

Application and Advances of Cell Membrane-Coated Nanoparticles in Diabetic Wound Healing

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Abstract: Wound healing in diabetes is a complicated and challenging task, which is affected by many factors. For example, microcirculatory disorders, inflammatory reactions, cell signaling disruption, abnormal fibrosis, and impaired immunity due to high blood sugar may have an adverse effect on wound healing. In order to address this problem, researchers have continued to explore a broad range of innovative approaches. Nanoparticles, as a novel repair material, are widely used due to their unique physical and chemical properties, particularly in the treatment of diabetes; however, they also have certain limitations. Cell membrane-coated nanoparticles, with their inherent biocompatibility and precise drug delivery capabilities, have emerged as a novel and highly effective strategy for treating diabetic wounds. Among these, nanoparticles coated with macrophage membranes and mesenchymal stem cell membranes have demonstrated the most significant therapeutic effects in wound anti-inflammation, vascular regeneration, and tissue repair. They can effectively improve the local pathological microenvironment, offering a novel and highly effective nanotherapeutic strategy for the treatment of chronic wounds. This paper systematically reviews research progress on nanoparticles coated with red blood cell membranes, macrophage membranes, stem cell membranes, and exosome membranes for treating diabetic wounds. It comprehensively organizes findings based on membrane source classification, mechanisms of action and in vitro/in vivo evidence. Compared to existing reviews, this paper's primary innovations and contributions lie in establishing a comprehensive membrane classification system, deeply analyzing the synergistic logic of multi-mechanism actions, and it provides a comprehensive analysis of practical challenges in areas such as reproducibility, safety, immunomodulation, large-scale production, regulatory compliance, and clinical translation. It provides theoretical support and practical references for developing more precise and safer wound repair strategies in the future.

Keywords: diabetic wound repair, nanoparticles, cell membrane

Introduction

Diabetes is a metabolic disorder characterized by hyperglycemia, which can result from insufficient insulin secretion, impaired insulin biological function, or both.

Diabetes includes a wide range of sub-types, including type 1 and 2 diabetes, adolescent diabetes (MODY), gestational diabetes, neonatal diabetes, and steroid-induced diabetes.¹⁻³

High blood glucose levels can cause a variety of complications, including diabetic nephropathy, neuropathy, cardiomyopathy, and skin ulcers.⁴

Today, as society advances and lifestyle changes, diabetes rates around the world have been increasing year after year, affecting billions of people around the world.⁵ In addition, it is estimated that one out of five people with diabetes will experience a chronic, non-healing injury, such as a DFU, over the course of their lives, with a surprisingly high rate of recurrence.⁶ It is common for diabetes to develop into chronic, hard-to-heal ulcers, as a result of a persistent infection due

to cellular dysfunction, microcirculatory disturbances, high oxidative stress, and hypoxia. These ulcers are a major factor leading to amputation and disability in patients.⁷

The outer skin and inner dermis form a part of our skin and have close association with the external environment. It is involved in a range of physiological processes, including maintaining the temperature and detecting external factors. The most crucial is that most parts of the body are covered with the skin that forms one of the main barriers of protection against mechanical damage, microbial infection, Ultraviolet Radiation, and extreme temperatures.^{8,9}

The process of wound healing is a dynamic activity that is split into four stages: hemostasis, inflammation, proliferation, and maturation that overlap each other and are precisely regulated. Importantly, it involves a large-scale cellular activity collaboration in order to heal damaged tissue. The complications of diabetes mellitus being one of the most severe in diabetes are serious problems because of the complexity of its environment which comprises infectious biofilm, over inflammatory response and poor angiogenesis.⁹ Figure 1 illustrates the normal wound healing mechanism and the wound healing mechanism in diabetes.¹⁰

The diabetic predisposed hyperglycemia state can lead to an increased use of bacteria nutrients and even weakening of immune systems. A great number of cellular, metabolic, and biochemical determinants of impaired wound healing exist. Although debridement, surgical debridement and skin grafting are all conventional treatment methodologies that can reduce the symptoms, the extent to which they can permanently resolve the diabetic wounds is still quite low.¹¹ Moreover, being one of the most chronic diseases, diabetes cannot be treated in a short period causing severe challenges to the psychological, physical, and financial well-being of patients. At the same time, the variety, multifacetedness, and plasticity of the cells which play a role in wound healing are a significant impediment to our profound research on the healing process. Therefore, so many innovative methods of treatment keep on coming out.⁹

Nanoparticles have an amazing effect on healing wounds caused by diabetes. Due to its excellent biocompatibility, degradation, and long circulation time within the body, they have emerged as a novel diagnostic and therapeutic system.¹² By exploiting the interaction between nanomaterials at different stages of wound healing, a new approach has been developed to facilitate the healing of chronic wounds. Nowadays, it has been widely used in the treatment of

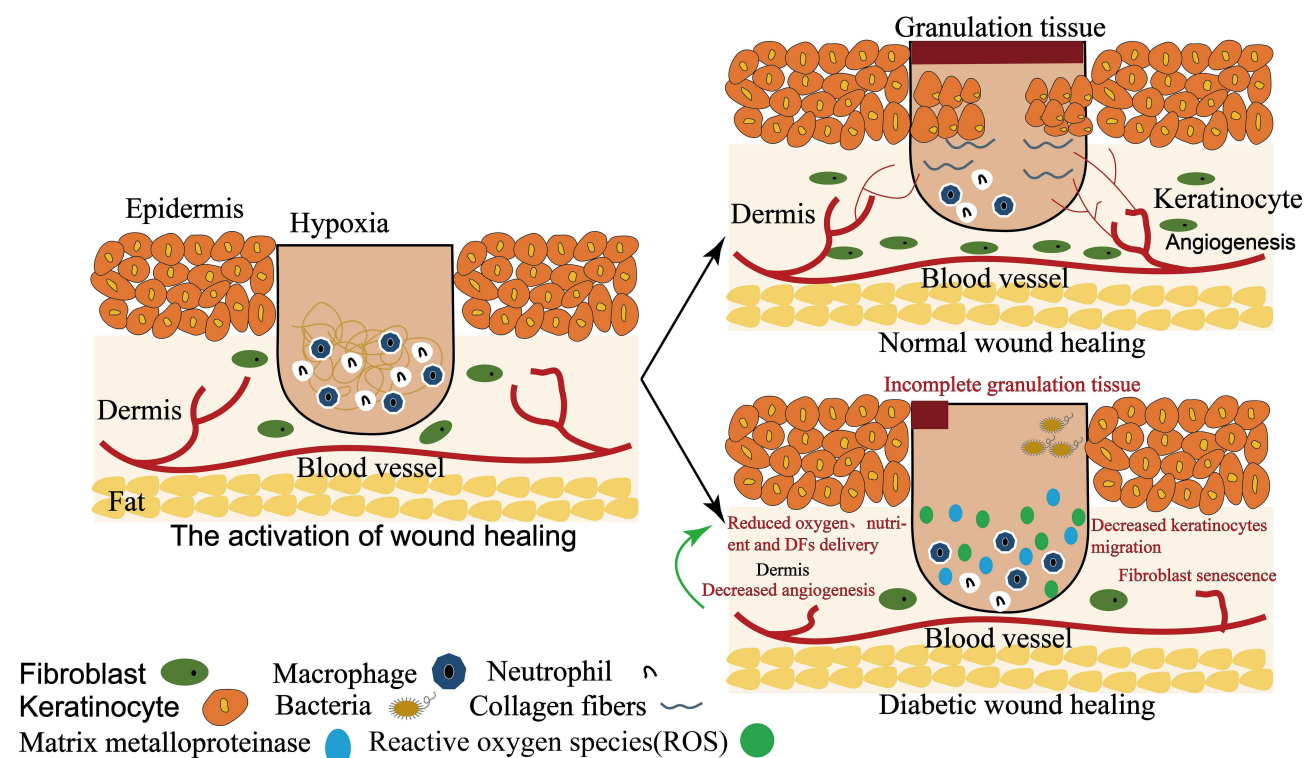


Figure 1 Normal Wound Healing Mechanism vs. Diabetic Wound Healing Mechanism. Adapted from Bai Q, Han K, Dong K, Zheng C, Zhang Y, Long Q, Lu T. Potential Applications of Nanomaterials and Technology for Diabetic Wound Healing. *Int J Nanomedicine*. 2020 Dec 3; 15:9717–9743. Creative Commons.

wound healing in diabetes because of its anti-inflammatory, antibacterial, and antioxidant properties. At the same time, nanoparticles are able to enter the body via a variety of pathways due to their unique properties. They can also be encapsulated, modified, and loaded to precisely target diseased sites, thus achieving therapeutic objectives. That's why nanoparticles are so popular.

Nanoparticles are new kinds of wound healing materials. Nanoparticles have extensive applications in the healing of diabetic wounds and exhibit excellent healing effectiveness.¹³ Nanoparticles can simultaneously load one or multiple drugs (eg exogenous growth factors, nucleic acids, antibiotics, antioxidants, etc.) and achieve sustained-release at the target tissue. Nanoparticles can improve the pharmacokinetics and chemical stability of drugs (small molecules, peptides, proteins, etc.).¹⁴

Although traditional uncoated nanoparticles have demonstrated certain application potential in drug delivery and wound repair, but it also has some limitations, for example, it tends to be recognized by the immune system as a foreign body, causing an inflammatory reaction or being cleared by the macrophages, thus decreasing the therapeutic effect. The presence of RES and MPS poses a major challenge in the delivery of nanoparticles.¹⁵ It is also difficult to accurately target the wound site, which may result in deposition in non-target tissues and increase the risk of toxic side effects. Especially in the treatment of diabetic injuries, nanoparticles are prone to degradation in the hyperglycemic microenvironment. Under high glucose and oxidative stress conditions, nanoparticles degrade or agglomerate faster, resulting in early inactivation and preventing sustained therapeutic efficacy. Thus, we require modification and encapsulation of nanoparticles to allow them to be delivered efficiently into the body and directed to the site of delivery. We chose to encapsulate nanoparticles within cell membranes to avoid the inherent limitations of nanoparticles themselves. By making use of the natural components of the cell membrane, nanoparticles can be “disguised” to avoid detection by the immune system, thus reducing inflammation and elimination. This approach improves security while at the same time improving targeting and stability.¹⁶

In recent years, various cell membrane-coated nanoparticle systems have been developed, featuring unique characteristics and functions to support resident cells. These cell membranes can originate from red blood cells, platelets, white blood cells, cancer cells, or bacteria, and function by binding to various synthesized nanoparticles.^{17,18} The hyperglycemic microenvironment is a key factor hindering wound healing in diabetes and severely compromises the stability of unmodified nanocarriers. Hyperglycemia-induced oxidative stress, inflammation, and abnormal enzymatic conditions readily lead to premature degradation, structural disruption, or immune clearance of nanocarriers. This reduces their accumulation at the wound site and diminishes therapeutic efficacy, limiting clinical application. Therefore, developing interference-resistant, highly stable nanodelivery systems is crucial. Cell membrane coating technology can provide nanocarriers with a biomimetic shell, enhancing their stability within pathological microenvironments and reducing non-specific clearance. This offers a reliable strategy for efficiently repairing diabetic wounds. In the field of diabetic wound treatment, significant progress has been made in the application of cell membrane-coated nanoparticles. Figure 2 illustrates the key steps and mechanisms of using different types of cell membrane-encapsulated nanoparticles for diabetic wounds. However, current research primarily focuses on single cell membrane types, single therapeutic functions, or independent nanomedicine systems. Although nanoparticle systems are relatively well-classified, their application in diabetic wound treatment remains constrained by critical issues such as immune clearance, inadequate targeting, and weak microenvironment regulation capabilities. This research approach suffers from fragmented perspectives, a lack of systematic mechanism summarization, and insufficient specialized analysis of the diabetic wound microenvironment. Cell membrane coating, as a biomimetic modification strategy, can fundamentally optimize the therapeutic behavior of nanocarriers in diabetic wounds. On one hand, it achieves immune evasion and prolonged retention by mimicking natural cell membranes. On the other hand, it enables precise targeting of wound sites, mitigates oxidative stress damage, and modulates inflammatory responses. To this end, this paper provides a systematic review of the field based on membrane-derived classification, mechanisms of action, and *in vitro/in vivo* evidence. Furthermore, unlike existing reviews, this study analyzes practical challenges in areas such as reproducibility, safety, immunomodulation, large-scale production, regulatory compliance, and clinical translation, with the aim of offering more targeted, systematic, and forward-looking guidance for this field of research.

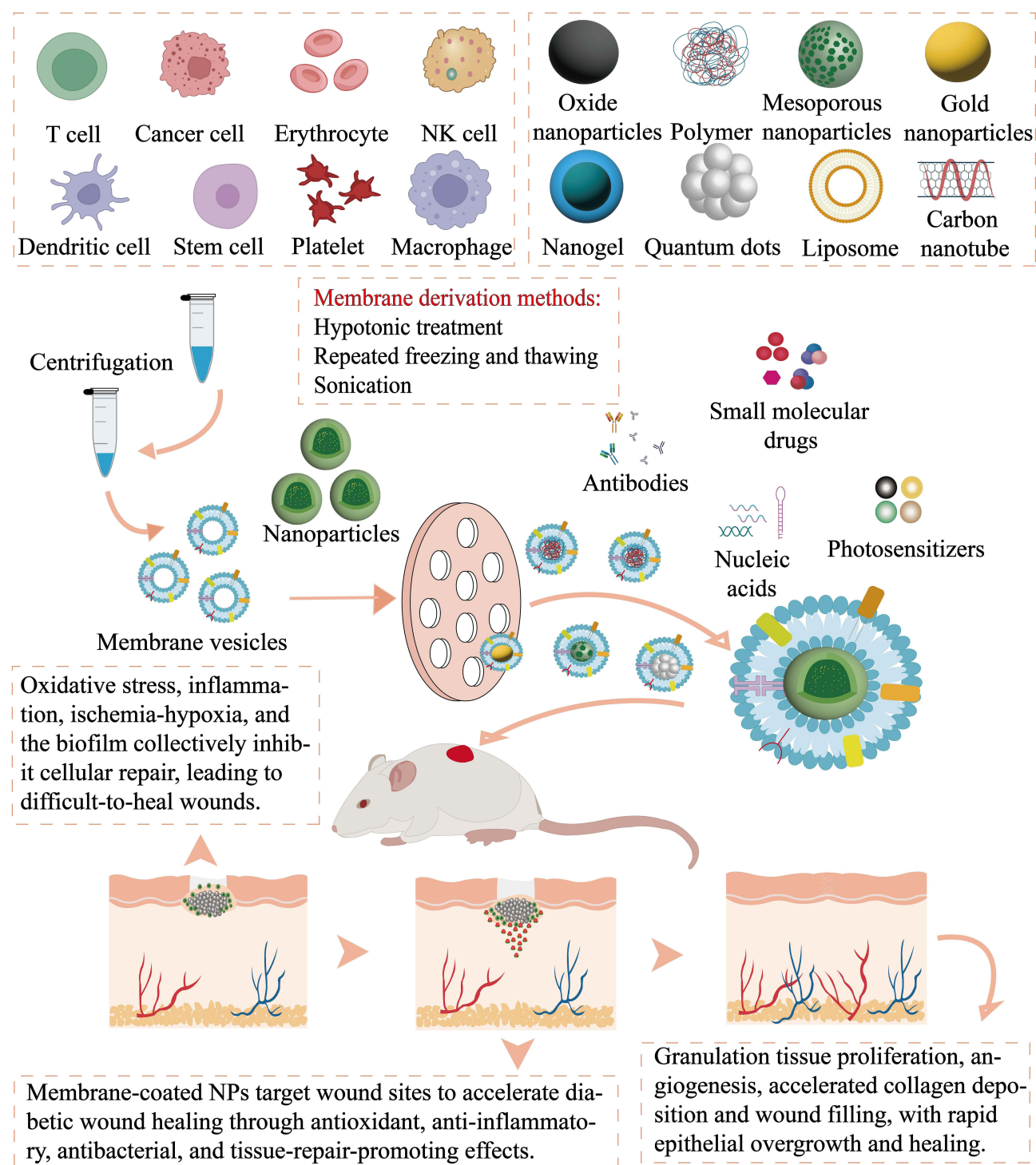


Figure 2 Mechanism Diagram of Cell Membrane-Coated Nanoparticles for Diabetic Wound Healing.

