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Application of Silk Fibroin Hydrogel in Bone Tissue Engineering

Zijin Wang

Northwestern Polytechnical University, Xi'an, China
*Corresponding author: qingqingzi@mail.nwpu.edu.cn

Abstract:

Silk fibroin (SF) hydrogel has emerged as a promising biomaterial for bone tissue engineering (BTE) due to its excellent biocompatibility, controllable degradation, and versatile processing capabilities. This review summarizes recent advancements in the application of SF hydrogel and its composites in BTE, focusing on its properties, preparation methods, and innovative modifications to enhance mechanical strength and biofunctionality. The shape of hydrogel improves the biocompatibility of SF material, making it better used in bone tissue engineering. SF hydrogel has demonstrated significant potential in addressing bone defects, osteoarthritis, periodontal regeneration, antibiotic delivery, and stem cell therapy. Composite materials, such as collagen, chitosan, and alginate, further expand its applications by improving mechanical and biological performance. The introduction of more composite materials further enhanced the application of SF hydrogel in bone tissue engineering. Despite these advancements, challenges remain, including the need for improved mechanical properties, reduced immune responses, and more extensive clinical validation. Future research should prioritize large-animal studies and clinical trials to facilitate the translation of SF hydrogel-based therapies into clinical practice.

Keywords: Silk fibroin hydrogel, Bone tissue engineering, Composite materials.

1. Introduction

In recent ten years, the incidence rate of various bone diseases has been increasing rapidly. Bone diseases and bone defects may lead to physical function defects, which will affect the ability of patients to take care of themselves. However, the repair ability of bone tissue is limited, and high-level defects are difficult to self-repair. Therefore, bone injury repair has been considered a major challenge in the field of clinical repair. More and more bone substitutes are widely used in surgical procedures, with over 2 million bone transplant surgeries performed worldwide each year. Bone replacement biomaterials have a market value of over 2.7 billion US dollars. Allogeneic bone transplantation and autogenous bone

transplantation are common clinical bone transplant techniques, but both have certain limitations. Autologous bone transplant patients have a high risk of infection, difficult collection conditions, and are only suitable for small-sized bone tissue injuries. However, allogeneic bone transplantation carries the risk of infection and disease transmission and may lead to immune reactions . Therefore, the development of artificial synthetic bone tissue fillers for bone tissue regeneration and repair has broad clinical needs and practical significance.

Silk fibroin is a high-quality natural protein extracted from silk, and its high strength and toughness are mainly derived from the highly oriented crystalline phase along the fiber axis. Silk fibroin has good processability, biocompatibility, and controllable degradability, making it an excellent material for bone tissue engineering (BTE). Although natural silk fibers have strong mechanical properties, most biomaterials made from pure silk fibroin SF solution lack flexibility and stretchability and are fragile and prone to breakage. Hydrogel has the characteristics of elasticity, softness, water swelling and transparency, which can effectively overcome the defects of poor flexibility and low tensile strength of SF materials.

Hydrogel is a three-dimensional cross-linked network composed of polymer, which is a network cross-linked structure composed of hydrophilic groups and hydrophobic groups. It can be prepared by chemical or physical cross-linking. Hydrogel has the characteristics of water retention and has the advantages of soft texture and stable shape. It is a good material structure used to replace bone tissue. The external gel structure can also provide a three-dimensional microenvironment to simulate the extracellular matrix, thus playing a role in regulating cell behavior and tissue function.

Therefore, compared with other silk-based materials such as sponge, film, fiber and particle, silk hydrogel has a better application prospect in bone tissue repair engineering. Low mechanical strength is one of the main obstacles to the performance of traditional silk fibroin hydrogels. Its problems include insufficient adhesion, lack of energy dissipation mechanism, irreversible mechanical properties, and responsiveness to the environment. These problems limit its application in bone tissue engineering. In recent years, the multifunctional silk fibroin hydrogel with high strength, adhesiveness, environmental stimulus reactivity, self-healing ability and injectability has been successfully prepared by using the technology of regulating silk fibroin protein at the molecular level. The research on combining silk fibroin with other materials to prepare new composite materials to improve their mechanical properties has also made breakthroughs.

