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Advances in Hydrogel Applications in Wound Healing and Tissue Regeneration

Siyan Shen[1, *]

[1]Model High School, Rome, GA, 30161, USA
*Corresponding author: siyanshen24@gmail.com

Abstract:
Hydrogel has received wide attention in the field of biomedicine in recent years due to its high-water content, good biocompatibility and structural characteristics similar to human tissues. This article reviews the classification, basic properties and application of Hydrogel in wound repair and tissue regeneration. According to the material source and functional characteristics, hydrogel can be divided into natural hydrogel, synthetic hydrogel and smart hydrogel. Studies show that hydrogel can accelerate wound healing by maintaining a humid environment, exerting antibacterial and anti-inflammatory effects, and promoting cell proliferation and angiogenesis. At the same time, hydrogel has also shown good application prospects in the fields of skin regeneration, bone regeneration and cartilage repair. Although hydrogel still has problems such as insufficient mechanical strength, difficult to accurately control the degradation rate and limited clinical application data, with the continuous development of material design and preparation technology, the new smart hydrogel and the research of multifunctional hydrogel is constantly advancing. In general, as a biomaterial with development potential, hydrogel has a broad application prospect in the fields of regenerative medicine and tissue engineering in the future.

Keywords: Hydrogel; wound healing; tissue regeneration; biocompatibility; tissue engineering.

1. Introduction

With the development of modern medicine, wound healing and tissue regeneration have become important research directions in the field of biomedicine. Problems such as burns, trauma, surgical wounds and chronic wounds are very common in clinical practice. These injuries often take a long time to recover, and may be accompanied by complications such as infection and tissue necrosis.

Therefore, how to promote wound repair and improve tissue regeneration efficiency has become an important topic for researchers [1].

Although traditional wound dressings such as gauze can play a protective role on wounds, their main function is to cover and isolate the external envi-

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ronment, and it is difficult to actively promote the tissue repair process [1]. In order to solve this problem, researchers began to explore biological materials with better performance, among which hydrogel has attracted wide attention for its unique structure and properties [2].

Hydrogel is a material with a three-dimensional network structure and a large amount of water.

Its composition and softness are similar to those of human tissues [3]. Due to its good biocompatibility, flexibility and moisturizing ability, hydrogel is widely used in biomedical research and clinical treatment [4]. Maintaining a moist wound environment is conducive to cell proliferation and tissue repair, and can also reduce the discomfort of patients. In addition, hydrogel can also absorb wound exudate and allow oxygen to enter the damaged tissue, thus creating a more suitable microenvironment for wound healing [5].

According to the material source and functional characteristics, hydrogel can be divided into natural hydrogel, synthetic hydrogel and smart hydrogel [3]. Among them, natural hydrogel (such as chitosan and gelatin) has good biocompatibility and degradability, and is often used in wound dressings and drug carriers; synthetic hydrogel (such as PEG and PVA) has good mechanical properties and is suitable for tissue engineering; while smart hydrogel can respond to external stimuli such as temperature and pH, showing a broad application prospect in the field of precision drug release and regenerative medicine [3].

In recent years, a large number of studies have shown that hydrogel can not only maintain a suitable wound microenvironment, but also carry antibacterial agents, anti-inflammatory agents and a variety of biologically active factors, so that they promote cell growth, angiogenesis and tissue repair [5]. In addition to wound treatment, hydrogel is also widely used in skin repair, bone tissue regeneration and cartilage repair, showing good development potential [2].

Nevertheless, hydrogel still has some limitations. For example, some natural hydrogels (such as gelatin-based hydrogel and alginate-based hydrogel) have low mechanical strength and are prone to structural rupture in large wounds or frequently moving parts. At the same time, its degradation rate is relatively fast, which may not meet the long-term treatment needs [3]. In addition, the preparation process of some highly functional smart hydrogel is relatively complex and the production cost is relatively high, which also limits their large-scale clinical application [2]. Therefore, further improving the stability, functionality and clinical applicability of hydrogel is still an important direction of current research.