Nanoparticles

In the treatment of various diseases, whether patients can be successfully cured depends on whether drugs can be delivered to specific sites. Current therapeutic methods still cannot concentrate drugs at the lesion site; instead, drug molecules simply distribute and diffuse throughout the body. This often leads to adverse side effects in the human body and wastes large amounts of medication.^{19,20} In long-term research on drug delivery, scholars have discovered that

nanoparticles have become suitable carriers for overcoming the limitations of conventional drug formulations and their associated pharmacokinetic constraints.²¹

Nanoparticles refer to particles with dimensions less than 100 nm in any dimension, exhibiting numerous unique physical and chemical properties.²² Due to its extremely small particle size, it exhibits a large specific surface area, quantum size effects, and macroscopic tunneling effects. These properties enable nanomaterials in the nanoparticle state to exhibit significantly enhanced optoelectronic, thermodynamic, and magnetic physical properties.²³ Meanwhile, the high specific surface area of nanoparticles makes them highly promising for applications in reaction catalysis, drug delivery, and biotherapy.²⁴

Nanoparticles are the primary building blocks of nanostructures. Its size and other properties of nanoparticles are characterized by small particle size, high antibacterial activity, high cellular uptake, low cytotoxicity, high biocompatibility, and biodegradability. The main applications of nanoparticles are drug and gene delivery, tissue engineering and fluorescent biomarking.^{10,25,26}

Nanoparticles can be classified in many ways. Namely, based on the type of nanoparticle constituents, it can be separated into organic nanoparticles, inorganic nanoparticles and synthetic nanoparticles. Within the category of wound healing, three key types of nanoparticles can be identified: First, nanoparticles that can be utilized as drug delivery systems; Second,²⁷ nanoparticles that possess wound-healing effects on their own, the main benefits of which include controlled and sustained delivery, which increases the half-life of drugs and improves bioavailability; Third, nanoparticles which can be integrated into scaffolds.²⁸

Nanoparticle Delivery System

Nanotechnology can overcome the limitations of traditional drug delivery through methods such as cell-specific targeting, transporting molecules to specific organelles, and intracellular transport. Nanoparticles also represent an innovative and promising platform for developing drugs and drug delivery carriers in modern medicine.²⁹ Therefore, nanoparticles hold promising potential for application in diagnosis, treatment, and prevention within the biomedical field.²²

A promising field of application is drug delivery systems, in which nanoparticles can be used as carriers to transport drugs to specific cells or tissues within the body, with their pathways designed to suit targeted delivery.^{30,31} Nanoparticles can improve the stability and solubility of the encapsulated drugs, promote the transport of transmembrane, and extend the cycle time, and thus enhance the safety and effectiveness of the drug. These carriers can transport DNA, RNA and GFS, all of which are involved in chronic wound healing.^{28,30,31} Because of their small size and physical and chemical properties, nanoparticles are able to transport these biomolecules or drugs into the cells, thereby protecting them from degradation and increasing their penetration into wounds and prolonging their half-lives. This reduces the number of applications needed and reduces the total cost. Additionally, drugs and biomolecules encapsulated within nanocarriers can exhibit distinct drug release profiles, thus meeting the requirements for wound healing.²⁸

It is also a strategy that enhances the concentration of therapeutic drugs in cells or tissues and thereby low doses are used especially where efficacy and toxicity occur incompatible places. At the same time, a high concentration of drugs at the target site has the potential to increase the therapeutic effects or tolerance to chemotherapy drugs by the body. Above all, non-water soluble therapeutic drugs can also be conjugated to nanoparticles, thus they can traverse physiological barriers to increase their bioavailability.³¹

Lipid Nanoparticles (LNPs)

Lipid nanoparticles (LNPs) represent a key technology within lipid-based drug delivery systems and have emerged as a significant advancement in oligonucleotide-based therapeutics.³² As a delivery system, lipid-based nanoparticles encompass various structural subclasses, but the most typical are spherical platforms. These offer numerous advantages, including simple formulation, self-assembly, biocompatibility, high bioavailability, and a range of physicochemical properties that can be controlled to modulate their biological characteristics.³³ Figure 3 shows schematic diagrams of different types of liposome drug delivery systems.³⁴

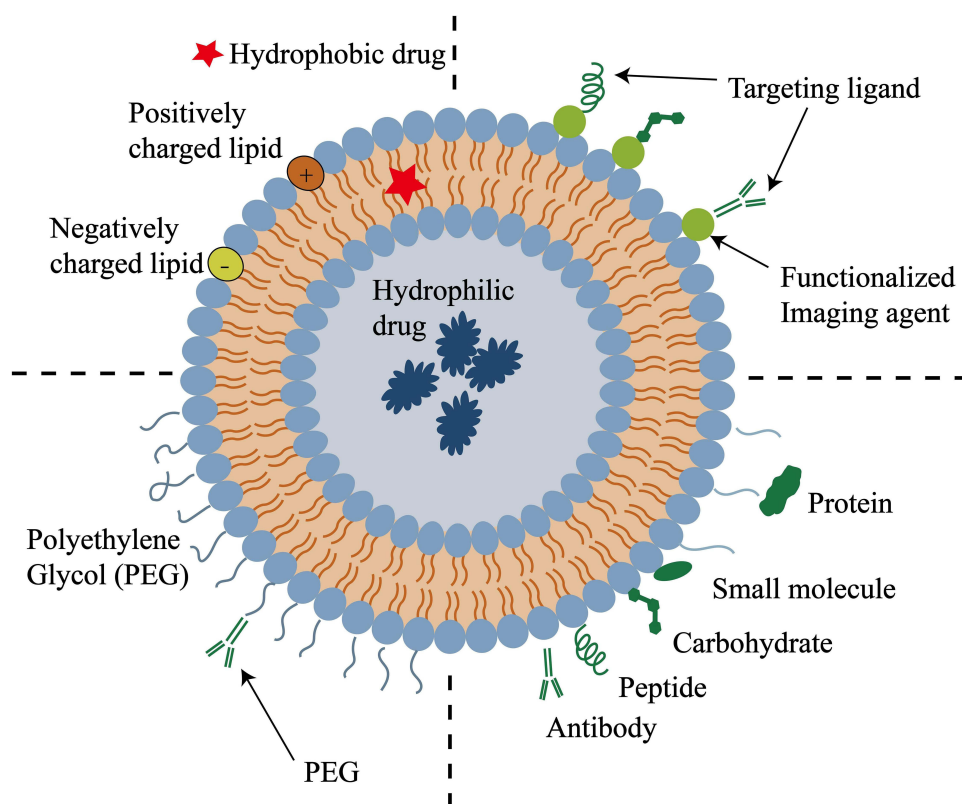


Figure 3 Schematic Diagram of Different Types of Liposome Drug Delivery Systems. Adapted from Sercombe L, Veerati T, Moheimani F, Wu SY, Sood AK, Hua S. *Advances and Challenges of Liposome Assisted Drug Delivery*. *Front Pharmacol*. 2015 Dec 1;6: 286. Creative Commons.

The key difference between LNPs and conventional liposomes is that a micelle structure is formed in the core, which can be modified according to the formulation and synthetic parameters. LNP is composed mainly of four components: cationic or ionizable lipids (which are associated with negatively charged genetic material and facilitate endosome escape), phospholipids (for the structure of the particles), cholesterol (for stability and fusion of the membrane), and the lipids modified by polyethylene glycol (for increased stability and circulation).^{35,36}

Cationic lipids were the first lipid nanoparticles, and they have the ability to bind negatively charged nucleic acids. This cationic lipid-based delivery system is however, highly toxic and immunogenic in both in vivo and in vitro.³⁷ PEGylated lipids are another very important constituent of lipid nanoparticles. PEGylated lipids eg, DMG-PEG 2000 and DSPE-MPEG-2000, are produced by the large-scale conjugation of hydrophilic polyethylene glycol to hydrophobic alkyl chains through the phosphates, glycerol or any other connection. By creating a spatial barrier that creates an unbinding of the liposomal constituents to the plasma proteins that would trigger liposomes to be quickly clear of the circulation system by the reticuloendothelial cells, the polyethylene glycol-modified lipids have the ability to extend the circulation period of liposomes. Such a change also makes it possible to control the size of nanoparticles. Cholesterol is also hydrophobic and rigid and can therefore occupy the space between the lipids in the liposome membrane and can stabilize the vesicles including DSPC and DOPE. It promotes endosomal release and cellular uptake by promoting fusion with cell and endosomal membranes.³⁸

Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are the most commonly used core carriers for constructing cell membrane-coated biomimetic nanomedicines. Their particle size, zeta potential, hydrophilicity/hydrophobicity, degradability, and drug loading capacity directly determine the efficiency of cell membrane coating, colloidal stability, and delivery efficacy within the microenvironment of diabetic wounds.³⁹ Polymeric nanoparticles can be categorized into synthetic degradable polymer systems and natural polymer systems.⁴⁰

Among synthetic biodegradable polymer systems, PLGA is the most commonly used nanomedicine carrier for cell membrane encapsulation. It exhibits excellent biocompatibility and degradability, with degradation products cleared via the tricarboxylic acid cycle. By adjusting the lactic acid-glycolic acid ratio, controlled degradation over 1–4 months can be achieved, enabling precise regulation of drug release rates.⁴¹ PLGA nanoparticles exhibit uniform size, stable structure, and moderate hydrophobicity, enabling effective encapsulation of various cell membranes. They are particularly suitable for long-circulation, anti-inflammatory, and antioxidant diabetic wound repair systems.⁴² Polycaprolactone (PCL) also offers excellent mechanical strength, structural stability, and prolonged degradation properties, making it suitable for ultra-long-acting drug delivery.⁴³ Utilizing PCL as a carrier to slowly release antimicrobial agents and anti-inflammatory factors achieves the goal of treating diabetic wounds. Introducing PEG segments onto nanoparticles effectively reduces protein adsorption on the nanoparticle surface. This decreases the clearance rate of nanoparticles in the external environment, thereby prolonging their circulation time within the body and lowering immunogenicity. The steric hindrance effect of the polyethylene glycol segments enhances the adhesion of cell membranes to the particle surface, making them more firmly attached and less prone to detachment.⁴⁴

In natural polymer systems, chitosan exhibits multiple bioactivities such as antibacterial, anti-inflammatory, procoagulant, and adhesion properties, making it particularly suitable for wound repair in diabetic infections. The material's positive charge enables efficient adsorption to negatively charged electrodes via electrostatic interactions, significantly enhancing coating efficiency.⁴⁵ Chitosan-based nanoparticles can simultaneously load hydrophilic drugs, growth factors, and nucleic acids, achieving pH-responsive drug release within inflammatory microenvironments. As a key component of the extracellular matrix (ECM), hyaluronic acid (HA) specifically binds to the CD44 receptor on the surface of inflammatory cells at the wound site, enabling targeted therapy for diabetic wounds.⁴⁶ HA nanoparticles exhibit high biocompatibility, modulate macrophage polarization, and promote angiogenesis, making them a novel cell membrane carrier that integrates “core functionality” with “targeting capability”.

In summary, the common advantages of polymer nanoparticles as cell membrane coatings for cores include highly tunable physicochemical properties that precisely match the encapsulation requirements of different cell membranes, excellent biocompatibility and degradability suitable for long-term repair of diabetic wounds, broad drug loading capacity, highly efficient encapsulation of diverse bioactive molecules such as anti-inflammatory, antioxidant, antimicrobial, and regenerative agents,⁴⁷ structural stability that protects cell membrane integrity and prolongs retention time of nanodrugs within the wound microenvironment, and ease of large-scale preparation meeting clinical translation requirements. However, certain limitations exist. Single polymers struggle to simultaneously meet requirements for encapsulation efficiency, stability, bioactivity, and responsiveness.⁴⁸ Synthetic polymers lack biological recognition signals, while natural polymers exhibit significant batch-to-batch variability. The complex diabetic wound microenvironment (high ROS, high inflammation, high enzyme activity, high glucose) may accelerate core degradation.⁴⁹ Additionally, batch-to-batch consistency after cell membrane encapsulation, storage stability, in vivo distribution, and metabolism require systematic investigation.

Nanomaterials That Promote Wound Healing

Among various nanomaterials, nanoparticles (NPs) have emerged as effective therapeutic strategies for wound healing due to their capabilities as therapeutic agents and carrier systems. Their small size and high surface-to-volume ratio enhance the potential for bio-interactions and facilitate penetration into wound areas, aiding cellular interactions, proliferation, signaling, and angiogenesis.⁵⁰ Currently, nanoparticles used for wound healing in diabetic patients primarily include metallic and metal oxide nanomaterials, as well as non-metallic nanomaterials.⁵¹ However, to our knowledge, Currently, specialized reviews on cell membrane-coated nanoparticles for diabetic wounds remain relatively limited. Based on existing literature, we summarize the applications of metal and metal oxide nanoparticles in wound healing (Table 1).