The purpose of this review is to summarize the progress in the application of silk fibroin hydrogel and its composites in bone tissue engineering. First, the source, properties and structure of silk fibroin hydrogel will be introduced. Secondly, the preparation methods of silk fibroin hydrogel related to bone tissue engineering were summarized. After that, this review summarized the latest progress in the application of silk fibroin hydrogel in bone tissue engineering in the past five years and the research on improving the properties of silk fibroin hydrogel by combining with other materials. Finally, the challenges and opportunities of silk fibroin hydrogel in the clinical application of bone tissue engineering are discussed.

2. Silk Fibroin

2.1 Source of Silk Fibroin

Extraction from silk is the main way to obtain silk fibroin, and the protective cocoon secreted by silkworms is the main source of silk. In the cocoon structure, sericin protein accounts for 75%, while sericin protein accounts for the remaining 25%. The process of removing sericin from silkworm cocoons in alkaline solution is called degumming. The lithium bromide dissolution method is currently the most commonly used method for degumming and extraction. Dissolve silk in lithium bromide solution and remove insoluble components by centrifugation and filtration. After ion liquid dialysis, a low concentration SF aqueous solution can be obtained [1, 2], as shown in Figure 1. The calcium chloride organic acid system is also a common method for extracting SF molecules, but the process is more complex due to the toxicity of its solvent.

Fig. 1 Schematic diagram of the extraction program for silk building blocks at different levels [2].

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2.2 Properties and Advantages of Silk Fibroin

As an extract from natural biomaterials, silk fibroin has low immunogenicity, low antigenicity, and low cytotoxicity, and does not cause inflammatory reactions in the body, thus demonstrating good biocompatibility. In addition, SF degradation is controllable, and the degradation rate of SF can be regulated by changing external conditions (implantation site and patient's physiological and pathological status, type and quantity of hydrolytic enzymes) and internal properties of SF (such as filament type, molecular beta fold content, crystallinity, cross-linking degree, and morphological characteristics) . According to reports, SF also has strong mechanical properties, with a stiffness of 10-17 GPa, ultimate tensile strength of 0.3-0.74 GPa, fracture strain of 4-16%, and toughness of 70-78 MJ/m [3], which is superior to common natural fibers and composite fibers. Due to the above characteristics, silk fibroin is a good material for bone tissue engineering applications.

2.3 Preparation of SF Hydrogel

Physical cross-linking and chemical cross-linking are classic methods for preparing SF hydrogels. Physical gel takes a long time and requires ultrasound, vortex, PH adjustment and other methods to speed up the gel rate, while traditional chemical gel has cytotoxicity and high cost, which is not conducive to large-scale production. In recent years, 1-ethyl - (3-dimethylaminopropyl) carbodiimide (EDC) and diglycidyl ether (BDDE) have been used as novel crosslinking agents to reduce toxicity (Figure 2) [4]. In recent years, Lee, et al. have successfully applied 3D printing to the synthesis of SF hydrogel, but it is still in the early stage of development and faces the challenge of commercialization [5]. Electrospinning technology has also been applied to the synthesis of SF hydrogel, further improving its mechanical properties and facilitating the growth of surface cells.

