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Recent Approach for Speeding up the Wound Healing

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Abstract

Healing wounds is an important physiological process in the body followed by trauma, burn injuries, post-surgery complications or different diseases that can damage the skin and tissues. Millions of people struggle with their healing process every year and some of them pass away according to the World Health Organization (WHO). Wound healing is done by different processes that are divided into hemostasis/inflammation phase, proliferation phase, and remodeling phase. The pathophysiology of these processes and the factors affecting them is explained. There are two general factors including systemic and local factors contributing, both explained in this research. Many resources have been reviewed regarding the factors that can enhance the healing process. All the information collected to fulfill one of the important purposes of this research. The enhancing factors which are discussed include therapeutic strategies for enhancing angiogenesis in wound healing like using growth Factors, Non-Growth Factor Protein Delivery, gene, and nucleic Acid-Based therapies for wound angiogenesis. Stem cells therapy one of the most recent topics that is being researched a lot in the wound healing subject and potentially gives hopes to healing enhancement, although more clinical trial and experiments need to be done especially on the human body to be able to get more specific results, hopefully can be proved and used to benefit the people who suffer from this problem around the world.

Keywords: Wound Healing; Wound Angiogenesis; Fast Wound Healing; Growth Factors; Stem Cells Therapy

Abbreviations: WHO: World Health Organization; ER: Emergency Room; Extracellular Matrix; TGF: Transforming Growth Factor; EGF: Epidermal Growth Factor; ROS: Reactive Oxygen Species; NO: Nitric Oxide; MMP: Matrix Metalloproteinases; DHT: Dihydrotestosterone; DHEA: Dehydroepiandrosteron; GC: Glucocorticoids; MMPs: Metalloproteinases; EPC: Endothelial Progenitor Cells; AS-IV: Astragaloside IV; Mscs: Mesenchymal/Stromal Stem Cells; SVF: Stromal Vascular Fraction.

Introduction

Wound healing is a vital physiological process for preserving skin integrity following trauma, whether accidental or intentional [1].

Every year, millions of people have scars because of skin injuries following surgery, trauma, or skin burns. Significant unfavorable physiological and psychological repercussions follow these skin injuries. More than 11 million burn injuries are recorded annually in the world, according to the World Health Organization [2].

According to the World Health Organization, 5.8 million individuals pass away from injuries each year [3].

Traumatic wounds (injuries that result in wounds) range from abrasions and minor skin cuts or rips to wounds that

result in substantial tissue loss or damage, as well as harm to bone and internal organs [3].

The mechanism of the injury affects how much tissue damage occurs. Traumatic wounds can be brought on by animal bites, crush injuries, blast injuries, burns, degloving injuries (when a large amount of skin gets torn from the deeper tissues), and penetrating injuries (like stabbings and gunshots). The requirement for immediate assessment and management of concurrent severe, life-threatening injuries frequently dictates the necessity for early management of traumatic wounds [3].

Our skin, a highly adapted, multifunctional organ that shields us against a daily onslaught of chemical, physical, and ultraviolet radiation challenges, was produced via millennia of evolution. It should hence be no surprise that our skin has sophisticated reparative systems that enable it to heal fast and effectively. The harsh external environment frequently causes injuries to the skin. Despite having a strong natural capacity for repair, a person's injury response could become compromised in many ways at the cellular level, impairing wound healing. The pathological alterations in the body that are most frequently the cause of this attenuation include those brought on by uncontrolled diabetes or senior age. Indeed, the two main risk factors for having a chronic wound are age and diabetes (i.e., a wound which takes more than 12 weeks (about 3 months) to heal Unfortunately, there is a large clinical need for treatment for these chronic wounds, which mostly include venous ulcers, pressure sores, and diabetic foot ulcers. They are also significantly worsening globally. Our skin is designed specifically to interact with the outside world and performs several crucial homeostatic tasks, such as controlling thermostability and perceiving external stimuli. Importantly, the skin serves as a major defense barrier, guarding against mechanical, chemical, thermal, and photic harm to internal tissues as well as desiccation [4].

