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CURRENT DEVELOPMENTS OF NANOTECHNOLOGY IN MENDING CHRONIC WOUNDS

Singamareddy Sai Deepthi*,Megavath Srikanth Naik, Uggirala Mounika and Chandu Babu Rao.

Priyadarshini Institute of Pharmaceutical Education and Research, 5th Mile, Pulladigunta, Guntur-522017.Andhra Pradesh, India.

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Abstract

A number of reasons inhibit the healing process in the wound healing phase, which is a natural and well-designed process. Millions of individuals worldwide are impacted by poor wound healing, which raises the associated mortality rates. Modern medicine and nanotechnology work together to generate new materials and gadgets at the nanoscale, which could revolutionize the way that macroscale treatments are now provided. Through antibacterial, anti-inflammatory, and angiogenic activities that transition the wound milieu from nonhealing to healing, nanomaterials can activate a variety of cellular and molecular pathways that support wound healing. The tiny nanomaterials, nanoscaffolds, nanofibers, and biomaterials utilized in nanotechnology for topical medication administration to promote wound healing. Prior research has shown that nanotechnology has numerous benefits for medical treatment. This review aims to demonstrate how biodegradable and nanoparticle-based materials can aid in the healing of wounds. the future paths of existing technology while going over possible approaches that can help the area of wound healing progress. This article focuses on the pathophysiology and mechanics of wound healing.

Keywords: Nanomaterials, Chronic wounds, Nanotechnology, Nanoscaffolds, Nanopart.

***Corresponding Author**
Siramshetty Sai Deepthi

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1. Introduction

The wound healing process is classically defined as a series of continuous, sometimes overlapping, events. These are haemostasis, inflammation, proliferation, epithelisation, maturation, and remodelling of the scar tissue. Nanoparticles allow for the external delivery of substances that are constantly produced at the site of injury (1). One such important endogenous molecule is nitric oxide [NO], with a maximum half-life in seconds. In delayed, non-healing wounds such as diabetic wounds/ulcers, the delivery of exogenous NO at the site of injury is an extremely promising therapy; the practical applications are limited due to lack of operative delivery molecules [2]. Most of the common features of chronic wounds include an extended inflammatory phase, existence of persistent infections, formation of bacterial bio-films, as well as higher levels of proteases and reactive oxygen species (ROS). Furthermore, dermal and/or epidermal cells residing in chronic wounds fail to respond to reparative stimuli(2). These cells present phenotypic abnormalities such as lower expression of growth factor (GF) receptors, as well as lower mitogenic potential, preventing their response to external environmental causes. Nano biotechnology which involves the use of nano-sized particles in biological systems represents the convergence of several scientific fields, including chemistry, biology, physics, optics, and nanoscale science and technology.

1. Wound:

A wound is a break in the integrity of the skin or tissues often associated with disruption of structure and function.

- A cut or break in the continuity of any tissue, caused by injury or operation.
- Wound is defined as a break in the skin or internal organs.

Types of Wounds:

There are two types of wounds;

- Acute wounds
- Chronic wounds

Acute Wound:

- Initial phase:

- 1. primary haemostasis and scab formation
- 2. Neutrophil infiltration
- Healing phase:
- 3. Re-epithelization
- 4. Angiogenesis
- 5.fibroblastsmigrationandactivation
- 6. collagen deposition

Chronic Wound:

1. Infection / biofilm
2. Persistent inflammation
3. Impaired angiogenesis
4. Fibroblast senescence

2. Physiology of Wound Healing:

The restoration of skin is a complicated physiological procedure, which involves the complex organization of numerous diverse cell types, chemokines, and various growth factors in a chronological manner (3). The function of platelets, neutrophils, macrophages and fibroblasts are considered in detail. It is essential that conventionally, the wound healing process is categorized into four phases:

A) Hemostasis B) Inflammation C) Proliferation D) Remodeling

3. Types of Phases: There are four types of phases in chronic wound healing (4).

3.1. Hemostasis phase:

The objective of the hemostasis phase of wound healing is to stop any bleeding. When your blood clots at the opening of a wound, it prevents you from losing too much blood and it is the first step of wound healing. The time of surgical incision, vascular injury occurs on a microvascular scale. the immediate response of the body. the function of various biomolecules involved in wound healing(5). the wound healing stage through the stimulation of epithelial cells, employing fibroblasts for collagen deposition and encouraging the restoration of injured tissue.