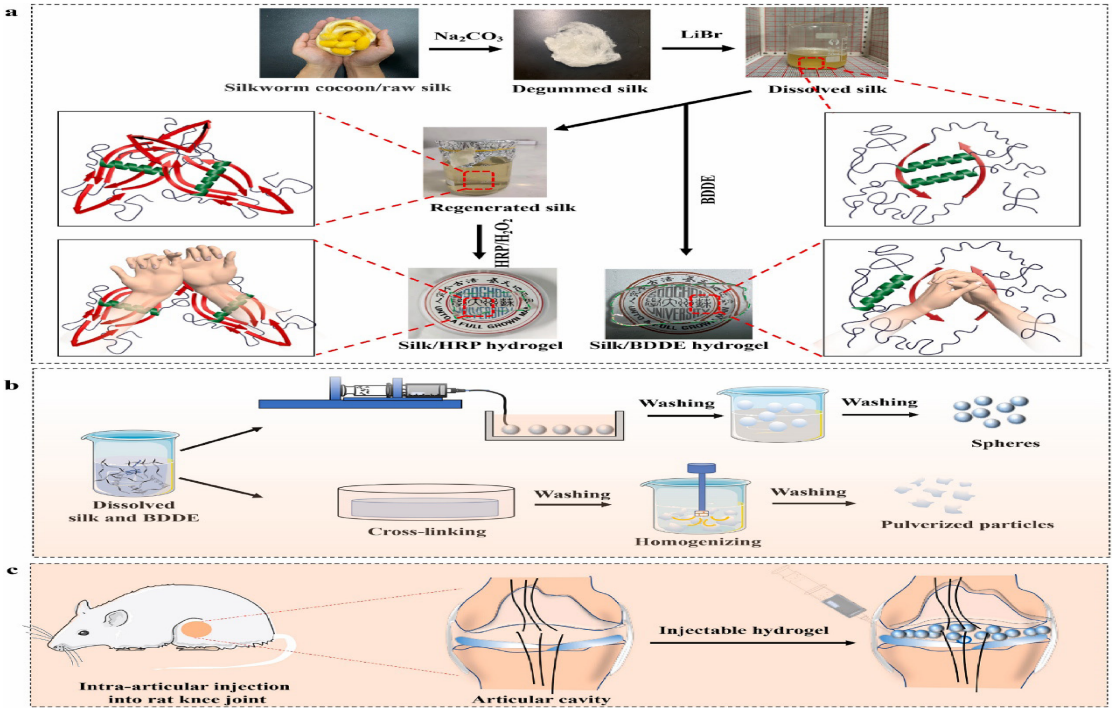

Fig. 2 Schematic diagram of crosslinking process and mechanism of BDDE/silk hydrogel [4]

3. Silk Fibroin Hydrogel Composites

Hydrogels are complex 3D networks formed by natural or synthetic polymer chains. In the past decade, hydrogels have become a very promising category of biomaterials in the biomedical field, because they have moisturizing properties, the ability to simulate the environment and functions of living human tissues, and customizable physical and biochemical properties. SF hydrogels suitable for different applications are compounded with different materials to prepare composite materials with rich and different characteristics.

3.1 Collagen

Collagen is considered the backbone of the extracellular matrix (ECM), which is a fibrous protein synthesized by animal fibroblasts and characterized by unbranched, opaque, and white color. It is widely present in animal

cartilage, tendons, skin, ligaments, and other connective tissues. Its main application areas include tissue regeneration, angiogenesis, and inflammatory response. Adjusting the proportion of polymers enables hydrogels to simulate 3D dynamic ECM of various tissues, which can be used to improve the biocompatibility of SF hydrogels, but their mechanical properties are poor [5].

3.2 Chitin and Chitosan

Chitosan and chitin have strong breathability, which can activate macrophages and promote wound healing. Therefore, they are widely used as biological dressings for wound dressings. Their antibacterial, hemostatic, and anti-inflammatory properties can be improved by combining them with SF hydrogel, making them available for wound healing [6]. A double network CS/SF hydrogel for cartilage repair, first uses 1- (3-dimethylaminopropyl) -3-ethylcarbodiimide hydrochloride (EDC) as a crosslinking agent and N-hydroxysuccinimide (NHS) as a stabilizer to couple thionates to CS, which has biocompatibility and can activate carboxyl groups and form amide bonds. Then mix the thiolated CS with SF at different mass ratios [7].

3.3 Alginate

The main raw material for alginate wound and skin dressing materials is insoluble alginate. Its main components are sodium carboxymethyl cellulose and calcium alginate. It has the characteristics of hemostasis, gel, high moisture absorption, softness and easy folding, and is an ideal filler. Insoluble calcium alginate can be converted into soluble sodium alginate through ion exchange when in contact with the wound surface and can absorb exudate equivalent to twice its own weight and 5-7 times that of ordinary gauze, providing a moist environment to promote wound healing. At the same time, calcium ions are released into the wound to induce platelet activation and accelerate wound healing. It can also absorb bacteria, prevent them from entering the wound, and activate macrophages to resist the invasion of pathogenic microorganisms. The application of SF hydrogel can promote postoperative wound and Chronic wound with high exudate [8].

3.4 Alginate

Glue is a kind of protein material, which is composed of denatured and partially hydrolyzed natural collagen and combined with SF hydrogel. It can promote basic cellular functions such as differentiation, migration, and proliferation by integrating cell-mediated enzyme degradation and cytokine mediated cell adhesion. According to reports, Kim A's team successfully prepared silk fibroin/gelatin microcarrier scaffolds, and the Young's modulus of the blended material was significantly higher than that of SF alone. In order to achieve reproducible production of SF/G mixture microcarriers with specified diameters, the team also developed an axisymmetric flow focusing device composed of ready-made parts and attachments. Under dynamic culture conditions, these SF/G microcarriers effectively promoted the adhesion of rat mesenchymal stem cells. After culturing in osteogenic differentiation medium, the cells exhibited typical characteristics of osteoblasts [9,10].

