Nanomaterials applied in wound healing: mechanisms, limitations and perspectives

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Abstract

Internal and external factors cause various types of wounds on the skin. Infections, nonhealing chronic wounds, and aesthetic and functional recovery all cause challenges for clinicians. The development of nanotechnology in biomedicine has brought many new materials, methods and therapeutic targets for the treatment of wounds, which are believed to have great prospects. In this work, the nanomaterials applied in different stages to promote wound healing and systematically expounded their mechanisms were reviewed. Then, the difficulties and defects of the present research and suggested methods for improvement were pointed out. Moreover, based on the current application status of nanomaterials in wound treatment, some new ideas for subsequent studies were proposed and the feasibility of intelligent healing by real-time monitoring, precision regulation, and signal transmission between electronic signals and human nerve signals in the future were discussed. This review will provide valuable directions and spark new thoughts for researchers.

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different stages to promote wound healing and systematically expounded their mechanisms were reviewed. Then, the difficulties and defects of the present research and suggested methods for improvement were pointed out. Moreover, based on the current application status of nanomaterials in wound treatment, some new ideas for subsequent studies were proposed and the feasibility of intelligent healing by real-time monitoring, precision regulation, and signal transmission between electronic signals and human nerve signals in the future were discussed. This review will provide valuable directions and spark new thoughts for researchers.

Key words: nanomaterials, wound healing, mechanism, intelligent healing challenges

1. Introduction

The skin covers the surface of the human body and is itslargest organ. The surface area of an adult is approximately 2 m^2. The skinfunctions as a protective barrier between the human body and the external environment, playing an important role in moisturizing, temperature control, sensory perception, humoral balance maintenance and external pathogensresistance(Dabrowska et al., 2018). Due to long-term exposure, the skin bears the brunt of various external stimuli. The wounds caused by destruction of the skin's integrity facilitates the occurrence of diseases. The most common wounds are burns, surgical incisions and cuts, bruises, and lacerations caused by trauma. There are signs of healing in most of these wounds within 3 months due to the self-healing properties of the organism. However, in some cases, such as an uncontrolled infection, these acute wounds can develop into chronic wounds, which last for months or even years(Hoversten et al., 2020). Recently, with the prevalence of chronic diseases such as obesity, diabetes and vascular dysfunction that have risen significantly over time, an increasing number of patients suffer from chronic wounds. Diabetic patients have a 15-25% risk of developing diabetic chronic ulcers(Spampinato et al., 2020). In addition, some infectious skin diseases, such as hidradenitis suppurativa, swimming pool granuloma, sporotrichosis, certainautoimmune skin diseases includingBehcet'ssyndrome, dermatomyositis,some physical skin diseases, such as radioactive dermatitis, bedsores, and some malignant skin tumors, can also make patients vulnerable to chronic wounds. The subcutaneous tissue of chronic and nonhealing wounds is exposed to the external environment for a long period of time, which predisposes patients to bleeding and osteomyelitis. This leads tothe risk of amputation or death for patientsin serious condition. The existence of chronic wounds not only reduces the quality of life of patients and increases their economic burden but also results in adverse mental, motor and psychosocial problems. Expanded medical resources have contributed to a growing burden on the healthcare system. Chronic wounds are so common that they are called silent epidemics(Lindholm et al., 2016).

Wound healing has always been a difficult problem for clinicians, and new materials and methods are urgently needed. With the rapid development of nanotechnology in this century, the nanomaterials produced by the combination of multiple disciplines have beenapplied in the fields of medicine, pharmacy, chemical industry and national defense. Nanomaterials (usually less than 100 nm in diameter) exhibit special physicochemical properties due to their unique structure, which leads to small size effects, surface effects, and macroscopic quantum tunneling effects. In recent years, nanomaterials have also been widely used in wound healing due to their excellent adsorption capacity and antimicrobial properties(Berthet et al., 2017). Wound dressings, which work as temporary skin substitutes, play an important role in hemostasis, infection control and the promotion of wound closure. Various dressing materials have been developed since immemorial time. Traditional wound dressings, such as gauze and bandages, just fill the skin defect(Mihai et al., 2019). The ideal dressing should not only simulate the extracellular matrix (ECM) to provide a moist environment but also have antimicrobial properties and promote cell proliferation and angiogenesis, thus requiring special materials with excellent properties (Table 1).The very large market demand for these materials has accelerated the development of nanomaterial dressings(Han et al., 2017). Currently, new nanomaterial dressings such as hydrogels, nanofibers and films are being widely used. The global market for these products is expected to exceed $20.4 billion by 2021(Homaeigohar et al., 2020).

Although an increasing number of new nanomaterials have been reported for use in wound healing in recent years, their mechanisms have not been comprehensively summarized. Here, we review the potential mechanisms and recent application progress of nanomaterials that promote wound healing fromdifferent aspects,

as well as their possible toxicity. Importantly, we propose the limitations of the current clinical applications and mechanistic research of the nanomaterials in wound healing and provide solutions and new research ideas, which may be research directions in the future.

2. Hemostasis

A rapidhemostasis process is vital in the first phase of wound healing. Nanomaterials have been widely used in wounds due to their excellent hemostatic properties. Compared with traditional gauze, nanoscale sponges have porous structures and a strong capability to absorb water. Nanomaterials cancover the wound surface and promote the formation of blood clots from wetted blood. Both endogenous and exogenous coagulation systems are activated to stop bleeding, and the possible mechanisms of this process have been explored.Nanomaterials recruit blood cells, including erythrocytes, platelets and leukocytes, through electrostatic adsorption or the interaction between sulfhydryl groups and blood cells. The aggregation of erythrocytes occludes the blood vessels and increases the blood viscosity to facilitate the margination of platelets. Expression of the adhesion molecule PECAM-1 increases, which enhances the interaction betweenendothelial cells and platelets(de la Harpe et al., 2019). At the same time, the nanomaterials initiate the activation of platelets by inducing interactions with glycoprotein IIb/IIIa receptors and the influx of extracellular Ca^{2+}(Simak et al., 2017). As the platelets aggregate, blood clots are formed, and subsequently, the nanomaterials accelerate the coagulation cascade by regulating the expression of prothrombin(Onwukwe et al., 2018). On the other hand, the nanomaterialspromote the adhesion and migration of fibroblasts and the crosslinking of fibrin stabilizesthe clot. In addition to the hemostatic ability of the nanomaterials themselves, they are can also be used for wound hemostasis by loading hemostatic drugs. Thrombin-loaded scaffolds potentiate the release of thrombin and activation ofplatelets to reduce bleeding time. The nanomaterials mediate rapid and effective hemostasis to promote wound healing (Figure 1A). Compared with traditional gauze and hemostatic methods, nanomaterials can facilitate clotting through their physical and chemical properties.They show unique advantages for the hemostasis of acute wounds with poor hemostasis effects by suture bleeding and patients with blood coagulation disorders. Thus, the use of nanomaterials is a convenient and effective hemostatic method for chronic open wounds with microvascular bleeding.