Wound healing is a crucial but challenging process that involves several overlapping but sequential phases, including hemostasis/inflammation phase, proliferation phase, and remodeling phase [1]

Following a skin injury, the exposed sub-endothelium, collagen, and tissue factor stimulate platelet aggregation, which leads to degranulation and the release of chemokines (chemokines) and growth factors (GFs), which form the clot [1].

The first cells to show up at the site of an injury, neutrophils clear away debris & bacteria to provide a favorable environment for wound healing. Following, macrophages gather, aid in the phagocytosis of germs, and cause tissue damage [1]

Typically, the hemostasis & inflammatory phase lasts 72 hours (about 3 days). The accumulation of many cells and an abundance of connective tissue are characteristics of the subsequent proliferative phase. Fibroblasts, keratinocytes, even endothelial cells are present in the wound. To replace the initial clot formation, the extracellular matrix (ECM), which contains proteoglycans, hyaluronic acid, collagen, & elastin, produces granulation tissue [1].

The remodeling phase, which comes after the apoptosis of existing cells but before the synthesis of new cells, is the final stage of wound healing. This phase, which lasts for a few months or years, is crucial for the gradual breakdown of the abundant ECM and the immature type III collagen and the development of the mature type I collagen. Any deviation during this phase could result in chronic wounds or excessive wound healing [1].

Trauma affects millions all over the world, these traumatic injuries often have severe outcomes such as infection, sepsis and even mortal outcomes, hence it is important to know factors which can help with increasing the speed of the normal physiological aspects of wound healing, as well as target all types of wounds we see on a day to day basis from homes to the emergency room (E.R), in order to come up with a faster and much more effective treatment plan benefitting most of the ER physicians, trauma facilities, paramedics and rescue teams, and overall patients.

Pathophysiology

The time of acute injury will herald the start of the wound healing process, the initial response to injury that causes damage to the blood vessels and extravasation of red blood cells from the intravascular space, is hemostasis to prevent exsanguination from vascular damage [5]. This is achieved by vascular contraction and by formation of a fibrin clot. Platelets are the principal cell type involved in hemostasis and fibrin clot formation; they are activated by vascular endothelial damage. The surface receptors on the platelets interact with the extracellular matrix proteins (fibronectin, collagen and von Willebrand factor), inducing the cascade that eventually leads to the coalescing of platelets to form an insoluble clot (eschar) of fibrin, fibronectin, vitronectin and thrombospondin forms [4]. Although the most basic function of this clot is to prevent bleeding, it also serves as protection from bacterial invasion into the bloodstream, acts as a scaffold for incoming immune cells and releases proinflammatory cytokines such as transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF) to attract immune cells to the area of injury [4]. After a brief period of vasoconstriction, vasodilation occurs

which will cause local hyperemia and edema [6].

Once bleeding is controlled there are 3 main phases of the wound healing process that proceed.

Inflammation

Innate inflammation is the primary defense against pathogenic inflammation and is characterized by the sequential infiltration of neutrophils, macrophages, and lymphocytes [7]. The proinflammatory such as mast cells, Langerhans cells, T cells and macrophages, are activated by the release of damage-associated molecular patterns (DAMPs) by necrotic cells and damaged tissue, and pathogen-associated molecular patterns (PAMPs) from bacterial components. As well as acting as chemoattractant signals for proinflammatory cells, these proinflammatory molecules enhance vasodilation which, along with the expression of endothelial cell adhesion molecules, such as selectins, facilitates neutrophil and monocyte adhesion and diapedesis [4]. Neutrophils being the initial recruits to the injured area, arrive within the first 24 hours and persist for 2 to 5 days, the chemotactic movement is mediated by the release of interleukin 1 (IL-1), tumor necrosis factor-alpha (TNF-α) and bacterial endotoxins, such as lipopolysaccharide (LPS) [4]. They initiate phagocytosis which serves to kill local bacteria and debride necrotic tissue and is mediated by the release of reactive oxygen species (ROS). Phagocytosis is then continued by macrophages.

