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Hydrogel dressing in diabetic wound healing

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Abstract. With the intensification of social ageing, the number of geriatric patients continues to increase. Among them, the problem of diabetic patients whose wounds cannot heal for a long time and even cause amputation has received widespread attention. Excessive inflammation caused by adverse exogenous and endogenous factors that interfere with the regulation of wound inflammation is the main factor in the failure of the wound to heal according to standard procedures. As a polymer with a three-dimensional structure, the hydrogel is expected to be a new type of chronic wound dressing with good potential due to its good biocompatibility and drug loading. Summarizing the advantages of new functional hydrogel dressings and the progress of research in diabetic wounds, it is expected to provide some new ideas for clinical research and functional improvement of hydrogels.

Keywords: hydrogel, diabetes, wound healing, anti-inflammatory

1. Introduction

As the largest organ and outermost layer of tissue in the human body, the skin is the main barrier against external environmental stimuli [1]. Therefore, research on the rapid healing and regeneration of injured skin is of great significance in effectively improving the quality of life of patients and reducing wound pain. In some cases, the appearance of acute inflammation caused by a bacterial infection or other factors causes chronic wounds not to be repaired in a timely and orderly manner according to the normal healing stage, which poses a great challenge to the clinical treatment of chronic wounds such as diabetes [2]. Therefore, the development of hydrogel dressings combined with novel antibacterial and anti-inflammatory technologies has become a key means to solve the problems of wound healing and skin repair.

2. Problem of wound healing

2.1. Wound healing stage

Wound healing is a complex physiological process, which is generally divided into four stages - hemostasis, inflammation, proliferation and remodeling [3], and the orderly progress of each stage can ensure wound healing.

As soon as the skin is damaged, the exposed collagen triggers an intrinsic and extrinsic clotting cascade [4]. The release of coagulation factors can stimulate fibrin matrix deposition, platelet aggregation and trigger vasoconstriction to reduce blood loss, and after 5-10 minutes of vasoconstriction, platelets and leukocytes migrate into the temporary matrix. Platelets release chemical signals that allow

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white blood cells to migrate from blood vessels in the direction of injury. Platelets kill bacteria by activating the clotting cascade, which stimulates the wound to produce inflammatory cells. In addition, platelets secrete proteins such as thrombospondin and growth factors such as insulin growth factor (IGF), platelet-derived growth factor (PDGF), and transforming growth factors (TGF-a, TGF-B)) to assist in the wound healing phase after hemostasis [5]. The early stages of inflammation involve the activation of the innate immune system, and locally released growth factors (GFs) and cellular mediators recruit inflammatory cells such as neutrophils and monocytes to the wound site, inducing the activation of intracellular signaling pathways, resulting in the expression of a large number of genes such as cytokines, chemokines, and antimicrobial peptides to initiate and maintain the inflammatory response, thereby achieving the effect of removing foreign bodies, bacteria, and harmful endogenous tissues. In the later stages of inflammation, macrophages produce cytokines and growth factors that help fibroblasts and endothelial cells proliferate and begin to enter the proliferative phase. The proliferative stages include granulation tissue formation, vascular regeneration, and reepithelialization. Granulation tissue is composed of a large number of fibroblasts, granulocytes, macrophages, and blood vessels, which partially restore the structure and function of the injured skin. Fibroblasts play a central role in the formation of granulation tissue, fibroblasts proliferate in large quantities through mitosis, synthesize and secrete a large number of collagen fibers and matrix components from 4~5 or 6 days, and form granulation tissue together with new capillaries, fill wound tissue defects, and create conditions for the coverage of epidermal cells [6]. During the proliferative phase, new blood vessels are formed, and the synthesis of enhanced collagen fibers begins. Epithelial cells, fibroblasts, and keratinocytes build granulation tissue. Complete repair of skin wounds can take weeks or even more than a year. The exact duration depends on the patient's age and health.