3.Anti-wound infections

Wound infection is the most common complication in wound healing. Because of the damaged skin barrier, external microorganisms easily invadeinto wounds. The infection impedes wound healing and involves muscles and bones when the infection spreads. Therefore, controlling wound infection is a prerequisite for the promotion ofwound healing.

3.1 Antimicrobial properties

Studies have examined the antimicrobial actions of nanomaterials against bacteria and fungi.Common pathogenic microorganisms of wound infections, such as*Staphylococcus aureus* , *Escherichia coli* and*Candida glabrata,* wereinhibited by nanomaterials in vitro(Pena-Gonzalez et al., 2017). The mechanism of action of nanomaterials showa wide range of antimicrobial abilities.Nanomaterials can increase bacterial cell membrane permeability by piercing with their sharp edges or interacting with membrane proteins. This loss incell membrane integrity leads to the leakage of cytoplasmic components and eventually bacterial lysis(Liao et al., 2019).On the other hand, the nanomaterialscan infiltrate bacterial cells to destroy proteins, DNA and lipids by binding via sulfurbonds or inducing oxidative stress(Mihai et al., 2019; Singh et al., 2020)(Figure 1B). The widespread abuse of antibiotics has led to bacterial resistance, which is related to microbial target modification, antimicrobial agent modification and the pumping out of the drug from the cell(Mofazzal Jahromi et al., 2018). However, an in vitro study found that there was no significant difference in the bacteriostatic efficacy of nanomaterialsbetween methicillin-resistant *S. aureus* (MRSA) and nonantibiotic-resistant *S. aureus* (Mohamed et al., 2020).Thisresult demonstrated that nanomaterials have the advantage of avoiding antimicrobial resistance mechanisms and are effective against resistant microorganisms.

In addition, microorganisms exist in the form of biofilms in most chronic wounds. In a biofilm, one or

multiple bacterial communities are closely linked together in a dynamic and orderly manner, forming an enclosed film outside the cells. The biofilm develops a reactive oxygen-dependent state that is insensitive to oxidative stress and protects the bacteria from attack by the host immune response. Studies have explored the antibiofilm mechanisms of nanomaterials. A nanosystem made from theF-127 surfactant, tannic acid and polymetforminnanoparticles(FTPNPs), has hydrophilic poly(ethylene glycol) (PEG) chains on the surface of the NPs. The PEG chains assistthe NPs in infiltrating into the biofilms todestroy themby increasing membrane permeability(Li et al., 2020).Moreover, nanomaterials can inhibit the formation of biofilms by reducing interbacterial adhesion through surface charge, hydrophobicity and surface morphology, as well as disturbingquorum sensing (QS)(Ong et al., 2019; Qais et al., 2020).

Notably,most of the current research has focused on common microorganismsthat are usually curable by traditional treatments. However, the challenge of wound healing lies in complex infectionsfrommultidrug-resistant microbes, including bacteria and fungi. Although studies have indicated that nanomaterials have inhibitory effects againstboth bacteria and fungi, there is a lack of in vivo studies fungal wound infections due to difficulty in establishing animal models. Most studies use only a single pathogenic biofilm model. However,synergistic effects among different microorganisms can increase virulence, so it is necessary to evaluate the antimicrobial efficacy of mixed infections. The chronic fungal skin diseasessuch as chromoblastomycosis, sporotrichosis and penicilliosismarneffeiare usually accompanied by skin wounds. There are few drugs with long treatment cycles and high costs for the treatment of wounds with chronic fungal infections. It will be of great benefit to patients if nanomaterials can have clearantifungal effects and greatly shorten treatment time.

In addition, most in vivo wound biofilm models are constructed by inoculation of microorganisms onto excision wound sites. These microorganisms may just be planktonic on the wound surface without an orderly arrangement to form a biofilm(Li et al., 2020). Becauseof various factors, including the host immune response, there are individual differences between differentin vivo biofilm studies. A stable in vivo model and an ideal in vitro model are still needed to explore the antibiofilm mechanism of nanomaterials. Moreover, we should be concerned about the potential risk ofnanomaterials that may lead to microbial variation. Nanomaterials have the ability to cause DNA damage and epigenetic changes. Studies have shown that nanomaterials can lead to drug resistance mutations, and further potential side effects should be considered in addition tofocusing on their antimicrobial properties(Bainomugisa et al., 2018).

3.2 Antimicrobial drug delivery

For a long time, antibiotics have been the first choice for the treatment of wound infections. Considering the impaired blood circulation in chronic wounds, an efficient local delivery system may be an appropriate way to improve the sterilization efficiency of drugs.The high surface area of nanomaterials allows them to deliver antimicrobials to the wound for infection control. Ceftriaxone, gentamicin and itraconazole have been loaded intonanomaterials to develop nanocomplexes with high loading capacities and a slow sustained release of theantimicrobial(Alhowyan et al., 2019; Chen et al., 2020).Moreover, nanomaterials have synergistic antibacterial effects by enhancing the internalization of the antibiotics. Nanomaterialscan increase membrane permeability by affecting the membrane potential and ultrastructure of bacterial cells, which makes infiltration by antibiotics easier(Vazquez-Munoz et al., 2019).

However, with the evolution of antibiotic-resistant bacteria, nanomaterials as drug carriers cannot solve the problem of antibiotic resistance. Antibiotic delivery nanosystems are being replaced by nonantibiotic active ingredient-loaded nanomaterials. It has been proven that tetrahedral framework nucleic acids (tFNAs)can increase the bacterial absorption of antimicrobial peptides by promoting instability of the bacterial membrane. tFNAsalso protect antimicrobial peptides from degradation in the protease-rich extracellular environment(Liu et al., 2020).A number of antimicrobial agents are being developed for wound infections, such as defensins, therapeutic microorganisms (bacteriophages and probiotics) and photodynamic therapy (PDT)(Mofazzal Jahromi et al., 2018). There are currently few studies on nanomaterials as carriers or protectants for these antimicrobial agents.

4. Immunoregulation

Local ischemia, necrosis and microorganisms in wounds trigger the inflammatory response. At this stage, macrophages and neutrophils invade the wound to inhibit the microorganisms and clear necrotic tissue and cells. Nanomaterials can promote beneficial inflammation and immune regulation, making them a new therapeutic strategy for wound treatment.

4.1 Acute wounds

The inflammatory period of acute wounds, such as traumatic wounds and surgical wounds, usually lasts 2-3 days. In this stage, macrophages and neutrophils are recruited and secrete inflammatory factors such as IL-1, IL-10 and TNF-α to clear local microorganisms and necrotic tissue, which is considered to be conducive to wound repair(Vigani et al., 2019).

Nanomaterials have the potential to stimulate innate immunity. Some metal nanomaterials,including TiO_2 NPs, CuONPs and carbon-based nanomaterials, such as graphene,have beenreported to recruit and activate macrophages and neutrophils. This may be related to activation by the nanomaterials that mimic pathogen-associated molecular patterns (PAMPs), inflammatory receptors such as the Toll-like receptors (TLRs), and nucleotides combined with the oligomeric structure domain (NOD) receptor NLRP3(Boraschi et al., 2017; Kinaret et al., 2020).Therefore, we can infer that application of these nanomaterials in the early stage can promote the inflammatory period of clean wounds. However, little attention has been paid to this aspect because the release time of proinflammatory nanomaterials is not controllable, which may cause a continuous inflammatory response and impede wound healing. For this reason, proinflammatory nanomaterials can be applied within 3 days of a clean acute wound or nanomaterials loaded with neutrophil and macrophage activators such as IL-8 and IFN-γ can be developedfor release over the first 3 days to achieve short-term effects. The actual effects need further experimental confirmation.

