


# Recent Advances in Nano-Formulations for Skin Wound Repair Applications

Yue Lin<sup>1,\*</sup>, Zheyang Chen<sup>2,\*</sup>, Yinai Liu<sup>3</sup>, Jiawen Wang<sup>2</sup>, Wang Lv<sup>1</sup>, Renyi Peng<sup>1</sup>

<sup>1</sup>Department of Emergency, The Third Affiliated Hospital of Shanghai University & Wenzhou No. 3 Clinical Institute Affiliated to Wenzhou Medical University, Wenzhou People's Hospital, Wenzhou, People's Republic of China; <sup>2</sup>Department of Plastic Surgery, The Third Affiliated Hospital of Shanghai University & Wenzhou No. 3 Clinical Institute Affiliated to Wenzhou Medical University, Wenzhou People's Hospital, Wenzhou, People's Republic of China; <sup>3</sup>Institute of Life Sciences, College of Life and Environmental Science, Wenzhou University, Wenzhou, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Renyi Peng, Tel +86 159-5771-6937, Email 20170032@wzu.edu.cn

**Abstract:** Skin injuries caused by accidents and acute or chronic diseases place a heavy burden on patients and health care systems. Current treatments mainly depend on preventing infection, debridement, and hemostasis and on supplementing growth factors, but patients will still have scar tissue proliferation or difficulty healing and other problems after treatment. Conventional treatment usually focuses on a single factor or process of wound repair and often ignores the influence of the wound pathological microenvironment on the final healing effect. Therefore, it is of substantial research value to develop multifunctional therapeutic methods that can actively regulate the wound microenvironment and reduce the oxidative stress level at the wound site to promote the repair of skin wounds. In recent years, various bioactive nanomaterials have shown great potential in tissue repair and regeneration due to their properties, including their unique surface interface effect, small size effect, enzyme activity and quantum effect. This review summarizes the mechanisms underlying skin wound repair and the defects in traditional treatment methods. We focus on analyzing the advantages of different types of nanomaterials and comment on their toxicity and side effects when used for skin wound repair.

**Keywords:** nanomedicine, nanomaterials, nano-formulations, skin injury, wound repair

## Introduction

As the body's largest organ, skin constitutes the first barrier between the body and the environment. The main function of skin is to act as a protective barrier to protect the human body against harmful stimuli such as microorganisms, radiation, and chemical and physical stimuli in the external environment. Moreover, it has other important functions, such as maintaining body fluid balance and body temperature, synthesizing vitamin D, transmitting and detecting changes in the external environment and regulating immune responses.<sup>1-4</sup> In summary, as skin is an indispensable tissue in the human body, the integrity of its structure is a prerequisite for the performance of the above normal physiological functions.

In daily life, due to the large area of the skin and its direct exposure to the external environment, burns, wounds, infections, accidents and skin trauma resulting from medical surgery cannot always be avoided. According to reported statistics, tens of millions of people around the world suffer skin injuries from accidents or surgeries every year. In addition, with the increasing number of patients with diabetes, the number of patients with chronic or acute skin injuries resulting from diabetes or other causes is also increasing significantly.<sup>5</sup> According to the International Diabetes Federation (IDF), the number of people living with diabetes worldwide reached 537 million in 2021, and it is expected that the number will surpass 783 million by 2045, among whom approximately 10% suffer from foot ulcers, refractory wounds or other complications. Chronic diabetic skin wounds are one of the main diabetes-related causes of death or disability.<sup>6,7</sup> Currently, acute and chronic skin wounds caused by various factors have become a public health problem of worldwide concern, bringing great economic and social burdens to patients' families, medical and health systems and

society. Additionally, the hyperplasia of scar tissue caused by wounds will also cause a great psychological burden for patients. Therefore, skin wounds caused by various factors are a serious challenge in clinical practice.

Due to the number of accidental injuries and the increasing number of patients with chronic or refractory wounds caused by diabetes, paraplegia or local radiation exposure and the skin being prone to trauma, wound repair has always been a research focus in the medical field. With social progress, people's desires for beauty have gradually increased, the current level and quality of wound repair cannot meet the requirements of patients, and the contradiction between them has become increasingly sharp. Hence, it is necessary for researchers to further elucidate the mechanism and various influencing factors of wound repair, improve existing treatment methods and discover new treatment methods.<sup>8–10</sup>

In recent years, with the joint efforts of medical workers and researchers, the basic research and clinical treatment of wound repair have made substantial progress. The development and implementation of a large number of drugs,<sup>11</sup> dressings,<sup>12</sup> skin grafts,<sup>11,13</sup> physiotherapy,<sup>14</sup> other treatments have greatly enriched our options for repairing various acute and chronic injuries, and have achieved positive results.

At present, the clinical treatment methods for skin wound repair mainly include medical surgical sutures, medical limb adhesives, drug-carrying dressings, tissue-engineered skin, physical therapy and miRNA treatments promoting skin wound repair. However, each treatment method has a certain application scope and side effects that cannot be ignored. For instance, (1) surgical suture is the most commonly used clinical treatment for acute skin wounds, but it may cause secondary damage to the skin and other soft tissues. In addition, it shows low efficiency; it is difficult to control the absorption period and ensure that the sutures begin to degrade after wound healing.<sup>15–17</sup> (2) Medical adhesives, widely used in clinical practice, are prone to promoting rash or skin abnormalities after use, and some of them exhibit defects, such as a brittle adhesive layer, formaldehyde production during decomposition and poor air permeability.<sup>18,19</sup> (3) Although wound dressings can temporarily protect the wound, prevent contamination, promote healing and provide a suitable environment for the process of wound healing and treatment, they have the defects of a short efficacy duration and uneven sustained release.<sup>20</sup> (4) Tissue-engineered skin has good application prospects in the study of treatment of skin wounds caused by acute or chronic skin trauma, but it also displays some disadvantages, such as immature multicell coculture technology and a simpler structure than that of real skin.<sup>21–23</sup> (5) Physical therapy is noninvasive and has the advantages of noninvasiveness, simple operation, no complications, wide indications and others but is usually only an auxiliary means to other therapies to promote wound repair.<sup>24–26</sup> (6) Recently, miRNA technology that promotes skin wound repair has attracted the attention of researchers, and some progress has been made in research on the role of miRNA in the repair of acute skin wounds, chronic diabetic injury, scar hyperplasia and other pathophysiological processes, but there is still a long way to go before clinical application will be possible.<sup>27–29</sup> In view of the above problems and challenges that have not been completely solved clinically, the design and development of new multi-functional wound treatment methods to accelerate and improve wound repair has important clinical application value.

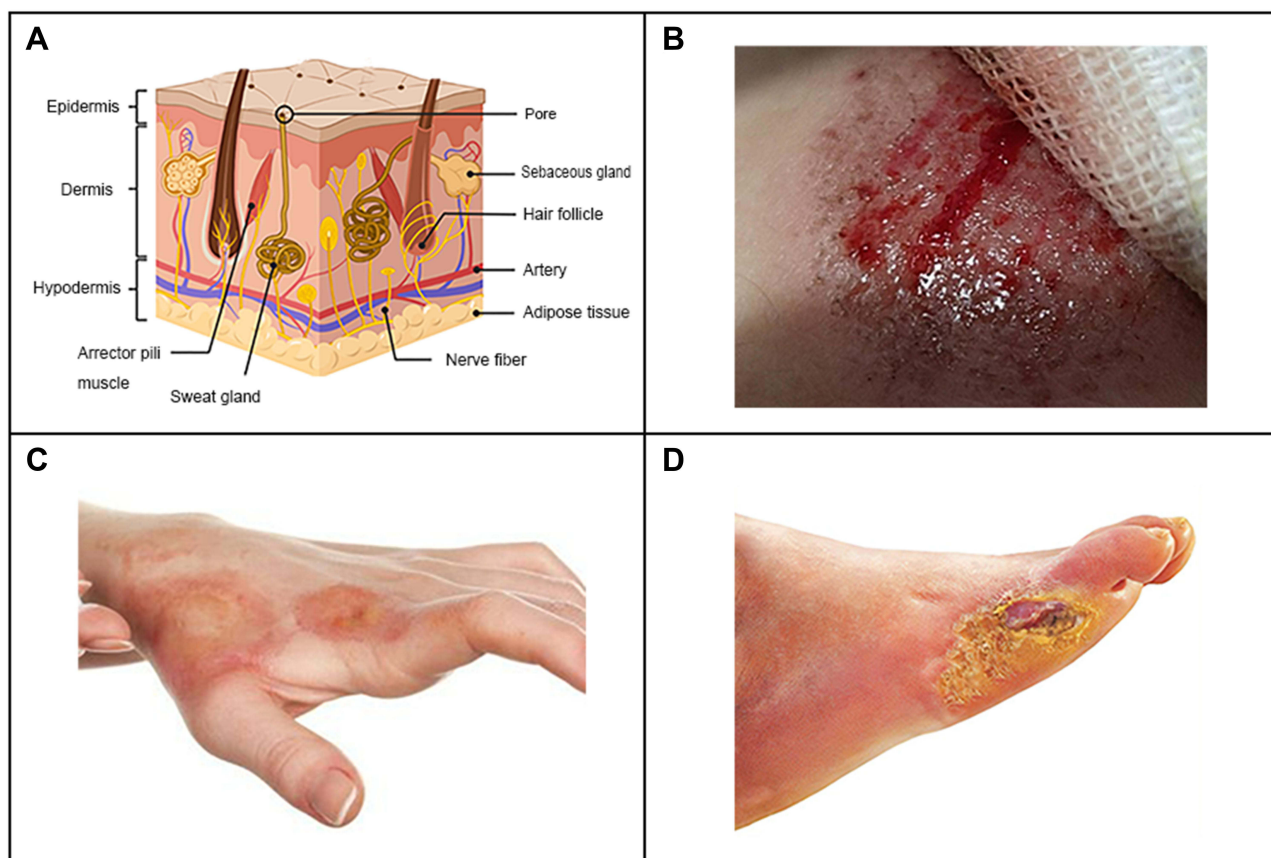
Nanomaterials have attracted increasing attention from researchers and have been widely studied in tissue engineering and biomedicine due to their good biocompatibility, controllable preparation methods, and unique physical, chemical, and biological properties.<sup>30–32</sup> In the past few years, the research and development of nanomaterials and nanotechnology have provided many novel solutions and strategies for the treatment of acute or chronic skin wounds, which not only effectively overcome the defects of traditional treatments but also utilize the unique functions and properties of many nanomaterials.<sup>33,34</sup> Compared with traditional materials, nano materials can effectively enter the human body by changing the drug dosage form, improving the drug concentration in blood, controlling the drug release rate or delivering the drug to the wound site, and the special physical and chemical properties of nanomaterials show more advantages in the field of wound repair.<sup>35,36</sup> For example, modified nanomaterials with pH, charge and microenvironmental effect and other characteristics are conducive to eliminating the obstacles of physiological barriers to drug transport, enhancing the targeting of drug delivery system and reducing drug dosage, thus improving drug absorption, regulating drug release rate, enhancing drug targeting, improving bioavailability and reducing drug toxicity and side effects.<sup>37–39</sup> With research efforts deepening and improvements in the understanding of the mechanism of action and biological safety, the use of nanomaterials will likely continue to be developed, and there is hope that nanomaterials may be the next generation of medical materials for acute or chronic skin wound therapy. This review summarizes the mechanisms underlying and key factors influencing skin wound repair, and we focus on the promotion and development of skin wound repair by nanomaterials.