Table 1 Applications of Metal and Metal Oxide Nanoparticles in Wound Healing

Metal ions	Name	Mechanism of Action	References
Silver	AgNPs	Possesses unique anti-inflammatory properties and demonstrates resistance to multidrug resistance while exhibiting antimicrobial activity. It promotes cell proliferation and migration, regulates inflammatory responses, thereby accelerating wound healing.	[52–54]
Gold	AuNPs	It exhibits excellent biocompatibility, high surface reactivity, antioxidant properties, and antibacterial characteristics, making it widely used in tissue regeneration, wound repair, and the delivery of bioactive substances. It also possesses outstanding physicochemical properties, such as stability within biological systems and the ability to absorb near-infrared light.	[55–57]
Copper	CuNPs	Activate signaling pathways such as vascular endothelial growth factor (VEGF) to promote proliferation, migration, and lumen formation of vascular endothelial cells, thereby supplying ample oxygen and nutrients to the wound site and accelerating granulation tissue growth.	[58–62]
Zinc	ZnO-NPs	Demonstrates excellent antibacterial potential, rapid epithelialization, wound contraction, mild inflammation, and no infection at the wound site.	[63,64]
Titanium	CMCS-CEBT	Possesses anti-inflammatory, anti-angiogenic, and antibacterial properties while accelerating wound healing, stimulating angiogenesis, increasing collagen deposition, and enhancing the expression of anti-inflammatory factors.	[65]
Iron	Fe/PDA@GOx@HA	Synergistically inhibits bacterial growth and suppresses pro-inflammatory responses, thereby enhancing wound healing.	[66]
Selenium	OD-PP@SeNPs	Induce M2 polarization in macrophages through the PI3K/AKT/NF- κ B and MAPK pathways to reduce inflammatory cytokines, exert anti-inflammatory effects, and remodel the inflammatory microenvironment.	[67]
Cerium	CeO ₂ @Tau@Hydrogel@Microneedle	CTH@MN mitigates oxidative damage and inflammatory responses in macrophages by inhibiting the ROS/NF- κ B signaling pathway. Concurrently, CTH@MN activates autophagy-mediated anti-aging activity, creating a favorable immune microenvironment for tissue repair.	[68]
Manganese	GA/HD/MDP	Reduces wound inflammation and oxidative stress, alleviates hypoxic conditions, promotes collagen deposition, induces vascular regeneration, and exhibits excellent anti-fatigue properties, photothermal antibacterial activity, reactive oxygen species scavenging, oxygen release, and angiogenesis characteristics.	[69]
Boron	MB NPs	It creates a localized alkaline microenvironment, enhances metal cation-induced bacterial death, and suppresses excessive inflammation triggered by dead bacteria both in vitro and in vivo, thereby accelerating wound healing.	[70]
Gallium	Cu-LMNP	Possesses excellent printability and biocompatibility, accelerating the healing of chronic infected wounds. The sustained release of multiple ions and EGF promotes epithelial regeneration, collagen deposition, and neovascularization, thereby accelerating wound healing.	[71]

Metal Nanoparticles

Silver Nanoparticles

The most widely used metal nanoparticles are silver nanoparticles (AgNPs) due to their unique anti-inflammatory properties, resistance to multidrug resistance, and antibacterial activity, which promote wound healing. The sustained release of Ag^{2+} is considered the sole cause of its antibacterial activity. Due to the affinity and electrostatic attraction of sulfoproteins, Ag^{2+} adheres to cell walls and cytoplasmic membranes, increasing their permeability, disrupting membrane integrity, inactivating respiratory enzymes, and generating reactive oxygen species.⁵² The disruption of cell membranes and DNA damage (through interactions with sulfur and phosphorus in DNA molecules) leads to replication and reproduction issues, resulting in microbial death—this represents the primary mechanism of action for Ag^{2+} .⁵³

Additionally, AgNPs can promote cell proliferation and migration, regulate inflammatory responses, thereby accelerating wound healing. Studies indicate that dressings loaded with AgNPs can effectively reduce wound infections and shorten healing time.⁵⁴

Currently, dressings containing AgNPs have been widely adopted in clinical practice. For instance, the low-Ag-concentration RPS-AgNPs nanocomposite developed by Mario Alberto Pérez-Díaz et al by impregnating silver nanoparticles onto radioactively sterilized pig skin inhibited bacterial growth and prevented biofilm formation. This approach enhances wound healing by inoculating conforming nanoparticles.⁷² Researchers such as Zhi yong Qian developed a moist wound dressing using a composite material of exosomes and silver nanoparticles (CTS-SF/SA/Ag-Exo dressing). This dressing promotes wound healing by accelerating collagen deposition, angiogenesis, and nerve repair.⁵²

Gold Nanoparticles

Gold nanoparticles (AuNPs) are widely used in tissue regeneration, wound healing, and the delivery of bioactive substances due to their excellent biocompatibility, high surface reactivity, and antioxidant properties. The antibacterial mechanism of AuNPs primarily involves bactericidal and bacteriostatic effects. When AuNPs come into contact with cells, they disrupt the membrane potential on the cell surface, thereby accelerating the production of reactive oxygen species and ultimately promoting cell death. AuNPs are widely used in tissue repair due to their anti-inflammatory and antioxidant effects.⁵⁵ AuNPs can also bind to bacterial DNA, blocking DNA unwinding during transcription, thereby inhibiting various drug-resistant bacteria such as *Escherichia coli*, *Enterobacter cloacae* complex, *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA), and others.

Gold nanoparticles also exhibit outstanding physicochemical properties, such as stability within biological systems, near-infrared light absorption, and tunable surface plasmon resonance (SPR) characteristics, making them promising for applications in gene and drug delivery. Mona G Arafa et al prepared thermal responsive gels containing AuNPs, namely PF127 (AuNPs-PF127) and PF127 combined with HPMC (AuNPs-PF127-HPMC). They investigated the efficacy of gold nanoparticles embedded in these thermal responsive gels against the Gram-positive bacterium *Staphylococcus aureus* to achieve antibacterial and wound-healing effects. Here, the antibacterial and photothermal properties of gold nanoparticles have been fully demonstrated, achieving excellent wound healing effects.⁵⁶ Adriana Martínez-Cuazitl et al prepared a nano-formulation (AuNP-BP) by conjugating purslane (*B. procumbens*) (BP) with gold nanoparticles (AuNPs) to deliver, stabilize, and mitigate the adverse effects of drugs or plant extracts. This formulation was designed to exert anti-inflammatory effects, accelerate collagen deposition, and promote skin healing.⁵⁷

Copper Nanoparticles

Copper (Cu) is one of the necessary microelements in the human body and plays an important role in many physiological mechanisms and also plays an important role in wound healing. Copper (including copper ions, copper nanoparticles, and other forms) can directly contact bacterial cell membranes. It disrupts the integrity of the membrane through physical perforation or electrostatic interaction, resulting in the release of bacterial contents and ultimately causing cell death. At the same time, the copper ions (Cu^{2+}) released into the bacterial cell can inhibit the activity of the enzyme and interfere with the replication of DNA and the synthesis of proteins. This is especially effective against common wound pathogens like *S. aureus* and *E. coli*. Since controlling infection is essential for wound healing, copper's intrinsic antimicrobial properties allow the design of a variety of copper nanoparticles to facilitate wound healing.⁷³ Copper coordination

polymer nanoparticles (Cu-CPN) were synthesized through self-assembly without compromising the Cu-CPNs' simulated glutathione peroxidase (GPx) and superoxide dismutase (SOD) activity. Integration of ϵ -polylysine (EPL) into the Cu-CPN structure through a simple one-pot self-assembly process improves its antimicrobial activity, making it a promising option for the treatment of chronic wound infections due to drug resistance.⁵⁸

Copper nanoparticles have also been linked to the enhancement of tissue repair, inflammation regulation, and antioxidant function. Copper ions can activate VEGF (VEGF) signaling pathway, and promote the proliferation, migration and lumen formation of VEGF. This provides sufficient oxygen and nutrition to the wound site, speeding up the growth of granulation tissue. The Anu Gopal group prepared chitosan and cupric nanocomposites (CCNC). CCNC regulates VEGF (VEGF) and transforming growth factor- β 1 (TGF- β 1), which reveals its function in the promotion of angiogenesis, the proliferation of fibroblast and the deposition of collagen. Histologic assessment showed that the CCNC therapy increased the proliferation of fibroblast, the deposition of collagen and the complete re-epithelialization of the rat.^{59,60} Wound healing requires an inflammatory phase, but excessive inflammation delays repair. Research shows that copper modulates the activity of immune cells, balancing the inflammatory response (increasing the immune clearance of pathogens at the initial stage and suppressing excessive inflammation in the later stages),⁶¹ At the same time, copper is able to remove excess reactive oxygen (ROS) at the wound site by acting in a manner analogous to that of antioxidant enzymes, thus reducing cellular oxidative damage and protecting healthy tissue. CuNPs show excellent catalytic activity for scavenging H₂O₂ and O₂⁻ due to the strong quantum confinement of electrons, demonstrating excellent catalytic properties.⁶² Tengfei Liu developed ultra-fine Cu₅.4O nanoparticles (NPs) (Cu₅.4O USNPs) with multi-enzyme mimetic activities and wide spectrum ROS scavenging ability in the treatment of ROS-related diseases.⁷⁴

Non-Metallic Nanoparticles

Oxidized Nanoparticles

Non-metallic nanomaterials have recently been demonstrated to promote angiogenesis and accelerate wound healing in diabetic conditions.^{75,76} Graphene oxide (GO) is oxidized from graphene and graphite. Graphene oxide flakes primarily consist of carboxyl and carbonyl groups at the edges, along with hydroxyl and epoxy functional groups on the basal plane.^{77,78} Sudip Mukherjee et al proposed that the formation of intracellular reactive oxygen species (ROS) and reactive nitrogen species (RNS), along with the activation of phosphorylated eNOS and phosphorylated Akt, may represent potential mechanisms by which graphene oxide and reduced graphene oxide induce angiogenesis. This further demonstrates that ROS can influence Akt phosphorylation by inducing eNOS (upregulation of phospho-eNOS), thereby activating the NO signaling pathway. This process enhances intracellular NO production, ultimately triggering angiogenesis.⁷⁹ Ponrasu Thangavel et al leveraged the pro-angiogenic properties of graphene oxide to propose developing reduced graphene oxide-loaded composite nanomaterials for promoting the healing of diabetic wounds.⁷⁷

The biomedical uses of mesoporous silica nanoparticles (MSNs) have been well-known due to its simple structure and compositions, multifunctional nature, and excellent biocompatibility, as well as, its unique structural benefits, which include mesoporous channels, high specific surface area, and surface modifiability.⁸⁰ The mesoporous silica nanoparticles that have been produced by the team of Meng-Meng Lu not only exhibit great adhesive properties, but also exhibit a tremendous antimicrobial behavior. The reasons behind these properties are the high specific surface area of the MSNs, broad surface functionalization as well as high biocompatibility.⁸¹

Polymer Nanoparticles

Polymer nanoparticles refer to polymeric materials with dimensions ranging from 10 to 1000 nm. They possess unique properties such as large specific surface area and excellent adsorption capacity, finding extensive applications across multiple fields. It demonstrates significant advantages in wound healing due to its excellent biocompatibility, controllable degradability, and multifunctional loading capacity.⁸² The primary materials and application forms are mainly based on natural polymers (nanoparticles made from chitosan, sodium alginate, gelatin, etc.) and synthetic polymers (such as PLGA, polyethylene glycol (PEG), etc). The primary core mechanisms of polymer nanoscale particles in wound healing applications are: 1. Drug delivery and controlled release 2. Promotion of tissue regeneration and barrier protection 3. Creation of a moist healing environment for wounds.⁸³ Compared to traditional wound dressings, polymer nanoparticles

exhibit “localized targeting + multifunctional synergy” characteristics. Their bioavailability can be enhanced through particle size regulation and surface modification. Extensive research has been conducted on their application in chronic wounds such as diabetic foot ulcers and burns.

Chitosan is a natural polysaccharide with excellent biocompatibility, antibacterial properties, and the ability to promote cell adhesion.³⁹ Chitosan nanoparticles can bind to biomacromolecules such as DNA and proteins through electrostatic interactions, enabling the delivery of genes and drugs.^{84,85} In wound healing, chitosan nanoparticles can promote fibroblast proliferation and collagen synthesis, accelerating the wound epithelialization process. They have also been studied for their antibacterial activity and wound-healing properties. Yu-Hsiang Lee et al prepared a chitosan-based multiphase composite hydrogel encapsulating perfluorocarbon emulsion, epidermal growth factor (EGF)-loaded chitosan nanoparticles, and polyhexamethylene biguanide (PHMB) for the repair of diabetic wounds.⁸⁶ Qinqin Huang et al developed a multifunctional chitosan-based spray nano-gel (Ag-G@CS) to synergistically inhibit bacterial infection, eliminate biofilms, and reduce inflammation in diabetic wounds.⁷⁵

Poly(lactic-co-glycolic acid) (PLGA) exhibits excellent biocompatibility, biodegradability, low immunogenicity, low toxicity, and good mechanical strength. PLGA is used to manufacture sustained-release drug microspheres, bone repair materials, bone fixation materials, scaffold materials, surgical sutures, implants, intraoral implants, artificial catheters, and more. Injectable formulations such as nano capsules, microspheres, and gels prepared using PLGA as a carrier material can protect drugs, enhance drug solubility, and improve bioavailability. They achieve sustained-release and controlled-release effects over extended periods, offering broad development prospects.⁸⁷

Taking advantage of the slow-release properties of PLGA, Yifan Zhang's team encapsulated curcumin in PLGA microparticles. These were combined with a microneedles consisting of gelatin-methacrylate hydrogels, allowing controlled release of curcumin in an optimum time to facilitate wound healing and minimize hypertrophic scar formation.⁸⁸ At the same time, PLGA has been widely used as a scaffold for wound healing. Chaotao Hu et al used PLGA as the scaffold carrier, adding PHMB and rhVEGF to scaffold (DS-PLGA @ PHMB/rhVEGF) to endow the scaffold with antibacterial and angiogenic functions. The DS-PLGA @ PHMB/rhVEGF scaffold exhibits strong antibacterial properties, which effectively inhibits the growth of bacteria and provides favorable conditions for wound healing. In vitro studies have shown that the scaffold can accelerate wound healing by suppressing inflammation, stimulating collagen formation, and enhancing angiogenesis.⁸⁹

Liposome

Liposomes, as nanoscale vesicles composed of lipid bilayer structures, have shown remarkable advantages in wound healing due to their excellent biocompatibility, degradation, and drug loading ability. First, it can be used for the delivery and controlled release of a variety of therapeutic drugs. Through modification of the liposomes surface, the release of the drug may be induced by the acidic environment of the wound (in the inflammation phase) or by body temperature. This increases the concentration of the drug locally, reduces the systemic side effects, and simultaneously achieves antibacterial and anti-infective effects while promoting tissue regeneration.⁹⁰ Yong Wang's group has developed a dermal replacement (GDS) with a gene liposome encapsulate nanocomposites. This innovative biological material combines the merits of liposomal nanocomposites with dermal substitutes, providing a more accurate and efficient therapeutic option for chronic diabetes. Using new liposomes as scaffolds, it is possible to deliver gene and therapeutic agents to wound sites, promote angiogenesis, and speed up wound healing.⁹¹ Second, the liposomes provide optimal wound dressing capabilities and can be incorporated into composite dressings. Through the combination of liposomes with cell membranes, hydrogel, electrospun membranes, and other dressing materials, they maintain the moisture content of the wound and allow continuous release of the drug through liposomes.⁹² This enhances the dressing's antimicrobial and tissue-repair capabilities. Qinghan Tang et al developed a curcumin-loaded Red Blood Cell Membrane (RBCM) (called RC-Lip) for the treatment of diabetic wounds. The RC-Lips were successfully prepared by thin film dispersion, and the fusion of RBC membrane with liposomal membrane was confirmed by surface protein analysis.⁹³ At the same time, a group of researchers developed a biological active material (GelMA-MY Lipo, or GML) by combining liposomes with hydrogel to produce a dressing that maintains the moisture in the wound, thus facilitating the healing of the skin and increasing the tensile strength.⁹⁴