Macrophages, which are induced by LPS and interferon-gamma (IFN-γ), play a number of roles in the inflammatory phase, with their primary role being phagocytosis. They clear apoptotic cells (including neutrophils), replacing them as the primary inflammatory mediator and initiating the transition out of the inflammatory phase. These macrophages, as they phagocytose the apoptotic cells, transition to a reparative state that stimulates keratinocytes, fibroblasts, and angiogenesis to promote tissue regeneration [7-9]. Macrophages also play a role in the release of proinflammatory cytokines that recruit and activate additional leukocytes early in the inflammatory phase [7]; later in the inflammatory phase, they also enhance their anti-inflammatory role by releasing growth factors that promote re-epithelialization, fibroplasia, and angiogenesis [4].

Although neutrophils and macrophages are the principal characters involved in the inflammatory phase of wound healing, the role of T cells in this phase cannot be ignored. Circulating T cells are recruited to resolve inflammation and peak during the late-proliferative/early-remodeling phase. The precise role of the T cell in this process has not been delineated, however studies have shown decreased T cell concentration and delayed T cell infiltration to be associated with impaired wound healing [7].

Proliferation

This phase, which begins approximately 3 to 10 days (about 1 and a half weeks) after injury, is characterized by formation of granulation tissue and restoration of the vascular network, through activation of keratinocytes, fibroblasts, macrophages, and endothelial cells, with the predominant cells being fibroblasts [4,6]. This process is mediated by various cytokines and growth factors, such as transforming growth factor-beta family (TGF-beta, including TGF-beta1, TGF-beta2, and TGF-beta3), interleukin (IL) family as well as angiogenesis factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor-basic (bFGF) and the serine protease thrombin in order to provide adequate perfusion during cell proliferation.

Vascular restoration takes place through two methods: Angiogenesis and Vasculogenesis. Angiogenesis is a process where new vessels sprout from the endothelium of the adjacent, mature vessels, whereas vasculogenesis involves the de novo formation of vessels through stem cell (endothelial progenitor cells) differentiation [6]. The mobilization of these stem cells begins after injury by Nitric oxide (NO), VEGF, and matrix metalloproteinases (MMP), mainly MMP-9.

Keratinocytes are activated by changes in mechanical tension and electrical gradients, as well as exposure to pathogens, cytokines and growth factors can migrate laterally across the wound to reform the epidermal layer in a process termed re-epithelialization. The keratinocytes migrate across the wound bed through their interactions with structural proteins of the preliminary matrix, particularly with MMP-1 and MMP-9. Migration of keratinocytes on opposing edges continues until they establish physical contact with each other.

The final step in the phase is the replacement of the provisional fibrin-rich matrix with granulation tissue by fibroblasts. The granulation tissue consists of fibroblasts, granulocytes, macrophages, capillaries, and loosely organized collagen bundles and classically possesses a red hue due to its highly vascular nature [6]. These fibroblasts respond to a myriad of signaling molecules, including transforming growth factor (TGF-β) and PDGF, which induces them to either become pro-fibrotic, laying down ECM proteins, or differentiate into myofibroblasts which drive wound contraction [4,10].

Remodeling

This is the final phase of wound healing, beginning on day 21 and lasting up till a year post-injury. cessation of granulation tissue formation and maturation of the wound begins, collagen type III is replaced by collagen type I, acting to increase the tensile strength of the developing scar. Proteoglycans aid the construction of mature, cross-linked collagen fibrils and act as a conduit for cell migration. However, the integrity and architecture of the scar extracellular matrix never fully resembles that of unwounded skin, the collagen fibrils in the dermis of the scar adopt large parallel bundles, while a basket weave orientation is observed in uninjured skin fibrils [4,11,12]. The collagen synthesis continues for up to 5 weeks, oxygen and ascorbic acid are essential to this process, with hypoxia or vitamin C deficiency leading to decreased wound strength. MMPs have significant roles in the remodeling of local matrix microenvironments, however, in this phase it is imperative to maintain a precise balance between synthesis and degradation of the new tissue and this is achieved through temporal regulation of key MMPs [4].