## Mechanisms Underlying and Factors Influencing Skin Wound Repair

Wound repair is a complex dynamic form of skin repair after an injury and is important for maintaining the integrity of the skin structure and its normal function; both the speed and quality of repair are affected by various factors.

### Mechanisms Underlying Skin Wound Repair

The skin is the largest organ and covers the outermost layer of the human body, and it is mainly composed of three parts: epidermis, dermis and hypodermis.<sup>40,41</sup> Keratinocytes are the main components of the epidermis, accounting for more than 80% of epidermal cells, and keratin can be produced in the process of differentiation. Keratinocytes and their substructures are connected by desmosomes and hemidesmosomes. According to the differentiation stage and characteristics, the epidermis can be divided into five layers, which from inside to outside are the basal layer, spinous layer, granular layer, transparent layer and horny layer.<sup>42,43</sup> The hypodermis accounts for most of the skin structure, and the dermis has a thickness of approximately 0.2 cm and can be divided into two layers, namely, the papillary layer and the reticular layer, which are mostly composed of proteins including collagen and elastin, with the addition of nerves, sweat glands, sebaceous glands and hair follicles.<sup>41</sup> Subcutaneous tissue is the loose connective tissue and adipose tissue below the skin, which connects the skin and muscle. It is vulnerable to trauma and ischemia, especially during inflammation, which can cause degeneration and necrosis (Figure 1A).<sup>41</sup> Skin wounds caused by various accidents and medical surgery constitute common phenomenon due to the large area of the skin and its direct exposure to the external environment. Additionally, skin diseases and diabetes can also cause skin wounds. The common skin wounds mainly include physical wounds (Figure 1B), chemical wounds (Figure 1C) and pathological wounds (Figure 1D). Most physical wounds in daily life are caused by scratching, scraping or superficial cuts, which damage the epidermis and dermis, while hair follicles and sweat glands are intact. Different degrees of wounds correspond to different skin injuries.<sup>44</sup> Chemical damage is the



**Figure 1** Schematic diagram of skin structure (A), physical trauma (B), chemical trauma (C) and pathological trauma (D).

acute skin damage caused by skin contact with certain chemicals, such as erythema, blisters, eschar and so on. Some studies have found that the skin irritation by anionic detergent sodium lauryl sulphate which causes chemical damage of the stratum corneum and interrupts skin barrier function.<sup>45</sup> Pathological wounds, such as diabetic foot ulcers, can be classified according to their size (area and depth), infection and ischemia. Ulcers in the early stages are limited to the skin and subcutaneous tissue, and in severe cases they can reach muscles, tendons or deeper.<sup>46</sup>

Wound repair is a complex dynamic self-repairing process of the skin (or other organ tissues) affected by interactions among multiple repair cells, growth factors and the extracellular matrix after an injury occurs, and it usually comprises three stages.<sup>47,48</sup> The first stage is hemostasis and inflammation.<sup>49</sup> Vasoconstriction, platelet aggregation and fibrin clot formation occur immediately after skin trauma and participate in wound hemostasis. Inflammation is caused by the formation of fibrin clots and the degranulation of aggregated platelets, which release chemokines. These chemokines recruit white blood cells (mainly neutrophils), macrophages or mast cells from the blood into the wound.<sup>50–53</sup> The inflammatory response begins to decrease a few days after trauma, accompanied by apoptosis of inflammatory cells, and tissue fragments and invasive microorganisms are removed during the inflammatory response.<sup>11,48,54</sup> The second stage is cell proliferation and differentiation: in the inflammatory stage, the remaining inflammatory cells, migrating epithelial cells and dermal cells induce and maintain cell proliferation and start cell migration via autocrine, paracrine and other growth factors.<sup>11,55,56</sup> In this stage, vascular endothelial cells begin to form, and vascular endothelial cells degrade the basement membrane under the mediating effects of vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF-2) and platelet-derived growth factor (PDGF); the cells migrate to the wound, proliferate, form intercellular contacts, and finally form blood vessels. At the same time, fibroblasts proliferate in the wound, synthesize extracellular matrix and form granulation tissue with rich neovascularization.<sup>48,57,58</sup> The entire stage is characterized by dynamic and interactive feedback between cells and the extracellular matrix mediated by growth factors and cytokines.<sup>59</sup> Tissue reconstruction or scar formation is the final stage of wound repair. The newly formed granulation tissue is reconstructed into scar tissue. The matrix temporarily formed in the above stage mainly contains collagen III, fibronectin and hyaluronic acid and is gradually replaced by the extracellular matrix, which mainly contains collagen I. Then, the migration of fibroblasts and myofibroblasts and the subsequent reconstruction of granulation tissue matrix leads to wound contraction.<sup>58</sup> Finally, fibroblasts undergo apoptosis to form scar tissue with very few cells, and the tensile strength of the scar tissue is similar to that of normal skin tissue (Figure 2).<sup>60</sup>