4.2 Chronic wounds

Chronic wounds, such as burn wounds and diabetic wounds,are usually trapped in a state of persistent inflammation due to burn stimulation and chronic infection, which is characterized by increased levels of proinflammatory cytokines and a nonhealing ability. Current studies have suggested that persistent inflammationis mainly caused by the disordered transition of macrophages from the M1 to M2 phenotype. Macrophages that are trapped in the M1 phenotype continuously secreteproinflammatory factors, which leads to severe tissue damage. Researchers have explored several ways to reverse thissituation. Some nanomaterials, such asTiO_2 NPs and nanofibrous scaffolds, can promote the transition from the M1 to the M2 phenotype. IL-10, a polyamine secreted by M2 macrophages, has anti-inflammatory and tissue repair effects to promote wound healing(Dukhinova et al., 2019; Kaymakcalan et al., 2018; Sun et al., 2018). Moreover, further mechanistic studies have shown that nanomaterials could activate the complement system in wounds by regulating the TLR/NFκB, MAPK/mTOR, and KGF2/p38 signaling pathways, reducing the expression of proinflammatory cytokines such as TNF-α, IL-1 and IL-6, and increasing the expression of anti-inflammatory cytokines such as IL-4 and IL-10 (Sun et al., 2019; Zhang et al., 2020)(Figure 1C).

The application of nanomaterials to regulate the inflammatory state of chronic wounds is a feasible treatment strategy. However, this approach has its limitations. For example, the inflammatory factors in burn wounds are mainly TNF-α, IL-1β and IL-6, while high expression of IL-18 is always observed in diabetic wounds. Nanomaterials such as silver nanoparticles (AgNPs) and nanofibers have beenreported to reduce the levels of IL-1β and IL-6, but the inhibitory effects of IL-18 havenot been verified, suggesting that these nanomaterials may have poor anti-inflammatory effectsagainstdiabetic wounds. Therefore, nanomaterials with excellent anti-inflammatory properties should be developed in the future for the treatment of various kinds of wounds(Mohammadi et al., 2019; Wasef et al., 2020). In addition, the inflammatorystage usually overlaps with the proliferation stage, and it is difficult to identify the end point of the inflammatoryperiod. Therefore, the negative effects of nanomaterials on proliferation should be taken into consideration when being applied for the immunoregulation ofchronic wounds. Further research could identify a marker that denotes the transition from theinflammatory phase to the proliferation phase to indicate the usable time of

animmunomodulatory nanomaterial.

4.3 Immunological wounds

Immune factors can also cause skin woundsthat patients with immune skin diseases are often accompanied by ulcers. For example, allergic vasculitis is accompanied by activation of the NFκB pathway and increases in TNF-α and IL-6, and dermatomyositis shows a proinflammatory phenotype with elevated levels of IL-6 and IL-10 after activation of TLR7. Behcet's disease and pyoderma gangrenous also displayelevated expression levels of IL-1 and IL-6(Chen et al., 2014; Kozono et al., 2015; Piper et al., 2018; Talaat et al., 2019; Wallach et al., 2018).Immune disorders are the main cause of wound formation in theseconditions, so immunotherapy plays a crucial role in wound healing. For this purpose, we can obtain inspiration from the anti-inflammatory properties of nanomaterials. For example, AgNPs and nanofibers can reduce the expression levels of IL-1, IL-6 and TNF-α, and metal nanomaterials such as ZnO NPs and TiO_2 NPs can inhibit the TLR and NFκBpathways by activating the transcription factorsPPARγ and arginase 1. Therefore, it can be inferred that nanomaterials may play a role in controlling immunological skin wound inflammation through the above pathways, but there is still a lack of relevant research(Chen et al., 2019; Dukhinova et al., 2019; Zhang et al., 2020). On the other hand, immune skin wounds are often accompanied by an adaptive immune response. The activation of $CD4^+$ and $CD8^+$ T cells and the decline in Treg cells are considered tobe associated with the pathogenesis of immune skin diseases(Hoeppli et al., 2019; Leccese et al., 2019; Quaglino et al., 2016). Treg cells maintain peripheral immune tolerance in the body and can secrete anti-inflammatory factors or exosome vesicles to reduce T cell proliferation and promote T cell apoptosis. Therefore, we propose a new concept of nanomaterial-mediated immune tolerance for the treatment of immune wounds. Similar to the principle of nanovaccines, specific antigens carried by peptides can betransmitted through nanomaterials. The antigens are then recognized and presented by immature dendritic cells (DCs), inducing Treg cell proliferation but not a proinflammatory response. Immature DCs then transmit tolerance signals by default to maintain peripheral tolerance(In't Veld et al., 2017).This method has been studied in patients with multiple sclerosis. If the desired effects in patients with immune skin diseases are achieved, it will be of great help to patients in the stable stage to prevent recurrence.

5. Reconstruction phase

Woundsareruptures or defects of the skin. After the local infection is controlled, the proliferation of skin and subcutaneous tissue is the most important process duringwound healing and involves the formation of blood vessels, the proliferation of fibroblasts and keratinocytes, andthe regeneration of skin appendages. Overthe past few decades, many studies have focused on the proliferation effects of nanomaterials themselves or their use as carriers on wounds. Different from traditional wound dressings, the porous structure of a nanomaterial can provide a scaffold for new cells and proteins. The nanomaterialcan interact with the tissues around the wound, activate the repair system in the body, and stimulate the secretion of various growth factors to promote wound healing.

5.1 Granulation tissue

Initial wound repair relies on the accumulation of granulation tissue. Fibroblasts together with new capillaries proliferate rapidly and synthesize collagen fibers and matrix components.Many studies have shown that nanomaterials can promote the formation of granulation tissue. Inorganic nanomaterials such as ZnO and terbium hydroxide NPscould induce oxidative stress in vascular endothelial cells(VECs). The accumulated ROS in VECs activate the p38 MAPK/Akt/eNOS signaling pathway, leading to the formation of NO, which stimulates angiogenesis(Nethi et al., 2019). Alternatively,these inorganic nanomaterialscould activate the Notch signaling pathway in VECs, the Notch1, Notch3, and Notch ligands Dll 1 and Jagged 1 and their target genes Hes 1 and Hey 1, which is another mechanism to promote angiogenesis by nanomaterials(Zhao et al., 2018a). Moreover,nanomaterials could also promote the proliferation of fibroblasts. Human skin fibroblasts were treated with composite nanofibers containing chitosan and AgNPs in vitro. After exposure to the nanofibers, the cell cycle progressed from stationary G0/G1 phase to S and G2 phases with active DNA synthesis and division. During this process, the TGF-β1/SMAD signaling pathway was activated, and the

results could be reversed by TGF-β1 receptor inhibitors(Zi-Wei et al., 2017).Moreover, the nanomaterials prevented the apoptosis of fibroblasts. A hyaluronic acid-based nanosystem was found to shield cell death receptorsandprevent cell apoptosis by activating the CD44 receptor in the cell membrane. In addition, the activation of CD44 stimulates the signaling cascade of the RHAMM receptor and tyrosine kinase 2 pathways, which leads to increased cell motility and growth (Vigani et al., 2019)(Figure 1D). The proliferation of blood vessels and fibroblasts is synchronous. For chronic old wounds with reducedblood supply, nanomaterials can be used as wound dressings to promote the repair of wound defects. However, the timing and duration of administration should be taken into consideration. A clean wound is a prerequisite for granulation growth. Insufficient proliferation of granulation will lead to the collapse of the wound surface, while excessive proliferation of granulation will hinder the process of epithelialization or lead to scar hyperplasia. Future research could explore the indicators that signify the treatment endpoints to guide the administration duration of use in practical applications.