Application of Nanoparticles Embedded in Scaffolds

With the continuous advancement of nanoparticle research, nanoparticles offer significant advantages as drug delivery systems. They enable controlled sustained-release of drugs, substantially extending the circulation lifespan of pharmaceuticals.⁹⁵ However, during drug delivery, biological barriers prevent the accumulation of nanomedicine carriers at the site of disease, thereby limiting the effective therapeutic response. This poses a significant challenge to researchers, and embedding multifunctional nanoparticles into deliverable scaffolds offers a solution to this problem.^{11,96}

Literature has proved that therapeutically active nanoparticles can be entrapped in scaffolds such that they are delivered in vivo to maintain sustained/controlled release of the nanoparticles. The use of metal nanoparticles in hydrogel scaffolds has been reported to improve antimicrobial effect and wound healing, which include gold nanoparticles, silver nanoparticles, and copper nanoparticles. Jun Xiang et al developed polycrystalline silver nanoparticles that are functionalized with cationic ions as well as a copolymer of sulfonated betaine methacrylate and dopamine methacrylate, with better antibacterial properties. Addition of these into a hydrogel scaffold cast of a precursor mixture of gelatin methacrylate (GelMA) and polyvinyl alcohol (PVA) led to a hydrogel scaffold having a good antibacterial performance upon the release of nanoparticles. Moreover, cationic modification had further blood compatibility improvement. Blend of (GelMA) and polyvinyl alcohol (PVA). When nanoparticles were released, the hydrogel scaffold proved to have great antibacterial activity. At the same time, the zwitterionic modification increased hemocompatibility and biocompatibility, inflammation mending, and the wound healing process.^{97–100}

At the same time, metal oxide nanoparticles are also potential candidates for nanoparticle-embedded scaffolds. Manganese oxide (MnO₂) has been demonstrated to alleviate oxidative stress by catalyzing the decomposition of H₂O₂ into O₂, thus effectively providing targeted relief from hypoxia. The study of Qian Wang et al on the effect of MnO₂ nanoparticles on the wound healing of patients with chronic diabetes showed that they had the advantages of reducing high blood sugar, promoting hemostasis and creating optimal wound environment. This reduces inflammation, speeds up the formation of granulation tissue and re-epithelialization, and accelerates the healing of the wound. Encapsulating MnO₂ nanoparticles in a PDA/AM hydrogel scaffold with poly (dopamine/acrylamide) can speed up wound healing and vascular regeneration in diabetes patients.¹⁰¹ Another study by Qian Wang et al showed that in Dex-SA-AEMA (DSA) hydrogels, Polydopamine (PDA) and Manganese Dioxide (MnO₂) could be used to convert endogenous H₂O₂ into O₂ in the microenvironment of diabetes. This process is effective in providing oxygen, reducing inflammation, speeding up the deposition of collagen and promoting angiogenesis.¹⁰²

Cell Membrane

The cell membrane is an elastic, semipermeable membrane primarily composed of phospholipids. It selectively facilitates the exchange of substances, absorbing nutrients and secreting and transporting proteins. Research indicates that the abundance of membrane proteins on the cell membrane surface enables membrane-coated nanoparticles to inherit a wide range of functions associated with the source cells. While retaining the complex biological functions of the cell membrane, these nanoparticles also exhibit multiple biological activities. High biocompatibility, capable of undergoing repeated cycles within the human body without causing adverse reactions.¹⁰³ As shown in Figure 4 schematic diagrams of various cell membranes.¹⁰⁴

Cell Membrane Drug Encapsulation and Delivery Systems

Cell membrane-based drug delivery systems are a new drug delivery technology that has proven to have an incredible capacity in the treatment of an illness because they have excellent biocompatibility, targeting properties, drug protection, as well as the capability to serve as a sustained-release “switch”. The delivery systems of drugs through cell membrane-based platforms will also be able to increase the use of drugs and decrease the side effects, which will be an advantage to medical practitioners and patients.¹⁰⁵ Its main principle consists of employing the peculiarities of the structure and the functions of the cell membrane, which can be generally achieved by physical or chemical ways of encapsulating the drugs into the cell membrane.^{106,107} To get even closer to achieving the desired results of drug delivery and a successful treatment, it is possible to modify drug delivery systems and attach the appropriate targeting molecule to the cell

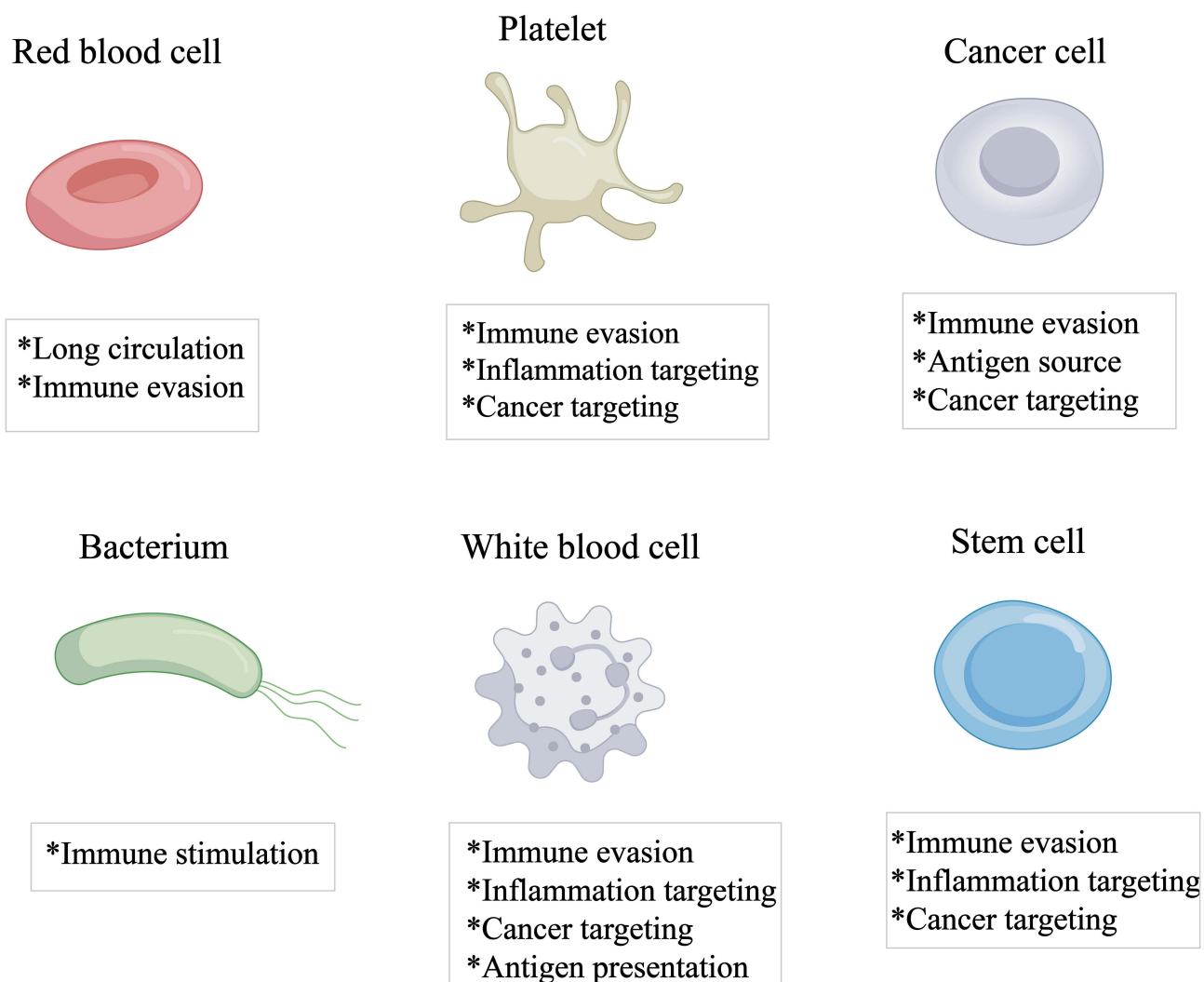


Figure 4 Various cell membranes. Adapted from Fang RH, Gao W, Zhang L. Targeting drugs to tumours using cell membrane-coated nanoparticles. *Nat Rev Clin Oncol*. 2023 Jan; 20(1):33–48. Creative Commons.

membrane. These molecules which are called the signposts help the drug delivery system to reach the target site with a high degree of accuracy.²⁹ The cell membranes of the drug delivery system are similar in structure and composition to those of biological cells liberated by the system when it enters the body and this allows it to evade recognition and clearance by the immune system and promotes the level of time it will take on the body.^{104,108} After effective access to the target site, the drug immerses the diseased cells releasing the medication and thus enforcing its therapeutic impact.¹⁰⁹

Additionally, the cell membrane-based drug encapsulation and delivery system can select different cell membranes based on varying drug delivery requirements and therapeutic needs. Table 2 summarizes the advantages of each cell membrane drug encapsulation method.

The key advantages of various cell-membrane-based drug delivery systems are their intrinsic biological properties — for example, targeting, immunomodulation, and barrier penetration. These systems allow accurate delivery of drugs and increased therapeutic efficacy by preserving functional proteins or receptors on the surface of the cell membrane, providing novel strategies for the treatment of cancer, inflammation, infection, and refractory diseases. Bo Liu et al Poly (lactic-co-glycolic acid) (PLGA) micelles disguised as RBC) membranes were used as potential long term controlled release systems for local administration of drugs.¹²³ Yue Zhao et al produced a nasal drug delivery system with Macrophage-encapsulated Ast nanoparticles (M0@Ast-NPs) to treat acute pulmonary injury (ALI) M 1in the context of Ast-NPs retain macrophage nativehoming property, enabling micro-delivery of the chosen drug into the

Table 2 Summary of Drug Delivery Advantages by Cell Membrane Encapsulation Methods

Name	Load Policy	Advantages	References
Red blood cell membrane	Physical encapsulation, surface functionalization	Excellent biocompatibility, abundant and readily available sources; membrane surface expresses CD47 protein, enabling evasion of immune clearance and prolonging circulation time in vivo; absence of a nucleus reduces immunogenicity, making it suitable for systemic administration.	[12]
Tumor cell membrane	Carrier-free high-drug-load nanoscale suspensions, homologous tumor cell membrane encapsulation, active targeted modification	Retaining tumor cell surface-specific antigens (such as N-cadherin and integrins), it exhibits "homologous targeting" properties, enabling precise recognition and enrichment within homologous tumor tissues. Simultaneously, it activates the body's immune response (such as dendritic cell maturation), combining targeted therapy with tumor vaccine functionality.	[110]
Platelet membrane	Physical embedding	Naturally targets damaged vascular endothelium, inflammatory sites, and tumor microenvironments (by binding fibrinogen via GPIIb/IIIa receptors on cell membranes); evades immune clearance, prolonging circulation time, making it particularly suitable for targeted therapy of thrombosis, atherosclerosis, and metastatic tumor sites.	[111]
Macrophage membrane	Bionic Targeting, Core Drug Delivery	Leveraging the "inflammatory chemotaxis" and "tumor homing capability" of macrophages (via recognition of tumor vascular adhesion molecules through integrin $\alpha 4 \beta 1$), it efficiently penetrates the tumor stroma. Membrane-surface receptors such as TLR4 enhance interactions with immune cells, facilitating immune combination therapy.	[112,113]
Mesenchymal Stem Cell Membrane	Physical embedding, in-membrane embedding	Preserving the tissue-repair chemotaxis of stem cells enables targeted delivery to sites of inflammatory injury (such as myocardial infarction and cerebral ischemia) and tumor microenvironments. With diverse sources (eg, bone marrow, umbilical cord), they are easily scalable for large-scale production, exhibit high biosafety, and are suitable for long-term administration	[114,115]
T cell membrane	Extrusion fusion method, In-situ physical package included.	Leveraging T cells' antigen recognition capabilities (such as TCR-specific binding to tumor antigens) to precisely target tumor cells; capable of penetrating the tumor's immunosuppressive microenvironment while simultaneously delivering immune checkpoint inhibitors (such as PD-I antibodies) to enhance T cell killing activity.	[116–118]
Neutrophil membrane	Physical embedding, membrane coating	Demonstrates potent chemotaxis toward acute inflammatory foci (eg, bacterial infections, postoperative inflammation) via the chemokine receptor CXCR2; membrane-bound Fc receptors enhance binding to pathogens, making it suitable for targeted anti-infective therapy	[119]
Bacterial cell membrane	PH Gradient Remote Load Method	Mimicking pathogen characteristics, it can be preferentially phagocytosed by antigen-presenting cells (such as macrophages), thereby activating innate immune responses. When used as a vaccine carrier, it efficiently delivers antigens and enhances immunogenicity, making it suitable for infectious disease vaccines or therapeutic cancer vaccines.	[120]
Neural stem cell membrane	Physical embedding	Possessing blood-brain barrier permeability and neurotropism (via CXCR4 receptors on cell membranes), it enables targeted drug delivery to brain lesions (such as gliomas and Parkinson's disease), addressing the challenge of brain drug administration.	[121]
Endothelial cell membrane	Double Emulsification Solvent Evaporation Method, Extrusion Method	Preserving the adhesive properties of vascular endothelial cells enables targeting of damaged vascular endothelium (eg, atherosclerotic plaques); vascular endothelial growth factor receptors (VEGFR) on the cell surface can specifically bind to tumor neovascularization, facilitating tumor-targeted delivery	[122]

inflammatory lung parenchyma and enhancing anti-inflammatory efficacy of astaxanthin (Ast).¹²⁴ Andreas Czosseck et al used mesenchymal stem cells to encapsulate porous materials, thus achieving hypoxia protection and promoting angiogenesis.¹²⁵

Cell Membrane Products

Cell membrane based clinical products make use of the unique functions of cell membranes to pioneer new therapeutic pathways in disease treatment. R&D is focused on exploiting the intrinsic properties of cell membranes to overcome the limitations of conventional treatments, making significant advances in a wide variety of areas.

Drug-loaded Vesicle-Mediated Tumor Targeted Therapy (DTMI) is one of the most innovative therapies for cancer. It is used as a carrier for the encapsulation or loading of small molecule chemotherapy drugs. Through a variety of mechanisms — including targeted drug delivery, chemotaxis and activation of neutrophils, the reversal of macrophage polarization phenotype, and the promotion of tumor antigen presentation — it can effectively kill tumor cells. Professor Huang's group has now discovered a new mechanism by which drug-loaded vesicles fight cancer. Now they are conducting clinical trials and trials, bringing hope to patients around the world.

