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Wound Healing and Skin Regeneration: Present Status and Future Directions

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ABSTRACT

Wound healing and skin regeneration involve intricate interactions between various cellular, molecular, and biochemical factors. This narrative review aims to provide an in-depth analysis of the present status of therapeutic strategies for wound healing and skin regeneration. The literature review was performed using the Google Scholar search engine with the help of relevant keywords. Selected publications were used to synthesize different sections of the narrative review. The quest for innovative therapeutic approaches to accelerate wound healing and enhance skin regeneration has led to remarkable advancements in recent years. The landscape of therapeutic approaches for wound healing and skin regeneration is evolving rapidly, driven by groundbreaking discoveries and interdisciplinary collaborations. From advanced wound dressings and growth factor therapies to stem cell-based interventions and gene editing techniques, the arsenal of tools at our disposal continues to expand. As researchers continue to unravel the intricate mechanisms underlying wound repair and regeneration, the potential for transformative therapies to revolutionize patient care remains immense. Through a combination of

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innovative technologies, personalized approaches, ethical considerations, and global accessibility, the future of wound healing holds promise for improving the lives of countless individuals worldwide. Despite significant advancements, several knowledge gaps persist in the field of wound healing and skin regeneration. Further elucidation of cellular and molecular mechanisms governing wound repair, inflammation resolution, and scar formation is warranted. Exploring the crosstalk between wound healing and the microbiome and the influence of ageing and systemic diseases will unravel new therapeutic targets and strategies. As researchers delve deeper into understanding the intricate mechanisms underlying wound repair, the development of novel therapies and their clinical translation become increasingly promising. With a multidisciplinary approach and ongoing advancements in technology, biology, and medicine, the future holds great potential for transforming the field of wound healing and skin regeneration.

1 Introduction

Wound healing is a fundamental physiological process crucial for maintaining tissue integrity and restoring normal function following injury (Gonzalez et al. 2016). Skin plays a pivotal role in protecting underlying tissues and organs from external factors (Herskovitz et al. 2016). Impaired wound healing can lead to chronic wounds, infections, and severe health complications. Over the years, various therapeutic approaches have been developed to promote wound healing and skin regeneration (Frykberg and Banks 2015). This article offers a comprehensive overview of the current landscape of wound healing therapies and envisions the potential directions for future research and development. Wound healing comprises distinct phases, including hemostasis, inflammation, proliferation, and remodelling. Each phase involves orchestrated interactions between immune cells, growth factors, cytokines, and extracellular matrix components (Gonzalez et al. 2016). Therapeutic interventions targeting specific phases aim to expedite healing and minimize scar formation. Traditional approaches, such as wound dressings, antibiotics, and surgical techniques, have paved the way for advanced therapies that harness the body's innate regenerative potential (Kolimi et al. 2022).

Modern wound dressings have evolved beyond basic wound coverage. Bioactive dressings incorporate growth factors, antimicrobial agents, and extracellular matrix components to create a favourable microenvironment for wound healing (Yu et al. 2022). Alginate, hydrocolloid, and collagen dressings have effectively enhanced wound closure and reduced infection risk (Sood et al. 2014). Furthermore, emerging smart dressings equipped with sensors and drug delivery systems enable real-time monitoring and controlled release of therapeutic agents (Pang et al. 2023). Growth factors are crucial in cell proliferation, angiogenesis, and tissue repair (Raica and Cimpean 2010). Topical application or controlled release of growth factors accelerates wound closure and enhances tissue regeneration (Kwon et al. 2006). However, challenges include short half-lives, potential side effects, and dose optimization. Combinatorial approaches and sustained-release formulations promise to overcome these limitations (Kalaydina et al. 2018).

Stem cells have garnered immense interest for their regenerative potential in wound healing (Banu et al. 2023). Mesenchymal stem cells (MSCs) exhibit paracrine effects, immunomodulation, and differentiation capabilities contributing to tissue repair (Bist et al. 2021; Peer et al. 2022; Sivanarayanan et al. 2023). Encouraging results from preclinical studies have paved the way for clinical trials exploring stem cell-based therapies (Sharun et al. 2020; Bist et al. 2021; Peer et al. 2022; Sharun et al. 2022; Sivanarayanan et al. 2023). However, standardization of protocols, ethical considerations, and long-term safety assessments remain crucial challenges. Advancements in biomaterials science have revolutionized wound healing and skin regeneration. Scaffolds, grafts, and skin substitutes composed of natural and synthetic polymers provide structural support, encourage cell adhesion, and facilitate tissue integration (Negut et al. 2020). Decellularized matrices retain native tissue architecture and signalling cues, promoting host cell infiltration and functional tissue restoration. Three-dimensional bioprinting technology enables precise deposition of cells and materials, offering personalized solutions for complex wounds (Liang et al. 2023).