## Factors Influencing Skin Wound Repair

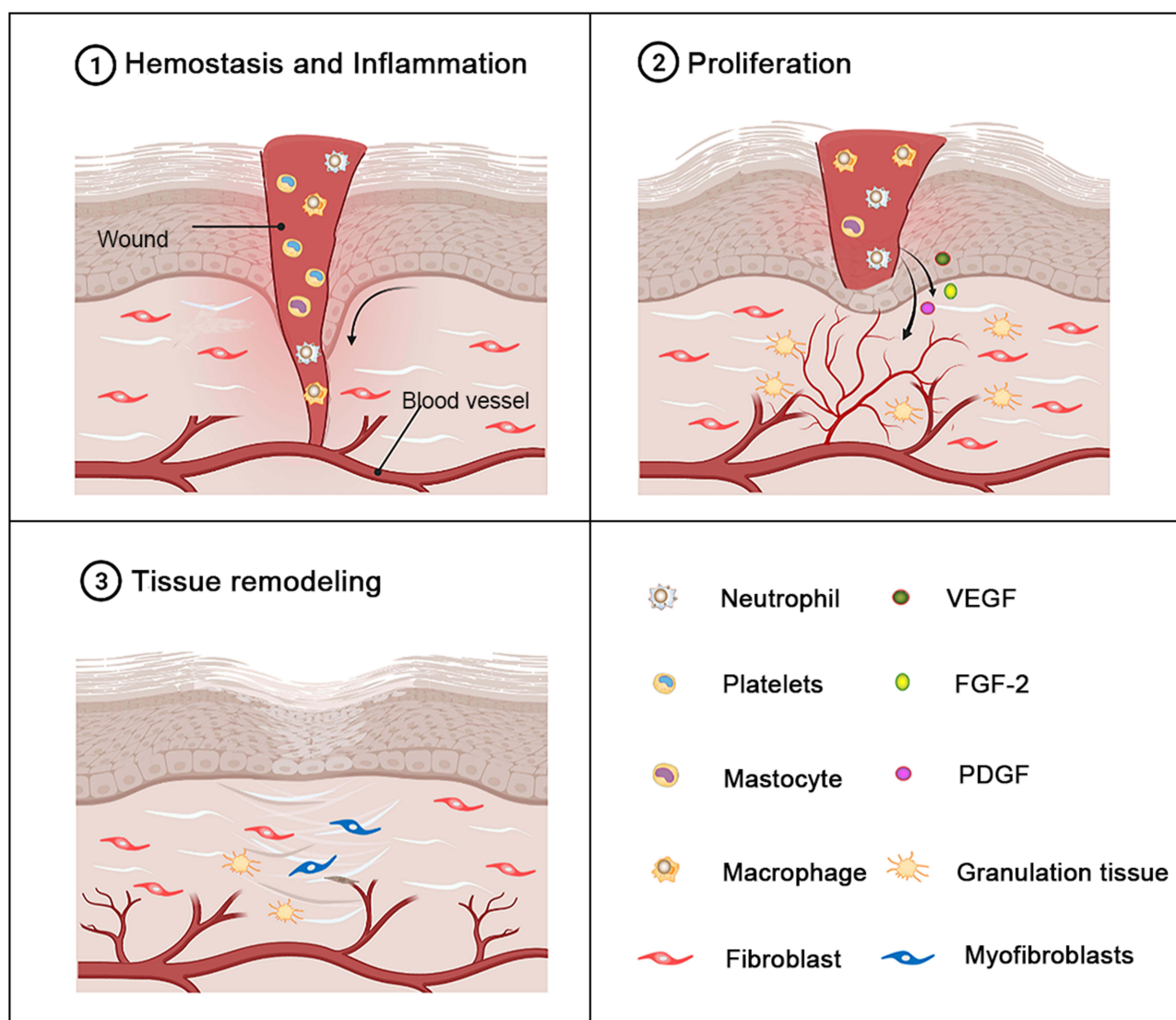
### Key Influence Factors

The speed and quality of wound repair are affected by the interaction of various factors, and further study of these factors could lead to the development of new and effective treatments. In general, the influencing factors can be divided into local factors and systemic factors. Local factors can directly affect the characteristics of the wound itself to influence the wound repair process, while systemic factors mainly influence the pathological, psychological and physiological states of the body, thereby affecting wound repair ability.<sup>61,62</sup> Local factors affecting wound repair mainly include temperature,<sup>63,64</sup> infection,<sup>62,65</sup> oxidative stress levels.<sup>66</sup> Systemic factors mainly include age,<sup>67</sup> healthy state,<sup>68,69</sup> autoimmune disease,<sup>70</sup> genetic factors,<sup>71</sup> psychological factors,<sup>72</sup> living habits<sup>73</sup> and so on. Normally, these factors are interrelated, and systemic factors affect the wound repair process mainly through their effect on local wounds. The above factors can delay or promote the process of wound healing by affecting one or more aspects of the process and thus become the focus of attention in the process of wound treatment.

### Influence of the Local Microenvironment of Wounds

In recent years, a number of studies have shown that skin wound repair not only is regulated by growth factors, nucleic acids, cells and other active components but also is affected by the microenvironment of the wound site.<sup>74</sup> In the process of wound healing, these active components of the wound site interact with the wound microenvironment in a continuous and bidirectional way, which plays a key role in accelerating wound repair speed and driving regenerative repair.<sup>75</sup> For example, the accumulation of excessive reactive oxygen species (ROS) caused by hyperglycemic stimulation and a chronic inflammatory response is one of the characteristics of skin wounds in patients with chronic diabetes and hinders the repair process.<sup>76</sup> Moreover, continuous exposure of endogenous proteins, nucleic acids, lipids and other





**Figure 2** The different stages of normal wound healing. Normal wound healing is a complex biological process that can be divided into three stages: the hemostasis and inflammatory stage, the proliferation stage and the tissue remodeling stage. The inflammatory stage occurs shortly after injury and is characterized by the influx of inflammatory factors. In response to inflammatory signals, neutrophils, macrophages and mast cells are migrate to the wound. As the inflammatory stage subsides and the proliferative phase of tissue repair begins, the dermis and epidermal cells migrate and proliferate excessively in the wound bed. Epithelialization, collagen deposition, angiogenesis, and formation of granulation tissue occur during this stage. The beginning of the stage of tissue remodeling is characterized by matrix remodeling and decreased cell density. At this stage, the wound undergoes contraction to form a scar.

important biomacromolecules at the wound site to high concentrations of ROS may lead to irreversible damage to their structure and function, thus leading to impaired wound repair.<sup>77</sup> Studies have shown that in a microenvironment characterized by inflammation and oxidative stress, the proliferation and redifferentiation of stem cells is significantly reduced and apoptosis can be induced, limiting their regenerative function.<sup>78,79</sup> A large number of studies have found that reducing the level of excessive ROS and oxidative damage at the wound site and improving the wound microenvironment are significantly conducive to repairing various skin wounds.<sup>80</sup>

### Influence of Pathogen Infection

In the process of wound repair, the infection of external bacteria will lead to the delay of wound healing.<sup>81,82</sup> Therefore, the prevention and treatment of wound infection is one of the focal issues in the process of skin wound repair, especially the wounds caused by burns and scalds, which are prone to the infection of Gram-positive bacteria such as *Staphylococcus aureus*.<sup>83,84</sup> Moreover, the use of inadequately sterilized surgical instruments increases the risk of

infection during wound repair surgery. For instance, infections caused by Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Enterococcus* and *Acinetobacter* are more common in the healing of chronic wounds, while inflammation caused by bacterial infection will delay the healing of wounds, form chronic wounds, increase the medical costs of patients, and affect the physical and mental health of patients.<sup>83,85,86</sup>

## Biological Nanomaterials for Skin Wound Repair

Nanomaterials are natural or artificial materials consisting of basic particles in powder form or clumps. One or more dimensions of this basic particle are between 1 nm and 100 nm, and the total number of this basic particle accounts for more than 50% of the total number of all particles in the material as a whole. Furthermore, nanomaterials composed of nanocrystals have a set of innovative physical properties, such as a small size effect,<sup>87</sup> interface effect,<sup>88</sup> quantum effect and quantum tunneling effect.<sup>89,90</sup> Naturally, nanomaterials used in skin wound repair have different functions according to their physical and chemical properties and structures.

## Nanomaterials with Biological Activity

Bioactive nanomaterials, usually with relatively clear chemical structures and surface properties, can interact with proteins, cells or tissues and cause biological reactions, which directly affect the interaction between materials and tissues or cells. In recent years, many bioactive nanomaterials have been developed for wound repair or tissue regeneration, and these nanomaterials have antibacterial, antioxidant, nano adhesion and other biological activities and have good effects with regard to accelerating wound healing, eliminating ROS on the wound surface and inhibiting infection.<sup>91–94</sup>