Professor Zhang Tong and the group of Researcher Ding Yue from the School of Chinese Medicine have developed a kind of biomimetic nanomedicine system (G/R-MLP), which is coated with a membrane of Gallic acid (GA) and Ginsenosides Rg3 (Rg3). This dual-targeting approach leverages tumor cell-mediated homotarget and glucose transporter targeting via glucosyl groups on Rg3's glycan chain. It has been shown that it is capable of avoiding and targeting tumor microenvironment, enhancing antitumor, anti-angiogenic, and immunomodulatory effects. This synergistically enhances the efficacy of Rg3 and GA against triple-negative breast cancer, providing an effective treatment strategy for breast cancer.¹²⁶

Siyang Cao and his team have researched a kind of bioengineered chondrocyte membrane-coated liposomes containing ferroptosis. It was found that they could function on the membrane of the chondrocytes treated with drugs, and then encapsulated them on the surface of liposomes. Employing a “Trojan horse” strategy, the liposomes targeted chondrocytes within articular cartilage, prolonging drug retention in the articular cavity. At the same time, iron dependent lipid peroxidation can be inhibited to alleviate the progression of osteoarthritis.¹²⁷ These results show that cell membrane-based drug packaging and delivery systems have an obvious advantage in increasing therapeutic efficacy and reducing toxic side effects, and are poised to lead the way in drug delivery.

Cell Membrane-Coated Nanotechnology

Mechanism of Action of Cell Membrane-Coated Nanoparticles

Cell-membrane-coated nanoparticles (NPs) offer advantages such as immune evasion, prolonged circulation time in vivo, specific molecular recognition, and cellular targeting. They have become a research hotspot in the field of nanomedicine and are also widely applied in wound healing.¹²⁸

The phospholipid bilayer on the cell surface acts as a barrier linking the intracellular structure with the extracellular environment, regulating the movement of materials inside the cell. Recent research has revealed that most nanoparticles enter cells via endocytosis. This process involves nanoparticles coming into contact with the cell membrane, becoming enclosed within the cell, and then detaching from the membrane to form vesicles that then enter the cell interior.

Cell membrane-coated nanoparticles exert their effects primarily by enhancing biocompatibility through “mimicry”, enabling targeted delivery of functional molecules, and regulating wound pathophysiological processes. By mimicking the surface characteristics of source cells, they achieve highly efficient promotion of wound healing. First, regarding biocompatibility and immune evasion, the use of cell membranes (such as red blood cell membranes or macrophage membranes) as a shell mimics the biological properties of natural cells. This reduces the likelihood of nanoparticles being recognized as foreign bodies by the immune system, thereby decreasing inflammatory responses and clearance rates while prolonging their retention time at the wound site. Concurrently, natural proteins on the cell membrane surface (such as adhesion molecules) enhance the affinity between nanoparticles and wound tissue, improving local enrichment efficiency and effectively serving as a “camouflage” mechanism; Secondly, by leveraging specific adhesion molecules

and homing signals on cell membranes, coated nanoparticles can actively target the inflammatory wound microenvironment, enhancing enrichment efficiency at the lesion site to achieve precise delivery and targeted therapy. Therefore, the cell membrane coating strategy overcomes the limitations of traditional nanocarriers in diabetic wound treatment across multiple dimensions—including in vivo stability, targeted homing, microenvironment regulation, and tissue regeneration—providing a crucial direction for constructing efficient and safe biomimetic drug delivery systems.

Certain cell membranes (such as modified bacterial membranes) can provide nanoparticles with a physical barrier function, isolating the wound surface from external pathogens. Simultaneously, we can load antimicrobial drugs onto cell membranes or modify membrane surfaces with antimicrobial peptides to directly inhibit bacterial infection at the wound site, thereby reducing the risk of infection. Finally, in regulating the wound microenvironment, cell membrane-coated nanoparticles can exert anti-inflammatory effects, promote angiogenesis, and accelerate tissue repair. Based on these advantages, various cell types including red blood cells (RBCs), macrophages, mesenchymal stem cells, platelets, white blood cells, cancer cells, and even bacteria have been utilized as sources for cell membranes.^{24,128,129} The following summarizes several diagrams related to cell membranes: Table 2 outlines the advantages of various cell membrane-based drug delivery systems. Table 3 provides an overview of the targeted enrichment mechanisms of multiple cell membrane-coated nanoparticles. Table 4 summarizes the immunomodulatory and microenvironment-responsive release mechanisms of various cell membrane-coated nanoparticles.

Table 3 Summary of Cell Membrane-Coated Nanoparticle Mechanisms of Targeted Enrichment

Cell Membrane Types	Core Nanomaterials	Key Mechanism of Action	References
Red blood cell membrane	PLGA NPs	Red blood cell membrane adhesion molecules (such as CD36) recognize inflammatory mediators (such as TNF- α) in diabetic wounds, leveraging the EPR effect of nanoparticles to achieve dual targeting at the wound site.	[130]
Macrophage membrane	PLGA, Natamycin	Macrophage membrane receptors (CCR2, CX3CR1) recognize inflammatory cytokines (TNF- α , CCL2) highly expressed at diabetic wounds, chemotaxis to the core of inflammation and locally accumulating via nanoparticle EPR effects.	[131]
Mesenchymal Stem Cell Membrane	Polydopamine (PDA)	MSC membrane receptors (integrin $\alpha 5 \beta 1 / \alpha v \beta 3$, CXCR4) recognize inflammatory mediators (TNF- α /IL-6) and hypoxia signals in diabetic wounds, targeting and enriching repair sites.	[114]
Bacterial cell membrane	Bacterial double-layer membrane-derived nanovesicles	Bacterial cell membrane components (LPS, fimbrin) bind to receptors on the surface of inflammatory cells (eg, neutrophils) at diabetic wounds, chemotactic factors in the infected area, achieving dual-targeted enrichment for inflammation and infection.	[120]
T cell membrane	PEG-b-PLL(Poly(ethylene glycol)-b-poly(L-lysine))	T cell membrane receptors (TCR, CCR5/CXCR3) recognize inflammatory antigens (eg, DAMPs) and factors (IL-12/IFN- γ) highly expressed at diabetic wounds, chemotaxis toward the core inflammatory zone to achieve precise targeting.	[117]
Neutrophil membrane	MONs	Neutrophil membrane receptors (CXCR1/CXCR2) recognize inflammatory cytokines (IL-8/TNF- α) highly expressed at diabetic wounds, while adhesion molecules (LFA-1/Mac-1) bind vascular endothelial cells. This dual targeting mechanism of “chemotaxis + adhesion” enables enrichment within the core inflammatory zone.	[119]

(Continued)

Table 3 (Continued).

Cell Membrane Types	Core Nanomaterials	Key Mechanism of Action	References
Tumor cell membrane	Carrier-free nanosuspension	Tumor cell membranes highly express adhesion molecules (ICAM-1/ integrin $\beta 1$) that actively target inflammatory factors (TNF- α /IL-8) in diabetic wounds, leveraging nanoparticle EPR effects to enhance local accumulation.	[110]
Platelet cell membrane	PLGA NPs	Platelet membrane GPIIb/IIIa and GPIB-IX glycoproteins target and bind to collagen fibers and fibrinogen in diabetic wounds, while CXCR4 receptors enhance local enrichment in response to inflammatory signals.	[111]
Endothelial cell membrane	PLGA	VEGFR and integrin $\alpha v \beta 3$ on the endothelial cell membrane surface can specifically recognize ischemic hypoxia signals and sites of vascular injury in diabetic wounds. Membrane-bound ICAM-1 binds to vascular endothelial cells at the wound site, enabling precise targeted enrichment.	[122]
Neural stem cell membrane	PLGA	NSC membrane surface CXCR4 and CCR5 recognize inflammatory mediators (TNF- α , IL-6) and neurotrauma signals at diabetic wound sites, actively targeting wounds and neurotrauma locations. Leveraging the EPR effect, it enhances local enrichment.	[121]

Table 4 Summary of Cell Membrane-Coated Nanoparticle Mechanisms of Immune Modulation and Microenvironment-Responsive Release

Types	Key Mechanism of Action	References
Red blood cell membrane	CD47 on the membrane binds to SIRP α on macrophages, signaling “don’t eat me” to prevent rapid clearance of nanoparticles and prolong their circulation time at the wound site.	[12]
Tumor cell membrane	Membrane surface TAAs can activate the local innate immune response, suppress M1 macrophage activation, promote M2 polarization, and break the chronic inflammatory cycle at the wound site.	[110]
Macrophage membrane	Immunoregulatory molecules such as CD206 and IL-10 receptors on the membrane surface suppress M1 macrophage activation, promote their polarization toward M2, reduce IL-6 and ROS release, and break the chronic inflammation cycle.	[113]
Mesenchymal Stem Cell Membrane	Inhibition of PD-L1, HLA-G, and TGF- β receptors on the membrane suppresses M1 activation, promotes M2 polarization, reduces oxidative stress damage, and breaks the chronic inflammation cycle.	[8]
T cell membrane	The synergistic action of CD28 and CTLA-4 on the membrane surface suppresses abnormally activated effector T cells, promotes Treg proliferation, reduces TNF- α and IL-17 release, and breaks the chronic inflammation cycle.	[116]
Red blood cell membrane, Tumor cell membrane, Macrophage membrane, Mesenchymal stem cell membrane, T cell membrane	The drug release suppresses inflammatory secretion and reduces oxidative stress, promoting fibroblast proliferation and epithelial cell migration while accelerating granulation tissue formation. The carrier exhibits sensitivity to wound acidity (pH 5.5–6.5) and high ROS levels, triggering precise membrane rupture to release anti-inflammatory drugs (eg, dexamethasone) and antimicrobial peptides, thereby addressing both inflammation and infection.	[8,12,110,116,131]

Cell Membrane-Coated Nanoparticles for Diabetic Wound Repair

Recently, the development of nanoparticles has attracted considerable attention, especially because of its unique advantages in the treatment of diabetes. However, the application of nanoparticles in the body also presents a number of challenges. For example, although our goal is to use nanotechnology to encapsulate drugs in nanoparticles to increase bioavailability and reduce toxic side effects, the high surface energy of nanoparticles makes them vulnerable to environmental conditions like temperature, humidity, and PH. Additionally, they face issues like low local therapeutic concentrations and poor systemic targeting capabilities.^{103,106,109} In order to solve these problems, some experts have suggested that nanoparticles be encapsulated in appropriate cell membranes, thus increasing their ability to target diseased tissues.

Cell membrane-coated nanoparticles are increasingly being applied in disease detection and treatment. This novel nanotechnology is characterized by its ability to evade phagocytosis, exhibit longer circulation times, and effectively target specific regions.¹³² Different cell membranes can confer entirely distinct biomedical functions to nanoparticles made of the same material. Therefore, in practical applications, cell membranes should be selected based on their specific characteristics and functions. Simultaneously, the critical identification of cell membrane-coated nanoparticles is paramount. Currently, common methods for validating successful membrane coating include: transmission electron microscopy (TEM) observation of core-shell structures; dynamic light scattering (DLS) detection of particle size and potential changes; Western blot validation of membrane protein presence; and fluorescence co-localization observation of membrane markers with nanoparticle carriers. Beyond qualitative validation, the field currently lacks unified evaluation standards. Establishing standardized protocols is essential to advance cell membrane-coated nanoparticles from laboratory research to clinical application. Figure 5 shows the characterization of IR780@PLGA@HM nanoparticles. These nanoparticles were prepared by fusing breast cancer cell membranes with bacterial outer membrane vesicles to form hybrid membranes (HM), then encapsulating IR780-loaded PLGA within the HM (Figure 5A). The resulting IR780@PLGA@HM nanoparticles exhibit tumor targeting, immunomodulatory, and photodynamic functions.¹³³ Figure 5B is TEM observation of OMVs, 4T1 membrane, HM, IR780@PLGA, and IR780@PLGA@HM. Figure 5C shows confocal laser scanning microscopy (CLSM) images of 4T1 cells taking up HM and IR780@PLGA@HM nanoparticles. Figure 5D–F show Western blot validation of HM and IR780@PLGA@HM nanoparticles, along with their particle size and zeta potential. Figure 5G shows the size and polydispersity index (PDI) of IR780@PLGA@HM nanoparticles after 7 days in PBS at 4°C. Figure 5H–J show the UV absorption spectra of free IR780 and IR780@PLGA@HM nanoparticles, the concentration-dependent behavior of the nanoparticles under ultrasonic irradiation (2 W/cm², 1 MHz), and the time-dependent generation of reactive oxygen species (ROS).

Nanoparticles Coated with Red Blood Cell Membranes

Recent studies have shown that nanoparticles (NPs) are a new kind of nanomaterials. Of these, RBC membrane is the most widely used membrane source. Owing to the fact that RBC membranes are one of the most common sources of cell membranes, their advantages in the application of RBC membranes for wound healing are mainly due to their inherent biological properties.¹³⁴ First of all, since the RBC membrane is derived from auto- or allogenic RBC, its natural composition ensures high tissue compatibility, minimizing irritation or rejection at the wound site. In addition, the surface of the membrane is rich in CD47, which binds to the SIRPα receptor on the surface of macrophage and sends a “self-recognition” signal. This prevents the removal of nanoparticles by the immune system, thus extending their action time at the wound site, thus improving biocompatibility and reducing immunogenicity. In addition, red blood cells have a long circulation lifespan in the bloodstream (approximately 120 days). Their membrane structure maintains anti-clearance properties, allowing the coated nanoparticles to remain stable at the wound site. This makes it less likely that they will be metabolized or cleared quickly, thus increasing the utilization efficiency of drugs or functional molecules. Because of their structure, RBC membranes are able to efficiently encapsulate nanoparticle cores, and at the same time provide sustained release capabilities for loaded drugs (eg, antibiotics or growth factors). This will avoid local overconcentration or adverse reactions due to the abrupt release of the drug, thus achieving long term treatment.¹³⁵

The main mechanism by which RBC membrane-encapsulated nanoparticles function is to regulate wound healing. When they are loaded with antibacterial agents, they create a highly concentrated drug environment at the wound site,