Additionally, heightened expression of TGF-β and mechanical tension stimulate differentiation into myofibroblasts. These types of fibroblasts are characterized by an abundance of alpha-smooth muscle actin (α-SMA) allowing for generation of a contractile force in the process of wound contraction. This force opposes the wound edges and allows for wound closure, after the wound becomes fully epithelialized, the myofibroblasts will undergo apoptosis. Persistence of myofibroblasts after epithelialization leads to fibrosis and scar formation [6,10]. Finally, the angiogenic response ceases and the acute metabolic activity in the wound concludes.

Factors Affecting the Healing Process

There are some factors which usually slow down the process of healing like some diseases or conditions like aging etc... These factors are divided to systemics and local factors that have different physiologic effects on the body.

Systemic Factors

A chronic wound may develop when wound healing does not proceed normally, which places a tremendous strain on both the patient and the healthcare system. An individual diabetic ulcer is thought to cost close to $50,000 USD [13]. Some of the systemic factors affecting wound healing include non-modifiable factors like age, gender and some of the modifiable factors include diabetes, anemia, alcohol consumption, smoking, obesity, medications, and malnutrition.

According to the World Health Organization (WHO) the old population—defined as those over 60—is expanding more quickly than any other age group. Older age is a major risk factor for poor wound healing. Numerous cellular and molecular investigations conducted on humans and animals have looked at age-related alterations and delay in wound healing. It is well known that in healthy adults, the effects of aging simply temporarily slow wound healing, not affecting the healing process itself [5]. An altered inflammatory response, such as delayed T-cell infiltration into the wound area with changes in chemokine production and decreased macrophage phagocytic capacity, is linked to delayed wound healing in the elderly [7].

Some deficiencies in wound healing are related to sex hormones for instance aged males have been found to heal acute wounds more slowly than aged females. The fact that male androgens testosterone and 5-dihydrotestosterone (DHT) and their steroid precursor dehydroepiandrosterone (DHEA) appear to have considerable influence on the wound-healing process is one explanation for this [7]. By controlling a number of genes related to regeneration, matrix synthesis, protease inhibition, epidermal function, and the genes predominantly linked to inflammation, estrogen influences wound healing [7].

As a result, wounds brought on by peripheral vascular disease as well as situations where vascular impairment may be a factor, like a diabetic ulcer, require special attention [13].

Diabetes has a complicated pathophysiology combining vascular, neuropathic, immunological, and metabolic components that leads to impaired recovery [14].

Hyperglycemia is associated with stiffer blood vessels, which impede blood flow and lead to microvascular dysfunction, which results in less oxygen reaching the tissues [14].

Diabetes-related blood vessel changes are also responsible for decreased leukocyte migration into the wound, making it more susceptible to infections [14].

Even the presence of high blood sugar can impair leucocyte performance. Peripheral neuropathy can also cause numbness and a loss of pain perception, which can result in creation of chronic wounds that are not promptly identified and treated [14].

Generally, the oxygen supply and tension in the wound bed are crucial factors in physiologic wound healing. To interact with a variety of cytokines, supply the cells that are actively proliferating, and act as an effector again for

neutrophil respiratory burst, oxygen is necessary for wound healing. According to estimates, for a wound to heal, the tissue oxygen tension must be at least 20 mm (about 0.79 in) Hg [13]. Oxygen tensions as low as 5 mm (about 0.2 in) Hg have been observed in non-healing lesions [13]. These effects appear to be additive; in conditions of low oxygen tension, not just will there be more necrotic debris to support bacterial development, but the immune system's main defense mechanism against these germs is also weakened.

