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Application of Hydrogel in Skin Repair

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Abstract: Skin repair has been one of the greatest challenges in human history. Today, with the dramatic increase in chronic diseases and surgical procedures, the demand for wound dressings has gradually increased. Hydrogel, due to their excellent hydrophilicity, biocompatibility and three-dimensional (3D) porous structure, are widely used in wound dressings. In this paper, the process of skin wound healing, the application of hydrogel in skin repair and other applications of hydrogel are introduced. Finally, the development of hydrogel materials in the field of wound healing is prospeced.

Keywords: Skin repair; wound dressing; hydrogel.

1. Introduction

As the largest organ in the human body, skin plays a vital role in sensing external stimuli, regulating body temperature, controlling evaporative water loss, protecting tissues/organs from physical or chemical damage, and resisting pathogens[1]. Therefore, when skin lesions or injuries are caused, the lack of graftable autologous skin often leads to chronic wound healing delay, seriously damaging the appearance and physiological function of the skin[2].Large-scale skin defects can also induce systemic diseases, such as metabolic aggravation, excessive diffusion of water and proteins, immune system dysfunction, disability, and even death in severe cases[3]. In addition, without proper wound treatment, in the later stage of skin wound healing, pathological scars will form and seriously damage the appearance and function of the patient[4]. To manage skin wounds, a variety of wound dressings have been developed on the market, including gauze, film, foam, nanofibers, hydrophilic colloids and hydrogels. Hydrogels have received much attention due to their natural extracellular matrix (ECM)-mimik structure, tunable mechanical properties, and simple bioactive substance delivery capabilities. They show great potential for application in skin wound repair. In this paper, the process of wound healing and the latest research progress of conventional natural wound dressings and hydrogel dressings for skin wound repair were introduced. Finally, the future development of hydrogel materials in the field of wound healing is proposed.

2. The Process of Wound Regeneration

As shown in Figure 1, wound healing is divided into four stages: hemostasis, inflammation, proliferation and remodeling.

Hemostasis is the body's instantaneous response to injury to ensure that other functions of the body function properly. The body responds to injury in a series of ways. First, blood vessels compress to limit blood flow, and then platelets gather to close the rupture of the blood vessel. Eventually, clotting occurs and the platelet thrombus is strengthened with fibrin threads[5].

The inflammatory stage usually occurs before the clotting stage is complete, and tissue swelling occurs after the damage has occurred. The swelling fluid promotes the movement of repair cells to the wound site and promotes healing. Inflammation is normal, and pain and swelling in the wound is usually due to enzyme and white blood cell activity.

In the proliferative stage, the fibroblasts and keratinocytes of the wound will produce some pale pink tissue to fill the defect. These pale pink tissues are called granulation tissue because they are similar in shape to granulation. As new tissue, composed of collagen and extracellular matrix (ECM), builds up, the wound begins to contract. When the entire wound is covered by epithelial cells, it marks the completion of re-epithelialization. Collagen is also deposited at the wound site.

The final stage of wound healing is the remodeling stage, which occurs when the wound begins to close as a result of collagen remodeling from type III to type I. At this stage, cells that have served their purpose and are no longer needed are removed[6]. In addition, collagen fibers are cross-linked to improve the strength of the skin around the wound[7].

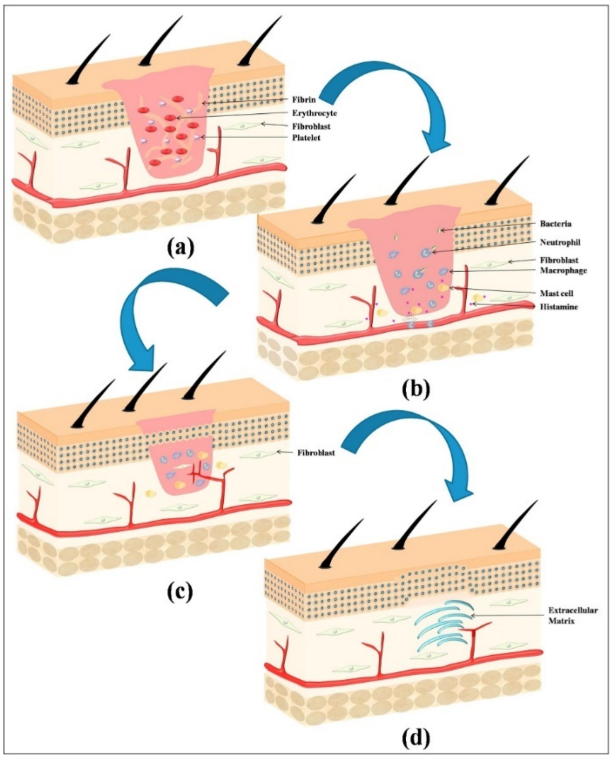

Figure 1. Four stages of wound healing: hemostasis, inflammation, proliferation, and remodeling[8]