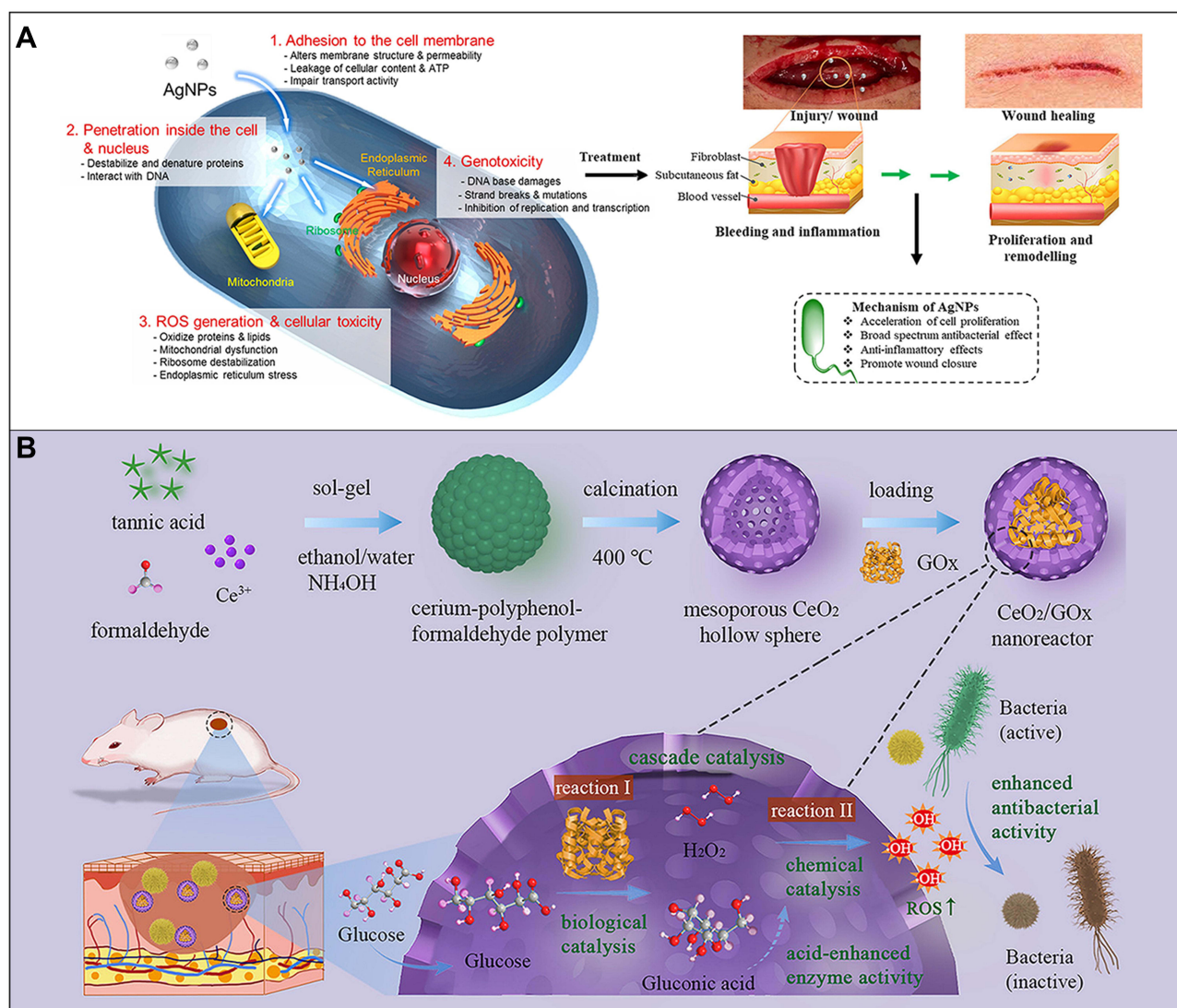
### Metal and Metal Oxide Nanomaterials

#### Silver Nanomaterials

Silver nanomaterials (AgNPs) are used as therapeutic agents for wound healing mainly because of their significant anti-inflammatory and antibacterial properties.<sup>95,96</sup> The main mechanism underlying the antibacterial activity of AgNPs can be simplified to the high surface area of Ag<sup>+</sup> released by them. AgNPs in the aqueous environment are oxidized in the presence of oxygen and protons, and Ag<sup>+</sup> is released when the surface of a particle dissolves. Ag<sup>+</sup> can interact with mercaptan groups in key bacterial enzymes and proteins and disrupt cell respiration, resulting in cell death.<sup>97,98</sup> The specific mechanisms are considered to be as follows. 1. AgNPs adhere to the surface of the cell membrane, which leads to the destruction of the cell membrane and changes in transport activity. 2. AgNPs enter the cell and interact with many organelles (mitochondria, etc.) and biomolecules (protein, DNA, etc.), resulting in its dysfunction. 3. AgNPs induce cytotoxicity and oxidative stress by producing ROS and free radicals. 4. Genotoxicity is induced by AgNPs and Ag<sup>+</sup>.<sup>97,99,100</sup> A large number of studies have shown that by reducing the expression levels of proinflammatory cytokines, such as interleukin 6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and so on, AgNPs can inhibit a variety of pathogenic microorganisms, including fungi, different types of bacteria and even viruses and have shown excellent anti-inflammatory activity, which means that they can be used to prevent or reduce wound infection.<sup>101–104</sup> Similarly, in diabetic wounds, AgNPs accelerate wound healing by activating the proliferation and migration of keratinocytes and helping fibroblasts differentiate into myofibroblasts, thus promoting wound contraction and accelerating the healing of diabetic ulcers. AgNPs are widely used in wound healing because they accelerate cell proliferation, possess broad-spectrum antibacterial and anti-inflammatory activities, and promote wound healing (Figure 3A).<sup>105–107</sup> Additionally, unlike conventional antibiotic therapy which faces the challenges of multiple resistance and biofilm formation, silver nanoparticles do not pose these difficult problems.<sup>108</sup>

#### Copper Nanoparticles (CuNPs)

Compared to other metallic nanomaterials such as silver and gold nanoclusters, CuNPs with good biocompatibility can be prepared quickly and produced at a low cost.<sup>109,110</sup> Moreover, CuNPs may interfere with viral activity and have a broad spectrum of antibacterial properties by producing oxidative stress that leads to the breakdown of viral or bacterial membranes.<sup>111,112</sup> It has been found that 1  $\mu$ M 80 nm CuNPs promote acute full-layer skin defect wound healing quickly by accelerating skin cell migration, proliferation, and new blood vessels.<sup>113</sup> In addition, phenytoin-loaded copper



**Figure 3** (A) Schematic diagram of the antibacterial mechanism and wound healing mechanism of silver nanoparticles. Exposure to silver nanoparticles (AgNPs) prevents bacterial colonization and inflammation in the wound, thereby promoting wound closure. Adapted with permission from: Lee SH, Jun BH. Silver nanoparticles: synthesis and application for nanomedicine. *Int J Mol Sci.* 2019;20(4):E865. doi:10.3390/ijms20040865.<sup>97</sup> © 2019 by the authors. Licensee MDPI, Basel, Switzerland (<http://creativecommons.org/licenses/by/4.0/>). And from: Nqakala ZB, Sibuyi NRS, Fadaka AO, Meyer M, Onani MO, Madiehe AM. Advances in nanotechnology towards development of silver nanoparticle-based wound-healing agents. *Int J Mol Sci.* 2021;22(20):11272. doi:10.3390/ijms222011272.<sup>125</sup> Copyright © 2021 by the authors. Licensee MDPI, Basel, Switzerland. Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>). (B) Establishment of a mesoporous ceria hollow sphere/enzyme nanoreactor and schematic diagram of cascade catalytic antibacterial therapy. Reproduced with permission from: Qin J, Feng Y, Cheng D, et al. Construction of a mesoporous ceria hollow sphere/enzyme nanoreactor for enhanced cascade catalytic antibacterial therapy. *ACS Appl Mater Interfaces.* 2021;13(34):40302–40314. doi:10.1021/acsmi.1c10821.<sup>124</sup> Copyright © 2021, American Chemical Society.

nanoparticles have been shown to accelerate epidermal regeneration and stimulate granulation and tissue formation in rats.<sup>114</sup> Therefore, CuNPs is a material with great potential for effective and rapid wound healing.

### Ceria Nanomaterials

Ceria nanomaterials display good biocompatibility and high antioxidant capacity and can be used to remove ROS in the lesion site. As a nano antioxidant enzyme with excellent performance, ceria materials have a large number of oxygen defects on the surface, and  $Ce^{3+}$  and  $Ce^{4+}$  can be rapidly transformed into each other, which confers on them antioxidant enzyme activity and a renewable ability to remove a variety of ROS.<sup>115–118</sup> Numerous in vitro and in vivo studies have shown that ceria nanomaterials can protect tissue cells from oxidative damage, prolong cell life in the oxidative microenvironment, promote cell proliferation and migration, and reduce the activity of functional enzymes such as

those involved in inflammation.<sup>119–121</sup> Ceria is considered an antibacterial agent that kills bacteria by a Fenton-like reaction in the presence of H<sub>2</sub>O<sub>2</sub>.<sup>122,123</sup> Qin et al<sup>124</sup> established a mesoporous ceria hollow sphere/enzyme nanoreactor by preparing ceria hollow sphere nanozymes loaded with glucose oxidase. The nanoreactor can effectively convert nontoxic glucose into highly toxic hydroxyl radicals through a cascade catalytic reaction, thus seriously destroying the cell structure of bacteria and preventing the formation of biofilms. In addition, gluconic acid can reduce the local pH value and further improve the peroxidase-like catalytic performance of mesoporous ceria. At the same time, *in vivo* experiments showed that the nanoreactor eliminated up to 99.9% of the bacteria in the wound tissue to prevent persistent inflammation and did not damage normal tissue (Figure 3B).

### Metal-Organic Frameworks (MOFs)

MOFs are inorganic-organic hybrid porous nanomaterials self-assembled from metal ions/clusters and multi-tooth organic ligands.<sup>126</sup> Compared with traditional organic and inorganic drug delivery systems, drug carriers based on MOFs have higher drug load and the possibility of chemical functionalization, which can enhance drug affinity.<sup>127,128</sup> They are widely used in biological fields such as drug delivery and biomarker detection due to their large pore volume, pore size and surface area, as well as adjustable surface functionality, and the metal-ligand bond strength is determined by the properties of metal ions and ligands, and is also the key to determining the hydrothermal stability of MOFs.<sup>127,129,130</sup> Recently, Yao et al<sup>131</sup> prepared a Zn-MOF encapsulated methacrylated hyaluronic acid (MeHA) microneedles (MNs) array. This MNs array has excellent antibacterial activity and considerable biocompatibility. It can significantly accelerate epithelial regeneration and neovascularization, promote wound healing, and play an important role in promoting wound healing.

### Upconversion Nanoparticles (UCNPs)

Among many nanomaterials, UCNPs with luminescent properties show unique advantages, which are light stability, persistent luminescence, deep tissue penetration and self-fluorescence inhibition and so on in medical diagnosis and treatment.<sup>132</sup> In order to make UCNPs have good water dispersion and biocompatibility, a large number of studies have been conducted to functionalize them by exchanging oleic acid ligands with DNA, which has great advantages in drug delivery targeting and imaging function in recent years.<sup>133,134</sup> Sun et al<sup>135</sup> reported an antibacterial nanocomposite film containing UCNPs. After 5min was irradiated by near-infrared light, UCNP in the nanocomposite film could trigger the release of ROS by photosensitizer, thus rapidly killing *Gram-positive Staphylococcus aureus* (94.5%) and *Gram-negative Escherichia coli* (93.2%). This work provides a new strategy for designing new antibacterial materials for anti-infection and wound healing.