5.2 Epithelization

After the granulation tissue fills in the wound defect, keratinocytes proliferate to form an integrated epidermis. In vivo studies in rats have confirmed that nanomaterials can promote the viability and proliferation of keratinocytes and accelerate the epithelialization of wounds. They can upregulate the expression of repair-related genes, such as TGF-β, Smad2, KRT6a, and IVN,in HaCaT cells and activate the TGF-β-VEGF-MCP 1, TGF-β-Smad2,and HER2-ErbB2 pathways to promote the epithelialization process. In addition, nanomaterials can stimulate the secretion of various growth factors,such as FGF2, PDGF and EGF, activate the ERK and P38 signaling pathways and promote the proliferation and migration of fibroblasts and HaCaT cells (Bhattacharya et al., 2019)(Figure 1D). Keratinocytes are involved in the formation of the skin barrier, electrospun tilapia collagen nanofibers have been observed to upregulateinvolucrin, filaggrin and TGase1, which are important components of the skin barrier(Zhou et al., 2016).Therefore, in the later stage of wound repair, application of these nanomaterials can facilitate wound closure and repair the skin barrier. However, for some wounds with large areas, such as burn wounds, the healing speed of this approach may not be enough. Therefore, several methods should be combined. For example, platelet-rich plasma (PRP) is a natural repository of growth factors. PRP-containing nanoscaffolds have been developed to release PRP to promote epithelialization. In the future, PRP can also be loaded into nanomaterials with pro-epithelialization potential(do Amaral et al., 2019). Alternatively, new nanomaterial-based wound dressings can be developed by loading autologous, allogeneic, or tissue-engineered skin pieces to accelerate the adhesion of skin, the formation of skin paddles and the proliferation of keratinocytes.

5.3 Adipose tissue

Duringthe repair of some deep wounds, local collapse usually appears after wound closure. This collapse is probably caused by the dysplasia of subcutaneous adipose tissue during the healing process. Whether nanomaterials can be used to promote the reconstruction of subcutaneous adipose tissue defects has not yet been studied. The present research has explored the influences of nanomaterials on adipose-derived stem cells (ADSCs), which have multidirectional differentiation potential to differentiate into fat, cartilage and bone. Nanomaterials can promote the hypermethylation of the Dlg3 gene promoter, which leads to a decrease in Dlg3 expression. Downregulation of Dlg3 promotes the proliferation ofADSCs and reduces cell apoptosis(Lin et al., 2018a). On the other hand, nanomaterials can promote the adipogenic differentiation of ADSCs. The adipogenic markers of ADSCs, such as PPARγ and FABP4,aretypically expressed after culture with scaffolds made by electrospinning(Gugerell et al., 2014).This suggests that nanomaterials can be used in deep wounds to promote ADSCs proliferation and adipocyte differentiation, and that the accumulation of adipocytes can repair defective subcutaneous tissue. However, most of the current studies have beenin vitro experiments, and confirmation studies inin vivo models are still lacking. In addition, different types of nanomaterials have different influences on ADSCs. For example, nanoscaffolds and some new nanomaterials, such as tetrahedral DNA nanostructures (TDNs),have beenconsidered to promote adipogenic differentiation, while SiO_2 NPs and fullerenes were found to have the opposite effect(Saitoh et al., 2012; Yang et al., 2017).There is still a wide space for research on developing new nanomaterials to promote the reconstruction of subcutaneous

adipose tissue and the related mechanisms.

The application of nanomaterials in the wound healing process should follow the sequence of subcutaneous tissue repair promotion, granulation tissue hyperplasia and epithelialization, and different nanomaterials may be required for each stage. However, because of the different types and depths of wounds, the repair time of each stage is also different. Therefore, distinguishing the dividing point of these stages has currently become a difficulty. In the clinic,the dividing point usually relies on the subjective judgment of the physician. If a marker can be obtained, we can extract the local tissue of the wound to determine the stage of tissue repair and select an appropriate nanomaterial. In this way, accurate wound repair can be achieved in the future, which not only reduces healing time but also maintains aesthetics as much as possible.

5.4 Amelioration of the microenvironment

As nanomaterial research has developed, scholars have begun to pay attention to the impacts of these nanomaterials on the cellular microenvironment. It has been found that nanomaterials such as nanofibers and hydrogels have hydrophilic surfaces, exhibita high water retention capacity and provide a moist environment for wound healing(Fu et al., 2014). AgNPs, gold nanoparticles (AuNPs), copper nanoparticles (CuNPs) and other nanomaterials can reduce the expression of matrix metalloproteinasesMMP-1,MMP-3, andMMP-8 and inhibit their decomposition of collagen(Frankova et al., 2016; Lee et al., 2015).These nanomaterials accelerate the remodeling of the ECM by promoting the deposition of type I and III collagen and fibronectin, providing a beneficial environment for cell proliferation and wound repair. In addition, studies have been conducted to use nanomaterials, collagen extracted from marine fish skin or pig decellularized ECM to prepare composite materials. These nanodressings have high histocompatibility, which can reduce both irritation to tissue and the inflammatory response. These nanodressingsare especially suitable for wounds that require long-term coverageof the dressing, such as burn wounds and diabetic wounds(Lin et al., 2018b; Ramanathan et al., 2017).Nanomaterials can also monitor the physical and chemical status of the ECM. Some scholars developed a novel electronic dressing that can continuously display the pH changes in the wound environment and control the pH value through an electric field to keep it in a suitable range for cell proliferation(Nischwitz et al., 2019).This technique can be used to control wound infection by artificially regulating the pH value to inhibit the growth of microorganisms, and it can also guide the release of drugs by monitoring the pH value. Furthermore, in the future, we can develop electronic dressings that monitor the state of extracellular hypoxicconditions and Ca^{2+} concentration, which can affect MMP activity and the synthesis of collagen. According to the real-time status, we can adjust these parametersto be in the appropriate range. The implementation of these ideas heralds the advent of anera of wound repair with precision control(Khadjavi et al., 2015; Navarro-Requena et al., 2018).