This article will introduce the classification and basic properties of hydrogel, and focus on its application in wound healing and tissue regeneration, as well as future development trends and potential challenges. Different from traditional reviews that only summarize the application of single hydrogels, this article systematically compares the performance advantages and limitations of natural, synthetic and intelligent hydrogels. It further integrates the multiple mechanisms of hydrogel-mediated wound repair and comprehensively analyzes the latest progress of hydrogel in multi-tissue regeneration, including skin, bone, cartilage and nerve tissue.

2. Hydrogels

2.1 Natural Hydrogels

Natural hydrogels usually come from natural polymer materials, such as gelatin, alginate, chitosan and hyaluronic acid [6]. Because it comes from natural biological materials, it has good biocompatibility and biodegradability, and can interact well with human tissues [1].

Among them, chitosan is a natural hydrogel material that has been studied more at present. Studies show that chitosan not only has a certain antibacterial ability, but also can promote cell adhesion and tissue repair, so it is widely used in the development of wound dressings. Gelatin comes from collagen, which has a structure similar to human tissues [3]. In addition, alginate has strong water absorption ability and can absorb a large amount of wound exudate, so it is often used to treat wounds with more exudate [7].

Although natural hydrogel has good biocompatibility, its mechanical strength is relatively low, and it is prone to degradation or structural damage during long term use. Therefore, it usually needs to be modified with other materials in practical applications [3].

2.2 Synthesis of hydrogels

Synthetic hydrogel is mainly made of artificially synthesized polymer materials. Common materials include polyethylene glycol (PEG), polyvinyl alcohol (PVA), and polyacrylamide, etc [4].

Compared with natural hydrogel, synthetic hydrogel has better mechanical strength, stability and adjustability. Researchers can adjust the water absorption performance, degradation rate and mechanical properties of materials by changing their composition and cross linking, so as to meet the needs of different tissue repair [5].

For example, PEG hydrogel has good stability and safety, and is widely used in tissue engineering and drug delivery [2]. PVA hydrogel has high flexibility and mechanical strength, and has good application value in soft tissue repair and artificial bracket construction [4].

However, some synthetic materials themselves lack natural biological activity, so their ability to promote cell growth and tissue regeneration is usually weaker than that of hydrogels from natural sources [4]. In order to overcome this problem, researchers began to try to compound natural hydrogel with synthetic hydrogel. For example, combining chitosan or gelatin with good biocompatibility with PEG, PVA and other materials with high mechanical strength can achieve better biological activity and structural stability at the same time [3].

The research of Bertsch et al. pointed out that this composite hydrogel can not only improve the mechanical properties of the material, but also improve the effect of cell adhesion and tissue repair [2]. Therefore, the development of composite hydrogel with both biological activity and mechanical properties has become an important research direction at present.

2.3 Basic Physicochemical Properties of Hydrogels

The reason why hydrogel can be widely used in the field of biomedicine is closely related to its unique physicochemical properties [5].

First of all, hydrogel has a high water content. Most hydrogels contain a large amount of free water inside, and their water content can reach more than 70%, and some even exceed 90% [1]. This high-water content makes its structure similar to that of human soft tissue, thus improving the compatibility between materials and tissues.

Secondly, hydrogel has good biocompatibility. Most hydrogel materials do not produce obvious toxicity or irritation to human tissues, so they are suitable for wound dressings and tissue engineering support [5]. In addition, hydrogel also has strong absorption ability and breathability. When the wound produces exudate, the hydrogel can absorb excess liquid in time, while allowing oxygen to diffuse into the wound area, providing a suitable environment for cell growth [8].

In recent years, researchers have also developed a variety of smart hydrogels. Such materials can release drugs or change their own structure according to environmental changes, so they are getting more and more attention in the field of precision processing.

3. Mechanism of action of hydrogels in promoting wound repair

3.1 Maintaining a moist healing environment

During wound healing, an appropriate moist environment can promote cell migration and tissue regeneration. Traditional gauze is easy to cause the surface of the wound to dry out, and even damage the new tissue when changing the dressing [7].

In contrast, hydrogel has excellent water retention ability and can form a stable moist environment on the wound surface [8]. This environment helps to promote cell proliferation, reduce scab formation, and accelerate the process of epithelial tissue reconstruction. At the same time, a humid environment can also reduce the pain of patients and improve the comfort of treatment [1]. Therefore, maintaining a continuous and stable humid environment is considered to be one of the important mechanisms for hydrogel to promote wound repair [7].