3. Application of Hydrogel in Skin Repair

Hydrogels, due to their excellent hydrophilicity, biocompatibility, and three-dimensional (3D) porous structure, have become the most popular choice for wound dressings, while also attracting a lot of Sub-I attention. Over the past decade, research on hydrogels as wound dressings has been on the rise. In addition, the function of hydrogels has changed from a single physical coverage or a single function to the integration of multiple functions now, and shows a trend of becoming more intelligent.

3.1. Adhesion and hemostasis

Quick hemostasis is the first step in wound healing. If there is severe bleeding in the injured tissue and the blood loss reaches more than 30% of the body's blood volume in a short time, it will endanger life[9-10]. The hemostatic function of hydrogels is usually used in combination with their adhesive properties because of the adhesive properties of hydrogels, which enable them to adhere closely to wounds and play a hemostatic role. Studies have shown that hydrogels have hemostatic properties not only because they can physically seal wounds, but also because they can enrich coagulation factors by absorbing wound exudates[11-12].

A common method for preparing viscous hydrogels is to add sticky functional groups to their structure, which can interact with and bind to the surrounding tissue to achieve adhesion. Yu et al. successfully constructed a cluster of stable and uniform hydrogels (HPC) by mixing hyaluronic acid (HA) as a crosslinking agent with polyethylpyrrolidone to form hydrogen bonds (Figure 2). The dynamic and reversible hydrogen bond of HPC makes it injectable, self-healing and flexible.

In addition, many functional groups in hydrogels enhance the adhesion of hydrogels, making HPC hydrogels as hemostatic agents show good therapeutic effect.