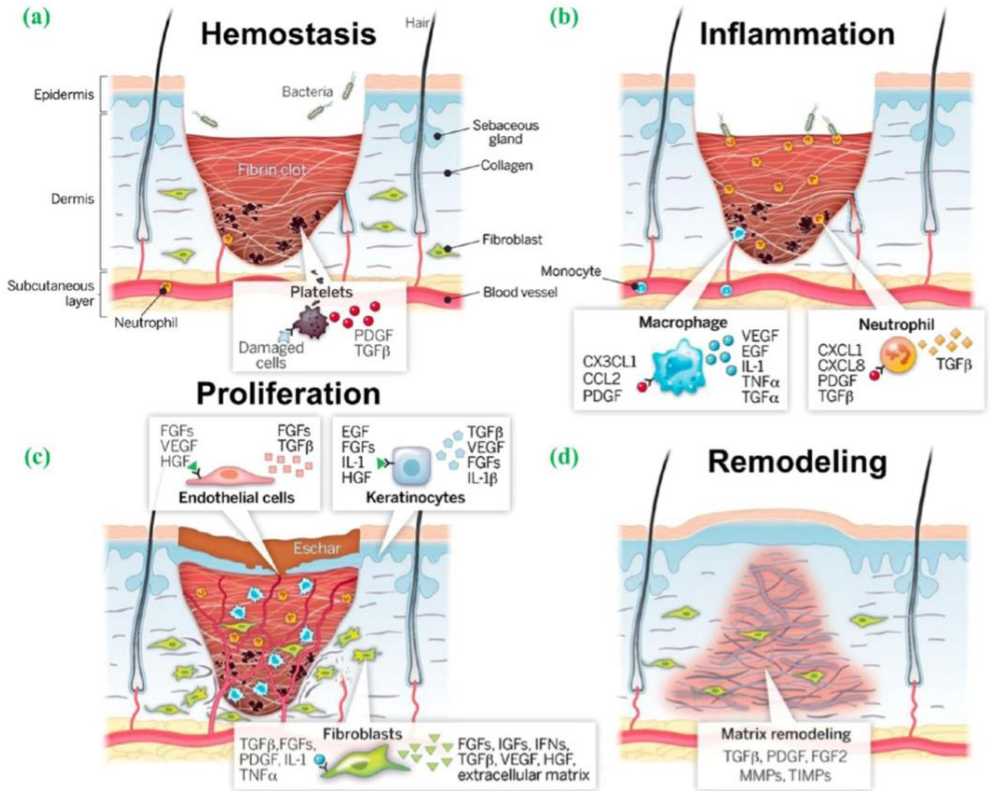

Figure 1. Four stages in wound healing: (a) hemostasis, (b) inflammation, (c) proliferation, and (d) remodeling [7].

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2.2. Chronic wounds

According to the nature of wound healing, it can be clinically divided into acute wounds and chronic wounds. Acute wounds are usually caused by mechanical or chemical injuries or burns, and the wound can heal completely, usually in 8-12 weeks. Chronic wounds are wounds that are caused by various pathological factors due to the presence of an underlying disease, deviate from the normal healing process of the wound in some way, and stagnate at a certain stage [8]. Chronic wounds have a high bacterial biofilm loading rate, with defects such as persistent inflammatory phases, excessive proteolysis, etc. Slow formation of new blood vessels, impaired angiogenesis, and inadequate supply of oxygen and nutrients to the wound site further delay the advancement of the wound healing process. Chronic wounds do not heal after 12 weeks and have no tendency to heal.

Studies have shown that the main causes of impaired healing of diabetic foot ulcers (DFU) [9] include vascular lesions, neuropathy and infection [10]. Hyperglycemia and abnormal glucose metabolism in diabetic patients lead to vascular-related diseases that affect the distribution of distal vessels emanating from the femoral artery, arch of the foot artery, and metatarsal artery. When the distal artery is unable to efficiently distribute oxygen and nutrients to the wound, defects in microcirculation, decreased capillary size, hardening of the basement membrane, and defects in arterioles occur. In addition, endothelial cell dysfunction can occur, reducing basic physiological activity, including nitric oxide synthase, and the inability of arteries and arterioles to dilate, resulting in abnormal blood flow and poor wound healing. In addition, diabetes mellitus can cause neuropathy, impairing the function of motor, sensory and autonomic nerve fibers, reducing their ability to detect pressure, and causing nerves to be insensitive to external heat, pressure and other stimuli from the wound. As a result, people with diabetes experience repetitive foot trauma that leads to poor wound healing. Besides, hyperglycemia [11] is the main source of infection, because high blood glucose concentration can inhibit the phagocytosis of white blood cells, reducing the ability to prevent infection, and the high sugar environment is a good medium for bacteria, so bacterial infections such as Escherichia coli and pneumococcus are extremely common in diabetic patients. When the body's resistance is weakened and a wound appears, bacteria will take advantage of the weakness and cause wound infection. Abnormal glycemic control can lead to immune dysfunction in the body, impair white blood cell activity and complement function, and accelerate the development of tissue infection. Therefore, diabetic patients are susceptible to infection and not easy to heal.