3.2 Antibacterial and anti-inflammatory effects

Infection and persistent inflammation are one of the important factors affecting wound healing.

When bacteria multiply, it will not only destroy the new tissue, but also stimulate the body to produce excessive inflammatory reactions, thus slowing down the wound repair process [8].

Many hydrogels have a certain antibacterial ability, among which chitosan-based hydrogel is a widely studied material. Chitosan is positively charged and can interact with bacterial cell membranes, destroying the cell membrane structure, thus inhibiting bacterial growth [9,10]. In addition, some functionalized hydrogels can also load silver ions, antibiotics or natural antibacterial ingredients to further enhance the antibacterial effect [9].

In addition to antibacterial effects, hydrogel also plays an important role in regulating inflammatory reactions. Studies have found that some hydrogel can reduce the expression level of pro-inflammatory cytokines such as TNF-α and IL-6, thus reducing local inflammatory reactions [8]. Studies by Huang et al. show that hydrogel with anti-inflammatory function can improve the wound microenvironment, reduce the excessive aggregation of inflammatory cells, and promote the subsequent tissue repair process [8].

Therefore, by using antibacterial and anti-inflammatory effects at the same time, hydrogel can create a more stable repair environment for wound healing.

3.3 Promotes cell proliferation and angiogenesis

Cell proliferation and angiogenesis are indispensable key links in the wound repair process. New blood vessels can provide oxygen and nutrients for damaged tissues, while cell proliferation helps to form a new tissue structure [6].

The three-dimensional network structure of hydrogel is similar to the extracellular matrix in the human body, so it can provide space for cells to adhere, grow and migrate

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[2]. In this microenvironment, repair-related cells such as fibroblasts and keratinocytes can more easily enter the damaged area and participate in tissue reconstruction [6].

In addition, some functional hydrogels can also load growth factors and continuously promote tissue repair through slow release [11]. Fu et al.'s research found that a natural bio adhesive hydrogel can regulate the functional state of macrophage, promote angiogenesis, and significantly improve diabetic wound. The wound closing speed in the model [9]. The research results show that the experimental group formed more new blood vessels and collagen tissue, indicating that hydrogel has a positive promoting effect on tissue regeneration [9].

Therefore, hydrogel can also accelerate the wound healing process by promoting cell proliferation and angiogenesis.

4. Application Effects of Hydrogels in Promoting Tissue Regeneration

4.1 Application in Skin Tissue Regeneration

Hydrogel has a wide application prospect in the field of skin regeneration. Due to its high-water content and good biocompatibility, hydrogel can simulate the natural extracellular matrix and provide a suitable environment for cell growth [2].

In recent years, a variety of hydrogels have been used to promote the repair of chronic wounds and burn wounds. The research of Fu and others has built a natural bio adhesive hydrogel and applied it to the diabetic wound model. The results show that the hydrogel can regulate macrophage polarization, promote angiogenesis, and significantly accelerate the speed of wound closure [9].

Compared with the control group, the experimental group formed more neovascular and collagen tissue, showing better tissue regeneration ability [9].

In addition, hydrogel containing chitosan can also reduce the risk of bacterial infection, thus further improving the quality of wound healing [10]. Therefore, hydrogel has become one of the important directions of modern wound dressing research.

4.2 Application in bone tissue regeneration

Bone regeneration is one of the important contents of tissue engineering research. Although traditional bone transplantation can repair bone defects, there are still problems such as limited donor sources and postoperative complications.

In recent years, biomimetic mineralized hydrogel has received wide attention. This kind of hydrogel can simulate the microstructure of natural bone tissue and provide a suitable environment for the proliferation and differentiation of osteoblast [12].

Research by Zhao et al. pointed out that mineralized hydrogel can promote calcium deposition and new bone formation, while improving the mechanical stability of the defect area [12]. Due to its good plasticity and biological activity, this type of hydrogel has great application potential in the field of bone defect repair in the future.

4.3 Applications in the repair of cartilage or nerve tissue

Compared with bone tissue, cartilage's self-healing ability is weak, so finding effective repair materials has always been a research hotspot [13]. The review of Hashemi-Afzal et al. points out that hydrogel can be used as a three-dimensional scaffolding material to provide a suitable growth environment for chondrocytes and promote extracellular matrix deposition [13]. Some can also release growth factors according to the changes in the surrounding environment, thus further promoting cartilage regeneration [11].