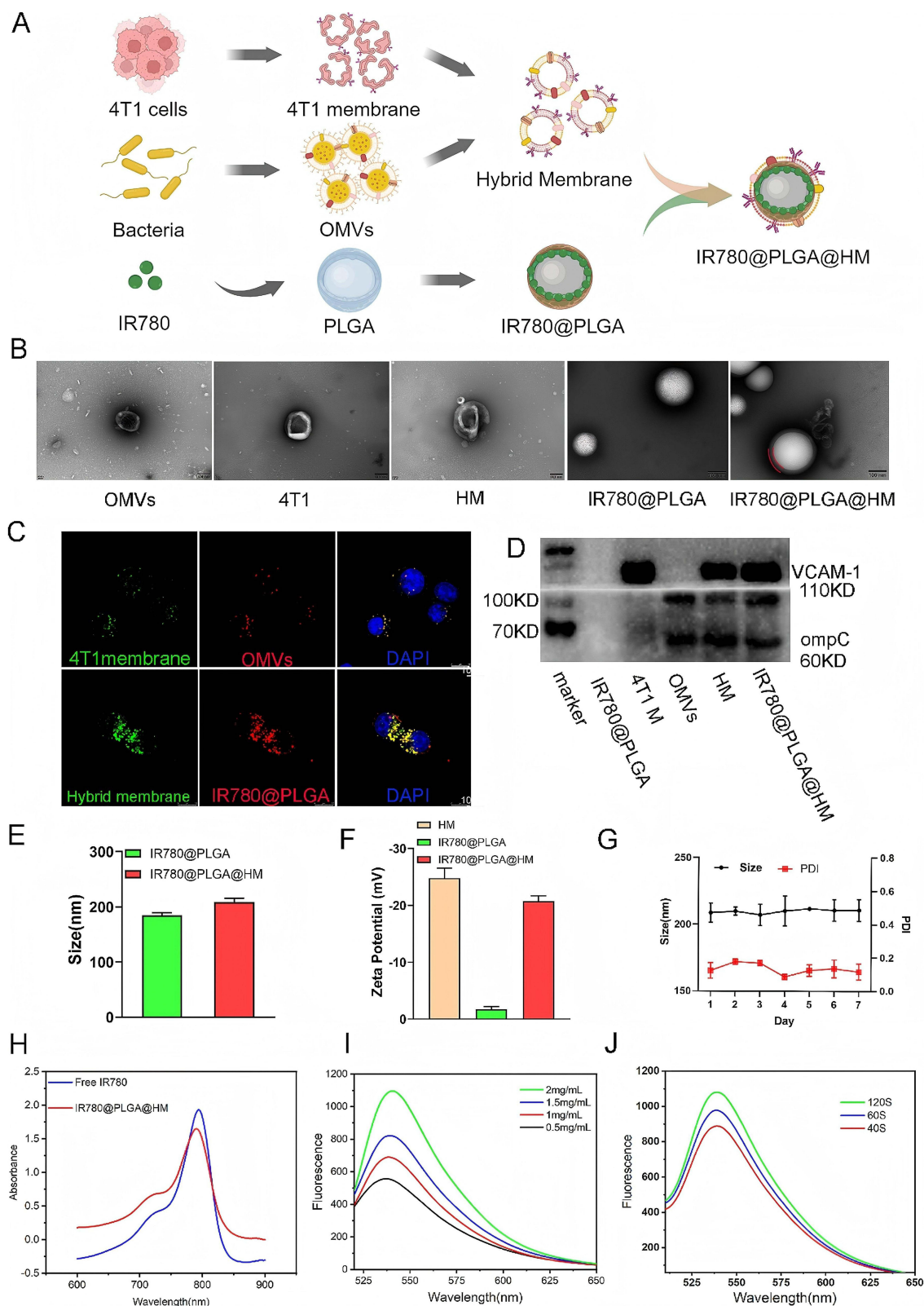


Figure 5 Characterization of IR780@PLGA@HM nanoparticles. **(A)** Schematic illustration of IR780@PLGA@HM nanoparticles construction. **(B)** TEM observation of OMVs, 4T1 membrane, HM, IR780@PLGA, and IR780@PLGA@HM (Scale bar = 100 nm. Red lines marked HM coating on nanoparticles). **(C)** CLSM images of 4T1 cells' uptake of HM (DiO labeled 4T1 membrane as green and Dil labeled OMVs as red) or IR780@PLGA@HM nanoparticles (DiO labeled HM as green and Dil labeled IR780@PLGA as red) (Scale bar = 10 μ m). **(D)** Western blot verification of HM and IR780@PLGA@HM nanoparticles. **(E)** Size and **(F)** Zeta potential of IR780@PLGA and IR780@PLGA@HM nanoparticles. **(G)** Size and PDI of IR780@PLGA@HM nanoparticles in PBS at 4°C for 7 days. **(H)** UV-vis-NIR absorption spectra of free IR780 and IR780@PLGA@HM nanoparticles. **(I)** Concentration-dependent and **(J)** Time-dependent ROS generation of IR780@PLGA@HM nanoparticles with US irradiation (2 V/cm², 1 MHz), with SOSG as fluorescence probe. Reproduced from Ref. (328 (2024)) (<https://doi.org/10.1186/s12951-024-02619-w>) with permission under a Creative Commons Attribution 4.0 License (<http://creativecommons.org/licenses/by/4.0/>).

and inhibit the growth of bacteria. At the same time, they can reduce excessive inflammation at the wound site by delivering anti-inflammatory drugs or by utilizing the innate immunomodulatory potential of the RBC membrane itself, while preventing long-term inflammation that hinders healing.¹² As demonstrated by Zhi yuan Fan and others, the presence of RBC membranes on the surface of the PLGA nanoparticles effectively mitigated the short-term inflammatory response of the loaded scaffold. Both the PLGA nanoparticles and the RBC membrane nanoparticles did not significantly influence the infiltration of neutrophils or macrophages into the scaffold. This may be attributed to the degradation or clearance of infiltrating cells by the nanoparticles.¹⁰⁹

RBC membrane coated nanoparticles can regulate inflammation during wound healing. As Aqib Iqbal Dar and others have demonstrated, the encapsulation of gold nanoparticles (AuNPs) in red blood cells to control the effect of inflammation on wound healing allows for a controlled inflammatory reaction in the early posttraumatic phase. This promotes accelerated wound closure and enhanced healing outcomes. The introduction of pro-inflammatory factors, such as TNF- α and IL-6, on the surface of the gold nanoparticles, allows targeted delivery to the wound site, enhancing the body's immune response and reducing the risk of non-specific protein binding. This further shows that the RBC membrane can prevent short term inflammation of the scaffold. In fact, some researches have suggested that RBC membrane-coated nanoparticles could avoid the immune clearance and utilize the natural membrane binding receptors for active targeting. This is due to the fact that the membrane itself contains a membrane protein called CD47, which acts as a marker for the recognition of red blood cells by the immune cell. It can reduce phagocytosis of macrophages through interaction with cell surface signaling proteins.¹³⁶ At the same time, the surface proteins on the RBC membrane can help to extend their circulation time in the body.

When we utilize growth factors carried by red blood cell membranes, they can stimulate fibroblast migration, proliferation, and collagen synthesis. Simultaneously, they promote neovascularization, accelerate granulation tissue growth and epithelialization, and facilitate tissue regeneration, thereby shortening the wound healing cycle. Lingbing Yang's team developed a hybrid cell membrane coating for macroscopic reticular fibers that acts as an immune coordinator, balancing immune responses with tissue regeneration. Using functionalized liposomes and click chemistry, they covalently bonded cell membranes derived from red blood cells (RBC) and platelets (PLT) to the fiber surface. Experimental results demonstrate that the hybrid cell membrane coating effectively prevents visceral adhesions and promotes muscle regenerative healing.¹²

In summary, applying nanoparticles coated with red blood cell membranes to diabetic wound repair addresses the issue of non-targeting in nanoparticles. This approach also enables nanoparticles to evade immune clearance, prolongs their circulation time in vivo, and promotes tissue regeneration. Most importantly, it can rapidly eliminate the foreign body rejection and inflammatory response triggered by nanoparticles against the carrier scaffold.

Macrophage-Coated Nanoparticles

Difficult-to-heal wounds are a major complication of diabetes. Chronic diabetic wounds can persist for extended periods with a high recurrence rate, leading to reduced quality of life and loss of skin and mucosal function.¹³⁷

The healing process of skin wounds involves distinct phases including hemostasis, inflammation, proliferation, and remodeling. Inflammation within the wound environment has been identified as a key aspect of chronic wounds in diabetes. The inflammatory phase is induced by pro-inflammatory mediators released from injured tissues and is crucial for controlling infection, clearing necrotic debris, and initiating the wound healing process.¹³⁸

Macrophages have been demonstrated to play a crucial role in wound healing. As a type of white blood cell, macrophages possess functions such as phagocytosis, participation in and promotion of inflammatory responses, and antigen presentation. They also exhibit a natural ability to be recruited to the inflammatory site of a wound.¹³⁹ Indifferent wound environments, macrophages can be categorized into two phenotypes: classically activated macrophages and alternatively activated macrophages.^{140,141} Macrophage dysregulation severely impairs wound healing in diabetic patients. In particular, uncontrolled inflammation and abnormal macrophage phenotypes are major factors hindering wound healing in diabetes.^{142,143} Xiu hong Huang et al (21) investigated the preparation of a novel nanoparticle that modulates mitochondrial function in M2 macrophages via the PI3K/HIF-1 α /vascular endothelial growth factor pathway, thereby promoting angiogenesis and accelerating wound healing in diabetic conditions.¹¹² Yuhang Jiang et al (23) The

literature proposes that precisely molecularly designed mannose-modified spherical lysine dendrimers (MGLDs) induce anti-inflammatory activity by targeting and reprogramming the M2 phenotype of macrophages. This promotes collagen deposition and angiogenesis while alleviating inflammation through the suppression of pro-inflammatory cytokine secretion and increased production of transforming growth factor- β 1, ultimately achieving the goal of promoting diabetic wound healing.¹¹³

Nanoparticles have found wide applications in promoting wound healing in diabetes patients. Many studies have shown that nanoparticles can significantly improve the pharmacokinetics and chemistry of drug loaded formulations, including small molecule drugs, peptides, and proteins.¹³² Recent studies have shown that nanoparticles coated with biological cell membranes can mimic cellular properties and exhibit natural targeting capabilities. Macrophage membranes, for example, have unique biological functions and offer advantages such as stability, continuous release, excellent biocompatibility, and long circulation. Within the body, macrophage membranes demonstrate active targeting capabilities and accumulate at sites of inflammation.^{144,145} Figure 6 demonstrates the properties of membrane-coated porous M-NPs/MLN4924 nanospheres, achieved by loading the drug into PLGA nanoparticles coated with biomimetic macrophage membranes (M-NPs/MLN4924). The macrophage membrane protects nanoparticles from clearance by the

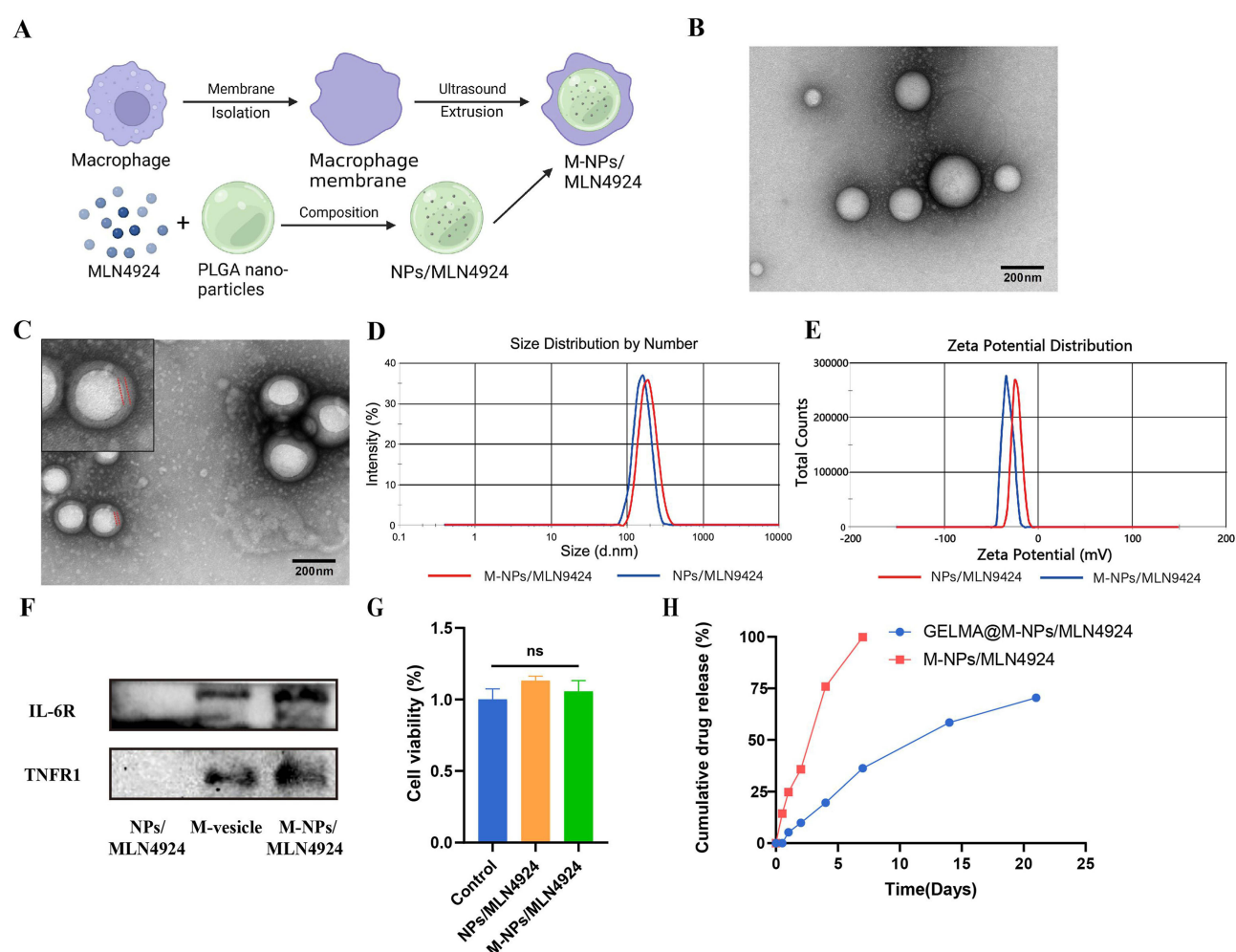


Figure 6 Study on the Properties of Membrane-Coated Porous M-NPs/MLN4924 Nanospheres. **(A)** This is a schematic representation of the synthesis process for M-NPs/MLN4924. The TEM images display nanospheres of **(B)** NPs/MLN4924, and **(C)** M-NPs/MLN4924 (the black box indicates a magnified electron microscope image, and the area highlighted in red demonstrates that the surface of the nanoparticles is covered with a uniform thin coating). **(D)** The dimensions and **(E)** zeta potential of porous NPs/MLN4924 nanospheres and M-NPs/MLN4924. **(F)** Western blots were performed on NPs/MLN4924 and M-NPs/MLN4924 to detect TNFR1 and IL-6R. **(G)** Biocompatibility was assessed by performing a CCK-8 assay after 24 h of cultivation (when compared to the control; ns: $P > 0.05$). **(H)** The release of MLN4924 from MNPs/MLN4924 and GelMA@M-NPs/MLN4924 was observed in PBS at 37°C and pH 7.4 for a duration of 21 days. "Neddylaton suppression by a macrophage membrane-coated nanoparticle promotes dual immunomodulatory repair of diabetic wounds" by Ruiyin Zeng is licensed under a CC BY-NC-ND 4.0 License (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).

reticuloendothelial system and antagonizes pro-inflammatory cytokines to mitigate inflammation in the surrounding area. Sustained release of MLN4924 from M-NPs/MLN4924 stimulates endothelial cell growth and tubule formation while promoting macrophage polarization toward the anti-inflammatory M2 phenotype.¹³² Figure 6A–C show a schematic diagram of the synthesis process for M-NPs/MLN4924, as well as transmission electron microscopy (TEM) images of the NPs/MLN4924 nanospheres and the M-NPs/MLN4924 nanospheres, in Figure 6C, the black box indicates a magnified electron microscope image, and the area highlighted in red demonstrates that the surface of the nanoparticles is covered with a uniform thin coating. Figure 6D and E show the size and zeta potential of the porous NPs/MLN4924 nanospheres and M-NPs/MLN4924. In Figure 6F, Western blot analysis was performed on NPs/MLN4924 and M-NPs/MLN4924 to detect TNFR1 and IL-6R. Figure 6G shows the evaluation of biocompatibility using the CCK-8 assay 24 hours after culture. Figure 6H shows that the release of MLN4924 from MNPs/MLN4924 and GelMA@M-NPs/MLN4924 persisted for 21 days in PBS at 37°C and pH 7.4.