As a result, the wound healing process in patients with hyperglycemia stalls at any of the four stages of normal wound healing, eventually manifesting as long-term symptoms of inflammation.

2.3. Treatment of diabetic foot ulcers

In modern life, a variety of methods have been shown to promote the healing of DFU and reduce the incidence of amputation, including local wound glycemic control, debridement of the wound site, foot decompression, hyperbaric oxygen therapy, electrical stimulation, negative pressure wound therapy, topical use of growth factors and dressings, etc.

Glycemic control: Abnormal blood glucose levels are a major cause of several complications in patients with diabetes and an important factor in impaired healing of DFUs. When the patient's blood glucose level > 11.1 mmol/L, neutrophil function is significantly impaired. At the same time, high blood sugar levels increase the rate of wound infection in patients. It also increases the incidence of peripheral arterial disease. Therefore, effective control of the patient's glycemic index is essential for the healing of DFU.

Wound debridement: Through debridement, necrotic tissue, protein fragments and infectious substances can be removed from the wound surface, effectively promoting the production of granulation tissue, reducing the number of wound infection bacteria, and stimulating the secretion of local growth factors to improve wound healing. Existing debridement methods include surgical debridement (performed by scalpel, tissue forceps, bending scissors, etc.), autolytic debridement (artificially creating a moist wound environment to activate the host's autonomic defense mechanisms), and enzymatic debridement (collagenase, papain, and dextran derived from animals such as crabs).

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Topical use of growth factors: Studies have shown that the addition of growth factors (such as insulin-like growth factor, fibroblast growth factor, platelet-derived growth factor, and epidermal growth factor) to dressings can effectively stimulate cell mitosis, improve cell chemotaxis, and accelerate wound healing. However, it should be noted that some growth factors are carcinogenic.

Dressings: Ideally, dressings for wound healing in DFU should have functions such as maintaining water balance at the wound site, stimulating the production of self-growth factors, antibacterial, and oxygen permeability. In addition, therapeutic dressings containing drugs should have a controlled drug release capacity. All things considered, the hydrogel is undoubtedly the most advantageous new wound dressing at this stage.

3. New wound dressing – hydrogel

3.1. Development of hydrogels

Traditional wound dressings mainly include gauze, bandages and foam dressings. Although these wound dressings have been successfully used in clinical practice for a long time, these traditional dressings have many defects, such as poor antibacterial effect, which make the traditional dressings not achieve the expected therapeutic effect. Therefore, the development of a novel dressing that promotes chronic wound healing has attracted great attention.

First of all, the hydrogel has a high-water content, which can provide the moist environment needed for wound healing while achieving the pain of cold compresses. Secondly, the hydrogel has good biocompatibility, is non-toxic and biodegradable, is safe to use, and will not cause rejection reactions such as hypersensitivity and inflammation. In addition, the three-dimensional network cross-linking structure of the hydrogel does not affect the gas exchange and normal respiration of cell tissues, which is conducive to the repair, growth and reproduction of cells at the wound. Its special structure can also be used as a carrier of functional materials, containing a variety of drug molecules that are beneficial to wound repair, preventing them from dissolving quickly, and controlling their continuous and efficient release at the target site.

