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Revitalizing Wound Healing Innovations Promoters Delivery Strategies

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Abstract: *Skin injuries have a significant impact on the global health system, imposing a substantial burden on the economy and society. The low cure rate reported for these injuries exacerbating the situation further. Skin wounds can be categorized as acute or chronic, and the immune response plays a crucial role in acute wound healing. During this process, activated immune cells and factors initiate inflammation, aid in wound cleansing, and facilitate tissue healing. However, dysregulation of the immune system during wound healing can result in persistent inflammation and delayed healing, leading to the formation of chronic wounds. Chronic wounds are characterized by a microenvironment that exhibits an abundance of pro-inflammatory macrophages, increased expression of inflammatory mediators like TNF-α and IL-1β, heightened activity of matrix metalloproteinases, and an excess of reactive oxygen species. Furthermore, chronic wounds are often complicated by bacterial biofilms, which perpetuate the inflammatory phase and make the healing process extremely challenging. In this review, the role of innate and adaptive immunity in the pathogenesis of both acute and chronic wounds is discussed. Additionally, recent immunomodulatory therapy strategies are reviewed, including the modification of macrophage phenotype, miRNA expression, and targeting of pro- and anti-inflammatory factors to enhance wound healing.*

Keywords– *Wound healing, Skin injuries, immune system, Delivery strategies*

I. INTRODUCTION

The wound healing process is a highly specialized and dynamic multi-phase process for repairing damaged or injured tissue through complex mechanisms. Failure in the normal wound healing process results in abnormal scar formation and a chronic state that is more susceptible to infection. Chronic wounds affect the quality of life of patients and increase morbidity and mortality, as well as being a huge financial burden on health systems worldwide, requiring specialized intensive biomedical care for their management. Clinical evaluation and management of chronic wounds remains a challenge despite the development of various therapeutic regimens, as they require complex long-term care and complex wound healing mechanisms. Various conventional approaches such as cell therapy, gene therapy, growth factor delivery, wound dressings, and skin grafts, etc., are used to promote wound healing in various types of wounds[1].

However, all the therapies mentioned above are not satisfactory for all wound types, therefore, there is an urgent demand for the development of competitive therapies. Therefore, there is a need to develop new and innovative treatment modalities for multipart therapeutic regimens for chronic wounds. Recent developments in advanced wound care technologies include nanotherapy, stem cell therapy, bioengineering skin grafts, and 3D bioprinting-based strategies to improve therapeutic outcomes with a focus on skin regeneration with minimal side effects. The primary aim of this review is to provide an up-to-date overview of advances in therapeutic options in the healing and management of chronic wounds over the years using innovative next-generation approaches. Here, we discuss the function and anatomy of the skin, wound processes and wound healing, followed by conventional treatment modalities for wound healing and skin regeneration. In addition, various emerging and innovative strategies to promote quality wound healing such as nanotherapy, stem cell therapy, 3D printed skin, extracellular matrix approach, platelet rich plasma approach, and cold plasma treatment therapy have been discussed and their advantages and disadvantages. Finally, the challenges of this innovative strategy are reviewed with notes on future prospects[2].

The incidence of chronic wounds is increasing due to an aging population and an increasing number of people with diabetes. With growing knowledge of the biological mechanisms underlying these diseases, there has been an increase in the development of medical technologies entering the conventional wound care market. Recent Advances: Several nanotechnology have been developed which exhibit unique characteristics that can overcome specific problems associated with wound repair mechanisms. In this review, we focus on the most recently developed nanotechnology-based therapeutic agents and evaluate the effectiveness of each treatment in in vivo models of diabetes associated with chronic wound healing. Critical Issues: Despite the development of potential biomaterials and nanotechnology-based applications for wound healing, this scientific knowledge has not translated into an increase in commercially available products containing nanomaterials. Future Directions: Further research is essential to provide insight into how scientific evidence of nanotechnology-based therapies can be applied in clinical settings[3].

Spatial and temporal tight regulation of the wound healing process involving various cell types is linked to epigenetic mechanisms in gene regulation, such as DNA methylation, histone modification, and chromatin reshuffling, as well as non-coding RNA. Here, we discuss the epigenetic changes that occur during wound healing and the rapidly growing understanding of how these mechanisms influence healing resolution in acute and chronic wound environments. We provide a focused review of current research regarding epigenetic regulators that contribute to wound healing by specific cell types. We highlight the role of epigenetic regulators in the molecular pathophysiology of chronic wound conditions. Understanding of how epigenetic regulators can affect function during normal and impaired wound healing may lead to new therapeutic approaches, and we highlight questions that can provide guidance for future research into epigenetic-based interventions to promote healing. Understanding the dynamic interactions between cellular subtypes involved in wound healing and epigenetic parameters during barrier repair will enhance our understanding of how to improve healing outcomes in patients affected by chronic non-healing wounds[4].