This review article provides an in-depth analysis of the present status of therapeutic strategies for wound healing and skin regeneration, highlighting their mechanisms of action, applications, and limitations. Additionally, it explores emerging trends and future directions in the field, encompassing cutting-edge technologies, biomaterials, and regenerative medicine approaches.

2 Skin

Skin is the largest organ by surface area, covering the entire external surface of the body (Rodrigues et al. 2019). Healthy skin plays a pivotal role in regulating the proper haemostasis of the body. Skin performs an array of functions like protection from external damage and Infection, thermal regulation, and fluid balance of the body. Skin plays a vital role in the production of vitamin D as well as in producing immune responses. Skin also assists in the smooth functioning of the joint by providing flexibility and rigidity wherever required (Sorg et al. 2017). The skin is an essential barrier to protecting from environmental influences like physical, chemical, and mechanical injuries (Bouwstra and Honeywell-Nguyen 2002). The epidermis forms the outermost structure of the skin, containing the keratinocyte layer and skin appendages. The keratinocyte layer forms the railing between the body and the external surface (Shaw and Martin 2009). Skin appendages in the epidermis consist of hair follicles and sebaceous glands (Takeo et al. 2015).

Histological features of the epidermis reveal 4 to 5 layers of stratified epithelium, including stratum corneum, stratum granulosum, stratum lucidum, stratum spinosum, and stratum basale (Strong et al. 2017). Stratum basale forms the basement membrane that separates the epidermis and dermis. The next layer is formed by the dermis, which is composed of fibroblasts, an extracellular matrix, nerves, lymphatics, and blood vessels (Shaw and Martin 2009). The dermis is divided into two layers: the superficial papillary layer and the deep reticular layer. Below the dermis lies the hypodermis, which contains adipose tissue and blood supply. Hypodermis acts as a thermal insulator and powerhouse of energy-supplying skin (Strong et al. 2017). The various skin components like the epidermis, skin appendages, and dermis contain stem cells essential for regulating normal haemostasis and skin regeneration (Ojeh et al. 2015).

3 Wound and types of wound

Loss of skin integrity due to illness or injury leads to cutaneous wounds (Clark et al. 2007). A wound is defined as damage or disruption in the normal skin anatomy. Irrespective of the causative agent, the wound alters the local environment surrounding the wound (Robson et al. 2001). The disruption of skin and the damage to the mucus membrane and organ/tissue is termed a wound (Young and McNaught 2011). Wound management is a critical clinical concern that significantly impacts the patient, their family, and the health care system (Witte and Barbul 1997). No standard system for wound classification exists. Based on the type of injury, the wound can be incised, sheared/de-gloving, crushed, burns, or contaminated wounds. Based on timing, the wounds are of three types: acute, early, and chronic wound. Acute wounds are less than 6 hours of age, early wounds are those that are less than 24 hours of age, and chronic wounds are those that are more than 24 hours old.

Based on depth, the wound can be either superficial or deep dermal wound. The wounds that are restricted only to the epidermis and papillary dermis fall under superficial wounds. Deep dermal wounds can be either partial-thickness or full-thickness wounds. A partial-thickness wound affects the deep layers of skin but does not involve whole skin layers. When a wound involves complete skin layers, including hypodermis, then such a wound is classified as a full-thickness wound (Percival 2002). Another important type of wound is a surgical wound. Depending on the level of gross contamination, surgical wounds can be categorized as clean, clean-contaminated, contaminated and dirty (Onyekwelu et al. 2017). The potential factors influencing the gross contamination of surgical wounds are the location of injury, presence or absence of acute inflammation, failure in aseptic technique, and Infection at the surgical site (Zinn 2012).

4 Wound healing

Wound healing is a complex process that aims to restore the injured/damaged tissue to normal. It involves the synchronized orchestration of sequential cellular and molecular events (Gonzalez et al. 2016). Cutaneous wound healing is a unique procedure involving the participation of various components like growth factors, cytokines, and many other cells. The target of physiological wound healing is to restore the integrity of damaged tissue. All wound healing procedures are mostly limited to wound repair only (Tottoli et al. 2020). Wound healing directs the activation and recruitment of various cells to the site. Therefore, any alteration in the immediate microenvironment, like the oxygen tension, chemokines, extracellular matrix, growth factor synthesis, and mechanical forces, can result in aberrant wound healing (Rodrigues et al. 2019). Wound healing has four phases: haemostasis, inflammatory, proliferative, and tissue remodelling (Figure 1) (Li et al. 2007). The inflammatory phase is the immediate phase following an injury and haemostasis that alarms to stop the damage. It involves cutaneous neurogenic inflammation and platelet haemostasis. Following an injury, the nociceptive receptors in the skin will activate and act via the peripheral nervous system to initiate vasoconstriction and inflammation.