4. Biomedical Applications in Bone Tissue Engineering

4.1 Regenerative Applications

In recent years, SF hydrogel, as one of the commonly used biomaterials for bone tissue engineering, has therapeutic potential in a variety of bone related diseases, mainly used for bone repair and anti-infection, including bone defects, osteoarthritis and periodontal tissue.

4.1.1 Bone defect

Disease, aging, or traumatic damage are the main causes of bone defects, typically involving damage to cartilage and subchondral bone. The scaffold applied to bone defects requires porosity, mechanical strength, and cell adhesion to promote cell adhesion, growth, differentiation, and migration. SF hydrogel has sufficient performance to support osteogenesis and oxygen transport. Porous and multi-scale SF hydrogel scaffold provides conditions for cell recruitment, nutrient transport and angiogenesis to promote bone regeneration. It is reported that Liu Qiuchen and others successfully prepared porous SF hydrogel scaffolds through 3D printing technology and used G-50 glucan gel particles (G50) as a porogen in silk solution to prepare hydrocolloid ink. The prepared Silk/G hydrogel is porous, and the pore size is very consistent with the optimal pore size, which enhances cell adhesion (Figure 3) [11]. Ao. Z et al. used low concentration of vitamin C to induce the degradation of MBG in sodium alginate/MBG/SF hydrogel, thus forming a porous structure in situ. In order to further stabilize the delivery of oxygen to tissues [12]. Meng L. et al. prepared a hydrophobic association bonded alginate SF hydrogel to improve the mechanical ductility, strength and toughness of the hydrogel. Under high strain, the hydrogel preferentially destroys the "sacrificial bond" formed by the cross-linking network of stearyl methacrylate (C18M) and SF, thus providing a lot of energy without destroying the integrity of the gel [13]. Xiaolin Wu et al. applied SF hydrogel to cartilage tissue regeneration, sealed the edges around the double-layer

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scaffold structure, made new cartilage grow to adjacent cartilage, and replaced the degraded bionic cartilage layer of adjacent cartilage, achieving a good fusion of artificial and natural tissue [14]. In order to achieve the regulation of SF hydrogel scaffold on cell behavior, silica nanoparticles can be added to it to stimulate osteoblast mineralization and effectively increase bone mineral density in vivo, or silicate nano clay can be added, such as Laponite (NAPO) as a bioactive agent to enhance biocompatibility [15].