6. Modifications after wound regeneration

After the remodeling stage, wound closure istraditionally complete.However, there are still some problems, such as scar hyperplasia, loss of hair follicles and sensory disturbances. In the past, post-healing repair was often overlooked. With the improvement of medical technology, more attention has been given to aestheticsand functional recovery. As a new therapeutic material, nanomaterials have also been developed and applied forthe post-healing repair of wounds.

6.1Scar prevention

Scarsmanifest as excessive fibroblastproliferation, disordered cell growth and abnormal collagen deposition, which not only affect the aesthetic appearance but also cause poor local traction and elasticity, resulting in limb dysfunction;there is also a risk of cancer. Currently,scars are mostly treated by surgical resection, local injection and radiation. Nanomaterials havebeen gradually applied in the treatment of scars. For example, some scholars developed glucocorticoid-loadedhydrogel particles to realize the long-term release of glucocorticoids, and the effectson the inhibition of scars has been confirmed in rabbits(Guo et al., 2018). AuNPs have been used as carriers of photosensitizersbecause ofthe photothermal effects of AuNPs and local surface plasmon resonance (LSPR) to enhance oxidative stress, leading to fibroblast apoptosis or necrosis(Zhang et al., 2017).However, these methods are used after the scar has formed, although ideally, scar formation would

be prevented before the wound is healed. Nanomaterials have been explored in this area. Studies have found that some nanomaterials, such as carbon nanotubes,can inhibit the excessive proliferation of fibroblasts by inhibiting the TGF-β-SMAD pathway. Moreover,these nanomaterials can regulate the expression of various enzymes in the cellular microenvironment, such as promoting the expression of MMP-1 and inhibiting collagen and fibronectin levels in the ECM. In addition, nanomaterials can induce the oriented movement of fibroblasts(Poormasjedi-Meibod et al., 2016; Weng et al., 2018).All of these observations indicate that nanomaterials have the potential to prevent scar formation before epithelialization. However, there is still a lack of in-depth mechanistic research, such as whether these nanomaterials can affect other scar pathways, such as Wnt/β-catenin, and regulate macrophage polarization to inhibit scarring hyperplasia (Hesketh et al., 2017; Yu et al., 2016)(Figure 2).In addition, most of the current studies have beenin vitro experiments, and there is a lack of in vivo confirmation studies, which are difficult to carry out. Reviewing the process of wound healing, the hyperplasia process of granulation tissue before epithelialization requires the activation of the TGF-β-SMAD pathway to promote the proliferation of fibroblasts. This processalso promotes the deposition of collagen during the remodeling phase, which is exactly the opposite of the antiscarring mechanism. Therefore, the application of nanomaterials to prevent scars before epithelialization may inhibit the active proliferation of granulation tissue. If we want to prevent scar formation before epithelialization, we need to consider other aspects. For example, we can implant nanotubes and other nanomaterials duringthe granulation tissue proliferation stage or use 3D printing technology to fill wound defects with nanoscaffolds to guide the directed and moderate growth of fibroblasts. We can also develop new nanomaterials to reduce the high levels of cytokines such as IL-6, IL-8, and IL-17 in the scar and adjust the expression of miR-146a, miR-21, neurotransmitters such as bradykinin, and substance P. Further experiments are needed as to whether these ideas are sufficient(Lebonvallet et al., 2018; Lee et al., 2018; Zhang et al., 2018).

6.2Hair follicle reconstruction

When the defect of the wound reaches the dermis, it will lead to loss of the hair follicle, so regeneration of the hair follicle is another part of wound healing. However, in wounds with skin substitute treatment and scar formation, regeneration of the hair follicles is the technical bottleneck for the complete restoration of skin structure and function. The application of nanomaterials in medicine has attracted the attention of scholars, who have begun to note the influence of nanomaterials on hair follicles. Synthetic composite electrospun membranes can promote the recruitment and proliferation of hair follicle stem cells by releasing zinc ions(Zhang et al., 2019). The nanofiber scaffold seeded with hair follicle stem cells can promote the attachment, proliferation and differentiation of hair follicle stem cells on the scaffold(Hejazian et al., 2012). These studies indicate that nanomaterials have the potential to promote hair follicle regeneration, but there are few studies in this field. Most of the studiesare in vitro experiments with limited types of nanomaterials. Although an in vivo study inSprague-Dawley (SD)rats showed that the number of hair follicles and hair follicle stem cells in the nanodressinggroupwas higher than that in the control group, further experiments are needed to explain the mechanism. The reconstruction and regeneration of hair follicles are difficulties that are faced in wound recovery(Zhang et al., 2019).Currently, surgical hair transplantation is widely used for hair follicle reconstitution, but the survival rate is limited. This may be related to factors such as damage to the transplanted hair follicle during the operation and local inflammation after transplantation. Inspired by the fact that nanomaterials can promote the proliferation of hair follicle stem cells and inhibit inflammation, we couldtry to use anti-inflammatory nanomaterials or composite nanomaterials loaded with stem cells, PRP and other drugs that promote the survival of hair follicles as auxiliary treatments to improve the viability and success rate of hair transplants (Figure 2).

After hair follicle reconstruction, whether nanomaterials can promote hair growth can also be studied in the future. It was reported that poly(glutamic acid) (PGA)NPscan increase the expression levels of the proteinscyclin D1 and CDK4 and induce the development of the hair follicle cycle by activating the Wnt/β-catenin pathway. These proteinsalso increase the expression of type II keratin and melanin and promote the proliferation of dermal papilla cells toencourage hair growth(Lee et al., 2019).However, most current studies have focusedon nanomaterials as drug carriers for hair loss, and there is still a lack of research on the effects of the nanomaterials themselves on hair growth. Because of itsspecial structure, drugs can be

stored within the hair follicle and slowly released for a long time. Nanomaterials are small in size and more easily enter the hair follicle for storage. Compared with other drugs for hair loss treatment, nanomaterials have the advantages of higher efficiency and longer lasting effects. Further exciting progress is expected in the exploration ofnanomaterials to promote hair growth.

6.3Skin sensory regulation

There are many cutaneous nerves and peripheral nerves in the skin, and skin wounds are bound to damage these nerves. Local infection, inflammation or improper nerve regeneration will cause paresthesia such as pain, itching, and hypoesthesia after healing, which affect the quality of life of patients.

Nanomaterials are widely used in the development of topical drug delivery systems due to their superior drug-carrying properties. To increase percutaneous drug penetration, prolong the release time and reduce side effects, some analgesics, such as nonsteroidal anti-inflammatory drugs, local anesthetics, capsaicin, and antipruritic drugs, such as glucocorticoids, have been developed as nanoemulsions, transfersomes, solid lipid nanoparticles (SLNs) and as other systems for the treatment of pain and itching after healing.In addition, topical ZnO NPs have been observed to have anti-itch effects(Aman et al., 2019; Andreu et al., 2018; Bikkad et al., 2014; Ghiasi et al., 2019; Nafisi et al., 2018).These formulations are feasible for most kinds of wounds, such as postoperative wounds, diabetic wounds, and burn wounds. However, postherpetic neuralgia woundsare a special circumstance. Neuralgia is severe and continuous and requires more powerful analgesics. We couldtry to apply an anestheticnanosystem for local pain relief or to develop delivery nanosystems for neuralgia drugs such as gabapentin and pregabalin. The actual clinical effects still need to be confirmed by further studies. In addition, there are few studies on whether nanomaterials can relieve pain and itching symptoms. The mechanisms of pain and itching overlap, and both are related to the sensory transmission of nerve cells mediated by neuropeptides, proteases and other mediators. Whether certain nanomaterials can achieve pain relief and antipruritus by inhibiting the secretion of these nerve mediators or inhibiting nerve signal transduction is a direction that can be explored in the future.