Alcohol use hinders wound healing and increases the risk of infection, according to clinical data and animal trials [7].

Alcohol use reduces host resistance and drinking alcohol while intoxicated at the time of an injury increases the likelihood of infection in the wound [7]. In response to an inflammatory stimulus, short-term acute alcohol intake suppresses the release of pro-inflammatory cytokines. In acute alcohol exposure, there is a correlation between lower neutrophil recruitment and phagocytic function and a higher likelihood of post-injury infection [7].

Apart from the increased risk of infection, any kind of exposure to ethanol influences the proliferative phase of healing [7].

By suppressing the early inflammatory response, wound closure, angiogenesis, and collagen formation, as well as changing the protease balance at the wound site, ethanol exposure can result in poor wound healing [7].

Patients who smoke after surgery experience a slower rate of wound healing as well as an increase in a number of problems, including infections, wound rupture, anastomotic leaking, wound and flap necrosis, epidermolysis, and a reduction in the tensile strength of wounds [7].

Given that nicotine can reduce tissue blood flow due to its vasoconstrictive actions, it is likely that nicotine reduces oxygen delivery via tissue ischemia [7].

Nicotine promotes sympathetic nerve activity, which releases adrenaline, which reduces tissue blood perfusion and produces peripheral vasoconstriction. Additionally, nicotine makes blood viscous due to decreased fibrinolytic activity and increased platelet adhesiveness. Smoke from cigarettes contains carbon monoxide, which contributes to tissue hypoxia in addition to nicotine's effects. A smaller percentage of oxygenated hemoglobin is present in the bloodstream as a result of carbon monoxide's aggressive, 200 times stronger attraction for hemoglobin than that of oxygen [7].

Numerous illnesses and health issues, such as coronary heart disease, type 2 diabetes, cancer, hypertension, dyslipidemia, stroke, sleep apnea, respiratory issues, and delayed wound healing are all known to be made more likely by obesity.Obese people typically experience wound complications, such as venous ulcers, pressure ulcers, hematoma and seroma development, skin wound infection, and dehiscence [7].

Adipose tissue was once thought to serve primarily as a caloric reserve. However, more recent research has shown that adipose tissue secretes a wide range of bioactive compounds known as adipokines. It is generally known that both adipocytes and the macrophages found inside adipose tissue create bioactive molecules such as cytokines, chemokines, and hormone-like substances like leptin, adiponectin, and resistin. The immune system and inflammatory response are significantly influenced by adipokines [5].

Even if there is not any concrete evidence to support it, the detrimental effects of adipokines on the body's immunological response appear likely to affect the healing process. Obesity has been linked to altered peripheral cytokine levels, reduced lymphocyte proliferation, and impaired peripheral blood mononuclear cell function [7].

Numerous drugs have the potential to alter how well wounds heal, including those that interfere with platelet function, clot formation, inflammatory responses, and cell proliferation [7].

Drugs called glucocorticoids Systemic glucocorticoids (GC), which are often used as anti-inflammatory medications, are well known for preventing the healing of wounds by suppressing cellular wound responses such fibroblast growth and collagen synthesis as well as overall anti-inflammatory actions. Systemic steroids produce incomplete granulation tissue and decrease wound contraction in the healing process of wounds [7].

A crucial transcriptional factor in the healing of wounds, hypoxia-inducible factor-1 (HIF-1), is also inhibited by glucocorticoids [7].

The majority of chemotherapeutic medications aim to block angiogenesis, fast cell division, and cellular metabolism, hence blocking many of the processes necessary for effective wound healing. These drugs prevent the production of DNA, RNA, or proteins, which reduces fibroplasia and neovascularization of wounds [7].

Chemotherapeutic medicines slow down cell migration into wounds, reduce the creation of the early wound matrix,

reduce collagen production, reduce fibroblast proliferation, and prevent wound contraction [7].