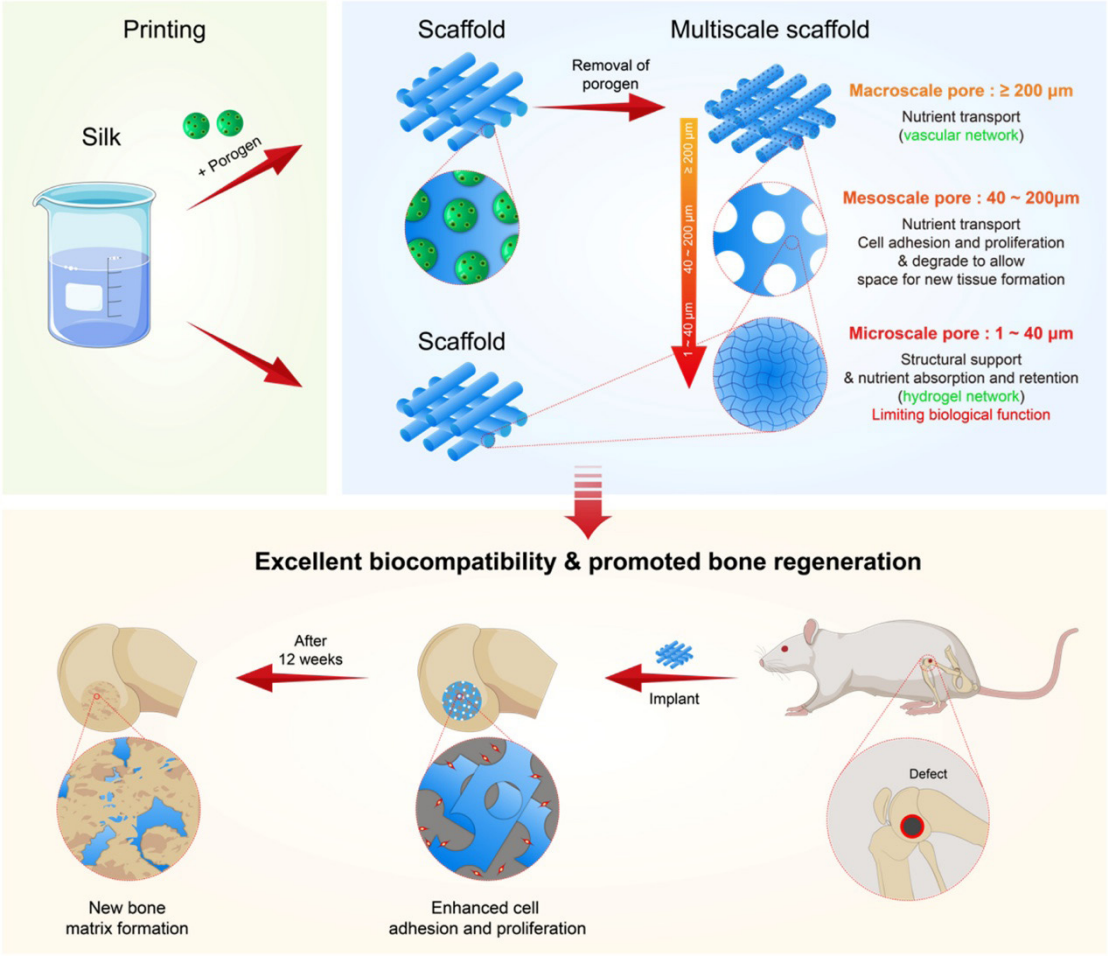

Fig. 3 Schematic illustration of a multiscale silk fibroin scaffold fabricated by 3D printing and its role in bone defect healing [11].

4.1.2 Osteoarthritis

Osteoarthritis (OA) is a degenerative disease of articular cartilage in the whole body caused by genetic factors, aging, obesity, high-intensity exercise and other factors, which causes intermittent severe pain. Implantation and injection of hydrogel can provide a platform for delivery of different growth factors and mesenchymal stem cells for in situ reconstruction, so it becomes one of the main strategies for repairing early cartilage defects. The research results of Tao Wang et al. show that the compression modulus of SF hydrogel prepared by BDDE is 166 ± 15.0 kPa, which has excellent stability, high elasticity and fatigue resistance [16]. After injecting it as a bio lubricant into the joint cavity of rats, significant therapeutic effects were observed, effectively reducing cartilage damage and alleviating pain. In order to reduce the immune response caused by the hydrogel filling process, Rui K. et al. used exosomes derived from olfactory mesenchymal stem cells encapsulated under 365 nm light irradiation(Exos@SFMA)Crosslinked with SF hydrogel, a modified hydrogel system was successfully developed, which further hindered the development of B cells and cytoplasm cells, reduced the production of antibodies, and thus regulated immune disorders (Figure 4) [17].