Vasoconstriction is followed by vasodilation due to the release of factors like the substance P. This causes an increase in blood flow to the sites, increases vascular permeability, oedema, and recruitment of inflammatory white blood cells (WBCs) to the site. Ultimately, the injured area will have redness and swelling by the end of the inflammatory phase (Cañedo-Dorantes and Cañedo-Ayala 2019). The primary goal of the proliferative phase is the closure of the wound and reduction in the size of the wound. This phase lasts from 48 hours to the 14th day after injury. The various events in this phase include angiogenesis, fibroplasia, and re-epithelialization. As a result of angiogenesis, the injured site will be covered with newly formed microvasculature. Fibroplasia follows the beginning of granulation. Fibroblast proliferates and produces collagen. Wound contraction also occurs simultaneously in this phase due to the action of myofibroblasts and as a result of fibroplasia. The hedgehog signalling pathway, responsible for differentiating endothelial cells into mesenchymal components, also occurs in this phase (Gonzalez et al. 2016).

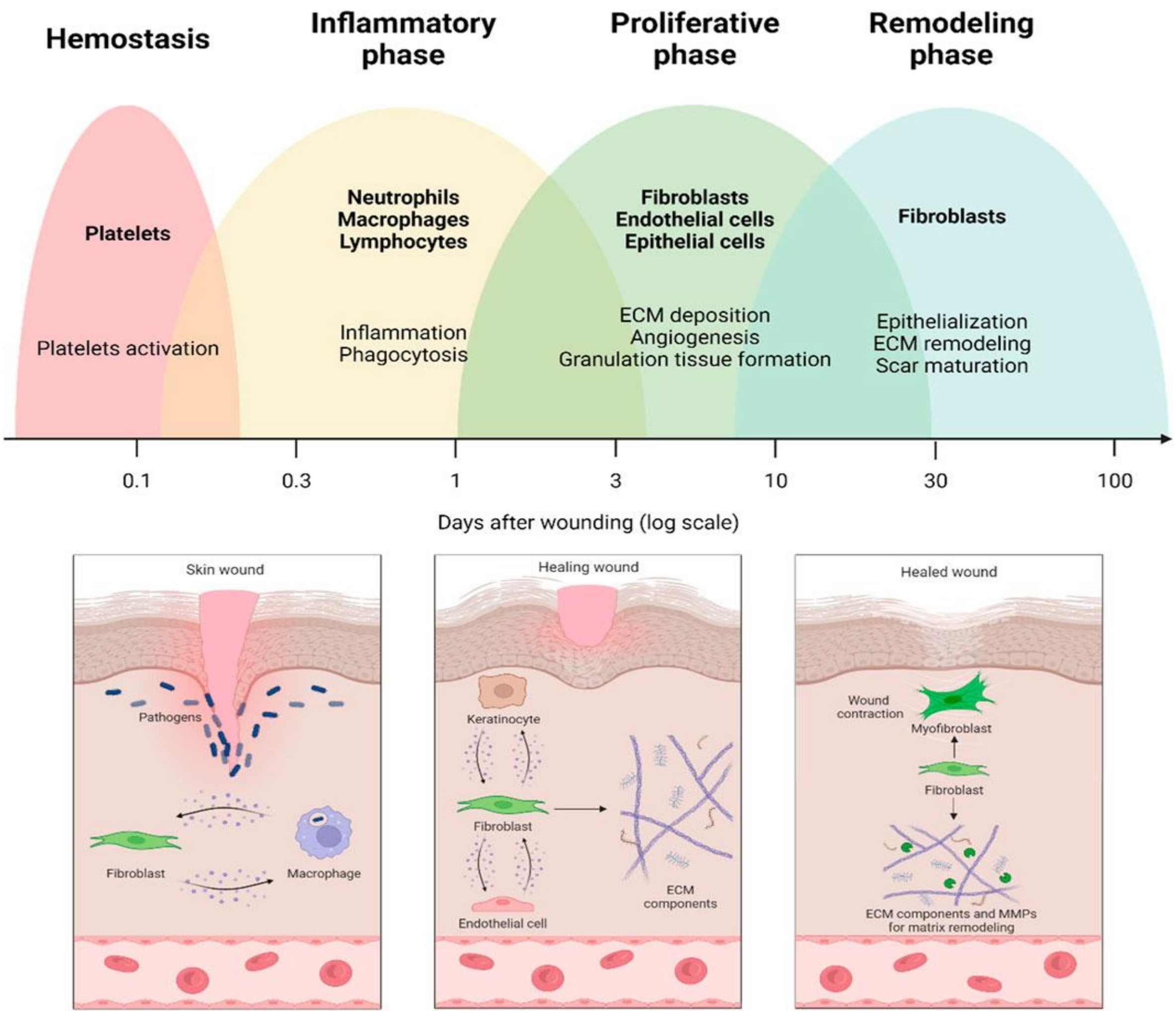

Figure 1 The wound healing process involves distinct phases, with fibroblasts playing a pivotal role. In the initial stages of wound healing, intricate communication takes place between fibroblasts and immune cells. Subsequently, fibroblasts synthesize key components of the extracellular matrix (ECM) while establishing communication channels with endothelial cells and keratinocytes. As the healing process progresses, fibroblasts contribute to the remodelling of the ECM through the secretion of matrix metalloproteinases (MMPs) and other matrix constituents. The figure was reproduced from Cialdai et al. (2022) under the Creative Commons Attribution License (CC BY) terms.

