate the toxicity associated with nanoparticle drugs but also increase the bioavailability of drugs, improving biocompatibility and targeting. Ma Baonan and others [27] have not only analyzed the drug loading characteristics of live cells, exosomes, and their delivery systems but also summarized their applications in tumor treatment, providing more therapeutic options for cancer treatment. Nanomaterials, through functionalization, offer new hope for targeted drug transport and combined cancer therapy.

The use of DNA for selective modification of nanomaterials shows promising applications in delivering anticancer drugs for tumor treatment [28]. Liu Rugui and others [29] prepared non-toxic poly (lactic-co-glycolic acid) nanoparticles encapsulating osimertinib, further modified with chitosan oligosaccharide for treating non-small cell lung cancer. The results indicated that these nanoparticles had a slow drug release rate, strong cytotoxicity, and significant tumor suppression effects, potentially improving the clinical treatment outcome of osimertinib by reducing drug resistance and disease recurrence in patients.

Breast cancer is the second leading cause of cancer-related deaths after lung cancer. A biofunctionalized electrochemical immunosensor was designed, utilizing immune cancer embryonic antibodies as probes for quantifying cancer embryonic antigens. Compared to traditional electrochemical immunosensors, the sensitivity of this sensor was increased by 3.5 times [30], showcasing its potential in detecting key cancer biomarkers. Drug release mechanisms can be activated by factors such as pH, the presence of enzymes, and temperature, significantly enhancing

the therapeutic effect on breast cancer [31]. Research has shown the synergistic anticancer effect of berberine oil and 5-fluorouracil with biodegradable nanomaterials against melanoma and breast cancer. Thus, encapsulating natural extracts with chemotherapy drugs in nanocarriers can reduce the treatment dosage, thereby diminishing the concentration of chemotherapy drugs, overcoming resistance, and toxicity drawbacks. This delivery system has a certain therapeutic effect on breast cancer cells [32]. Artemisinin and its derivatives have been proven to possess good anticancer biological activity. When encapsulated in various nanomaterial drug delivery systems and modified, these bioactive molecules can be targeted to cancer lesions, maintaining drug release and significantly improving therapeutic effects [33].

Prostate cancer is a common malignancy in the male urinary reproductive system. The team led by Liu Xueyi [34] introduced advanced nanomaterial drug delivery systems for treating prostate cancer and their future developments. Nanomaterial drug delivery systems enhance the passive accumulation at pathological sites through improved permeability and retention effects, extend circulation time in the blood, and control drug release, improving treatment outcomes. Huang Kexiang and others [35] have reviewed the progress of nanomaterial drug release systems in stomach cancer treatment. New nanocarrier-based drug delivery systems have shown to be effective and efficient in gastric cancer treatment, presenting a broad development prospect.

5. Conclusion and Outlook

With the research into biomaterials, silk fibroin nanomaterials have shown significant medical field implications due to their excellent biocompatibility, extending drug efficacy and improving drug utilization rates. Currently, silk fibroin drug delivery systems are mostly in the research stage, requiring long-term exploration and clinical trials for clinical implementation. This paper systematically introduces the application research of different functional silk nanomaterial drug carriers in cancer treatment, hoping to provide references for the clinical research of biomaterials in antitumor drug delivery.

Acknowledgments

Preparation of Intelligent Silk Fibroin Light Therapy Nanosystems and Their Antitumor Performance Evaluation, Project No. KJZD-K202304501, a key project of the Chongqing Municipal Education Commission Science and Technology Project.

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