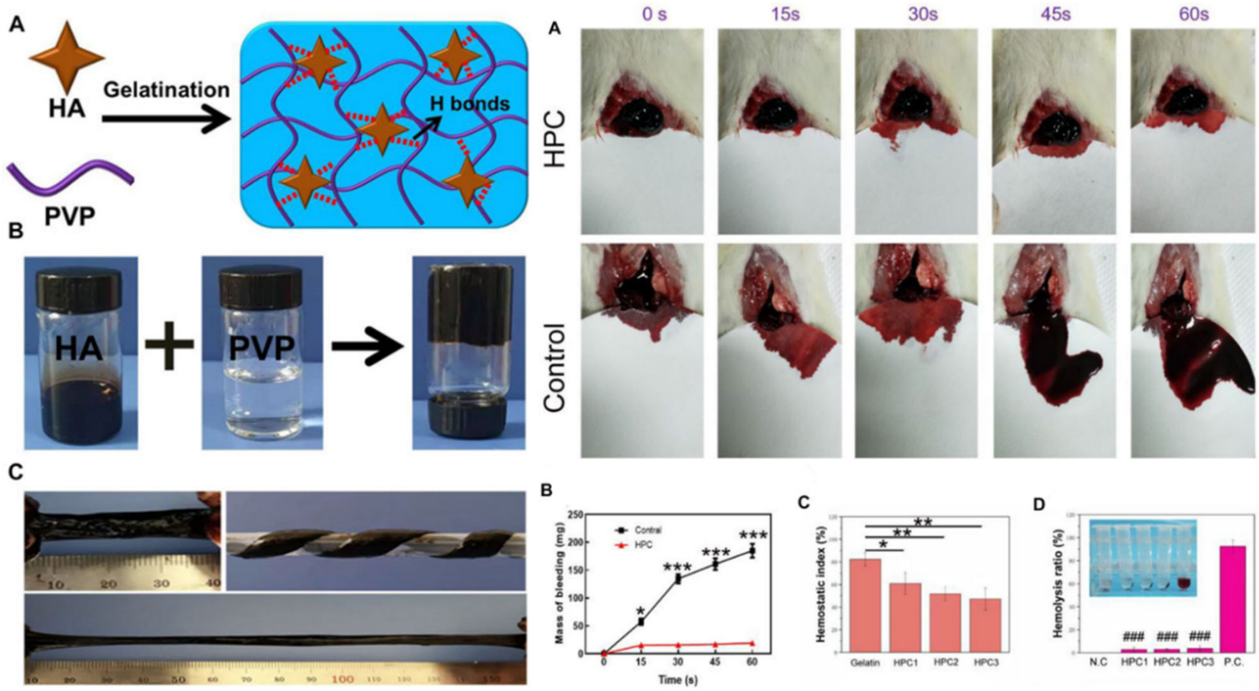

Figure 2. Stretchability, distortion and hemostatic function of HPC hydrogel[13]

3.2. Antioxidant and anti-inflammatory

The inflammatory stage is the second stage of wound healing and usually occurs within a few hours. Inflammatory mediators such as FGF, PDGF, tumor necrosis factor (TNF) α, and interleukin (IL) -1 are expressed in large quantities during the inflammatory phase to remove harmful substances and necrotic tissue. However, if the inflammatory response is too strong, it will delay the healing of the wound. The body can reduce ROS damage at the wound site by releasing the antioxidant system, or small molecules of antioxidants. However, many neutrophils infiltrate the injured site and release proteases, oxygen radicals, and inflammatory mediators, resulting in high levels of ROS, interfering with tissue remodeling, and leading to nonhealing.

Yang et al. developed a multi-functional dynamic boric acid crosslinked hydrogel, which inoculated gelatin (Gel) with 5-carboxyl-3-nitrophenylboric acid (NPBA) and epigallocatechin gallate (EGCG) to achieve rapid gelation at pH=7.4(Figure 3). The EGCG can interact with cations electrostatically. The loading of antimicrobial peptide (AMP) in hydrogel was realized. EGCG in Gel-NB/E hydrogel is released in high glucose and acidic environment through boric acid bond break to clear ROS, reduce inflammation, and regulate the function of macrophage polarization. In addition, because AMP is encapsulated in Gel-NB/E hydrogel, the hydrogel has excellent bactericidal ability.

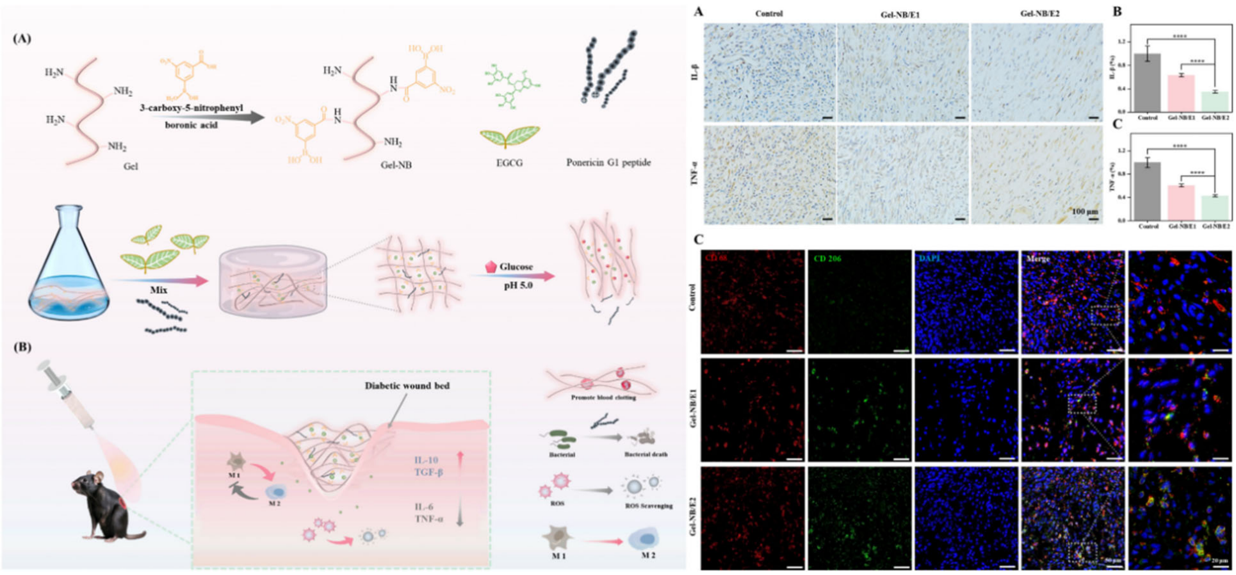

Figure 3. Gel-nb /E/AMP hydrogel dressings can be rapidly constructed to tightly cover diabetic wounds, promoting wound healing by stopping bleeding, antibacterial, reducing inflammatory response, and regulating macrophage polarization[14].