The remodelling phase aims to develop normal skin tissue and maturation of the scar. A balance between collagen synthesis and degradation accomplishes this phase. Nevertheless, the tissue achieves original strength, but approximately 80% of wound strength is achieved following long-term wound healing. Nutrition, hypoxia, chronic inflammation, Infection, and immunosuppression are important factors that influence wound healing. Therefore, a thorough understanding of the physiological events and factors affecting wound healing is necessary to reduce the morbidity and mortality of wounds (Singh et al. 2017).

5 Wound management

For achieving optimum wound healing, the foremost consideration is maintaining an aseptic state during wound care and using suitable antiseptics to lower the infection rate if the wound has been doubtful about its contamination. The chosen wound management method is also essential to minimize tissue necrosis. The wound management begins with providing adequate haemostasis, followed by further techniques like applying pressure bandaging. Finally, the traditional use of caustic and cauterization agents applied over the wound is replaced mainly with topical collagen, gelatin, thrombin, etc. (Brown and Zitelli 1993). According to Anderson (1996), there are six essential points to be considered while managing any wounds: preventing further wound contamination, debridement of necrotizing tissue, eliminating debris, foreign contaminants, and adequate wound drainage, ensuring the formation of a healthy vascular bed and selection of an effective method for closure of skin defect.

The underlying principle of wound management is to optimize the environment for wound healing. The treatment modality of wounds mainly depends on the size and type of wound. The initial procedure for wound management is decontamination, followed by debridement. These procedures allow for eliminating both infections and removing dead and devitalized tissues. The outcome of wound management aims to form a sound and viable wound bed that ensures wound closure (Anderson 1996). The wound healing rate, tissue return to normal function, final appearance, client satisfaction, etc., will ultimately depend on how the wound is managed. It also has miscellaneous topical applications of various agents like Aloe vera gel, honey, live yeast cell derivatives, etc. In addition, growth factors like epidermal growth factors and epidermal growth factors like peptide GF, PDGF, and TGF potentially enhance wound repair (Liptak 1997).

6 Factors Affecting Wound Healing

Impaired wound healing results from several factors that can participate in one or more phases of the wound repair process. Guo and DiPietro (2010) broadly classified these factors as local and systemic factors affecting wound healing.

6.1 Local factor

The local factors affecting wound healing include oxygenation, Infection at the wound site and high levels of metalloproteinases (MMPs).

6.1.1 Oxygenation

Oxygen is essential for preventing wound infection, inducing angiogenesis, keratinocyte differentiation, collagen synthesis, re-epithelization, and allowing normal wound contraction. Conversely, inadequate oxygenation induces temporary hypoxia and impairs wound healing (Rodrigues et al. 2019), and such impaired wounds result in the formation of chronic or ulcerated wounds.

6.1.2 Infection

Inflammation is the first phase in the process of normal wound healing. This process is essential to remove all the contaminating microorganisms. If there is a failure to effectively decontaminate the wound, the inflammation process will get prolonged along with improper microbial clearance. In the absence of an incomplete inflammatory process, there will be a prolonged elevation of pro-inflammatory cytokines such as interleukin-1 (IL-1) and TNF-α. This prolongs the inflammatory phase and increases the level of matrix metalloproteases (MMPs), a group of proteases that can degrade the extracellular matrix. In relation to the increased protease content, there will be a decrease in the level of protease inhibitors that occurs and results in chronic wounds (Menke et al. 2007).

6.1.3 Metalloproteinases

Elevated levels of MMPs, a group of enzymes capable of breaking down the ECM, coincide with a reduction in natural protease inhibitors. This shift in the protease balance can hasten the degradation of growth factors present in chronic wounds (Menke et al. 2007). Infections in wounds follow a pattern akin to other infectious processes, manifesting as biofilms—complex communities of aggregated bacteria encased in a self-produced extracellular polysaccharide matrix. Fully developed biofilms create shielded microenvironments, rendering them more resilient to typical antibiotic treatments (Guo and DiPietro 2010).

6.2 Systemic factors

The systemic factors affecting wound healing include the animal's age, stress, diabetes, sex hormones, medication, obesity, nutrition, etc.