## Nonmetallic Nanomaterials

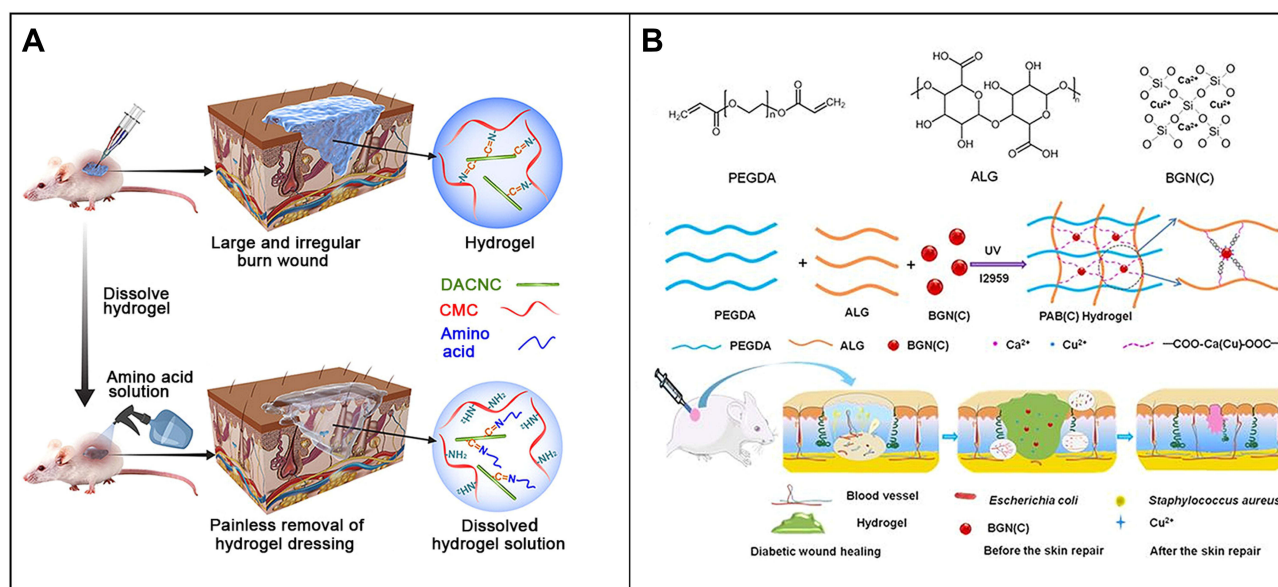
### Polymer Nanomaterials

Nanopolymers (especially natural ones), which have excellent biocompatibility and biodegradation, have been widely used in biomedical research.<sup>136–138</sup> For instance, as a kind of representative polymer nanomaterial, chitosan nanoparticles have good application prospects in the field of wound repair due to their excellent mucosal adhesion, anti-infection activity and hemostatic activity.<sup>139–141</sup> Huang et al<sup>142</sup> developed a nanocomposite self-healing hydrogel using water-soluble carboxymethyl chitosan (CMC) and rigid rod-like dialdehyde-modified cellulose nanocrystal (DACNC), which can be injected into irregular and deep burn wound beds. Once injected, it quickly heals, reforms a complete hydrogel, thoroughly fills the wound area and protects the wound from the external environment (Figure 4A).

### Silicon Oxide Nanomaterials

Meddahi-Pellé et al<sup>143</sup> discovered and demonstrated that aqueous silica nanomaterials had a nanobridge effect that enabled rapid and strong bonding in both skin wounds and organic deep wounds. Silica nanoparticle adhesive aqueous solution for wound repair has the advantages of quick and convenient use and it does not require complex and time-consuming operation.<sup>144</sup> Unlike polymer tissue adhesives, silica nanoparticle adhesives do not require complex cross-linking reactions; furthermore, they still have a good adhesion effect under the humid environment in the body.<sup>19</sup>





**Figure 4** (A) Carboxymethyl chitosan (CMC) combined with dialdehyde-modified cellulose nanocrystal (DACNC) nanocomposite hydrogel for irregular and deep burn wounds. Reproduced with permission from: Huang W, Wang Y, Huang Z, et al. On-demand dissolvable self-healing hydrogel based on carboxymethyl chitosan and cellulose nanocrystal for deep partial thickness burn wound healing. *ACS Appl Mater Interfaces*. 2018;10(48):41076–41088. doi:10.1021/acsami.8b14526.<sup>142</sup> Copyright © 2018, American Chemical Society. (B) Synthesis of bioactive silica-based nanocomposite (PABC) hydrogel scaffold and its potential application and hypothetical mechanism in diabetic wound healing. Reproduced with permission from: Li Y, Xu T, Tu Z, et al. Bioactive antibacterial silica-based nanocomposites hydrogel scaffolds with high angiogenesis for promoting diabetic wound healing and skin repair. *Theranostics*. 2020;10(11):4929–4943. doi:10.7150/thno.41839.<sup>146</sup> Copyright © The author(s). Creative commons attribution license (<https://creativecommons.org/licenses/by/4.0/>).

Moreover, unlike traditional suture, suture nail and other closed wound treatment methods, nano aqueous solution does not readily cause secondary damage to soft tissues or organs, such as the skin, liver and lung, and does not require subsequent stitch removal.<sup>145</sup> Li et al<sup>146</sup> reported a bioactive silica-based nanocomposite hydrogel scaffold (PABC scaffold) with high angiogenesis-promoting abilities for supporting diabetic wound healing and skin repair, including the main network formed by polyethylene glycol diacrylate (PEGDA) and an auxiliary dynamic network formed between copper-containing bioactive glass nanoparticles containing copper (BGNC) and alginate (ALG). The scaffold can significantly promote the viability, proliferation and angiogenesis of endothelial progenitor cells (EPCs) in vitro. In vivo, it can promote early angiogenesis/neovascularization, effectively repair the vascular network and significantly accelerate wound healing and skin tissue regeneration by increasing the expression levels of hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ )/VEGF and the deposition of collagen matrix in diabetic full-thickness wounds (Figure 4B).

### Carbon Nanomaterials

Carbon nanomaterials have the advantages of large drug load, good biocompatibility and strong targeting, especially which are modified.<sup>147</sup> Carbon nanotubes are ideal drug carriers for their large surface area, excellent optical properties and good compatibility with cells. Their water dispersion and biocompatibility coated with polymer materials are greatly improved, and their precious metal coordination and binding abilities are enhanced, which have significant advantages in drug delivery, biosensor and wound diagnosis.<sup>148</sup> Magnetic hollow carbon nanospheres with acorn as carbon source are prepared via high temperature calcination method, and the drug loading and release of ibuprofen show that they have good drug loading and release ability.<sup>149</sup> Carbon nanotubes have also been studied as potential antimicrobial agents with inherent antibiotic activity. Carbon nanotubes have effective bactericidal activity against *Enterobacter* and *Escherichia coli*, which can cause cell aggregation and microbial death.<sup>150</sup> This may be expected to be used in the process of wound repair.

### Nanofiber Materials

Nanofiber materials have a large specific surface area, high porosity and facilitate the transport of nutrients and oxygen, which led researchers to the idea of using them for drug delivery.<sup>151,152</sup> In recent years, breakthroughs have been made in

the research and preparation of starch nanofibers for drug loading and external application. For example, starch nanofibers prepared by crosslinking method have the advantages of controllable sustained release and good biocompatibility.<sup>153</sup> Xuan et al<sup>154</sup> prepared an injectable nanofiber polysaccharide self-healing hydrogel, which can significantly promote wound healing.

## Biological Nanomaterials for Topical Therapeutic Drug Delivery Carriers

Biological nanomaterials used for local therapeutic drug delivery carriers are mainly employed to transport nitric oxide, antioxidants, growth factors, nucleic acids, antibiotics, and other active ingredients to promote wound repair. Here, we focus on the following four types of active ingredients loaded in nanomaterials.