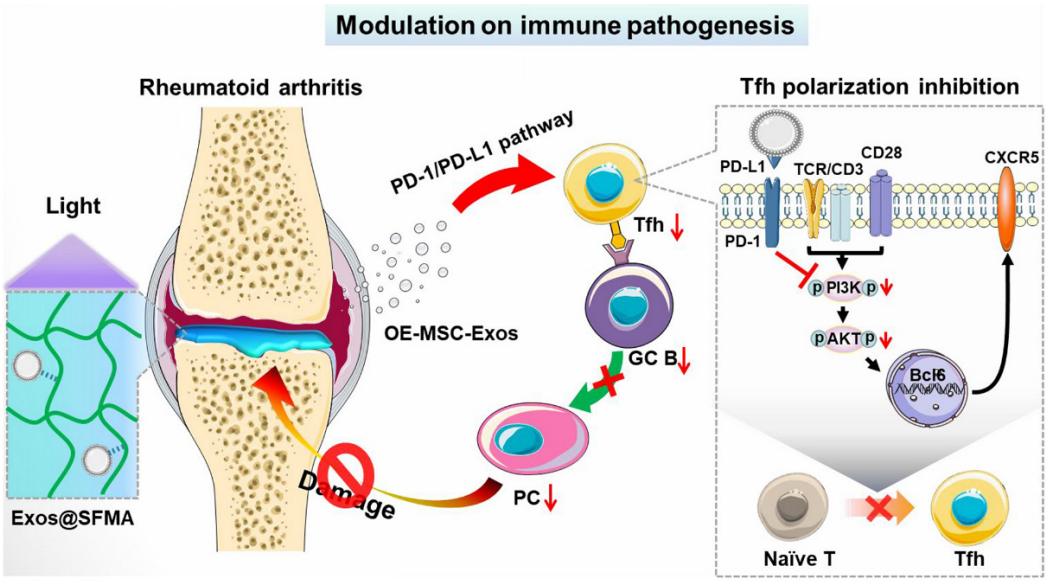

Fig. 4 Mechanism of SF hydrogel adhesion to bone tissue and treatment of arthritis [17].

4.1.3 Periodontium

In recent years, the demand for periodontitis, tooth extraction, and dental implantation has gradually increased, and the demand for repairing damaged alveolar bone and alveolar bone has also correspondingly increased. At present, the main demand for materials is focused on reducing inflammation and supporting the load-bearing capacity of dental implants. Wu's team used SF hydrogel chemically modified with glycidyl methacrylate (GMA) to repair alveolar bone tissue. This hydrogel with in situ gel capability can promote angiogenesis [18]. Chuysinuan P. et al. HAP/alginate/SF hydrogel was designed as a dental replacement treatment scaffold, and the bionic fiber gel like structure was successfully constructed, which provides mechanical support for alveolar bone repair and promotes the reconstruction of tissue microenvironment [19]. Du J.H's team designed an SF hydrogel with BRD9 degradation agent, which effectively alleviates the problem of jaw necrosis (ONJ) related to zoledronate (ZOL) and the problem of acute bone loss of local invasive periodontitis after tooth extraction induced by lipopolysaccharide (LPS) [20]. Jiaxuan Lyu team applied thiostreptococcus/silk fibroin hydrogel to treat periodontitis, showing significant antibacterial and anti-inflammatory properties against Porphyromonas gingivalis [21].

4.2 Anti-Infective and Stem Cell Delivery Applications

4.2.1 Antibiotic

In bone tissue engineering, biomaterials need to avoid bacterial adhesion that may cause tissue infection before the bone tissue fully heals. This demand is crucial for promoting bone integration while inhibiting infection to support effective bone repair. In the research of Peng Zhang et al., in order to use vancomycin to treat osteomyelitis, the SF protein microspheres of vancomycin were encapsulated in injectable SF hydrogel to create a sustained-release system [22]. The combination of SF hydrogel with metals and antimicrobial peptides is also one of the main research directions. Zhou M. et al. complexed it on the surface of AgNPs by hydrogen bonding to form a structure similar to protein corona and prepared a hydrogel made of antibacterial peptides with SF osteogenic fragments. They used SF's PH reactivity to intelligently identify bacterial invasion, destroy bacterial membrane structure and generate ROS. In addition, they also released silver ions to destroy bacterial genetic material and affect its protein synthesis, ultimately achieving dual effects of osteogenesis and antibacterial [23]. Marta R. et al. reduced bacterial adhesion by synergistically using gold and silver metals. The SF/HAP hydrogel was used as a carrier and reducing agent to enable silver ions and gold ions to be reduced to corresponding gold and silver nanoparticles (AuNPs and AgNPs) in situ, thus improving the antibacterial activity of the scaffold [24].

4.2.1 Stem cells

Stem cells have the ability to differentiate into multiple directions, and BMSCs are commonly used in BTE to effectively repair bone regeneration. Various forms of SF scaffolds have been used as substrates for loading BMSCs. Joseph's team used SF/nano hydroxyapatite bioink loaded with MSCS and thermoplastic ink formed from a paramagnetic iron doped bioactive glass polycaprolactone

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mixture for bioprinting [25]. MiRNAs extracted from extracellular BMSCs play a crucial role in bone formation and resorption processes. Ou et al. aimed to repair critical sized bone defects in rats without loading osteoblasts. They loaded miR-214 inhibitors onto PEI-GO complexes and assembled them into HAP/SF scaffolds. This attempt successfully controlled the release of miR-214 inhibitors and promoted cell proliferation and adhesion [26].