6.2.1 Age

The risk of impaired wound healing increases with age. In healthy elderly individuals, there is a delay in wound healing without altering the quality of wound healing (Gosain and DiPietro 2004). This delay is thought to be due to decreased macrophage function and reduction in the inflammatory response associated with old age (Swift et al. 2001).

6.2.2 Sex hormones

Sex hormones in aged individuals affect wound healing either positively or negatively. For example, it is observed that estrogen improves age-related impairment in wound healing, whereas androgens negatively influence cutaneous wound healing (Gilliver et al. 2007).

6.2.3 Stress

Studies suggest that there is stress-induced alteration occurs in the normal wound healing process by reducing the function of the immune system (Boyapati and Wang 2007).

6.2.4 Diabeties

The alteration of healing in diabetes individuals occurs due to hypoxia, fibroblasts and epidermal cell dysfunction, deviation of angiogenesis and neovascularization from normal, increased metalloproteases levels, reactive oxygen species induced damage, decrease in the immune resistance and neuropathy (Guo and DiPietro 2010).

6.2.5 medication

Different medications, such as glucocorticoids, NSAIDs, chemotherapeutic agents, etc., can affect the normal wound healing process. Systemic steroids are often used as an anti-inflammatory in wounds but can contribute to incomplete granulation tissue and reduced wound contraction (Franz et al. 2007). It also increases the risk of Infection. NSAIDs are also widely used agents in the treatment of wounds. However, short-term usage of NSAIDs has a less negative impact on wound healing, whereas long-term use causes anti-proliferative effects and impairs wound healing (Guo and DiPietro, 2010). Chemotherapeutic agents inhibit DNA, RNA, and protein synthesis, reducing fibroplasia and wound neovascularisation (Franz et al. 2007).

6.2.6 Obesity

Mostly, this will alter the functioning of the immune system and lower inflammatory response, thereby impairing the normal wound repair process.

6.2.7 Alcohol and smoking

These habits are found to have a negative impact on wound healing but are the least concern in veterinary practice.

6.2.8 Nutrition

Energy, fat, proteins, amino acids, micro-nutrients, etc., greatly influences the normal wound healing process. Energy sources provide the glucose precursor required for ATP synthesis and are essential for cellular repair. Protein is the most important nutrient needed for the normal wound-healing process. Among all the nutrients, micronutrients like vitamins and minerals have more influence on wound repair. Any inadequacy in the level of these nutrients alters the normal repair mechanism. For example, vitamin C and A deficiency impair re-epithelization, normal collagen synthesis, etc., whereas an excess of vitamin E impairs healing. A lower zinc level is essential for normal wound healing, but excess levels negatively affect healing (Guo and DiPietro 2010).

7 Dressing materials in wounds

Wound dressings have evolved through extensive development in recent years (Figure 2). In ancient times, dressing material was restricted to traditional natural products covered over the wound directly. But, over the years, there were significant changes, and newer dressing materials were developed to achieve specific functions (Zahedi et al. 2010). Recent studies suggested that simple gauze dressings are unsuitable for all types of wounds because the gauze absorbs all the moisture and exudates and can dry the wound environment. This causes further damage while the wound dressing is being replaced (Kucharzewski et al. 2019). The property of an ideal wound dressing material includes the capacity to attain rapid healing, low cost, and maximum comfort to the patient. There are several ways for the classification of wound dressing materials. Based on the functions of the dressing material used, it can be classified as debridement, antibacterial, occlusive, absorbent, or adherent dressing.