### Nanomaterials Loaded with Growth Factors

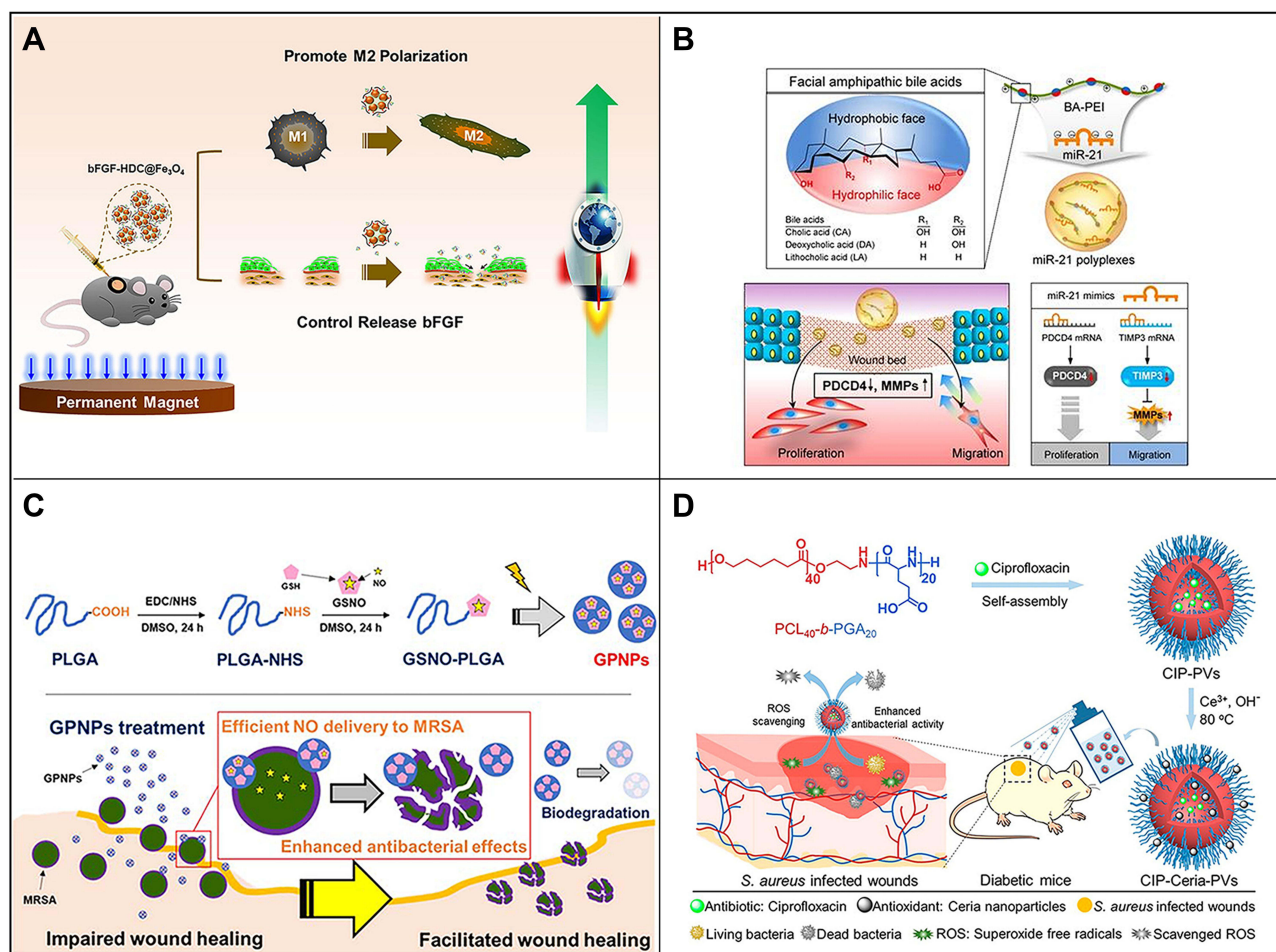
It is well known that growth factors play a key role in all stages of wound repair.<sup>56</sup> For example, recombinant human platelet-derived growth factor has been approved by the American FDA for the treatment of chronic diabetic foot.<sup>155</sup> Under normal physiological conditions, growth factors are not stable and are easily degraded by enzymes in the wound microenvironment. In addition, high local concentrations of these factors may even cause disorder in the wound repair process; however, loading growth factors into nanomaterials can effectively prevent these problems. Furthermore, they can achieve sustained release and improve the therapeutic effect of growth factors in the process of wound repair.<sup>156–158</sup> Choi et al<sup>159</sup> designed and established an electrospun nanocomposite containing human recombinant epidermal growth factor (EGF), which achieved continuous and effective release of EGF and achieved good results in diabetic wound repair. In addition, Wu et al<sup>160</sup> based on the Fe<sub>3</sub>O<sub>4</sub> nanoparticle, developed a basic fibroblast growth factor (bFGF) loaded Fe<sub>3</sub>O<sub>4</sub> nanoparticle (bFGF-HDC@Fe<sub>3</sub>O<sub>4</sub>) using a simple mussel-inspired surface immobilization method, which can stabilize bFGF under different conditions and exhibit a sustained release effect. It has been found that bFGF-HDC@Fe<sub>3</sub>O<sub>4</sub> can greatly promote wound healing by promoting M2 macrophage polarization and cell proliferation. Therefore, the continuous release of growth factors with regulatory behavior is achieved by modifying nanoparticles, which provides a broad prospect for their application to tissue regeneration (Figure 5A).

### Nanomaterials Loaded with Nucleic Acids

MicroRNAs (miRNAs) have been shown to be potentially involved in the entire wound healing process in a highly decisive and coordinated manner.<sup>161–164</sup> However, exogenous miRNA therapy has several limitations, including poor stability, low cell uptake rate, limited selectivity for target tissues and so on. To improve the local release of miRNAs and improve the efficiency of wound healing, the method of introducing nanomaterials to load nucleic acid molecules has been continuously studied.<sup>165–167</sup> Nanomaterials can also deliver DNA, siRNA, miRNA and other nucleic acid molecules to upregulate or inhibit the expression of target genes, thereby regulating of the skin wound repair process.<sup>168,169</sup> Randeria et al<sup>170</sup> connected thiolated siRNA to the surface of gold nanoparticles with a diameter of 13 nm, which was used to downregulate monosialoganglioside 3 synthase expression in diabetic ulcer sites. The experimental results showed that siRNA-loaded nanocomposites can promote keratinocyte migration and proliferation and thus effectively promote the repair of diabetic lesions. Wang et al<sup>166</sup> introduced miRNA-21 nanocarriers electrostatically complexed with three types of bile acid-attached polyethyleneimine (BA-PEI) conjugates, including cholic acid (CA), deoxycholic acid (DA), and lithocholic acid (LA) for treatment of skin wounds. This nanocarrier delivery system has been found to regulate programmed cell death protein 4 (PDCD4) and matrix metalloproteinases (MMPs) after transcription to promote cell migration and proliferation, which in turn helps to accelerate wound repair (Figure 5B).

### Nanomaterials Loaded with Therapeutic Gases

Endogenous gas signaling molecules, such as nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H<sub>2</sub>S), can affect vascular dilation, transfer information among cells, participate in neural development and regulate gene expression.<sup>171–173</sup> At the site of skin wounds, severe trauma often leads to damage to blood vessels, nerves and tissues, and wound repair requires the active participation of these gas signaling molecules.<sup>174,175</sup> As the earliest discovered and studied gas signaling molecule, NO has been applied in a large number of products for the clinical treatment of various diseases.<sup>176</sup> NO is an endogenous fungicide produced by a large number of macrophages and has broad-spectrum antibacterial properties. It has been reported



**Figure 5 (A)** Fe<sub>3</sub>O<sub>4</sub> nanoparticles loaded with basic fibroblast growth factor (bFGF) can greatly promote wound healing by polarizing M2 macrophages and promoting cell proliferation. Reproduced with permission from: Wu J, Zhu J, Wu Q, et al. Mussel-inspired surface immobilization of heparin on magnetic nanoparticles for enhanced wound repair via sustained release of a Growth Factor and M2 Macrophage Polarization. *ACS Appl Mater Interfaces*. 2021;13(2):2230–2244. doi:10.1021/acsmi.0c18388. <sup>160</sup> Copyright © 2021, American Chemical Society. **(B)** A schematic diagram of the use of miRNA-21 mimic nanocarriers in the treatment of skin wounds and the role of miRNA-21 mimics in wound repair by activating cell proliferation and migration. Reproduced with permission from: Wang SY, Kim H, Kwak G, et al. Development of microRNA-21 mimic nanocarriers for the treatment of cutaneous wounds. *Theranostics*. 2020;10(7):3240–3253. doi:10.7150/thno.39870. <sup>166</sup> Copyright © The author(s). Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>). **(C)** Schematic diagram of S-nitrosoglutathione-conjugated poly(lactic acid-glycolic acid) nanoparticles (GPNPs) synthesis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA)-infected skin wounds. Reproduced with permission from: Lee J, Kwak D, Kim H, et al. Nitric Oxide-Releasing S-Nitrosoglutathione-Conjugated Poly(Lactic-Co-Glycolic Acid) Nanoparticles for the Treatment of MRSA-Infected Cutaneous Wounds. *Pharmaceutics*. 2020;12(7):E618. doi:10.3390/pharmaceutics12070618. <sup>183</sup> Copyright © 2020 by the authors. Licensee MDPI, Basel, Switzerland. Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>). **(D)** Preparation of CIP-loaded and ceria-decorated polymer vesicles (CIP-Ceria-PVs) and combination of antioxidants-antibiotics in the treatment of diabetic infected wounds. Reproduced with permission from: Wang T, Li Y, Cornel EJ, Li C, Du J. Combined Antioxidant-Antibiotic Treatment for Effectively Healing Infected Diabetic Wounds Based on Polymer Vesicles. *ACS Nano*. 2021;15(5):9027–9038. doi:10.1021/acsnano.1c02102. <sup>195</sup> Copyright © 2021, American Chemical Society.

that NO can destroy bacterial cell membranes, proteins and DNA through the formation of active nitrogen species or direct nitrosation, resulting in bacterial cell death.<sup>177,178</sup> In addition to the antibacterial activity of NO, NO has attracted much attention as a new type of infectious wound healing drug because of its beneficial role in regulating inflammation and promoting wound healing, such as through promoting cell proliferation and tissue remodeling.<sup>176,179</sup> In the wound repair field, NO can promote angiogenesis at the wound site by activating signaling pathways related to vascular endothelial growth factor, basic fibroblast growth factor and transforming growth factor- $\beta$ .<sup>180,181</sup> It has been found that NO loaded in poly(lactic acid-glycolic acid)(PLGA)-doped polyethyleneimine (PEI) (PLGA-PEI) composite nanoparticles significantly improved the repair speed of wounds infected with methicillin-resistant *Staphylococcus aureus*.<sup>182</sup> Lee et al<sup>183</sup> synthesized S-nitrosoglutathione (GSNO)-conjugated PLGA (GSNO-PLGA) and used this new polymer to prepare GSNO-PLGA nanoparticles (GPNPs) for

the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA)-infected wounds. GPNPs had a higher NO load and showed stronger antibacterial activity against MRSA than did GSNO (Figure 5C).