Hypoesthesia after wound healing is difficult. Generally, physical therapy is used to improve symptoms, but the therapeutic effect is poor. In recent years, electronic skin represented by carbon-based nanomaterials has emerged in the field of body surface monitoring. Electronic skincan collect information of temperature, pain sensation, and even taste sensation from the skin and convert it into electronic signals for transmission(Qiao et al., 2018; Zhao et al., 2018b).Then,the application of this kind of equipment to patients with hypoesthesia after a large area of wound healing could be imagined. When the patientsare exposed to a harsh environment of heat, chemical damage and electrical stimulation, they cannot respond in time due to hypoesthesia. The application of electronic skin can transmit danger signals on a more appropriate timescale and protect the body from danger. Unfortunately, the current technology just convertsthese signals into digital signals, which cannot be directly transmitted to human nerves and fed back to the brain. If this difficulty is overcome, holistic functional wound healing wouldbe further realized(Ma et al., 2019).Moreover, before electronic skin is applied to the body, it is necessary to consider the harmonious symbiosis between the electronic skin and the surrounding normal nerves, muscles, lymphatics and glands, as well as ensure the precise transmission of nerve instructions. These may be the next directions for researchers (Figure 2).

7. The toxicity of nanomaterials in wound healing

Nanomaterials have an excellent ability to promote wound healing, and there is still great potential for their application and development in the future. However, it should be noted that the wound surface is not protected by intact skin. The nanomaterials directly contact the tissue inside the wound, and the biological safety of the products must be considered before application.

The most reported transdermal toxicities of nanomaterials are skin irritation and allergies(Ema et al., 2013; Palmer et al., 2019).Theseside effectshave individual differences and may be unavoidable. There havealso been frequent reports ofnanomaterials causingoxidative stress, autophagy and apoptosis in keratinocytes and fibroblasts(Wang et al., 2018). These toxicities depend on the particle size, shape, surface charge and concentration of the nanomaterial. Therefore, these factors should be adjusted to reduce toxicity to skin

cells when developing new nanomaterials used in wounds(Hashempour et al., 2019).In addition, it has been reported that nanomaterials cause DNA damage and decrease gene methylation, suggesting the potential of cell canceration(Ali et al., 2016; Sooklert et al., 2019).However, there is still no direct evidence to prove that nanomaterials can cause malignant transformations and inherited gene mutations in skin cells. Thisdoes not mean that nanomaterials are safe. It is not known whether the long-term percutaneous exposure and deposition of nanomaterials in the skin will cause severe consequences, which will need to be confirmed by long-term exposure experiments in the future.

Nanomaterials will come in contact with blood cells in ruptured blood vessels in wounds and enter the blood circulation. This phenomenonbrings two consequences, one of which is hemolysis. Some metal nanomaterials, such as AgNPs and ZnO NPs, have been found to cause hemolysis. To solve this problem, we can adjust the physical and chemical properties of the materials or wrap biologically active substances such as phospholipids and polysaccharides onto the surface of the nanomaterials(Bakshi, 2017).Another consequence is that the nanomaterials will spread throughout the body into various organs after entering the blood, causing multisystem effects. Compared with the original concentration of the nanomaterials, the concentration of nanomaterials after entering the blood circulation is greatly reduced, and they can be partly excreted through urine and feces. Weight loss and even death have been observed in animal experiments, but in practical use, there is no conclusive evidence regarding whether nanomaterials will cause organ failure and/or tumors, whether exposure during pregnancy will affect offspring and what the safe concentrationis(Hadrup et al., 2018).

In general, nanomaterial toxicity studies in wound healing havemainly concentrated on local acute adverse reactions. There are relatively few studies on systemic and chronic toxicity. On the other hand, most of the studied nanomaterials are metal nanomaterials, carbon-based nanomaterials and nanotubes, whereas nanofibers, films and other novel nanomaterials are still rarely studied(Teixeira et al., 2020).Future toxicity studies urgently need to solve these problems.

8.Outlook and future challenges

8.1 Limitations of the existing research

In summary, it has been demonstrated that nanomaterials have a positive effect duringeach process of wound healing. But most current studies have beenconducted in vitro, and the in vivo experiments need to be improved. The animals used for studies are rats, mice, rabbits and pigs. Due to the differences in animal cost, size and availability, rats and mice are most commonly used. However, the skin morphologiesand wound healing processes of these rodents are different from those of humans. In comparison, the skin of pigs is the most similar to that of humans. Because of the high cost and cumbersome operation of experiments with large animals, pigs are not widely used in wound healing research(Abazari et al., 2020).In addition, many wounds lack a standardized and controllable modeling method. For example, wound biofilms, diabetic wounds and wounds of immune skin diseases are usually imitated woundphenomena, and it is difficult to reflect the mechanism of human skin wounds.

Drugs and methods for wound treatment are changing rapidly, and nanomaterials are being applied to wounds in various formulations. However, the mechanism by which nanomaterials promote wound healing hasstill only been superficially studied. For example,macrophage polarization and the TGF-β1/SMAD signaling pathway are the most commonly reported pathways in the inflammatoryand proliferation phases, respectively. The related mechanism by which nanomaterials promote wound repair after reconstruction is rarely reported. There are many types of nanomaterials with different characteristics, and the mechanism of wound healing promotion should also be multifaceted. Deeper and more innovative mechanisms need to be explored in the future, which would behelpful to improve treatment methods and avoid unnecessary side effects(Dukhinova et al., 2019; Janjic et al., 2017).

8.2 Future challenges

Because nanomaterials have superior drug-carrying properties, an increasing number of new drugs have

beenloaded onto nanomaterials, such as stem cells and PRP. For the treatment of immune skin diseases, the emergence of a variety of biological agents has gradually replaced traditional drugs. If these monoclonal antibodies can be loaded onto nanomaterials, it may lead to an improvement in the absorption rate and efficacy of the drug.

Although the existing research has confirmedthat nanomaterials can play a positive role in all phases of the promotion of wound healing, the same materials cannot be beneficial throughoutthe whole process, and different types of materials may be required at different stages. Since it is impossible to visually judge the dividing point of each stage, it is important to develop a real-time indicator of the wound condition. In recent years,self-powered implantable electronic skins based on ZnO nanowires modified by enzymes (urease and uricase) have been developed for transcutaneous detection of human health, including blood pressure, temperature, humidity, electrolyte metabolites, etc(Asif et al., 2015; Ma et al., 2019).Through this technology, electronic skin that monitors the pH value, humidity, inflammatory factors and signaling pathway proteins can be developed in the future. Then, the therapist can accurately control the treatment of wounds and select appropriate nanomaterials according to the real-time situation.