3.2. Inflammation phase:

The inflammation arises instantly after the injury and frequently lasts for up to 3 days. Thrombin is one of the first products of the coagulation cascade occurring during haemostasis, and is responsible for platelet activation and aggregation, leading to the formation of the "platelet plug" and allowing cells and fluid to enter the wound bed. After 3–4 days of wound development, macrophages remove exhausted neutrophils via efferocytosis, averting a nonspecific breakdown of the tissue and perseverance of inflammation(6).

3.3. Proliferation phase:

The aim of growth factors is to promote cell migration into the wound site, stimulate the growth of epithelial cells and fibroblasts, start the formation of new blood vessels, and profoundly influence the remodelling of the scar. Four days after wound development, a proliferation stage begins and persists for ~21 days in chronic wounds(8). The proliferation stage is categorized primarily by granulation of tissue, wound reduction, and angiogenesis. PLA/PLGA/PEG/hyaluronan/gelatine nanoparticles embedded with different growth factors have been successfully applied on skin wounds.

3.4. Remodelling Phase:

The last stage of wound healing is maturation and remodeling. This phase starts about three weeks post wound development and can take one year or even more, based on the type of wound, resulting in the natural epithelium growth and scar tissue maturation. the collagen realignment into organized grids that upsurge the tensile strength of the tissue, accomplishing about 80% of unwounded skin(9). The stem cells cell-based therapies hold the potential to promote vascularization and tissue regeneration. The hVEGF gene was delivered through biodegradable polymeric nanoparticles: treated stem cells showed the engraftment of the tissue.

4. Pathophysiology of Wound Healing:

The skin establishes a high capacity for restoration that is controlled by the efficient and arranged order of cellular and molecular processes. Furthermore, a disturbance in the normal healing procedure may entirely stop wound healing, causing chronic wounds. The imbalance in the phases results in chronic, nonhealing wounds(10). Several investigators stated that 6–8 weeks are suitable for wound healing; beyond that, the wound should be considered a chronic/nonhealing wound. The Cells during acute wound healing are different (functionally and phenotypically) from that of chronic nonhealing wounds(12).

5. Role of Metal and Metal Oxide Nano Particles in Wound Healing:

Nanoparticles are based on metal are extensively applied in biomedicine owing to their benefits, such as easy synthesis with defined shapes and sizes, facile functionalization of the surface, enhanced biocompatibility, and superior physicochemical properties(13). The most extensively used NPs in the biomedical area are gold and silver. Gold NPs are broadly considered in biosensing due to their optical properties and for drug delivery as a nanocarrier.

5.1. Silver Nanoparticles:

Silver is a bactericidal agent and is generally used for the treatment of blisters, wound disease, and abscesses. For instance, silver nitrate is still used for the treatment of nonhealing chronic disease(14). The wound coverings loaded with AgNPs developed from diverse biocompatible polymers showed virtuous repressive activity against *Staphylococcus aureus, E. coli, S. epidermidis,* and *Salmonella typhimurium*.

5.2. Lipid Nanoparticles:

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) were representatives of lipid nanoparticles introduced to overcome the limitation of liposomes. Lipid NPs are propitious vehicles for medicinal agents, for example, drugs, growth factors, and small interfering RNA (siRNA). Two kinds of lipid NPs, i.e., solid lipid NPs (SLNs) and nanosized lipid carriers (NLCs), have

been formed as efficient carriers for wound treatment(14).