### Nanomaterials Loaded with Antibiotics

Traditional wound dressings mainly play a role in hemostasis, infection control, wound cleaning and exudate absorption. This method requires large doses of antibiotics and takes weeks to months. In addition, this treatment can produce drug-resistant pathogens in the body.<sup>184–186</sup> More effective antibiotic strategies have been developed. For example, antibiotics can be loaded in functional nanoparticles, such as micelles,<sup>187</sup> vesicles,<sup>188</sup> nanosheets<sup>189</sup> and so on, which can achieve slow release of antibiotics, resulting in a continuous antibacterial effect, and can also be functionalized through targeted modifications. These characteristics reduce the required dose of antibiotics, thereby reducing the chance of developing antibiotic resistance.<sup>190–192</sup> Due to their intrinsic biological activity and therapeutic efficacy, nanomaterials can regulate different stages of wound repair, which promises to be a new approach to wound treatment. Evidence verified that mesoporous silica nanoparticles (MSNs) loaded with the broad-spectrum antibiotic tetracycline in their channels and mixed with carboxymethyl cellulose hydrogel synchronously absorbed wound exudate and released antibiotics to prevent infection, which could effectively promote the skin wound repair process.<sup>193,194</sup> Wang et al<sup>195</sup> proposed a method to treat diabetic infected wounds based on polymer vesicles combined with antioxidant-antibiotic therapy. Polymer vesicles are self-assembled by amphiphilic block copolymers poly( $\epsilon$ -caprolactone)-block-polyglutamic acid. In this self-assembly process, ciprofloxacin (CIP) is loaded into the vesicles, and ceria nanoparticles grow in situ on the CIP-loaded polymer vesicles after self-assembly. These CIP-loaded and ceria-decorated polymer vesicles (CIP-Ceria-PVs) showed strong antibacterial activity and scavenging ability of superoxide anion free radicals in the treatment of diabetic infected wounds (Figure 5D).

Therefore, based on the various factors influencing the process of skin wound repair, a variety of multifunctional composite nanobioactive materials have been designed at the micro and nano scales to combine the unique advantages of each material, and when these composites are loaded with the appropriate therapeutic drugs, this approach is expected to result in new safe and effective wound treatment methods. In recent years, nanomaterials used as local drug delivery carriers have become a research hotspot in the biomedical field, but there are still some problems and challenges in the clinical transformation application. Although drug-carrying nanoparticles have some advantages in terms of particle size, synthesis method, surface modification and biocompatibility, it is still a challenge to study the behavior, toxicity, biological distribution and clearance mode of these nano-delivery systems in vivo before they can be used in clinic.<sup>196</sup> Therefore, the clinical transformation of making drug-loaded nanoparticles as drug delivery system is a key problem to be solved in the development of drug-loaded nanomaterials.

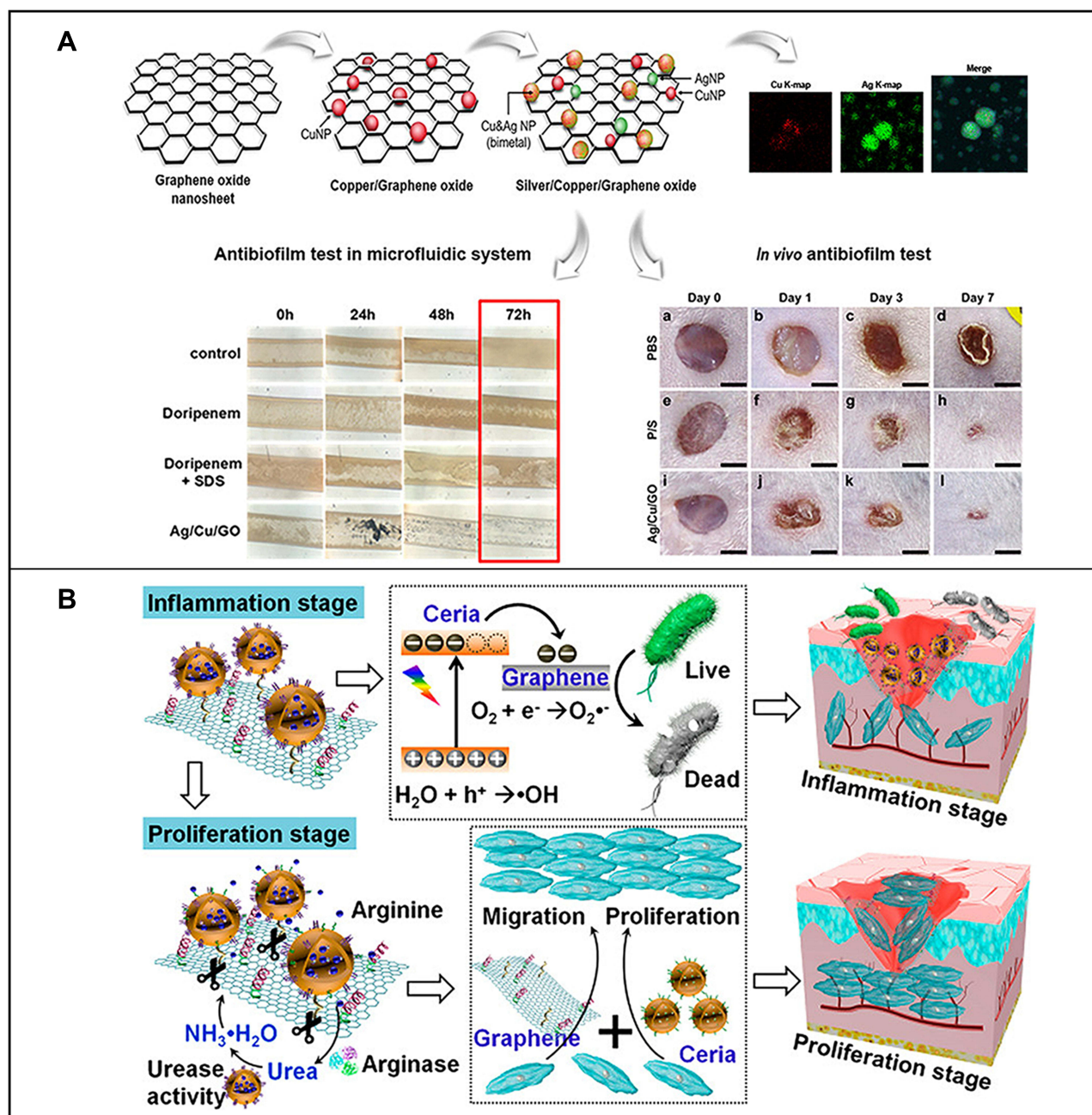
### Multifunctional Composite Biological Nanomaterials

In recent decades, considering that a single functional material or therapeutic has difficulty addressing the multiple factors of skin wound repair, the strategies of wound tissue repair and regeneration and local drug delivery, based on multifunctional nanocomposite materials, have gradually attracted the attention of researchers.<sup>197</sup> The establishment of multifunctional nanocomposites and local drug delivery systems can not only retain the biological activity of nanomaterials but also overcome the deficiency of the poor efficacy of single materials when carrying therapeutic drugs. Moreover, the overall performance of composite materials is optimized, and this approach is expected to open a new direction for skin wound repair and local drug delivery.<sup>146,198,199</sup>

For example, due to high surface charge density, silicate nanosheets can induce coagulation factor aggregation to promote coagulation; moreover, they can also greatly improve the physiological stability, injectability and hemostatic ability of nanocomposite hydrogels and have a good synergistic effect with a gelatin matrix.<sup>200</sup> A study showed that nanocomposite hydrogels with shear thinning properties can be used as injectable hemostatic agents by loading silicate nanosheets into a gelatin matrix.<sup>201</sup> Castleberry et al<sup>202</sup> established a nanocoating containing siRNA based on a nylon matrix using layer-layer self-assembly technology, which achieved the sustained release of siRNA in the wound site, thus successfully downregulating the expression of target gene metalloproteinase-9 and greatly promoting the repair of diabetic wounds. Jang et al<sup>203</sup> prepared silver and copper bimetallic nanoparticles on the surface of graphene oxide (GO) by a chemical reduction method (Ag/Cu/GO). To evaluate the potential of the antibacterial treatment in vivo, the effect of Ag/Cu/GO on the skin of mice subjected to trauma and infected with *Pseudomonas aeruginosa* was analyzed. It was found that local application of Ag/Cu/GO could effectively remove antibiotic-



resistant bacteria and quickly and effectively heal skin or wound diseases caused by bacterial infection and biofilm formation (Figure 6A). Cheng et al<sup>204</sup> designed an arginine-loaded and detachable ceria-graphene nanocomposites (ACG NCS). In the inflammatory stage, ACG NCS can effectively produce ROS and kill bacteria under white light irradiation. During the proliferative phase, ceria nanoparticles can be isolated from ACG NCS and absorbed by cells to remove intracellular ROS and promote cell proliferation, while the isolated graphene can be used as a scaffold to promote fibroblast migration to the wound site (Figure 6B). With the advantages of good biocompatibility and small particle size, nanomaterials can be combined with traditional dressings, thus showing advantages of easy fixation and removability in wound repair.<sup>205</sup>



**Figure 6 (A)** Preparation of silver/copper/graphene oxide nanocomposites and their antibacterial film effect and promotion of wound healing after *Pseudomonas aeruginosa* infection. Reproduced with permission from: Jang J, Lee JM, Oh SB, Choi Y, Jung HS, Choi J. Development of Antibiofilm Nanocomposites: Ag/Cu Bimetallic Nanoparticles Synthesized on the Surface of Graphene Oxide Nanosheets. *ACS Appl Mater Interfaces*. 2020;12(32):35826–35834. doi: 10.1021/acsami.0c06054.<sup>203</sup> Copyright © 2020, American Chemical Society. **(B)** Schematic diagram of the wound healing mechanism of arginine-loaded and detachable ceria-graphene nanocomposites (ACG NCS). Reproduced with permission from: Cheng Y, Chang Y, Feng Y, et al. Hierarchical acceleration of wound healing through intelligent nanosystem to promote multiple stages. *ACS Appl Mater Interfaces*. 2019;11(37):33725–33733. doi:10.1021/acsami.9b13267.<sup>204</sup> Copyright © 2019, American Chemical Society.