5. Challenges in Clinical Applications

At present, the use of SF based biomaterials still faces many challenges that need to be addressed. For example, SF still exhibits some adverse immune reactions in the human body, which may be caused by residual sericin protein, as it is a non autologous biomaterial. In addition, the mechanical properties of SF scaffolds are still poor compared to traditional scaffold materials, and their practicality needs further systematic research and clinical application verification. Speaking of which, a lot of work needs to be done to further clarify the long-term safety of SF scaffolds, as the degradation products of SF biomaterials may trigger the immune system. Therefore, although the bone regeneration ability of SF materials has been demonstrated in small animal models, there is still a lack of validation in large animal models. In addition, further research is needed on the osteogenic signaling pathway of SF. At present, products designed based on SF have not been widely applied in clinical practice, which may be due to a lack of data on the safety and efficacy of SF. At present, there are only 7 SF based design products successfully approved for medical devices in China, which are mainly used for skin dressings (4 cases) and abdominal, vaginal and dental bone fillers (1 case each), of which 3 cases are SF hydrogels. In addition, currently only 3 SF based product clinical trials have been completed globally, and 5 clinical trials are in an undeveloped or unfinished state [27]. The vast majority of related basic research focuses on in vivo or in vitro evaluation of small animal models of SF. Therefore, we urgently need data from large animal in vivo evaluation and randomized controlled human trials to promote the practical application of SF based hydrogels.

6. Conclusion

Silk fibroin hydrogel represents a highly versatile and effective material for bone tissue engineering, offering unique advantages such as biocompatibility, tunable degradation, and the ability to mimic the extracellular matrix. Recent innovations in composite materials and preparation techniques have significantly enhanced their mechanical properties and functional versatility, enabling applications in diverse clinical scenarios, from bone defect repair to osteoarthritis treatment. However, challenges related to mechanical strength, immune response, and clinical validation must be addressed to fully realize its potential. Future efforts should focus on large-scale preclinical studies and rigorous clinical trials to ensure the safety and efficacy of SF hydrogel-based therapies. With continued research and development, SF hydrogel holds great promise for revolutionizing bone regeneration and repair in clinical settings.

References

[1] Campana V, Milano G, Pagano E, et al. Bone substitutes in orthopaedic surgery: from basic science to clinical practice[J]. J Mater Sci: Mater Med, 2014, 25: 2445–2461.

[2] Yao X, Zou S, Fan S, Niu Q, Zhang Y. Bioinspired silk fibroin materials: From silk building blocks extraction and reconstruction to advanced biomedical applications[J]. Materials Today Bio, 2022, 16: 100381.

[3] Dickerson MB, Fillery SP, Koerner H, et al. Dielectric breakdown strength of regenerated silk fibroin films as a function of protein conformation[J]. Biomacromolecules, 2013, 14(10): 3509–3514.

[4] Wang T, Li Y, Liu J, et al. Intraarticularly injectable silk hydrogel microspheres with enhanced mechanical and structural stability to attenuate osteoarthritis[J]. Biomaterials, 2022, 286: 121611.

[5] Lee YJ, Lee JS, Ajiteru O, et al. Biocompatible fluorescent silk fibroin bioink for digital light processing 3D printing[J]. Int J Biol Macromol, 2022, 213: 317–327.

[6] Peng W, Li D, Dai K, et al. Recent progress of collagen, chitosan, alginate and other hydrogels in skin repair and wound dressing applications[J]. Int J Biol Macromol, 2022, 208: 400–408.

[7] Patel DK, Dutta SD, Hexiu J, et al. 3D-printable chitosan/silk fibroin/cellulose nanoparticle scaffolds for bone regeneration via M2 macrophage polarization[J]. Carbohydr Polym, 2022, 281: 119077.

[8] Liu J, Yang B, Li M, et al. Enhanced dual network hydrogels consisting of thiolated chitosan and silk fibroin for cartilage tissue engineering[J]. Carbohydr Polym, 2019, 227: 115335.

[9] Birmingham, E., Niebur, G. L., & McHugh, P. E. (2012). Osteogenic differentiation of mesenchymal stem cells is regulated by osteocyte and osteoblast cells in a simplified bone niche.