Hydrogel is also of great value in the field of neurological tissue repair. Because its soft structure is similar to that of nerve tissue, it can reduce mechanical damage after implantation and provide a supporting environment for axon regeneration [14]. Research shows that functionalized hydrogel with electrical conductivity can promote nerve signal conduction and improve the efficiency of nerve repair [14]. Therefore, hydrogel shows good application prospects in cartilage tissue and nerve tissue regeneration.

5. Current Problems and Future Development

5.1 Major research findings

As a class of high-water-content biomaterials with excellent biocompatibility and tissue-mimicking structure, hydrogels have shown unique superiority and irreplaceable application value in wound repair and tissue regeneration [1,5]. This paper systematically classifies hydrogels into natural hydrogels, synthetic hydrogels, and smart responsive hydrogels, and summarizes the respective characteristics of different hydrogel systems. Natural hydrogels possess outstanding biocompatibility and biodegradability, while synthetic hydrogels are featured with tunable mechanical strength and structural stability [2,4]. In comparison, emerging smart hydrogels can respond to external environmental stimuli, providing new ideas for precise regenerative medicine [11].

In terms of repair mechanism, hydrogels achieves efficient wound healing through a variety of collaborative ways [5]. It can maintain a stable and moist wound microenvironment and avoid scab formation and secondary tissue damage. At the same time, hydrogels can play a good antibacterial and anti-inflammatory effect by inhibiting bacterial proliferation and down-inflammatory cytokines [8,9]. In addition, the three-dimensional network structure of hydrogels can simulate extracellular matrix, provide support for cell adhesion, proliferation and angiogenesis, and ultimately accelerate tissue remodeling [10].

At the practical level of application, hydrogels have achieved good results in many types of tissue regeneration scenarios. In addition to the common skin wound repair, functional hydrogels also show great potential in bone defect reconstruction, cartilage repair and nerve tissue regeneration, which fully proves that hydrogel biological materials are used in tissue engineering and regenerative medicine. Broad development prospects in the field.

5.2 Existing defects and limitations

Although hydrogel-related research has developed rapidly and has a broad application prospect, there are still obvious shortcomings in materials, which limits their large-scale clinical transformation [15].

First of all, most natural hydrogels have insufficient mechanical properties. The structural strength is low, and it is prone to rupture and failure when applied to moving parts or high-stress wounds, which greatly reduces the stability of actual use.

Secondly, the degradation rate of hydrogels is difficult to regulate accurately. The degradation rate and the tissue repair process are prone to mismatch, which cannot provide long-term effective structural support for wound healing [4].

Finally, although multifunctional hydrogels and smart hydrogels have made a lot of progress in laboratory research, most of the existing experimental data are limited to animal models. Long-term biosafety evaluation and standardized clinical data are still scarce, and some material preparation processes are complex and expensive, which restricts their industrialization and large-scale clinical application [15,16].

5.3 Future development prospects

With the continuous progress of material modification technology and bionic design concept, hydrogel biological materials will develop in the direction of high mechanical stability, multifunctional integration and intelligent and accurate clinical treatment in the future [11].

First, composite hydrogel technology will continue to be optimized. Combining the biological advantages of natural hydrogels with the mechanical advantages of synthetic hydrogels, the development of modified composite materials that take into account biological activity and structural stability will become the mainstream research direction at present [2].

Second, the stimulus responsive smart hydrogels will continue to iterate and upgrade. Intelligent hydrogels that can respond to temperature, pH and biological signals can realize on-demand drug release and dynamic regulation of micro-environment, which is expected to achieve accurate and phased treatment of wounds [11,16].

Third, future research will focus on promoting the clinical transformation of hydrogel materials. On the basis of optimizing material performance, improve standardized biosafety testing, long-term efficacy verification and low-cost preparation technology, and further expand the clinical application scope of hydrogels in the field of wound repair and multi-tissue regeneration [15].

In summary, hydrogels are promising advanced biomaterials in regenerative medicine. Continuous optimization of material performance and in-depth clinical translational research will enable hydrogels to play a greater role in future tissue engineering and clinical wound treatment [15].

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