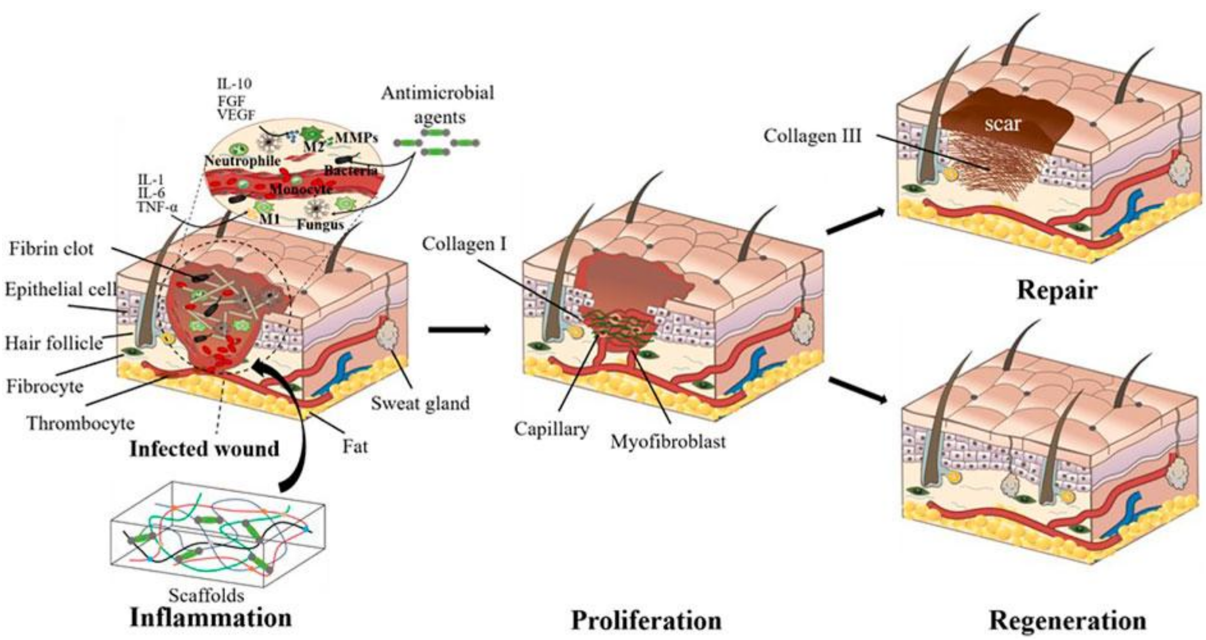

Figure 2 Tissue-engineered scaffolds have emerged as a promising approach for treating cutaneous wounds. Currently, wounds are addressed using two main types of scaffolds: conventional biological scaffolds and pro-regenerative counterparts. While both scaffold types contribute to wound healing, the pro-regenerative scaffolds exhibit a greater capacity for fostering complete and well-structured skin regeneration. In contrast, traditional biological scaffolds often result in the formation of scar tissue. The figure was reproduced from Qin et al. (2022) under the Creative Commons Attribution License (CC BY) terms.

Based on the materials used to produce the dressing they can be hydrocolloid, alginate, or collagen dressing. Depending on the physical form of the dressing material, it can be in the form of an ointment, film, foam, gel, etc. One of the important classifications of dressing is based on the physical contact that the dressing material makes with the wound. Dressings making direct contact with the wound surface are called primary dressings. Secondary dressings are those that are applied over the primary dressing. Island dressings exhibit an absorbent area at the centre of the dressing material surrounded by an adhesive region. The most commonly used dressing material classification is traditional, modern, advanced dressings, skin replacement material, and wound healing devices (Boateng et al. 2008).

The foremost function of dressing material is to protect the wound and provide the ambient environment for healing so that dressing material can contribute to cutaneous repair. There are various synthetic and natural dressing materials with satisfactory results. The natural dressing includes polysaccharides (chitin, chitosan, etc.), proteoglycans, and proteins (collagen, gelatin, eggshell membrane, etc.). The biocompatibility, biodegradability, and similarity with extracellular matrix contribute to the extensive use of natural dressing material. Synthetic dressing materials are obtained by electrospinning technique and are designed to exhibit specific and extraordinary functions. Examples of synthetic dressings include bio-mimetic micro/nanoscale fibres (Mogoşanu and Grumezescu 2014).

8 Eggshell membrane in wound healing

Many bio-materials, which are capable of managing wounds, have been developed. They help protect against microbial contamination and are also used to deliver therapeutic agents. Eggshell membrane (ESM) is a highly produced global waste that has potential applications in various fields (Banu et al. 2023). ESM is a thin layer of 100µm thickness lying between the eggshell and egg albumen. It is a double-layered membrane that has a light pink colour. ESM has a semi-permeable structure. The porous architecture is contributed by the peculiar arrangement of protein fibres (Mittal et al. 2016).

Structurally ESM is composed of 3 layers: outer ESM, inner ESM, and limiting membrane. The ESM can be separated by manual peeling, acid treatment, or dissolved air flotation (Yoo et al. 2009). ESM is composed of both organic and inorganic matrices. The organic components are proteins, including collagen (type I, V, X), osteopontin, keratin, proteoglycan, and glycoprotein (Sah and Rath 2016). The other important chemical constituents of ESM include glucosamine, chondroitin, hyaluronic acid, ovotransferrin, desmosine and isodesmosine, sialic acid, lysyl oxidase, lysozyme, β-N-acetylglucosaminidase (Ruff et al. 2009). ESM constitutes a protein network composed of collagen I, V, X, etc., which is responsible for enhanced tissue regeneration (Guha Ray et al. 2018). Tavassoli (1983) has established the biocompatibility of ESM with stromal cells. ESM exhibits properties that alter the quality and rate of wound healing (Amitha et al. 2023; Banu et al. 2023).