II. ACUTE AND CHRONIC WOUND HEALING

Skin injuries have a major impact on the global health system, creating a significant burden on the economy and society. In addition, the situation was exacerbated by the low cure rate, which was actually overestimated in the reports. Skin wounds are generally classified into acute and chronic. The immune response plays an important role during acute wound healing. Activated immune cells and factors initiate the inflammatory process, facilitate wound cleansing, and promote subsequent tissue healing. However, dysregulation of the immune system during the wound healing process leads to persistent inflammation and delayed healing, which ultimately leads to chronic wounds. The chronic wound microenvironment is characterized by high numbers of pro-inflammatory macrophages, increased expression of inflammatory mediators such as TNF-α and IL-1β, increased matrix metalloproteinase activity, and abundance of reactive oxygen species. In addition, chronic wounds are often complicated by a bacterial biofilm, which maintains the inflammatory phase. The persistent inflammation and microbial biofilm make healing of chronic wounds extremely difficult. In this review, we discuss the role of innate and adaptive immunity in the pathogenesis of acute and chronic wounds. In addition, we review recent immunomodulatory therapy strategies, including

modification of macrophage phenotype, regulation of miRNA expression, and targeting of pro- and anti-inflammatory factors to enhance wound healing[5].

Skin wound healing is a complex process involving a variety of immune and structural cells, in which the secretion of cytokines, chemokines, and growth factors regulates the stages of healing. Typical wound healing has traditionally been divided into four successive stages: hemostasis, which lasts from a few minutes to a few hours after skin injury, acute inflammation, which lasts 1 to 3 days, proliferation, which usually lasts from a few days to a month, and finally, skin remodeling or scar formation. Tissue damage is followed by rapid vascular contraction to prevent bleeding from vascular injury. Platelets, the main cellular mediators of hemostasis and coagulation, initiate healing as soon as they receive signals from the extracellular matrix (ECM) and local cells[6]. The ECM secretes proteins such as fibronectin, collagen, and von Willebrand factor, which attach to platelet receptors such as glycoprotein 6, thereby forming blood clots. Blood clots consist of platelets embedded in a network of fibrin, fibronectin, vitronectin, and thrombospondin, and are essential for protecting against bleeding. In addition, blood clots protect the injured environment from bacterial invasion and serve as a source of cytokines and growth factors released from activated platelets and necessary for recruitment of immune cells. Release of alpha-granules from platelets results in the release of certain factors, including platelet factor 4 (PF4), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), hepatocyte growth factor, and transforming growth factor-beta 1 (TGF-β1), which is important for the initiation of the inflammatory process. The most abundant component of alpha-granules is PF4, which facilitates neutrophil and macrophage recruitment, monocyte differentiation, and reactive oxygen species (ROS) formation. Platelet-derived TGF-β1 stimulates keratinocyte proliferation and remodeling and regeneration of the epidermal layer[7].

The physiological process of wound healing involves four steps: hemostasis, inflammation, proliferation, and maturation, which work properly and coordinately to ensure proper healing. However, if the wound fails to go through this organized process, healing of the skin tissue is delayed, and eventually leads to a chronic wound. Some common features of non-healing wounds are exudation, recurrent infection, tissue necrosis, incomplete re-epithelialization, decreased angiogenesis, and overproduction of ROS (reactive oxygen species). In general, chronic wounds can be categorized into three main categories: diabetic foot ulcers (DFU), vascular ulcers, and pressure ulcers[8]. These injuries are commonly found in older people who suffer from pathological conditions such as diabetes mellitus, vascular disease, and obesity. Diabetes mellitus affects all four steps in skin wound healing. Diabetic ulcers are associated with a high pro-inflammatory profile due to overexpression of inflammatory cytokines, such as TNF-α, and reduced production of pro-healing mediators, including IL-10 and TGF-β. This leads to polarization of macrophages towards the M1 phenotype, activation and degranulation of CD8+ T cells, resulting in tissue necrosis. Chronic wound healing is characterized by the prolonged presence of myeloid cell populations, such as macrophages, neutrophils, and monocytes, in the late stages of inflammation. In contrast, the percentages of Langerhans cells (LC), dermal cells, and eosinophils decreased during this process. Mastocytes are also involved in the development of chronic wounds. Cutaneous mast cells are degranulated in diabetic ulcers, and decreased activity accelerates wound healing. T cells also play a role in maintaining a pro-inflammatory profile in non-healing skin wounds[9].