The rate at which surgical and trauma wounds heal can be significantly impacted by malnutrition or specific dietary deficits. Patients who are malnourished and have chronic or slow-healing wounds frequently need specialized nourishment. The healing process can be impacted by energy, carbohydrates, protein, fat, vitamins, and mineral metabolism [7].

Local Factors

Oxygen: Oxygen is arguably the most essential element involved in cellular metabolism. It is crucial in the production of energy via ATP and plays a vital role in the wound healing process, for example, the synthesis of collagen by fibroblasts, which needed for wound closure requires the hydroxylation of proline and lysine, which cannot be accomplished without the presence of oxygen during the reaction. Proper oxygenation of the wound has been found to reduce the risk for infection [15], though delayed wound closure to prevent infection with anaerobic bacteria and through oxygen mediated superoxide production by polymorphonuclear leukocytes. Proper oxygen supply during the wound healing process has also been linked to induction of angiogenesis, increased keratinocyte differentiation, migration, and re-epithelialization, enhancement of fibroblast proliferation and collagen synthesis, and promotion wound contraction [7]. A study showed that animals breathing 10 percent oxygen should a significant decline in wound strength when compared with the control at 20 percent, however the group that received 40 percent oxygen had increased wound strength as compared with the control group [16], once again confirming the significant role that oxygen plays in the wound healing process.

Proper oxygen supply can be a difficult balance to achieve, due to vascular disruption from injury and the increased consumption by metabolically active cells in the healing process, the microenvironment of wounds is quite hypoxic. In addition to that, conditions such as peripheral vascular disease, obesity, diabetes, and advanced age can lead to compromised vessels, causing impaired blood flow and impaired wound healing. Hypoxia can also be caused by radiation induced vasculitis in cancer patients [15].

Although it has been established that lack of oxygen impairs wound healing, this relationship is not completely a straightforward one, temporary hypoxia is also known to enhance wound healing [7]. This is achieved through the hypoxia mediated production of cytokines such as PDGF, TGF-β, VEGF, tumor necrosis factor-α (TNF-α), and endothelin-1 by macrophages, fibroblasts, and keratinocytes [7].

Foreign Bodies: A foreign body, which has any abnormal mass or structure in the tissues will prevent healing of the wound, if present. The main problems caused by the presence of foreign bodies in a wound are their role as irritants and their relation to infection. Absorbable materials can promote inflammation which causes accumulation of free fluid and can act as a medium for bacterial growth, leading to infection of the wound site. Even with antibiotics, the risks for recurrence of infection are dependent on the porosity of the foreign material, porous materials can harbor bacteria, allowing re-infection of the site after the course of antibiotics [16].

The level of irritation caused by a foreign body and how well it is tolerated can be determined by the material. Reactive metals such as iron can show delayed reaction due to development of corrosion that causes irritation; organic materials such as wood, fibers from clothing, soil and grass are not at all well tolerated and often lead to a highly contaminated wound and development of a bacterial infection, even without bacterial, chronic inflammation is observed until the offending material in removed. Talcum powder from the inside of sterile gloves, if introduced into a wound can lead to formation of a granuloma, due to the insolubility of the talc. Insoluble materials like glass and gravel can remain encapsulated in the tissues, causing little to no reactions due to their inert nature. As mentioned above, porous materials are not very well tolerated as they act as a medium for bacterial growth and proliferation. The surface of the foreign object can also play a role in how well tolerated it is, non-reactive metals with smooth surfaces can remain in the tissues, causes little to no reactions, as seen in medical devices such as metal plates and screws, however, metals with rough surfaces will tend to cause more irritation to the surrounding tissues, leading to inflammation [16].