With the development of medicine, the treatment of wounds not only pursues the filling of defects but also requires comprehensive functional and aesthetic recovery. Nanotechnology is rapidly developing and is considered to be able to solve a number ofproblems in various situations. Currently, scholars have successfully applied nanomaterials to promote wound healing and prevent scar formation. Nanotechnology still has great potential in the regeneration of hair follicles, the regulation of paresthesia and the improvement of abnormal pigmentation. Especially with the emergence of electronic skin in recent years, the combination of nanotechnology and electronic technology has provided new ideas for the recovery of paresthesia after wound repair and brought an intelligent concept for wound healing.

9.Conclusion

In recent years, an increasing number of nanomaterials have been used to treat wounds. This work reviewed the possible ways that nanomaterials can facilitate wound healing and their related mechanisms, which improves our understanding of the role of nanomaterials in wound healing. We pointed out that most of the current studies have focused on promoting hemostasis, antiinfection, immunoregulation and proliferation, but there is a lack of research on the in-depth mechanisms and post-wound modifications. Additionally, we proposed some methods and new thoughts for subsequent studies, especially for functional and aesthetic problems after wound healing. We hope our work will provide inspiration for more exciting progress in the future.

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Table 1. Application of nanomaterials in wound healing.

NP	Matrix/Drug association	Model	Wound type	Result	Ref
ZnO NPs	Alginate/acacia	Rabbits	Full-thickness excised skin wound	Possesses good biocompatibility properties; increased deposition of collagen and calcium, more fibroblasts and few inflammatory cells; accelerated wound healing	(Manuja et al., 2020)
Polycaprolactone (PCL) nanofibers	Alfalfa	Human dermal fibroblast and keratinocytes in vitro; humansand mice	Ex vivo human skin wound model; mouse excisional wound splinting model	Promoted in vitro cellular growth of epidermal keratinocytes and dermal fibroblasts; promoted wound closure, re-epithelialization, and granulation tissue formation in mice and human models	(Ahn et al., 2019)
SiNPs	Curcumin	*S. aureus* and *Pseudomonas aeruginosa* biofilms in vitro	Scratch assay on human dermal fibroblast (HDF) cells	Enhanced antimicrobial and antibiofilm activities of curcumin SiNPs as a photosensitizer in antimicrobial PDT; showed a narrower denuded region of wounds in a scratch assay	(Mirzahosseinipour et al., 2020)

NP	Matrix/Drug association	Model	Wound type	Result	Ref
SiNPs		PRP and human blood plasma		SiNPs shortened coagulation time in activated partial thromboplastin time (APTT) and prothrombin time (PT)tests, increased the activation of factor X induced by Russell's viper venom, inhibited the aggregation of PRP induced by ADP	(Gryshchuk et al., 2016)
Nanobioglass	Chitosan hydrogel	Rats	Liver injury with biopsy punch; femoral artery injury punctured by needle	Formed stable blood clots in vivo; reduced blood clotting time when added to human whole blood in vitro	(Sundaram et al., 2019)
AgNPs	Curcuma	*S. aureus*, *Streptococcus pyogenes*, *E. coli*, P. *aeruginosa* and *Candida albicans*	Scratch assay on fibroblast cells (L929)	Exhibited remarkable decrease in the growth of microorganisms; promoted the cell proliferation and migration in the fibroblast cells	(Maghimaa et al., 2020)

NP	Matrix/Drug association	Model	Wound type	Result	Ref
AgNP hydrogels	Sodium alginate and gelatin	Rats; *P. aeruginosa*, and*S. aureus* in vitro	Biopsy punch	Showed significant bactericidal activity in vitro; promoted vascular granulation tissue without cellular fibrous scars and reduced wound size in vivo	(Diniz et al., 2020)
GO scaffold	Fe_3O_4NPs; polyhydroxybutyrate-co-hydroxyvalerate copolymer	Mouse fibroblast cells in vitro;E. coli, P. aeruginosa, S. aureus and B. subtilis	Scratch assay on fibroblast cells	Exhibit efficiency against gram-negative bacteria strains; significant cell adhesion, proliferation and accelerated wound contraction	(Pramanik et al., 2019)
TiO_2 nanotubes	IL-4	RAW 264.7 murine macrophage cells		IL-4 was slowly released during the early stage allowing M1 activation, promoted polarization from M1 to M2 macrophages after 72 h	(Li et al., 2018)
α-Gal–containing micelle NPs		Mice	Splinted excisional wound model	Enhanced polarization of macrophages toward the M2 healing phenotype, enhanced granulation tissue deposition, vascular growth and keratinization	(Kaymakcalan et al., 2018)

NP	Matrix/Drug association	Model	Wound type	Result	Ref
Nanofibrous membrane	Nanobioglass incorporated chitosan-polyvinyl alcohol (PVA)	Mice fibroblast cells; rat traumatic model and mice diabetic model	Full-thickness wounds	Upregulated growth factors including VEGF and TGF-β, downregulated inflammatory cytokines such as TNF-α and IL-1β· accelerated healing in terms of complete re-epithelialization, improved collagen alignment and formation of skin appendages	(Chen et al., 2019)
AgNPs		HDFs; human epidermal keratinocytes (HEKs)	Scratch assay on HDFs and HEKs	Downregulated inflammatory cytokines (TNF-α and IL-12) and MMP3	(Frankova et al., 2016)
AuNPs	Keratinocyte growth factor	HDFs and HEKs; rat wounds	A full-thickness dorsal excisional wound	Promoted the proliferation of keratinocytes and wound closure	(Pan et al., 2018)
AuNPs	Gallic acid, isoflavone and protocatechuic acid isoflavone	Rats	Surgical wound	Suppressed MMP-1 and promoted VEGF, angiopoietin-2 and collagen, increased dermal and epidermal thickness	(Lee et al., 2015)

NP	Matrix/Drug association	Model	Wound type	Result	Ref
CONPs		Rabbits	Rabbit ear hypertrophic scar model after full-thickness excisional wound	Improved the collagen arrangement; reduced scar by inhibiting hypertrophic scar fibroblasts proliferation and inducing apoptosis	(Xiao et al., 2019)