Therefore, research has proposed nanoparticles encapsulated within macrophage membranes, which can mimic the aggregation characteristics of macrophages in inflamed tissues. By regulating inflammatory responses, Caihong Lu et al also proposed using macrophage membrane-coated nanoparticles. These particles mimic the aggregation behavior of macrophages in inflamed tissues. The biological properties of the exogenous macrophage membrane provide the nanoscale system with excellent biocompatibility and enable evasion during systemic circulation.¹⁴⁵

Recent studies have further demonstrated that nanoparticles coated with macrophage membranes can promote the healing of diabetic wounds. As demonstrated in studies by Ruiyin Zeng et al, loading drugs onto PLGA nanoparticles coated with macrophage membranes prevents their exclusion by the reticuloendothelial system. The macrophage membranes protect the nanoparticles, counteract pro-inflammatory cytokines to reduce inflammation in surrounding areas, and prolong drug release. Furthermore, due to the presence of membrane antigens such as TNFR1 and IL-6R on the macrophage surface, macrophage-coated nanoparticles can effectively capture and sequester various pro-inflammatory cytokines and chemokines, thereby playing a crucial role in neutralizing inflammation during diabetic wound healing.¹³² Figure 7 shows the experiment demonstrating the accelerated healing of diabetic wounds in animals by GelMA@M-NPs/MLN4924.¹³² They added M-NPs/MLN4924 to the porous GelMA hydrogel during hydrogel formation (Figure 7A). To evaluate the efficacy of M-NPs/MLN4924 on diabetic wound healing, they established a mouse model of chronic diabetic wounds and the hydrogel of each group was applied around the wound by injection. The results showed that both GelMA@NPs/MLN4924 and GelMA@M-NPs/MLN4924 accelerated wound closure compared with the hyperglycemia group (Figure 7B and C). Figure 7D and E show the assessment of wound blood perfusion using small-animal Doppler imaging. The blood perfusion results are expressed as the ratio of the wound area (ROI-1) to the total area (Tot).

Generally speaking, macrophages play a key role in inflammation, and nanoparticles play an important role in the healing process of diabetes. Through the development of a new nanoparticle, which undergoes the coating of macrophage membrane, it can be actively recruited to the inflammatory site. This approach allows the nanoparticles to regulate inflammatory responses while also facilitating its function in diabetic wound repair, thus significantly enhancing wound healing.^{113,146}

Mesenchymal Stem Cell-Coated Nanoparticles

Mesenchymal stem cells (MSCs) are adult stem cells possessing regenerative capacity and multipotent differentiation potential.¹¹⁵ In recent years, numerous studies have demonstrated that mesenchymal stem cells (MSCs) play a crucial role in tissue regeneration and wound repair by promoting wound healing, facilitating wound re-epithelialization, stimulating angiogenesis, regulating inflammatory responses, and modulating extracellular matrix remodeling.¹⁴⁷

Research by Yi Liu et al has demonstrated that human umbilical cord mesenchymal stem cells (HUCMSCs) not only possess hypoglycemic effects but also protect vascular endothelial cells from diabetic injury through a paracrine mechanism mediated by MAPK/ERK signaling.¹⁴⁸ Jiayi Yang et al demonstrated that a combination of human umbilical cord mesenchymal stem cells (HUCMSCs) and composite hydrogels significantly accelerates wound closure rates, increases CD31 and Ki67 expression, promotes granulation tissue regeneration, and upregulates vascular endothelial growth factor (VEGF) and transforming growth factor beta-1 (TGFβ-1) expression.¹⁴⁷

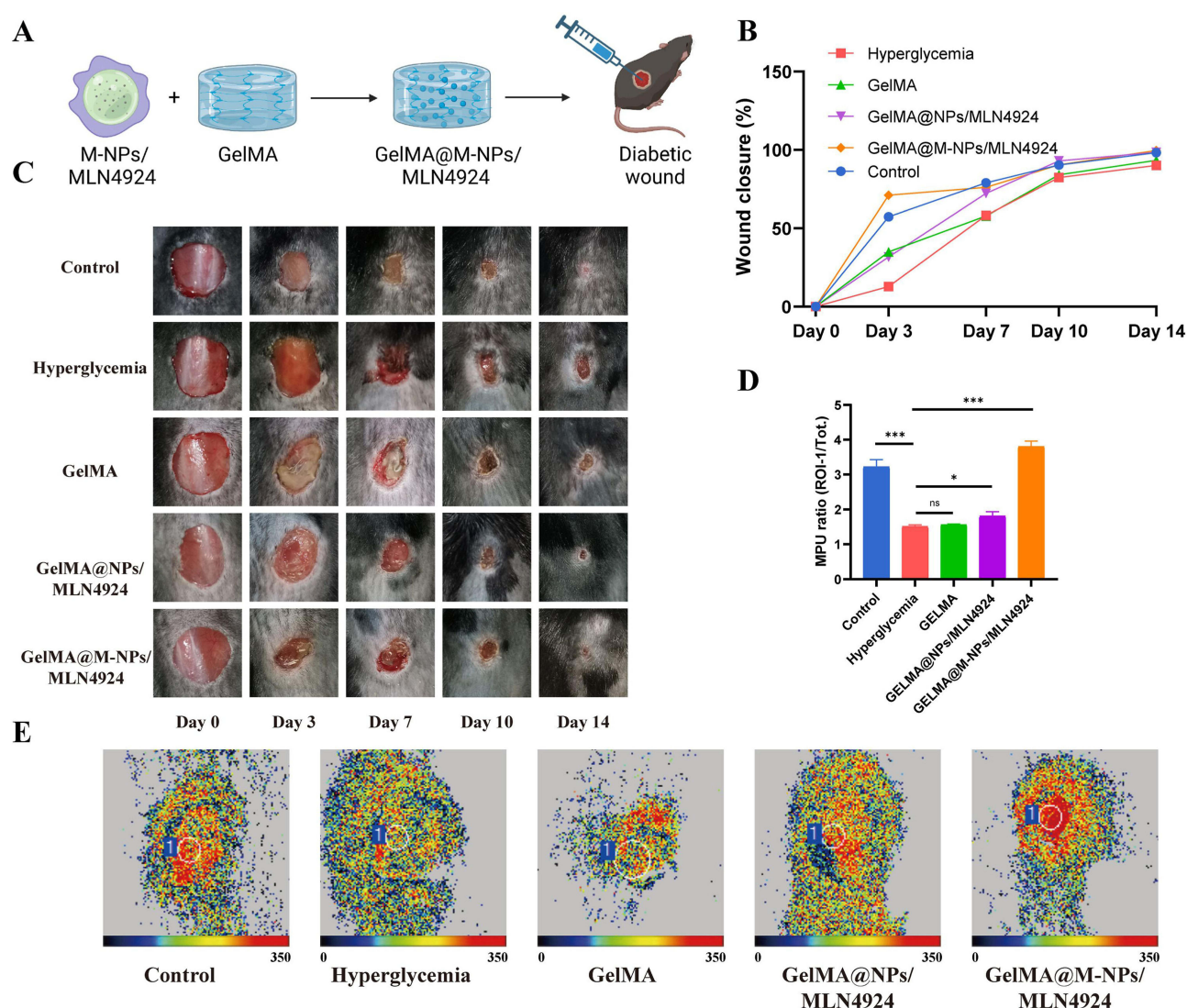


Figure 7 GelMA@M-NPs/MLN4924 Promotes In Vivo Healing of Diabetic Wounds. **(A)** The hydrogel mixed with nanoparticles is applied to the diabetic wound by injection. **(B)** Illustrative pictures showing full-thickness injuries in diabetic rats on days 0, 3, 7, 10, and 14 post-administration of PBS (Control), GelMA, GelMA@NPs/MLN4924, and GelMA@M-NPs/MLN4924. **(C)** The closure rates of wound healing in each group were computed through the utilization of the ImageJ software. **(D and E)** Small animal Doppler examination was used to evaluate the blood perfusion of wounds. The blood perfusion results are displayed as the proportion of the wound area (ROI-1) to the overall area (Tot). * $P < 0.05$; *** $P < 0.001$ (The circled area corresponds to "ROI-1" (Region of Interest 1), which is the delineated wound area). "Neddylation suppression by a macrophage membrane-coated nanoparticle promotes dual immunomodulatory repair of diabetic wounds" by Ruiyin Zeng is licensed under a CC BY-NC-ND 4.0 License (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).

The primary characteristic of MSCs is the presence of diverse receptors on their cell membranes, including cytokine receptors, chemokine receptors, growth factor receptors, and cell-matrix receptors. These receptors regulate protein synthesis between the intracellular environment and the cell nucleus, thereby influencing cellular metabolism and function.^{149,150} Studies indicate that CXCR4 expressed on the surface of MSCs exhibits strong inflammatory targeting properties. Additionally, chemokine and cytokine receptors expressed on the MSC membrane, such as CXCR1, CXCR2, CCR1, and CCR2, also play a crucial role in cell migration toward sites of inflammation.^{141,151} It also demonstrates that nanoparticles encapsulated by MSCs exhibit superior ability to penetrate the endothelial cell barrier compared to unencapsulated nanoparticles. Furthermore, these nanoparticles significantly reduce macrophage uptake of nanoparticles from 84% to 24%, indicating a low risk of increased inflammation.^{17,149,152}

Research by Yuanlong Li et al confirmed that nanoparticles coated with cell membranes derived from CD90+ MSCs reduce apoptosis via the FOXO pathway and influence the polarization of type II macrophages, thereby modulating

inflammatory responses by increasing IL-10 secretion.¹⁵¹ Shaoying Gao et al developed a nanoparticle that promotes the proliferation of bone marrow-derived mesenchymal stem cells (BMMSCs) and the migration of keratinocytes.¹⁷ When BMMSCs were co-cultured with the prepared nanoparticles, genes associated with wound healing were upregulated in BMMSCs. Subsequently, the authors coated the nanoparticles with bone marrow mesenchymal stem cell membranes. The study confirmed that the coated nanoparticles accelerated epithelialization, promoted collagen remodeling, counteracted oxidative stress, and enhanced angiogenesis in vivo, thereby accelerating diabetic wound healing.¹⁵³

Numerous studies have demonstrated that nanoparticles coated with mesenchymal stem cell membranes can simultaneously exhibit the dual properties of both mesenchymal stem cells and nanoparticles.¹¹³ When applied to diabetic wound repair, a composite nanoparticle that promotes wound healing can be prepared. Coated with a mesenchymal stem cell membrane, it exerts a dual effect to achieve a higher cure rate.¹¹⁵

Exosomes Encapsulating Nanoparticles

Exosomes refer to small membrane vesicles containing complex RNA and proteins, and are now predominantly defined as disc-shaped vesicles with diameters ranging from 40 to 100 nm. Most cells can secrete exosomes under both normal and abnormal conditions. These primarily originate from multivesicular bodies formed by the invagination of intracellular lysosomal particles. After fusion between the outer membrane of the multivesicular body and the plasma membrane, exosomes are released into the extracellular matrix. Exosomes are regarded as specialized secretory vesicles that participate in intercellular communication. They serve as crucial tools for intercellular signaling, transporting molecules such as miRNAs, mRNAs, or proteins from donor cells to recipient cells. This process influences intracellular signaling pathways and various biological processes.¹⁵⁴

In recent years, a large number of studies have shown that exosomes play a key role in wound healing. For example, studies by Muyu Yu et al have demonstrated that ATV treatment of exosomes derived from mesenchymal stem cells (MSCs) can up-regulate AKT/eNOS signaling pathway, thus increasing the pro-angiogenic function of MSC-derived exosome and speeding up the healing of diabetic wounds.^{154,155}

Yang et al demonstrated that exosomes from human umbilical cord mesenchymal stem cells stimulated with blue light promote wound healing by upregulating MEF2C signaling.¹⁵⁶ Another study by Ding et al indicates that deferoxamine promotes skin wound healing by MSC-Exos through enhancing angiogenesis in STZ-induced diabetic rat models. The literature by Peng Wang et al (136) also demonstrates that epidermal stem cell-derived exosomes (ESCS-Exo) promote wound healing by reducing inflammation, enhancing wound cell proliferation, stimulating angiogenesis, and inducing M2 macrophage polarization.¹⁵²

Exosomes provide a promising strategy for wound healing, which can reduce inflammation and promote angiogenesis, collagen deposition, cell proliferation and migration, and ultimately speed up wound healing.

However, as research progresses, there is still a limited understanding of the molecular mechanisms underlying the formation, release, uptake and function of extracellular vesicles. In particular, there is not enough research on the physiology, diversity, endocytosis, and molecular transport of extracellular vesicles.

Additionally, due to the short half-life and instability of exosomes in vivo, directly injecting free-floating exosomes into the wound site makes it difficult for them to remain at the wound site long enough to achieve satisfactory results.¹⁴¹

Given that nanoparticles also play a significant role in diabetic wound healing, literature has proposed encapsulating nanoparticles within exosomal membranes for use in diabetic wound repair. The combination of the advantages of nanoparticles and exosomes, while mitigating their respective limitations, is expected to produce superior results in wound healing. Excessive inflammation and damage of angiogenesis are the key factors that lead to poor healing in diabetes. Studies have shown that M2 macrophage-derived exosomes (MES) exert anti-inflammatory effects by regulating the phenotype of macrophages, showing great potential in biomedical applications.

Therefore, Junkai Zeng et al proposed a system utilizing composite nanoparticles constructed with MSE coating for diabetic wound treatment, achieving a dual effect of simultaneously suppressing inflammation at the wound site and promoting angiogenesis.¹⁴¹ Meanwhile, Feili Yan et al also noted in their study that nanoparticles coated with exosomes enhance their ability to circulate for extended periods. Di Wu et al developed a novel type of exosome by conjugating it

with magnetic nanoparticles. Both in vivo and in vitro, this approach promoted angiogenesis and enhanced fibroblast function, thereby upregulating miR-21-5p and further accelerating wound healing.^{115,157}

Numerous studies have demonstrated that combining exosomes with nanoparticles significantly enhances wound healing. Consequently, research on exosome-coated nanoparticles for diabetic wound repair holds considerable promise.