3.3. Antibiosis

Chronic wounds caused by bacterial infections have become a major medical threat and challenge. Bacterial infection can be triggered by the accumulation and growth of bacterial cells at the wound site[15]. Infection can pass through three successive stages: contamination, colonization, and infection[16-17]. Bacterial infection of the wound site leads to delayed wound healing and, in some cases, can lead to serious harmful effects that are life-threatening. Therefore, the need for wound dressings with antibacterial properties is urgent.

Nano-silver has excellent physicochemical properties and wide antibacterial spectrum, so it has become a research trend to apply nano-silver in wound dressing. Wang et al. embedded silver nanoclusters (AgNCs) and mangiferin (MF) molecules into CH hydrogels with 3D network structure (Figure 4). The hydrogel can form a high concentration of Ag ion on the surface of the gel, and the bacteria on the surface of the hydrogel can be captured by electrostatic interaction, which can improve the bactericidal performance of low dose but long term. In addition, MF molecules are conducive to the regeneration of wound capillaries/hair follicles/tissues, thus promoting wound healing.

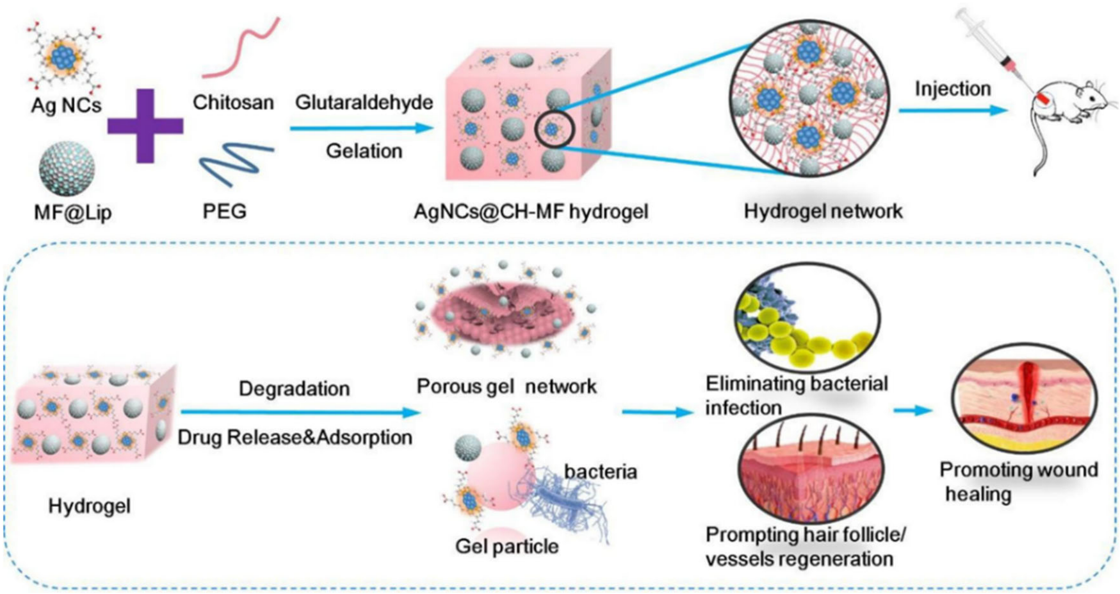

Figure 4. Eliminate bacterial infections and promote hair follicle/vascular regeneration by controlling the surface adhesion properties of AgNCs and MF release[18]

In addition, some cationic substances have also been shown to have antibacterial activity because the positive charge between them attracts bacteria with a negative surface charge, which then kills the bacteria by destroying the bacterial cell membrane[19]. For example, Han et al. prepared a coated gelatin based hydrogel (GelTHB-Fe) adhesive, avoiding the use of strong alkaline agents or strong oxidants(Figure 5). In addition, the introduction of the pyrogallol component gives the hydrogel antibacterial properties and promotes the healing of infected wounds as a tissue adhesive.