Polymer-based nanocomposites, as one of the multifunctional composites and mainly including hyperbranched polymers, liposomes and polymer micelles, have great application value in drug delivery systems due to their good biocompatibility and ability to load hydrophobic/hydrophilic drugs, proteins and other bioactive agents.<sup>206,207</sup> For example, polymer micelles are nano-agglomerates with shell/core structure formed by self-assembly of amphiphilic block copolymer in aqueous solution, and widely used in the field of wound repair.<sup>208,209</sup> Their hydrophobic core can encapsulate a variety of hydrophobic anti-inflammatory and antibacterial drugs and improve their stability and solubility without changing their chemical structure, so the hydrophilic shell and nano particle size are conducive to drug release and enrichment at the trauma site.<sup>209</sup> Another multifunctional nanocomposite materials are hydrogel nanocomposites used for drug sustained-release material, wound dressing and scaffold for tissue engineering during wound repair treatment, with good biocompatibility, shaping ability and performance characteristics similar to extracellular matrix.<sup>210,211</sup> However, the further development of hydrogels is still limited because of their poor mechanical properties and self-healing properties, which has great potential for improvement. The introduction of different types of nanoparticles into hydrogel nanocomposites, such as carbon-based, polymer-based, inorganic and metal-based nanoparticles, is a common method to obtain nano-composite hydrogels with excellent properties and customized functions, which can not only enhance the mechanical properties, self-healing properties and chemical properties, but also improve their stability.<sup>197,198,212</sup> Therefore, multifunctional nanocomposites have a good application potentiality in the field of wound repair.

Therefore, nanomaterials and physical materials with different physical and chemical properties, biological activities and drug loading capacities are synergistically integrated into nanocomposites, providing a new approach to wound repair, tissue regeneration and local drug delivery. Multifunctional nanocomposites take full advantage of the unique physicochemical properties and synergistic gains of therapeutic drugs, biomaterials and nanomaterials, and this approach is beneficial for addressing the diverse pathological mechanisms discovered in research and advancing the field of wound repair and tissue regeneration.

## Toxicity and Side Effects and the Challenges and Perspectives of Biological Nanomaterials in Wound Repair

At present, with the increasing frequency of the usage of nanomaterials, there is an urgent need to evaluate their biological safety. However, the establishment of a nanomaterial biosafety evaluation system is still in the exploratory stage, and the biosafety evaluation of nanomaterials mainly focuses on the toxicological study of their health effects, but there is still a lack of follow-up observation and evaluation after clinical wound repair. Nanomaterials can enter cells and affect the transmembrane process, cell division, proliferation, apoptosis and other basic life processes and the regulation of related signal transduction pathways, so as to produce certain biological effects at the cellular level.<sup>91,213</sup> It has been found that carbon nanotubes can easily enter human cells and affect the cell structure. At low doses, carbon nanotubes can stimulate the phagocytosis of macrophages, but at high doses, they can seriously reduce the phagocytosis of macrophages to exogenous poisons.<sup>214,215</sup> Cells treated with nano TiO<sub>2</sub> can be detected to leak large amounts of Ca<sup>2+</sup>, and studies have shown that nano TiO<sub>2</sub> can attack cell membranes, causing them to rupture, leading to cell death.<sup>216,217</sup> What's more, after entering human cytoplasm by virtue of the tiny properties, nano TiO<sub>2</sub> can oxidize and damage cellular genetic material depending on their high chemical activity. Research found that 8-hydroxyguanosine could be detected in RNA, which were separated from the cells treated by nano TiO<sub>2</sub>, thus resulting in that the expression of cell genetic information is affected indirectly via RNA.<sup>218</sup> ROS generation and oxidative stress response are important mechanisms of nanomaterials to induce a variety of biological toxicity effects.<sup>219</sup> The toxicity study of nano-ZnO shows that nano-ZnO has higher cytotoxicity and could significantly increase intracellular ROS levels, deplete glutathione, and significantly reduce malondialdehyde and superoxide dismutase contents.<sup>220</sup> Therefore, oxidative stress may be a major manifestation of the cytotoxicity of nanomaterials.

Many consumer products such as sunscreens and cosmetics may contain nano-TiO<sub>2</sub>, so it is meaningful to study the skin absorption of these nanoparticles. In one study, pig skin, considered most similar to human skin, was treated by nano-TiO<sub>2</sub>, and particle-induced X-ray fluorescence analysis was used to observe the distribution of nano-TiO<sub>2</sub> in the skin structure. The results showed that nano-TiO<sub>2</sub> can enter the granular layer below the epidermis through the cuticle,

especially in the epidermal germinal layer.<sup>221</sup> Moreover, deposits of ultrafine TiO<sub>2</sub> particles in sunscreen were found in the cuticle and dermal papilla of hair follicles.<sup>222,223</sup>

According to the current research results, nanomaterials have three main characteristics promoting skin penetration. The first is related to the particle size of nanomaterials, and the smaller the particle size, the easier it is for it to penetrate the skin. Second, the degree of skin irritation is determined by the properties of the nanomaterial entering the dermis. Third, nanoparticles or other extracts containing soluble substances and metals easily penetrate human skin.<sup>224–226</sup> Due to the use of various nanoparticle types and their different physical and chemical properties, even the same nanomaterial with different particle sizes will display different biological effects. Therefore, there is a particularly urgent need to evaluate the biosafety of the new nanomaterials emerging every year, and researchers and designers should try to avoid or lessen these toxic side effects when designing related nanomaterials.

Although some biological effects of nanomaterials have been assessed, the potential toxicity and possible effects are not clear. On account of the high yield of nanomaterials and the urgency of screening potential hazards, the current priority is to reach an international convention on the impact of nanotechnology on the human body and the environment, and establish scientific and perfect detection methods. However, there is no systematic study on the metabolism and biochemical reaction of nanomaterials toxicity *in vivo*. Therefore, the preliminary establishment of a structure-activity relationship model provides a scientific basis for comprehensive and accurate evaluation of the toxicity of nanomaterials. In recent years, flow cytometry, high throughput virtual screening and metabonomics all have been widely used in toxicological research, but the biggest problem is the uncertainty and randomness of evaluation methods, and there is no objective index that can directly reflect the toxicity of nanomaterials. Although nanomaterials may produce some toxic effects, the current research results and data are not sufficient to indicate that these toxic effects will become a major problem in wound repair, and they have great potential clinical application value, we should treat the impact of nanomaterials positively and objectively.

## Conclusions and Perspectives

Various acute and chronic skin wounds are common clinical problems; moreover, the mortality and disability rates caused by chronic diabetes wounds are high, which all result in substantial health problems and inconvenience for patients. Although the existing clinical wound treatment methods can control infection, stop bleeding and absorb exudates to some extent, various difficulties still exist, and the ideal wound repair effect still cannot be achieved. In recent years, nanomaterials with good biocompatibility, controllable preparation methods and unique physicochemical and biological properties have not only effectively overcome the shortcomings of traditional therapeutic methods but also show unique functions and properties.

This review summarizes three types of nanomaterials currently used in the treatment of skin wounds, namely, nanomaterials with inherent biological activity, nanomaterials used as local delivery carriers for therapeutic drugs, and multifunctional composite nanomaterials. Nanomaterials currently used in skin wound repair show ideal efficacy and advantages over traditional treatment methods. Moreover, the toxicity and side effects of related nanomaterials are also emphasized, and a sound biosafety evaluation system is expected to be established. We believe that with the development of biomedicine and materials science, additional innovations in skin wound repair nanomaterials with ideal repair functions and few toxic side effects will emerge, resulting in considerable reparative effects in skin wound patients.

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## Author Contributions

Yue Lin and Zheyang Chen contributed equally. Investigation, data curation, writing - original draft, writing - review and editing: Yue Lin and Zheyang Chen; supervision, writing - review and editing: Yinai Liu, Jiawen Wang and Wang Lv; conceptualization, project administration: Renyi Peng. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically



for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare no conflicts of interest in relation to this work.

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