III. INNOVATIVE TREATMENT STRATEGIES WOUND HEALING

The wound healing process is a highly specialized and dynamic multiphase process for repairing damaged or injured tissue through complex mechanisms. Failure in the normal wound healing process results in abnormal scar formation and a chronic state that is more susceptible to infection. Chronic wounds affect the quality of life of patients as well as increase morbidity, mortality and a large financial burden on health systems worldwide, thus requiring specialized intensive biomedical care. Clinical evaluation and management of chronic wounds remains a challenge despite the development of various treatment plans, because it requires long-term treatment that requires patience and the complexity of wound healing mechanisms. Various conventional approaches such as cell therapy, gene therapy, growth factor delivery, wound dressings, and skin grafts are used to promote wound healing in various types of wounds[10].

However, all of these therapies are not satisfactory for all wound types, so there is an urgent need for the development of more competitive therapies. Therefore, it is necessary to develop new and innovative

treatment modalities for a comprehensive treatment regimen for chronic wounds. Recent developments in advanced wound care technologies include nanotherapy, stem cell therapy, skin graft bioinjeneri, and strategies based on 3D bioprinting to improve therapeutic outcomes with a focus on skin regeneration with minimal side effects[11]. The main aim of this review is to provide an updated overview of the development of therapeutic options in the healing and management of chronic wounds over the years using innovative next-generation approaches. In this review, we discuss the function and anatomy of the skin, wound processes and wound healing, followed by conventional treatment modalities for wound healing and skin regeneration[12]. In addition, various new and innovative strategies to promote quality wound healing such as nanotherapy, stem cell therapy, 3D bioprinting skin, extracellular matrix based approach, platelet rich plasma based approach, and cold plasma processing therapy have been discussed with their respective advantages and disadvantages. . Finally, the challenges of this innovative strategy are reviewed with notes on future prospects[13].

Currently, effective and quality wound healing is a major challenge for clinicians as well as researchers and also incurs significant costs. This can be proven by the increasing market for global wound care products which reached around 12 billion US dollars in 2020 and is expected to reach 18.7 billion US dollars in 2027. In general, skin wound therapy is divided into "Conventional" or "Regenerative". In conventional wound therapy, healing involves controlling infection by changing bandages (twice daily) and weekly debridement of damaged tissue[14]. Conventional treatment methods for thick or full skin defects include thin-thickness skin grafts. Although such grafts can save lives, there are drawbacks associated with the need for repeated surgical interventions, limited available donor sites, formation of hypertrophic scars, and possible impairment of function. On the other hand, regenerative wound healing uses emerging biomedical research technologies such as smart wound dressings, bioactive biomaterial matrices, stem cell therapy, gene therapy, targeted drug/growth factor delivery, and bioinjury skin grafts to restore skin function after healing and recovery. damaged skin tissue[15]. This regenerative therapy approach allows better quality wound healing without scar formation. Previous approaches to wound healing have focused on regenerating the skin structure layer by layer into two main compartments, the epidermis and dermis, using skin substitutes involving a biological framework or hydrogels encapsulated with cells. Matrixes containing cells encapsulated with keratinocytes, fibroblasts, or various types of stem cells have shown promising results in accelerating wound healing with reduced scar formation. Although this approach is promising because it mimics the biological and morphological features of skin, there is still a lot of scope for improving skin substitutes in terms of cellular composition and spatial distribution to record the complex microarchitecture of native skin tissue[16].

IV. GROWTH FACTORS PROMOTERS OF THE WOUND HEALING PROCESS

Burns can be caused by a variety of factors and carry an increased risk of infection which can seriously hinder the wound healing process. Chronic wounds from burns are a major health problem. Wound healing is a complex process regulated by cytokines, growth factors, prostaglandins, free radicals, clotting factors, and nitric oxide. Growth factors released during this process are involved in cell growth, proliferation, migration, and differentiation[17]. Reactive oxygen species are released in acute and chronic burn injuries and play an important role in healing and regeneration. The main objective of this review is to present the role of growth factors, reactive oxygen species, and metformin in the healing process of burns. Currently, burns are the fourth most common type of injury, caused by several factors, primarily hot water, followed by hot tea or milk, hot objects, hot food, hot oil, chemicals, electricity, sunlight, embers, and fire[18].