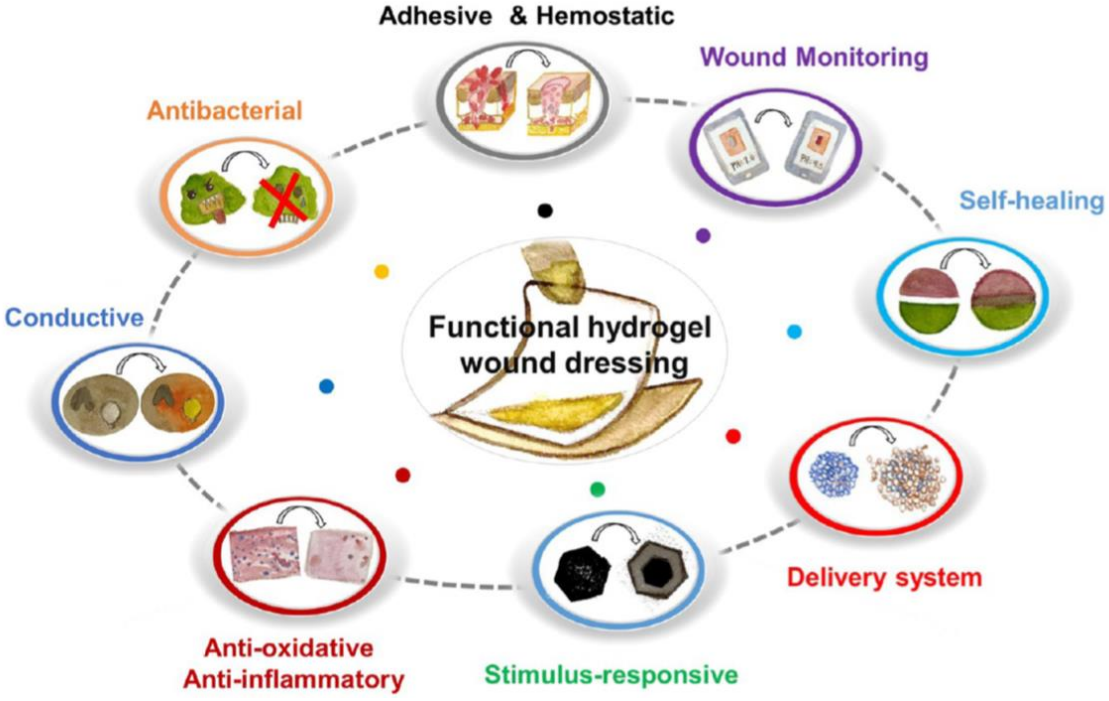

Figure 2. Advanced functions appeared in hydrogel wound dressing [12].

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3.2. The progress of antibacterial hydrogel

The development of antimicrobial agents combined with hydrogels as wound dressings is very promising. As research has evolved, many antimicrobial hydrogels have been developed, such as, nanoparticle hydrogels with metal ions (silver, copper, gold); metal oxide (zinc oxide, titanium dioxide, nickel oxide) nanoparticle hydrogel; Hydrogels containing antibiotics (ciprofloxacin, gentamicin, vancomycin); Bio-extracts (honey, curcumin, vitamin E) encapsulated hydrogels; Hydrogels containing antimicrobial polymers (chitosan, polylysine, polyethyleneamine); hydrogel containing antimicrobial peptides; Carbon materials (graphene oxide) are coated with hydrogels, etc. [13]. However, some antimicrobial materials have various defects due to their inherent properties, such as, if too much metal nanoparticles are used, they may cause symptoms such as dermatitis, redness, swelling, itching and ulceration of the wound skin; Long-term misuse of antibiotics has led to the emergence of drug-resistant bacteria (methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci) [14] and some intractable superbugs, which are resistant to a variety of antibiotics and seriously hinder wound repair and skin regeneration; Although bioextracts are non-toxic, they are clinically deficient due to their low water solubility, low stability, and poor bioavailability.

At this stage, the method of using photothermal technology to achieve an antibacterial effect is extremely advantageous. Photothermal therapy is mainly used for the treatment of a variety of common tumors, and the exploration of its antibacterial properties is still in the initial stage of research, and has great potential for development in the field of treating chronic skin wounds. The principle of photothermal antimicrobial technology is the photothermal effect, which usually uses near-infrared light to irradiate the surface of objects where bacteria are present, and uses appropriate photothermal agents to convert light energy into local physical heat, taking advantage of the sensitivity of bacteria to high temperatures, resulting in the death of bacteria by heat [15]. Through the efforts of researchers, multifunctional hydrogels with a variety of photothermal properties have been developed.