Clinical Applications of Cell Membrane Products

Compared to conventional wound healing treatments, cell membrane-coated nanoparticles have shown tremendous potential in clinical applications for wound healing. Based on clinical practice and patient acceptance, cellular membrane-coated nanoparticles have excellent biocompatibility and are unlikely to cause immune rejection in the body. This means that there is a lower likelihood of side effects in the patient and therefore more safety. Additionally, because of their minute size, nanoparticles can be administered via a variety of routes — whether by local application, injection, or other — so that they can be more adaptable to different wound types and offer more flexible treatment options for clinicians. The Jiangnan University School of Medicine, Prof. Lu Guozhong's group, published a paper in Nanobiotechnology. The research utilized the innate ability of macrophages to identify bacteria and the characteristic increase of ROS (ROS) at the site of infection to develop a new nanoparticle, Sa-MM @ Van-NPs, for targeted delivery and controlled release. The nanoparticles are effective in targeting the infected area and releasing vancomycin to remove the bacteria, thus facilitating faster wound healing. With excellent biocompatibility, they hold promise as a powerful strategy for precisely eradicating infections and accelerating wound recovery.¹⁵⁸

Below we summarize some clinical trial projects and patents for cell membrane products. Table 5 summarizes relevant clinical trials on cell membrane-encapsulated nanoparticles from the ClinicalTrials.gov website. Table 6 outlines patents related to cell membrane-encapsulated nanoparticles from the China National Intellectual Property Administration website.

Table 5 Clinical Study on the Application of Cell Membrane-Nanoparticles for Diabetic Wound Healing.

Table 5 Clinical Study on the Application of Cell Membrane-Nanoparticles for Diabetic Wound Healing

Trial Number	NCT07046767	NCT02120755
Trial name	CAMP RWE Trial: AmnionGrafts for Healing Hard-to-Heal Ulcers in RW Populations	A Randomized Comparison of "human amniotic tissue graft" Human Allograft Amniotic Membrane vs. Moist Wound Dressing in the Treatment of Diabetic Wounds
Condition	Diabetic Foot Ulcer (DFU) Venous Leg Ulcer Wound; Foot	Diabetic Foot Ulcers Wound Care
Intervention/treatment	OTHER: IP1: BioLab Membrane Wrap Lite IP2: BioLabTri-Membrane Wrap OTHER: IP2: BioLab Tri-Membrane Wrap	BIOLOGICAL: "human amniotic tissue graft" Human Allograft Amniotic Membrane
Sex	ALL	ALL
Age range	ADULT, OLDER_ADULT	ADULT, OLDER_ADULT
Sponsor	Capsicure, LLC	Liventa Bioscience
Enrollment	165	0
Study type	INTERVENTIONAL	INTERVENTIONAL
Trial phase	NA	PHASE4
Reference	(Chuengsamarn, Rattanamongkolgul, Luechapudiporn, Phisalaphong & Jirawatnotai, 2012)	(Adibian, Hodaei, Nikpayam, Sohrab, Hekmatdoost & Hedayati, 2019)

Table 6 Patent for Cell Membrane-Encapsulated Nanoparticles

Invention Title	Publication Number	Abstract
A Method for Preparing Macrophage Membrane-Coated Hair Nanoparticles and Its Applications	CN115581684A	Alkali extraction prepares hair nanoparticles (main components: melanin, keratin) photothermally sensitive for infected diabetic foot ulcers; ultrasonic fusion encapsulates in macrophage membranes, enhancing bacterial adhesion and efficiency in infected areas, high biocompatibility. ⁹⁴
Preparation Method and Application of Multifunctional Hydrogels for Preventing Postoperative Adhesions and Tumor Recurrence	ZL202311307736. 9	Cell membrane lipid-based protamine hyaluronic acid bionic nanocomposite particles prevent postoperative adhesions and tumor recurrence while promoting wound healing.
A Macrophage-Targeted Polydopamine Nanoparticle Drug Delivery System, Its Preparation Method, and Applications	CN116602935A	By loading naringenin onto polydopamine nanoparticles and encapsulating them within macrophage membranes, excellent therapeutic effects were demonstrated on skin wounds.
Bionic Nanoparticles Based on Cancer Cell Membrane Modification: Preparation Methods and Applications	CN115252581A	Cancer cell membrane-modified bionic nanoparticles: excellent targeting, potent antitumor activity, low cytotoxicity, inhibits tumor growth, superior tumor-targeted accumulation, prolonged circulation, effective tumor cell killing, plus its preparation method and applications.

Current Research Status and Future Prospects of Cell Membrane-Coated Nanoparticles in Diabetic Wound Healing

Diabetic chronic wounds exhibit pathological characteristics of high inflammation, high oxidative stress, high infection risk, high hyperglycemic toxicity, and poor healing. Traditional treatments struggle to simultaneously achieve anti-infection, immune regulation, tissue repair promotion, and targeted drug delivery. Consequently, clinical healing rates remain low, recurrence rates are high, and progression to ulcers or even amputation is common, making this a global clinical challenge.¹⁵⁹ Novel bionic drug delivery systems, exemplified by cell membrane-coated nanoparticles, possess inherent cell membrane properties due to their surface coating. This enables advantages such as evading immune clearance, prolonging wound retention, achieving targeted accumulation, and facilitating multi-modal synergistic therapy, making them a current research hotspot in diabetic wound repair.¹⁶⁰ However, translating these findings from basic research to clinical application still faces a series of critical scientific and engineering challenges. This chapter systematically reviews and outlines challenges surrounding large-scale production, reproducibility, safety, immunogenicity, regulatory pathways, and clinical translation barriers.

Feasibility of Mass Production

Cell membrane-coated nanomaterials show promising industrial application prospects for chronic wound healing in diabetes, yet systematic breakthroughs remain necessary in process scaling, quality control, cost management, biosafety, and safety oversight.¹⁶¹ Regarding raw material selection, readily available human red blood cells, platelets, and mesenchymal stem cells will be prioritized. Serum-free culture and fully automated membrane extraction systems will address issues of limited availability, heterogeneity, and immunogenicity.¹⁶⁰ Concurrently, medical biodegradable materials such as PLGA, gelatin, hyaluronic acid, and mesoporous silica exhibit broad application potential in wound repair. Cost-wise, enhancing production line recovery rates, leveraging economies of scale, and promoting domestic material sourcing will reduce per-dose costs to an acceptable range.¹⁶² Given the substantial clinical demand for diabetic wound care and potential healthcare coverage, its industrialization demonstrates clear economic and market viability. Future efforts to optimize membrane sources, develop continuous preparation processes, establish standardized quality control systems, and enhance material stability will significantly boost industrial feasibility, propelling these biomimetic nanomaterials from the laboratory to clinical application.

Reproducibility and Safety Assessment of Experimental Results

Currently, research findings on cell membrane-coated nanoparticles in the field of diabetic wound healing are increasingly abundant. However, there remain shortcomings in the reproducibility of experimental results and safety

assessments. First, regarding cell membranes, their sources exhibit significant heterogeneity.¹⁶³ Differences in cell lines, passage numbers, culture conditions, and extraction methods all lead to variations in membrane composition, membrane protein expression, and membrane structure. Simultaneously, regarding nanoparticles, preparation techniques, coating ratios, extrusion cycles, particle size ranges, and other parameters lack standardized protocols. Therefore, future efforts should shift research from exploratory work confined to individual laboratories toward standardized studies that are reproducible, verifiable, and scalable, thereby establishing a robust data foundation for subsequent clinical translation.¹⁶⁴

Of course, biosafety is equally important. Given that diabetic patients exhibit hyperglycemia, chronic inflammation, immune dysregulation, and liver and kidney abnormalities, these factors can influence drug distribution, retention time, and toxic effects within the body. At the same time, the preparation process for membrane-coated nanoparticles involves multiple steps, including cell membrane isolation and ultrasonic disruption. If sterile conditions are not strictly maintained during any of these steps, bacterial contamination can easily occur.¹⁶⁵ Furthermore, due to their sensitivity to high temperatures and disinfectants, traditional sterilization methods can easily damage the membrane structure and function, rendering them unusable. Macrophages are cells that recognize pathogens and readily bind to trace amounts of endotoxins such as LPS; however, membrane separation and purification methods struggle to completely remove these trace endotoxins.¹⁶⁶ As a potent inflammatory factor, endotoxins, if delivered to diabetic wounds alongside nanoparticles, can exacerbate local chronic inflammatory responses, thereby undermining the drug's anti-inflammatory and reparative effects. This makes it difficult to directly extrapolate traditional safety assessment results.¹⁶⁷ Therefore, we must maintain long-term vigilance regarding critical issues such as persistent toxicity, accumulation risks of degradation products, disruption of local microenvironments, and potential inflammatory activation. Moving forward, we should establish a safety evaluation system tailored to the pathological characteristics of diabetes.¹⁶⁸ This requires conducting systematic toxicological studies at the multi-dose, long-term, and large-animal levels to clarify the drug's effects on tissue toxicity, systemic toxicity, genotoxicity, and carcinogenicity. Such research will provide comprehensive and reliable safety evidence to ensure the drug's safe administration.¹⁶⁷

Research on Immunogenicity and Immune Evasion Mechanisms

Although cell membrane encapsulation strategies confer natural immune evasion capabilities to nanoparticles, reducing recognition and clearance by the mononuclear phagocyte system, the potential immunogenicity and long-term immunological safety of cell membrane-coated nanoparticles still require systematic and in-depth investigation. Diabetic patients inherently exhibit chronic low-grade inflammation and immune dysregulation, making exogenous carriers more likely to trigger complement activation, immune cell infiltration, and antibody production. Current understanding of the immune recognition patterns, signaling pathways, and long-term immunological fate of membrane-coated nanoparticles remains incomplete.¹⁶⁹ Therefore, future research should focus on elucidating the molecular mechanisms of immune evasion mediated by different cell membrane sources. By modifying membrane surface proteins and precisely regulating membrane composition, efficient and stable membrane material selection can be achieved.¹⁷⁰ This approach reduces exposure to foreign antigens, enhances innate immune evasion capabilities, and ultimately enables efficient and stable biological activity of cell membranes, providing novel insights and methods for treating diabetic wounds.

Regulatory Compliance Requirements and Challenges Encountered During Clinical Translation

Cell membrane-coated nanoparticles, as a biomedical material applicable to wound healing, must comply with relevant regulations governing pharmaceuticals, medical devices, and biological products. Currently, research in this field remains exploratory both domestically and internationally, primarily focusing on classification and definition, quality control, impurity limits, sterility requirements, and stability evaluation.¹⁷¹ In China, wound dressings for diabetic patients are generally classified as Class III medical devices, subject to stringent requirements regarding sterility control, impurity limits, stability, toxicokinetics, and long-term safety.¹⁷² However, transitioning from basic research to clinical application faces multiple practical challenges: high production costs, poor storage and transport stability, unclear mechanisms of wound microenvironment regulation, and insufficient large animal and clinical trial data.⁴ Moving forward, we will focus

on clinical needs by simplifying structural design, enhancing material stability, conducting multicenter preclinical studies, and promoting multidisciplinary collaboration between medicine and engineering. This approach will gradually overcome constraints in technology, cost, and clinical application.

Conclusion

Diabetes is a chronic metabolic disease that is becoming more and more prevalent, and the injury that is caused by it is often difficult to heal and carries the risk of related complications. The mechanism of wound healing in diabetic patients is complex, involving multiple pathways including cell, molecule, inflammation, immunity, and microcirculation.

In recent years, researchers at home and abroad have made great progress in treating diabetes. These include the use of biomaterials (using biological scaffolds, growth factors, and stem cells to promote wound healing in diabetes patients), surgical procedures supplemented by auxiliary techniques, and nanotechnology. Among them, nanotechnology has emerged as an especially outstanding field of research.

The application of nanoparticles (NPs) in diabetic wound repair has great potential. Nanoparticles provide strong structural support and deliver biological activity and signaling molecules to promote cell differentiation and function in the injured area during the process of reconstruction. However, due to certain limitations related to the individual use of nanoparticles, numerous studies have proposed using cell membrane-coated nanoparticles for diabetic wound repair. This method makes nanoparticles more compatible with living cells, thus reducing their potential toxicity and immune rejection. Secondly, cell membrane encapsulation enhances the stability and circulation life of nanoparticles within the body, facilitating their more efficient delivery to target tissues or cells. Additionally, cell membrane encapsulation can mimic the biocompatibility of natural cells, making nanoparticles more easily accepted and utilized by organisms. In this paper, we summarize the application and development of different kinds of membrane-coated nanoparticles in diabetic wound repair. Compared to existing reviews, this paper moves beyond material construction and basic pharmacodynamic summaries. Instead, it focuses on the pathological specificity of diabetic wounds, systematically elucidating the targeted repair mechanism of cell membrane-encapsulated nanoparticles. It provides a comprehensive analysis of practical challenges in areas such as reproducibility, safety, immunomodulation, large-scale production, regulatory compliance, and clinical translation. This provides more forward-looking and practical theoretical support for advancing the clinical translation of novel bionic delivery systems for diabetic wounds.

Research on diabetic wounds is a critical field requiring multidisciplinary collaboration and effort. Understanding the effects of diabetes on wound healing and exploring effective therapeutic approaches will help to improve the quality of life for patients with diabetes. Prevention and routine care are also an important way to reduce the suffering of patients and to reduce the burden on health systems. In future studies, we expect to see more discoveries in diabetes, which will open up more possibilities and opportunities for clinical therapy.

Abbreviations

MODY, Maturity-Onset Diabetes of the Young; DFU, Diabetic Foot Ulcer; RES, Reticuloendothelial system; MPS, Mononuclear phagocyte system; DNA, Deoxyribonucleic acid; RNA, Ribonucleic acid; GFS, Growth factors; LNPs, Lipid nanoparticles; DSPC, 1,2-Distearoyl-sn-glycero-3-phosphocholine; DOPE, 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine; PLGA, poly(lactic-co-glycolic acid); PCL, Polycaprolactone; PEG, Polyethylene Glycol; ROS, Reactive Oxygen Species; MRSA, Methicillin-resistant *Staphylococcus aureus*; VEGF, vascular endothelial growth factor; Enos, endothelial nitric oxide synthase; GDS, Gelatin Dermal Scaffold; RBC, Red Blood Cell; R&D, Research and Development; MSC, Mesenchymal stem cell; CCR1, C-C chemokine receptor type 1; CCR2, C-C chemokine receptor type 2; CXCR1/2/4, C-X-C chemokine receptor type 1/2/4; MSCs, Mesenchymal Stem Cells; FOXO, Forkhead box O.

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Disclosure

The authors report no conflicts of interest in this work.

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