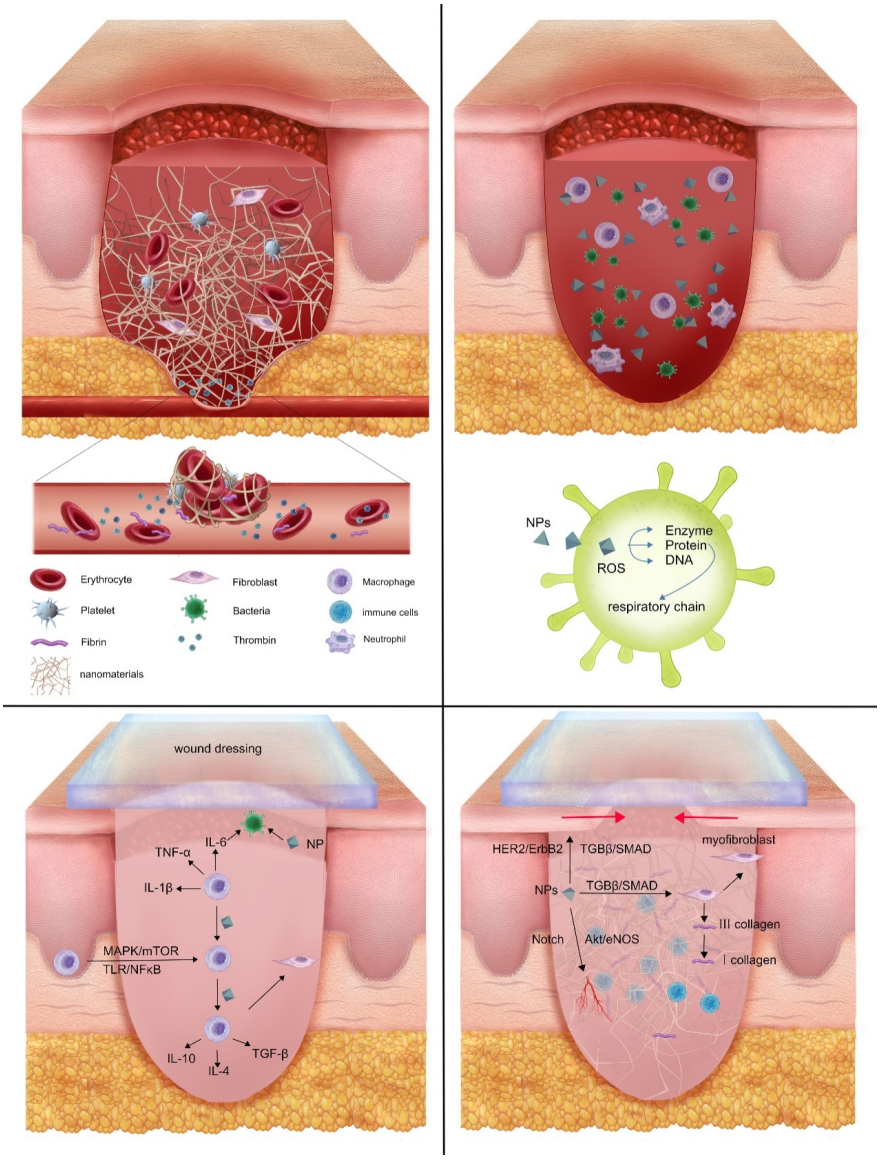

Figure 1. Possiblemechanisms of promoting wound healingby nanomaterials. A) Nanomaterials promote the accumulation of red blood cells, platelets and clotting factors at the damaged vasculature to form blood clots. B) Nanomaterials can kill microorganisms in the wound and promote the removal of necrotic tissue by macrophages. C) In the immunomodulatory stage, nanomaterials promote the phenotypic transformation of macrophages and regulate the expression of inflammatory factors in the wound. D) During the proliferation and reconstruction stages, nanomaterials promote angiogenesis, granulation tissue hyperplasia, epithelialization, and reorganization of the extracellular matrix.

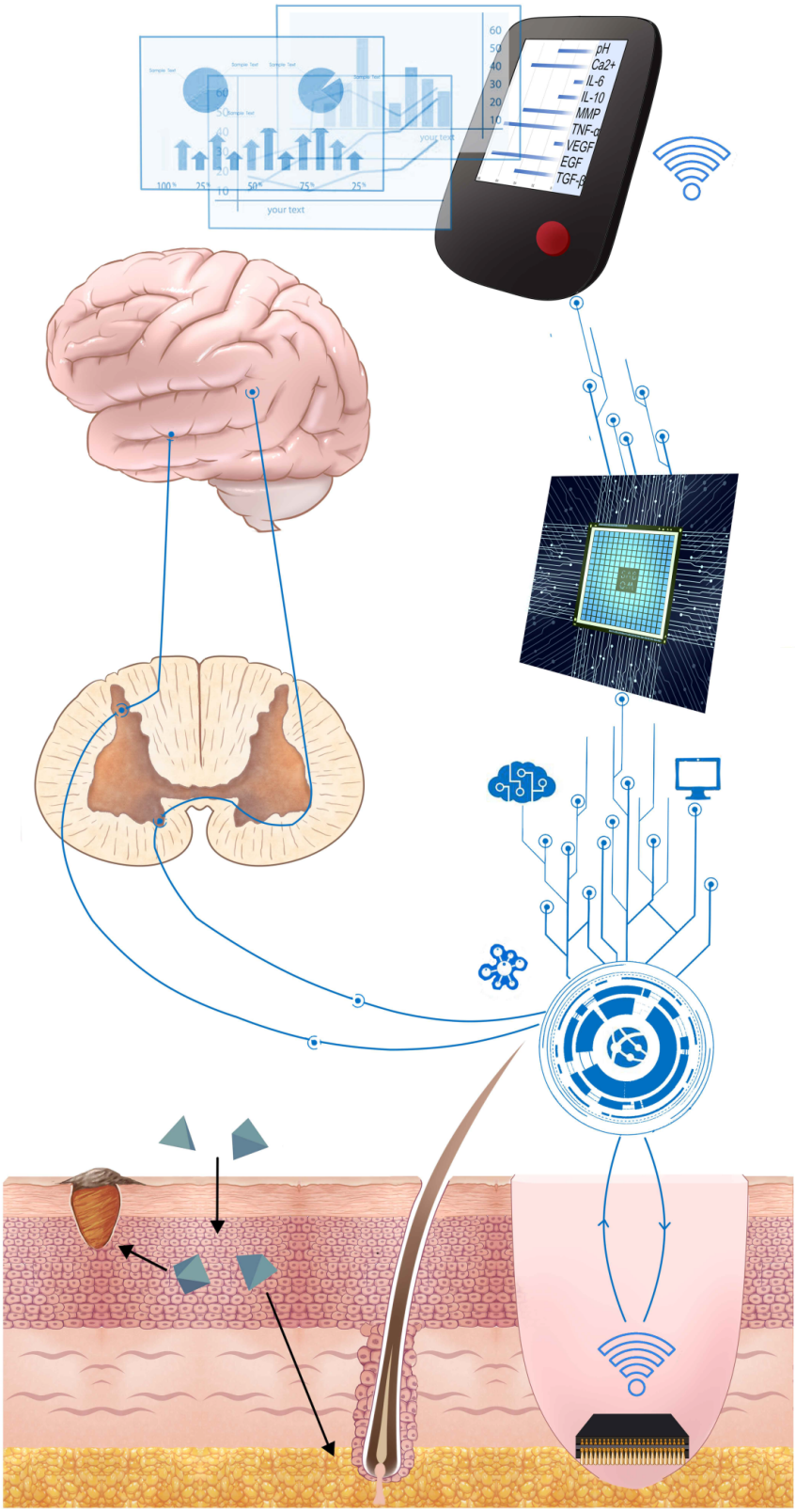

Figure 2. In the future, nanomaterials have great potential in preventing scarring, promoting hair follicle growth and resolving hypoesthesia.