Depending on the degree of damage, burns may be treated at home, by a pharmacist, or may require specialized care. Despite the existence of modern health services today, the death rate from burns is increasing every day. Unfortunately, burn patients are at increased risk of developing systemic and skin bacterial infections which can severely impede the wound healing process. Dead tissue and protein-rich exudate are present in the burn wound, providing a suitable environment for microbial development and colonization. When the skin is injured, various cell types such as keratinocytes, fibroblasts, functional cells, and growth factors (GFs) are recruited and involved in wound regeneration[19]. In both humans and animals, a wound can be defined as damage to or disruption of normal anatomical structure and function, which can be in the form of damage to the integrity of the skin epithelium, or it can be deeper, affecting the subcutaneous tissue and damaging several

structures, such as tendons, muscles, blood vessels, nerves parenchyma organs, and bones. Burn-related injuries can be acute or chronic, depending on how long they take to heal. Compared to acute wounds, chronic wounds have a negative impact worldwide, with high medical costs for patients and a higher risk of death. Chronic wounds are venous, arterial, and diabetic ulcers that are usually associated with burns, advanced age, and several systemic and circulatory diseases. Worldwide, diabetic foot ulcers are a major health problem in healthcare[20].

V. CONCLUSION

The review also highlights the role of epigenetic mechanisms in wound healing and the potential for epigenetic-based interventions to improve healing outcomes. The incidence of chronic wounds is increasing due to factors like an aging population and diabetes. Recent advances in nanotechnology and other innovative approaches offer promising strategies for enhancing therapeutic outcomes in wound healing. The wound healing process is a complex multi-phase process that involves various mechanisms and cell types. Failure in the normal wound healing process can lead to abnormal scar formation, chronic wounds, and increased susceptibility to infection. Chronic wounds have a significant impact on patients' quality of life, morbidity, mortality, and healthcare costs. Conventional approaches for wound healing include cell therapy, gene therapy, growth factor delivery, wound dressings, and skin grafts. However, these therapies are not satisfactory for all types of wounds, necessitating the development of new and competitive treatments. Recent advancements in wound care technologies, such as nano therapy, stem cell therapy, bioengineering skin grafts, and 3D bioprinting, show potential for improved therapeutic outcomes with minimal side effects. The review aims to provide an up-to-date overview of advances in therapeutic options for chronic wounds, focusing on innovative next-generation approaches. Epigenetic mechanisms, including DNA methylation, histone modification, and chromatin reshuffling, play a crucial role in wound healing and can influence healing outcomes in both acute and chronic wounds. Understanding the role of epigenetic regulators in cellular functions during wound healing can lead to novel therapeutic approaches.

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REFERENCES

[1] K. Raziyeva, Y. Kim, Z. Zharkinbekov, K. Kassymbek, S. Jimi, and A. Saparov, "Immunology of acute and chronic wound healing," *Biomolecules*, vol. 11, no. 5, pp. 1–25, 2021, doi: 10.3390/biom11050700.

[2] P. Kolimi, S. Narala, D. Nyavanandi, A. A. A. Youssef, and N. Dudhipala, "Innovative Treatment Strategies to Accelerate Wound Healing: Trajectory and Recent Advancements," *Cells*, vol. 11, no. 15, 2022, doi: 10.3390/cells11152439.

[3] D. Miricescu, S. C. Badoiu, I. I. Stanescu-Spinu, A. Ripszky Totan, C. Stefani, and M. Greabu, "Growth factors, reactive oxygen species, and metformin— promoters of the wound healing process in burns?," *Int. J. Mol. Sci.*, vol. 22, no. 17, 2021, doi: 10.3390/ijms22179512.

[4] C. G. Cárdenas-León, K. Mäemets-Allas, M. Klaas, H. Lagus, E. Kankuri, and V. Jaks, "Matricellular proteins in cutaneous wound healing," *Front. Cell Dev. Biol.*, vol. 10, no. November, pp. 1–20, 2022, doi: 10.3389/fcell.2022.1073320.

[5] H. Yu *et al.*, "Landscape of the epigenetic regulation in wound healing," *Front. Physiol.*, vol. 13, no. August, pp. 1–19, 2022, doi: 10.3389/fphys.2022.949498.