5.3. Polymeric Nanoparticles: Polymers are substances that are made up of small organic molecules (i.e., monomers) linked together in long, repeating chains(12). The polymer's chain length is determined by the molecular weight of separate monomers and the degree of polymerization. Amphotericin B nanoparticles resulted in equivalent or enhanced killing efficacy with 72.4–91.1% by 4 h for Clinical strains.

5.4. Gold Nanoparticles:

Gold nanoparticles are used in resonance scattering dark-field microscopy for the detection of microbial cells and their metabolites, the bio-imaging of tumor cells, and for the detection of receptors on their surface, and for the study of endocytosis(17). Unlike Ag, AuNPs by themselves do not show any antimicrobial activity. vancomycin-conjugated AuNPs improved the activity of vancomycin (50-fold) against vancomycin-resistant enterococci and presented substantial activity against *E. coli*.(18)

5.5. Liposomes:

Liposomes can be classified according to their size (from nm to mm), number of bilayers, or the method of fabrication. They are generally prepared from phospholipid and cholesterol. They observed an increase in wound closure rate, angiogenesis, and a reduced inflammation(19). Nanogels and nano emulsions have also been poorly explored in the field of wound healing. The results showed that the cationic elastic liposomes containing the growth factor complex significantly accelerated the wound closure rate in the diabetic mouse model, with the maximal shrink of wound size by 58% compared with the native growth factor complex.(20)

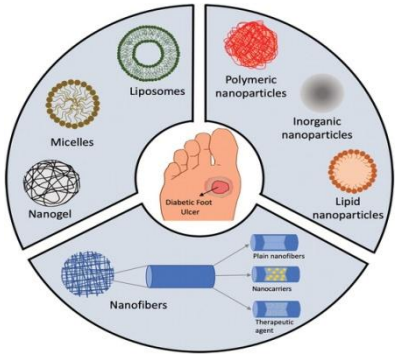

Fig.3.Schematic representation of Nano carriers used for chronic wound healing

6 .Current Treatments of Chronic Wounds:

The ultimate goal of the wound management is to prevent serious infection, accelerate wound healing and reduced scars and pain for patients. Currently, a set of strategies are available for wound management mainly including debridement, autografts and application of therapeutic agents(12). Current treatment of chronic wounds depends on the wound etiology. Antimicrobial peptides are able to control both inflammation and bacterial infection, acting as wound-healing peptides. These properties are highly desired in novel topical formulations for treatment of chronic wounds.(13)

7. Nanotechnology of chronic wounds:

the wound healing process is affected by several factors, including gene expression; cell functions such as migration, proliferation, and differentiation; the skin microenvironment; infection; ischemia–hypoxia; inflammation; and collagen formation and arrangement.(24) Tradition treatment methods for chronic wounds that show delayed Union involve local or systemic drug administration. However, the performance of these drugs is suboptimal owing to limitations such as low solubility and low bioactivity.

8. Future Directions:

The new chronic wound nanotherapeutics are multifunctional platforms that promote wound healing with minimal scar formation, avoid/treat bacteria contamination, and can even release the active biomolecules encapsulated at specific rates that match wound healing necessities.(25) The appearance of new biomolecules active in wound healing, such as GFs or nucleic acids, shows the necessity of designing new formulations to protect them from degradation and to deliver them at specific rates. It is also required that they are easy to apply into the wound, which means, for NPs and self-assembling carriers, to be included in another formulation.

Conclusion

In this article, the mechanisms underlying the latest developments in nanomaterials that promote wound healing have been reviewed. There are research gaps regarding the correct processes and post-wound modifications, despite the majority of the literature focusing on the promotion of hemostasis, anti-infection, immunoregulation, remodeling, and proliferation. Comparably, our understanding of the molecular and cellular mechanisms underpinning wound healing has advanced to the point that researchers are able to design novel therapeutic strategies that directly influence cellular and subcellular processes involved in the healing process.

Author contributions

All authors are contributed equally.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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