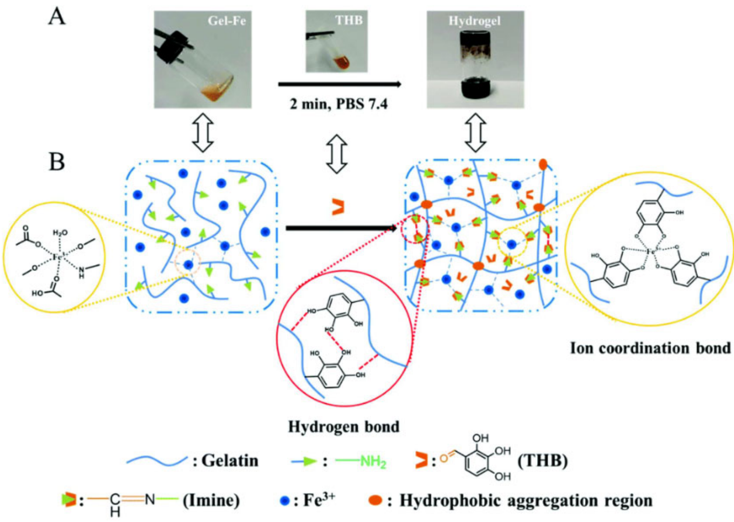

Figure 5. Preparation of GelTHB-Fe hydrogel with self-healing and antibacterial properties[20]

3.4. Regeneration promotion

The wound healing process involves a complex and extensive interaction of growth factors and cytokines that coordinate the recruitment and interaction of various cell types at the wound site. Growth factors are not only effective and safe in the treatment of acute skin wounds, but also promote wound healing without serious adverse reactions[21].

P. siok et al. loaded aspirin-triggered resolvinD1 (AT-RvD1) and IL-10, two key cytokines in controlling immune response, into the hydrogel formed by cross-linking PEG, RGD and VPM (Figure 6). Enrich the wound microenvironment with anti-inflammatory cells of the innate and adaptive immune system to enhance the regenerative response.

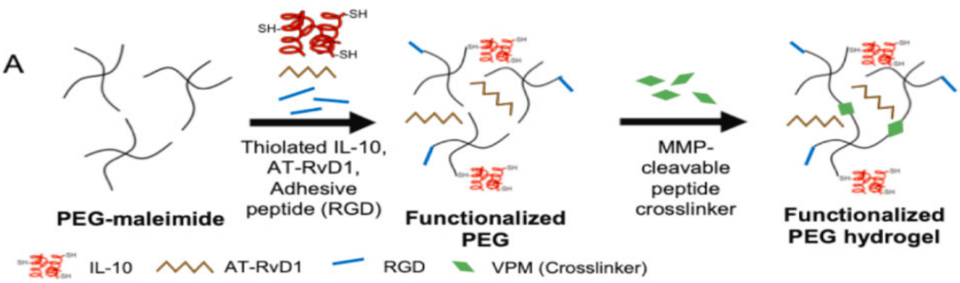

Figure 6. Preparation of PEG hydrogels loaded with IL-10 and AT-RvD1[22].

In addition, nitric oxide (NO), as an endogenously produced gaseous signaling molecule or gas transmitter, is responsible for a variety of systemic regulatory effects and host responses, and has also been proven to promote wound regeneration. Nitric oxide is produced by three subtypes of NO synthase (NOS) : neuronal NOS (nNOS), endothelial NOS (eNOS) and inducible NOS (iNOS), all through the L-arginine-nitric oxide pathway[23-25]. Among them, eNOS is mainly expressed in endothelial cells and plays a role in vasodilation, inhibition of platelet aggregation and adhesion, inhibition of white blood cell adhesion and vascular inflammation, control of vascular smooth muscle proliferation, activation of endothelial progenitor cells and stimulation of angiogenesis[23, 26]. Liu et al. developed a nanoparticle loaded with near-infrared laser-triggered nitric oxide (NO) release, while combining photothermal effects, to synergistically treat bacterial infected wounds(Figure 6).