[6] I. Gardikiotis, F. D. Cojocaru, C. T. Mihai, V. Balan, and G. Dodi, "Borrowing the Features of Biopolymers for Emerging Wound Healing Dressings: A Review," *Int. J. Mol. Sci.*, vol. 23, no. 15, 2022, doi: 10.3390/ijms23158778.

[7] X. T. Trinh *et al.*, "A Comprehensive Review of Natural Compounds for Wound Healing: Targeting Bioactivity Perspective," *Int. J. Mol. Sci.*, vol. 23, no. 17, 2022, doi: 10.3390/ijms23179573.

[8] Q. Bai *et al.*, "Potential applications of nanomaterials and technology for diabetic wound healing," *Int. J. Nanomedicine*, vol. 15, pp. 9717–9743, 2020, doi: 10.2147/IJN.S276001.

[9] F. Wang, W. Zhang, H. Li, X. Chen, S. Feng, and Z. Mei, "How Effective are Nano-Based Dressings in Diabetic Wound Healing? A Comprehensive Review of Literature," *Int. J. Nanomedicine*, vol. 17, no. May, pp. 2097–2119, 2022, doi: 10.2147/IJN.S361282.

[10] X. Deng, M. Gould, and M. A. Ali, "A review of current advancements for wound healing: Biomaterial applications and medical devices," *J. Biomed. Mater. Res. - Part B Appl. Biomater.*, vol. 110, no. 11, pp. 2542–2573, 2022, doi: 10.1002/jbm.b.35086.

[11] S. Bekeschus, T. von Woedtke, S. Emmert, and A. Schmidt, "Medical gas plasma-stimulated wound healing: Evidence and mechanisms: Mechanisms of gas plasma-assisted wound healing," *Redox Biol.*, vol. 46, no. August, p. 102116, 2021, doi: 10.1016/j.redox.2021.102116.

[12] S. Vitale *et al.*, "Phytochemistry and Biological Activity of Medicinal Plants in Wound," *Molecules*, vol. 27, no. 11, pp. 1–30, 2022.

[13] A. V Ljubimov and M. Saghizadeh, "Progress in corneal wound healing," *Prog Retin Eye Res*, vol. 49, no. 310, pp. 17–45, 2019, doi: 10.1016/j.preteyeres.2015.07.002.Progress.

[14] A. R. Kwilas, R. N. Donahue, K. Y. Tsang, and J. W. Hodge, "Therapeutic Strategies for Enhancing Angiogenesis in Wound Healing," *Cancer Cell*, vol. 2, no. 1, pp. 1–17, 2015, doi: 10.1016/j.addr.2018.09.010.Therapeutic.

[15] I. Pastar *et al.*, "Epigenetic regulation of cellular functions in wound healing," *Exp. Dermatol.*, vol. 30, no. 8, pp. 1073–1089, 2021, doi: 10.1111/exd.14325.

[16] B. Blanco-Fernandez, O. Castaño, M. Á. Mateos-Timoneda, E. Engel, and S. Pérez-Amodio, "Nanotechnology Approaches in Chronic Wound Healing," *Adv. Wound Care*, vol. 10, no. 5, pp. 234–256, 2021, doi: 10.1089/wound.2019.1094.

[17] H. H. Idrus *et al.*, "Molecular impact on high motility group box-1 (HMGB-1) in pamps and damp," *Indian J. Public Heal. Res. Dev.*, vol. 15, no. 4, 2019, doi: 10.5958/0976-5506.2019.02045.X.

[18] H. H. Idrus *et al.*, "Achras Zapota L Extract Reduces Levels of Soluble Tumor Necrosis Alpha (TNF-a) of Salmonella Typhi," in *International Conference on BioMedical Sciences (ICBMS19)*, 2019, pp. 2–8.

[19] H. H. Idrus, M. Mustamin, and Zulfahmidah, "Evaluation of a Multidisciplinary Extracurricular Event Using Kolb's Experiential Learning Theory: A Qualitative Study [Letter]," *J. Multidiscip. Healthc.*, vol. 16, pp. 39–40, 2023, doi: 10.2147/jmdh.s389932.

[20] H. H. Idrus, Sunarno, and S. Rijal, "Detection of Antibiotic Resistance Genes in Pseudomonas aeruginosa by Whole Genome Sequencing," *Infect. Drug Resist.*, vol. 15, pp. 7125–7126, 2022, doi: 10.2147/IDR.S389959.