[10] Klotz BJ, Gawlitta D, Rosenberg AJ, et al. Gelatin-Methacryloyl hydrogels: towards Biofabrication-Based tissue repair[J]. Trends Biotechnol, 2016, 34(5): 394–407.

[11] Luetchford KA, Chaudhuri JB, De Bank PA. Silk fibroin/gelatin microcarriers as scaffolds for bone tissue engineering[J]. Mater Sci Eng C, 2019, 106: 110116.

[12] Liu Q, Chen L, Liu H, et al. Promotion of bone defect repairs using multiscale 3D printed silk porous hydrogel scaffolds[J]. Acta Biomater, 2025.
[13] Meng L, Shao C, Cui C, et al. Autonomous Self-Healing Silk fibroin injectable hydrogels formed via Surfactant-Free Hydrophobic Association[J]. ACS Appl Mater Interfaces, 2019, 12(1): 1628–1639.
[14] Wu X, Zhou M, Jiang F, et al. Marginal sealing around integral bilayer scaffolds for repairing osteochondral defects based on photocurable silk hydrogels[J]. Bioactive Materials, 2021, 6(11): 3976-3986.
[15] Wu X, Zhou M, Jiang F, et al. Marginal sealing around integral bilayer scaffolds for repairing osteochondral defects based on photocurable silk hydrogels[J]. Bioact Mater, 2021, 6(11): 3976–3986.
[16] Cheng Y, Cheng G, Xie C, et al. Biomimetic silk fibroin hydrogels strengthened by silica nanoparticles distributed nanofibers facilitate bone repair[J]. Adv Healthc Mater, 2021, 10(9).
[17] Wang T, Li Y, Liu J, et al. Intraarticularly injectable silk hydrogel microspheres with enhanced mechanical and structural stability to attenuate osteoarthritis[J]. Biomaterials, 2022, 286: 121611.
[18] Rui K, Tang X, Shen Z, et al. Exosome inspired photo-triggered gelation hydrogel composite on modulating immune pathogenesis for treating rheumatoid arthritis[J]. J Nanobiotechnol, 2023, 21(1).
[19] Wu S, Zhou X, Ai Y. Pro-angiogenic photo-crosslinked silk fibroin hydrogel: a potential candidate for repairing alveolar bone defects[J]. J Appl Oral Sci, 2023, 31.
[20] Chuysinuan P, Nooeaid P, Thanyacharoen T, et al. Injectable eggshell-derived hydroxyapatite-incorporated fibroin-alginate composite hydrogel for bone tissue engineering[J]. Int J Biol Macromol, 2021, 193: 799–808.
[21] Du J, Liu Y, Wu X, et al. BRD9-mediated chromatin remodeling suppresses osteoclastogenesis through negative feedback mechanism[J]. Nat Commun, 2023, 14(1).
[22] Lyu J, Shen S, Hao Y, et al. The impact of Thiopeptide antibiotics on inflammatory responses in periodontal tissues through the regulation of the MAPK pathway[J]. Int Immunopharmacol, 2024, 133: 112094.
[23] Zhang P, Sun Y, Yang H, et al. Vancomycin-loaded silk fibroin microspheres in an injectable hydrogel for chronic osteomyelitis therapy[J]. Front Bioeng Biotechnol, 2023, 11.
[24] Zhou W, Bai T, Wang L, et al. Biomimetic AgNPs@ antimicrobial peptide/silk fibroin coating for infection-trigger antibacterial capability and enhanced osseointegration[J]. Bioact Mater, 2022, 20: 64–80.
[25] Ribeiro M, Ferraz MP, Monteiro FJ, et al. Antibacterial silk fibroin/nanohydroxyapatite hydrogels with silver and gold nanoparticles for bone regeneration[J]. Nanomedicine, 2016, 13(1): 231–239.
[26] Ou L, Lan Y, Feng Z, et al. Functionalization of SF/HAP Scaffold with GO-PEI-miRNA inhibitor Complexes to Enhance Bone Regeneration through Activating Transcription Factor 4[J]. Theranostics, 2019, 9(15): 4525–4541.
[27] ClinicalTrials.gov. Clinical trial database[EB/OL]. [n.d.]. Available: https://www.clinicaltrials.gov/search?term=silk%20fibroin&limit=50&page=1