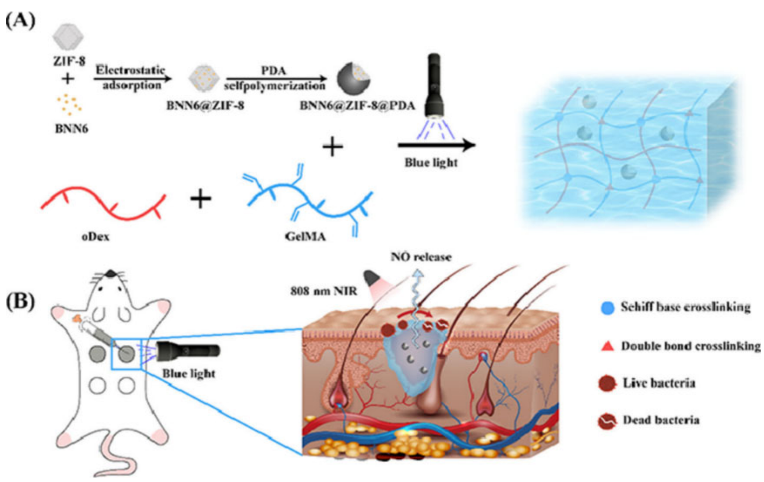

Figure 7. Antibacterial pro-regeneration hydrogels with photothermal effects and NO release properties[27]

4. Other Applications

In addition to being a wound dressing, hydrogels have a wide range of applications. For example, contact lenses are commonly used by more than 125 million people worldwide for eye treatment. Improving the materials for contact lenses is a rapidly evolving discipline. Due to their wide field of view, resistance to wet weather and aesthetics, contact lenses are used by millions of people around the world as an alternative to eyeglasses. There are some types of contact lenses such as soft contact lenses, rigid permeable (RGP) contact lenses, extended wear contact lenses, disposable contact lenses, professional contact lenses (orthokeratography), decorative contact lenses. Due to their rapid recovery and non-invasive use when in contact with biological fluids compared to other biological materials, they have been the subject of considerable research on their deposition levels.Based on their elasticity and modulus, contact lens materials can be roughly divided into rigid permeable (RGP) materials and aqueous gels.

In addition, the application of hydrogels in the skin care industry has gradually attracted attention. So far, a variety of hydrogel cosmetic formulations containing active cosmetic ingredients have been prepared. The selected hydrogel is suitable for cosmetic applications on the skin and is a suitable bioadhesive hydrogel formulation. The hydrogels used in the preparation of cosmetics can be based on a variety of biopolymers, including collagen, gelatin, hyaluronic acid, alginate, chitosan, xanthan gum, pectin, starch, cellulose and its derivatives. Biopolymer based hydrogels are used to develop new cosmetic products such as so-called "beauty masks". These masks claim to moisturize the skin, restore its elasticity, and promote anti-aging effects.

5. Perspectives

Skin wounds are one of the most common clinical diseases, and how to repair various skin wounds quickly and with high quality is still facing many challenges. With the rapid development and cross-fusion of materials science and biomedicine, hydrogels can integrate a variety of excellent properties through flexible structural modification and combination of different functional components, and are widely used in wound treatment and research. Although there have been some advances in wound repair research in terms of cell-derived and tissue-engineered skin construction, we still need to work hard to achieve the goal of "perfect" repair. Since the process of wound repair is a complex and dynamic biological process, it is difficult to use a functional hydrogel dressing to meet the needs of the whole process at the same time, so it is necessary to develop hydrogels with multiple functions and curative effects for different types of wounds and different stages of wound repair, so as to be more convenient for clinical wound repair. In addition, real-time monitoring of the changes of various parameters of the wound microenvironment is very important, and the preparation of new hydrogels that can be dynamically monitored and intelligently responded will be an important research direction in the future, so as to improve the speed and quality of wound repair more accurately and efficiently.

6. Concluding Remarks

In this paper, the stages of wound healing and the study of hydrogel wound dressing were described. Hydrogels have excellent performance in hydrophilicity and biocompatibility, can effectively relieve wound pain and promote healing, and have become an important material for wound repair. Today, technology is advancing at a rapid pace, and researchers are expected to develop smart hydrogel dressings that can monitor wound healing and work on demand to better meet clinical needs. Then, perhaps, healing will no longer bother people.

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