Infection: The growth and proliferation of microbes in a wound is one of the most common reasons for impaired wound healing [7]. Introduction of bacteria into a wound can be due to migration, though the opening in the skin, bacteria is able to move from an area it is normally present (e.g., on the surface of the skin) into the tissues where it is an abnormal presence; bacteria can also be introduced through the contamination of the wound by foreign material. Infection is seen as an imbalance in the normal equilibrium of bacterial quantity, the development of infection, especially in a surgical patient is determined more by the quantity of bacteria than the absolute presence of bacteria [17]. The development of an infection can also be determined by the species present, but also by the host immune response, the number of different species present and the virulence of the organisms [18]. The state of infection and replication

status of the bacteria present in the wound determines if the wound is classified as contaminated, colonized, or infected. A wound with non-replicating microorganisms is referred to as "contaminated," whereas colonization indicates the presence of replicating microbes. Infected wounds can be further classified as local infections, with microbe replication and initial local tissue response occurring and invasive, with major host injury [7,15]. The presence of bacteria can impair the wound healing process by arresting the wound in the inflammatory phase, leading to the formation of a chronic wound. Under normal conditions, inflammation is a self-limiting process, with the inflammatory process acting in a beneficial manner to debride the wound, however, when this process becomes chronic, it serves to only cause further injury to the wound site and prolong inflammation [19]. This can be achieved through the release of bacterial endotoxins that can cause a prolonged elevation of cytokines such as interleukin-1 (IL-1) and TNF-α. Chronic inflammation from infection induces tissue breakdown though the release of matrix metalloproteinases (MMPs) that degrade the extracellular matrix. A reduction in the production of protease inhibitors is also observed which can lead to the increased breakdown of growth factors that promote wound healing [7,18,20]

The development of biofilm is also a crucial factor in the hindrance of wound healing. Biofilms consist of many bacteria clustered together to form dense, mat-like structures that cover the wound's entire surface. The increased susceptibility to infection and the presence of necrotic tissue allowing easy bacterial attachment, make chronic wounds an ideal environment for biofilm formation. Mature biofilms act as a protective microenvironment for bacteria, making them more resistant to antibiotic intervention [21].

Venous Insufficiency: The symptoms of venous insufficiency are due to venous hypertension, this can be a result of valvular dysfunction. Valve failure may occur due to a weakening of the valves due to varicose veins, or damage to the deep veins secondary to venous thrombosis, trauma, or obstruction [22]. Inflammation from recruited leukocytes, mast cell degranulation as well as the activity of matrix metalloproteinase inhibitor and fibroblast differentiation into myofibroblasts participate in vain wall remodeling and varicose formation [21]. Chronic inflammation, maintained by proinflammatory factors: IL-1α, IFN-γ, and TGF-β1, as well as incompetent blood flow which promotes thrombus formation, leading to further fibrosis and valvular destruction, also contributes to the impaired wound healing seen in this condition [21].

Complications from hypoxia due to venous insufficiency can also result in formation of a wound, venous insufficiency ulcer. The mechanism by which venous insufficiency delays wound healing also affects this type of wound, causing it to be a chronic wound.

Factors Enhancing the Healing Process

Enhancing the healing process is a broad topic to be discussed in this research, so it is better to break it down into various aspects for better understanding of its purpose. Enhancing the healing process in non-healing wounds can be different from people with normal body system and normal wounds.

Enhancing the process in non-healing wounds sometimes works by just bringing the impaired system function back to normal, for example the most common cause of chronic, non-healing ulcers that put patients at higher risk for limb amputation is diabetes [23]. Reduced ability to regenerate microvasculature through the process of angiogenesis is a significant factor in non-healing wounds in diabetes and peripheral vascular disease [23]. This disruption of the normal healing process is a major therapeutic target for developing new treatments for non-healing and ischemic wounds because it contributes to the dysfunctional healing response [23]. So, some treatments like the delivery of growth factors, gene therapy, stem cell therapies, and mechanical/pressure-based stimulation have all been used as techniques and dressings with the aim of enhancing chronic wound healing [23]; to just help with the healing process to back to normal like if we consider zero as normal, coming from minus ten to zero that count as a progress, an enhancement. But enhancing the healing process in people who are in normal condition (already a zero) is somehow another deal because we want to make the progress from zero to +10 although there might be some correlation between these types as well, but the goal is enhancing the normal healing process farther more like using Adipose-Derived Stem Cells (ADSCs) and Mesenchymal Stem Cells (MSCs). There is not that much research and experiments have been done to show significant effect on the time of healing process, but we hope we can go farther in future as this is one of the important purposes of this research.