Zhou et al. [16] introduced gold nanoparticles into the mesoporous structure of mesoporous polydopamine and modified the hydrogel. Experiments have proved that the presence of hydrogels greatly reduces the toxicity of gold nanoparticles to the skin, making them have long-term biocompatibility. The combined use of two photothermal agents, mesoporous polydopamine and gold nanoparticles, results in an enhanced photothermal effect (approximately 70°C). Moreover, the hydrogel has excellent reproducible photothermal antibacterial ability. However, high temperatures can cause damage to the healthy tissue cells around the wound. Therefore, it is of great significance to reduce the effective antimicrobial temperature of PTT. Qiao et al. [17] prepared a self-healing hydrogel with certain photothermal stability, in which Fe3+ oxidized dopamine and polydopamine-encapsulated poly(thiophene-3-acetic acid) were added as active ingredients to stably increase the temperature by 23°C. After 10 minutes of near-infrared exposure, the survival rate of both E. coli and methicillin-resistant Staphylococcus aureus was less than 0.0001%. Experiments have proved that the combined application of photothermal antimicrobial technology and low concentration of antimicrobial agents can produce better antibacterial effect in hydrogel dressings while reducing the damage caused to the body. Although Qiao et al. [17] effectively reduced the temperature of PTT antimicrobial action, it still did not meet the ideal range (below 50°C) to prevent normal tissues from being destroyed by high temperatures. Zhao et al. used glycocalyx to simulate the function of phenylboronic acid to make the hydrogel specifically capture the bacteria on the surface of the hydrogel and destroy the bacterial membrane, which enhanced the sensitivity of bacteria to PTT, so that the hydrogel could achieve a good antibacterial effect at a temperature lower than 49.6°C. In addition, the use of non-covalent hydrogen bonding of polydopamine (PDA) with carboxymethyl chitosan and polyacrylamide (Fig. 3), the highly dynamic reversible borate covalent bonding of PDA to phenylboronic acid-functionalized graphene, and the stacking of PDA give the hydrogels good mechanical properties and self-healing ability.

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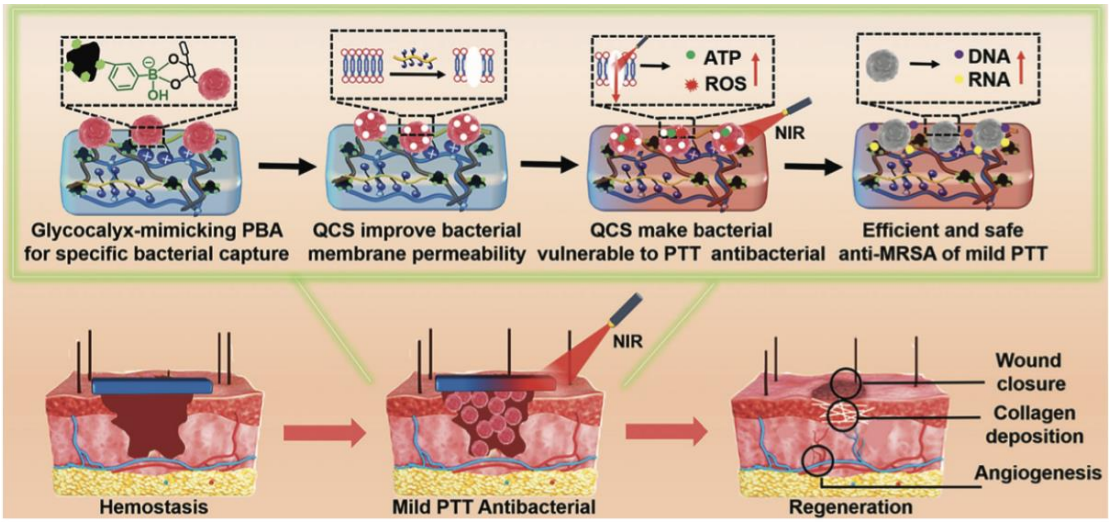

Figure 3. [17] Schematic diagram of photothermal antimicrobial repair performance of multifunctional hydrogel dressing First, glycocalyx mimicking phenylboronic acid can capture methicillin-resistant Staphylococcus aureus on the surface of hydrogels. The carboxymethyl chitosan will then disrupt the membrane of the trapped bacteria and achieve an effective antimicrobial effect through a mild photothermal effect at low heat (below 50°C) coordinated by photothermal 3- aminophenylboronic acid modified reduced graphene oxide (rGB). Biocompatible hydrogels accelerate tissue regeneration and healing of infected wounds.

3.3. Limitations of enhanced mechanical properties of hydrogels

It is important to note that the rupture of the hydrogel due to mechanical stretching significantly increases the risk of infection by external bacteria. Consequently, the quest for effective methods to enhance the mechanical strength of hydrogels while preserving their structural integrity has garnered significant interest within the scientific community. In recent years, self-healing hydrogels have been developed. As a new type of smart material, self-healing hydrogel has better mechanical properties than traditional hydrogels, and in addition, hydrogels have achieved self-healing functions and structural damage functions due to their dynamic and reversible three-dimensional polymer network structure prepared by physical or chemical cross-linking [18].