9 Fibrin glue

Fibrin glue is a tissue sealant that has been widely used as an adjunct to haemostasis for many years (Mooney et al. 2009). However, over decades, the significant functions of fibrin glue have been limited to being a tissue sealant and an agent for controlling bleeding. But recently, the potential of fibrin glue has been widely exploited as a drug delivery system. The use of fibrin glue as an agent for drug delivery involves effective drug-matrix interaction and controlled drug release (Spicer and Mikos 2010). The fibrin glue can be prepared either from PRP or by combining concentrated fibrinogen solutions with thrombin (Silver et al. 1995). Human fibrin glue comprises two different components contained in separate vials. This component includes freeze-dried clotting proteins (fibrinogen, fibronectin) and freeze-dried thrombin, which act as catalysts. The clotting factors are reconstituted in a solution containing aprotinin to inhibit tissue fibrinolysis. The thrombin portion is dissolved in a calcium chloride solution. These components play an inevitable role in haemostasis and wound healing.

The mechanism of action is through its capability to mimic the physiological coagulation process, serving its haemostatic and sealing action. Moreover, it evokes bio-stimulation that directs the formation of new tissue (Canonico 2003). When injected at the desired site, the two components club together in equal volumes, where the thrombin gets converted into the fibrinogen to fibrin. An enzymatic reaction mediates the conversion, and the rate of reaction is controlled by the thrombin concentration. Spotnitz et al. (1997) compared suture technique and fibrin sealant application and concluded that fibrin sealant is a suitable biological tissue glue that can effectively function as a potent adjunct to sutures. Fibrin sealant can be used alone or with sutures or tape to promote optimal wound integrity. In addition, these fibrin sealants can be used independently in wounds where sutures cannot control or aggravate bleeding. These adhesives' advantages include sealing tissue planes and eliminating potential dead spaces. It is interesting to notice that fibrin sealant has resulted in a low infection rate and has promoted healing. The effectiveness of fibrin glue dramatically depends on the intended surgical use. The fibrin glue causes a reduction in drainage and seroma formation, but these animal studies are not well predictive for clinical usage. Moreover, application methods like spraying or applying on a stream will significantly influence the effectiveness of fibrin glue. The major drawback with commercial preparation is that the constituent and outcome of fibrin glue may vary considerably (Clark 2003).

Fibrin glue has been proven to potentiate wound-healing effect on oral cavity wounds compared with traditional sutures (Yucel et al. 2003). Fibrin adhesives are highly useful for averting leakage and promoting healing in conditions like complex gastrointestinal surgeries, especially with intestinal anastomosis. The stumbling block of fibrin sealant application in such conditions is due to the high cost of these products. Fibrin glue has also been found to have osteoinductive potential (Abiraman et al. 2002). Takagi et al. (2001) established the prospects of using fibrin glue in tracheal anastomosis. Topical application of BM-MSCs and their conditioned media via fibrin glue vehicle effectively improved the quality of cutaneous wound healing in chronic excisional wounds in rats without any marked acceleration at the rate of wound closure (Mehanna et al. 2015).

10 Animal models for wound healing studies

In vitro and in vivo models have primarily contributed to the understanding and studying of the physiologic model and aberrant wound healing mechanism (Parnell and Volk 2019). The criteria for selecting an animal model include inter-species anatomical considerations and physiological attributes, differences in wound healing mechanisms among different animals, sample size, and analytical techniques applied for the study (Lindblad 2008). The other factors influencing the selection of an animal model for wound studies are availability, cost, ease of handling, and investigator familiarity. Small mammals are commonly used for wound healing and studies (Sullivan et al. 2001). Full-thickness wound models are the ones that are created by the complete removal of the epidermis, dermis, fascial planes, and even subcutaneous fat. Healing starts from the margins and progresses to the base of the wound.

The formation of the fibrin clot will be followed by the infiltration of granulation tissue and the migration of an epidermal tongue along the interface between the granulation tissue and the clot. This type of wound is created using standard equipment like a biopsy punch, scalpel, and dermatome. The major advantages of this model are a significant wound volume involving all dermal layers, epithelialization occurring from the margin of the wound, and the provision to assess chemistry, histology, and cell population within the wound site. The rate of wound healing is usually monitored through re-epithelialization rate, histological organization of connective tissue, angiogenesis, and extent of collagen or proteoglycan deposition. The major demerits of this model are excess bleeding and an increased chance of infections (Davidson 1998). Rabbits are widely used as experimental models in wound healing studies. Rabbits are loose-skinned animals where wound healing occurs primarily by contraction. The merits of this model are relatively inexpensive and highly prolificacy.

11 Assessment of wound healing

Wound healing studies are complex processes that integrate various cells and consist of various repair phases, such as inflammation, proliferation, re-epithelialization, and remodelling. The wound healing assessment can be done through non-invasive and invasive methods. The non-invasive protocols for wound healing estimation are done through wound tracing, photographic evaluation, biophysical techniques, etc. The invasive protocols require wound biopsies involving histopathological, biochemical, and immunological techniques of wound evaluation (Masson Meyers et al. 2020). Evaluation of wound healing is done generally through measurement of the size of the wound, morphological appearance of the wound, including wound bed and its relationship with tissue growth, the extent of scarring noticed, as well as vascular and pathophysiological conditions that may interfere with the healing (Falanga 2005). The use of digital photography and image analysis software helps in the assessment of healing and provides accuracy in choosing treatment protocols. This also helps monitor patients' treatment responses (Papier et al. 2000).