So far, researchers have developed multiple types of hydrogel dressings with different properties, and the current stage of hydrogel dressings has shown injectability, strong adhesive properties, good self-healing ability, efficient antibacterial ability, antioxidant capacity and drug release properties.

According to the healing mechanism, self-healing hydrogels can be divided into physical self-healing hydrogels and chemical self-healing hydrogels. Physical self-healing hydrogels reconstruct networks between molecules, oligomers, or polymer chains by forming dynamic non-covalent interactions [19] (e.g., hydrophobic interactions, host-guest interactions, hydrogen bonding, crystallization, metal-ligand synergies, etc.). Chemical self-healing hydrogels rebuild the network by forming dynamic covalent bonds such as hydrazide, phenylborate, disulfide, imine, metal-ligand coordination, reversible radical reaction, and reversible Diels-Alder cycloaddition reaction. Among them, Schiff base bonds, imine bonds, are widely used in self-healing hydrogels, and the structure is formed by the reversible condensation reaction of primary amines and active carbonyl groups [19] (such as aldehyde groups and ketone groups). Schiff base bonds are one of the few dynamic cobonds that can be formed without stimulation, and dynamic equilibrium can be achieved in the presence of water molecules. In addition, aromatic Schiff bonds are more widely used than aliphatic Schiff bonds due to their more stable structure.

Huang et al. [20] developed a self-healing hydrogel based on water-soluble carboxymethyl chitosan (CMC) and rigid dialdehyde-modified cellulose nanocrystals (DACNCs). Through dynamic Schiff bond cross-linking between CMC and DACNC, the hydrogel is self-healing in less than 5 minutes without external force. In addition, it has been found that the mechanical properties of hydrogels can be

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effectively improved by adjusting their concentration and crosslink density. Zhang et al. [21] introduced adipic acid, diacylhydrazide and calcium ion (Ca2+) into quaternary ammonium, carboxymethyl chitosan and aldehyde-modified hyaluronic acid to prepare a novel hydrogel. Through the synergistic effect of imine bonds, hydrazone bonds and coordination bonds, the mechanical properties and self-healing properties of hydrogels were significantly improved. Experiments have shown that the hydrogel has a compressive stress of up to 896.30 kPa. In addition to chitosan, other amino polymers, such as gelatin, can also be used to form imine bonds with aldehyde functionalized polymers to prepare dynamic hydrogels, which proves the versatility of imine bonds in practical applications.

Due to its high mechanical strength and self-healing ability, the self-healing hydrogel successfully ensures its structural integrity, making it less prone to tearing, reducing the risk of wound exposure and reinfection to a large extent, and avoiding further damage to the wound. It is worth noting that the hydrogel formed based on the dynamic Schiff base bond can be painless removal by using amino acid solution and reduce the pain of the patient when changing dressings [18], which is an advantage that other hydrogels do not have. However, it should be noted that as the crosslinking density increases [17], the pore size of the hydrogel decreases significantly, which reduces the swelling rate of the hydrogel, limits its ability to be used for drug delivery, and adversely affects cell growth.

4. Conclusion

In order to avoid the toxic effect of hydrogel dressings on the skin, most of the research teams adopted the strategy of using natural materials as the main body and modifying them to prepare hydrogels, which also achieved certain results in enhancing the antibacterial effect, shortening the wound healing time and reducing the pain of dressing change. However, the hydrogels on the market still cannot meet the various clinical needs for wound healing. In order to cope with the problems of insufficient toughness of hydrogels and long repair time after rupture, we can try to develop bilayer hydrogels with strong and weak bond layers in the future. The strong bond layer adopts a high-toughness structure, which is not easy to break, which limits the activity of the human wound to a certain extent and avoids wound rupture. The weak bond layer adopts a structure with self-healing properties to ensure the repair of the hydrogel after fracture. When stretched, the strong bond layer does not break, maintaining the integrity of the hydrogel, and the breakage of the weak bond layer improves the mechanical properties of the hydrogel, thereby reducing the risk of microbial infection during wound exposure. Studies have shown that mild stimulation at temperatures between 40-43°C can promote angiogenesis, and mild thermal effects should promote type I collagen deposition and neurovascular reintegration, aiding wound healing [22]. Therefore, in addition to high-temperature antimicrobial treatment using the photothermal effect, skin repair can also be carried out with gentle PTT. In the future, we can develop temperature-adjustable hydrogels that can achieve different effects of sterilization and skin cell regeneration at different stages of wound treatment.

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