Histopathology of wounds is a useful tool that helps exclude malignancy, evaluate healing progress during treatment, and understand the pathophysiology of non-healing wounds (Romanelli et al. 2013). In the immunological method of wound healing estimation, signalling molecules involved in the repair process are identified and quantified with the help of several techniques like immunohistochemistry and enzyme-linked immunosorbent assay (Carlson and Longaker 2004). The biochemical assays employed for wound healing assessments are hydroxyproline, myeloperoxidase (MPO) assay, N-acetylglucosaminidase (NAG), oxidative stress profile, etc. These are very helpful to monitor the progression of wound healing. One commonly employed assay is the hydroxyproline assay, which indirectly indicates collagen content and thereby comments on wound healing. An increase in the hydroxyproline content shows that there is an increased deposition of collagen. The higher the collagen synthesis and deposition, the more enhanced wound healing will be. Techniques like flow cytometry and macrophage polarization are used for wound healing assessment (Masson Meyers et al. 2020).

12 Conclusion and prospects

The wound healing and skin regeneration field has witnessed remarkable progress, driven by interdisciplinary collaborations and innovative technologies. Advanced wound dressings, growth factors, stem cell therapies, biomaterials, and gene editing tools have transformed the treatment landscape. While challenges persist, including standardization, safety, and ethical concerns, the convergence of cutting-edge approaches holds immense potential to revolutionize wound care and improve patient outcomes in the coming decades. In conclusion, therapeutic approaches for wound healing and skin regeneration have evolved significantly, offering innovative strategies to accelerate healing and promote tissue regeneration. As researchers delve deeper into understanding the intricate mechanisms underlying wound repair, the development of novel therapies and their clinical translation become increasingly promising. With a multidisciplinary approach and ongoing advancements in technology, biology, and medicine, the future holds great potential for transforming the field of wound healing and skin regeneration.

The era of personalized medicine is revolutionizing wound healing and skin regeneration. Advances in genomics, proteomics, and metabolomics enable the identification of patient-specific factors influencing wound healing outcomes. Biomarker profiling facilitates early diagnosis, prognosis, and treatment selection for optimal therapeutic responses. Pharmacogenomics guides drug selection and dosing, minimizing adverse effects and improving efficacy. Integrating patient-specific data with regenerative therapies empowers clinicians to tailor interventions, optimize wound healing trajectories, and enhance patient outcomes. Translating novel therapeutic approaches from bench to bedside requires rigorous preclinical studies and adherence to regulatory guidelines. Safety assessments, pharmacokinetics, and long-term outcomes must be thoroughly evaluated before embarking on clinical trials. Regulatory agencies play a critical role in ensuring the ethical and safe conduct of research, particularly in the context of gene editing, stem cell therapies, and novel biomaterials.

While wound healing and skin regeneration are poised for remarkable advancements, several challenges and ethical considerations warrant attention. Long-term safety assessments of emerging therapies are paramount to mitigate unforeseen risks and adverse effects. Standardizing protocols, outcome measures, and patient selection criteria is essential to ensure consistent and reproducible results across clinical trials. Additionally, ethical considerations surrounding gene editing, stem cell research, and human experimentation require thoughtful discourse and guidelines to balance scientific progress with societal and moral values. Wound healing therapies must be scientifically robust, economically feasible, and globally accessible. Developing nations face unique challenges in wound care, including resource limitations and healthcare disparities. Innovations in low-cost wound dressings, telemedicine, and community-based care models can bridge the gap and improve wound healing outcomes on a global scale. Collaborative efforts between researchers, clinicians, policymakers, and non-governmental organizations are pivotal in ensuring equitable access to cutting-edge wound healing technologies.

Despite significant advancements, several knowledge gaps persist in wound healing and skin regeneration. Further elucidation of cellular and molecular mechanisms governing wound repair, inflammation resolution, and scar formation is warranted. Integration of advanced imaging modalities, such as multiphoton microscopy and single-cell RNA sequencing, will provide unprecedented insights into dynamic cellular processes. Exploring the crosstalk between wound healing and the microbiome and the influence of ageing and systemic diseases will unravel new therapeutic targets and strategies.

Ethical approval

Not applicable.

Data statement

The authors confirm that the data supporting the findings of this study are available within the article.

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Declaration of Interest

All authors declare that no commercial or financial relationships exist that could, in any way, lead to a potential conflict of interest.

Authors' contribution

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