Therapeutic Strategies for Enhancing Angiogenesis in Wound Healing

The non-healing nature of diabetic foot ulcers and other chronic wounds is largely due to reduced angiogenesis. There are several theories to explain why the angiogenesis in these chronic wounds is reduced. Compared to non-diabetics and diabetics without foot ulcers, diabetic patients with foot ulcers have higher circulatory levels of PEDF in their plasma. Additionally, there is a notable decrease in syndecan-4 and glypican-1 in diabetic skin, two essential cell surface heparan sulfate proteoglycans required for efficient FGF-2 and other growth factors binding to their

appropriate receptors. Similarly, venous leg ulcer wound exudates have anti-angiogenic qualities despite increased expression of angiogenic factors. These analyses are in line with a proteomic analysis of venous leg ulcer exudates, which discovered increases in anti-angiogenic proteins in non-healing ulcers. Additionally, there were higher levels of soluble VEGFR-1 and VEGF-A proteolysis in chronic venous ulcers, which may be used to inhibit VEGF-A activity [23].

Growth Factors

Research on the use of growth factors for promoting angiogenesis and improving wound closure in chronic wounds has been ongoing for many years. Endogenous growth factors are necessary for efficient wound healing and play a crucial role in directing the wound-healing process. While the delivery of exogenous growth factors has demonstrated benefits for wound closure and angiogenesis in animal studies, nearly all growth factor-based agents for wound healing have not demonstrated definite benefits for improving wound healing in patients in clinical trials. One theory for why these trials failed is that as people age and develop vascular disease, they become resistant to the effects of angiogenic growth factors. It is also unclear whether a single growth factor therapy could promote wound healing. Clinical adoption of these treatments has been slowed by the inconsistent findings from clinical trials and the therapies' prohibitive costs, but work is still being done to create more potent protein therapies for wound healing [23].

Non-Growth Factor Protein Delivery

In preclinical models of wound healing, many other proteins showed therapeutic effects on wound angiogenesis. One important example of a protein hormone that has been demonstrated to regulate angiogenesis and wound healing is insulin. By promoting angiogenesis, the delivery of insulin from PLGA microspheres enclosed in an alginate sponge dressing improved healing and decreased scarring from burn injuries in rats. Additionally, insulin injection into mouse skin caused angiogenesis, indicating that it is a viable option for ischemic wounds. Additionally, topical insulin delivery to diabetic skin ulcers facilitated faster wound healing in a double-blind, placebo-controlled clinical trial. This finding suggests insulin as a less expensive option to growth factor therapies [23]. It has been demonstrated that the hormone erythropoietin (EPO), a non-growth factor protein, promotes angiogenesis. EPO topical application or infusion was shown to significantly increase angiogenesis rates in mice and rats compared to the control group in a model of second-degree burn injury where a massive portion of the original vasculature was lost or severely damaged. Additionally, compared to the control group, the EPO-treated rats' wound closure rates were accelerated, with an average wound closure rate of 98.8% by day 7. Additionally, EPO has been used to treat ischemic injuries, where significant revascularization is necessary to reestablish adequate blood flow, and it has been hypothesized that EPO and VEGF collaborate to encourage angiogenesis at the site of the wound. On the other hand, EPO has been linked to tumor angiogenesis in hepatic tumors and Lewis lung carcinoma tumors, so similar precautions should be taken as with many growths factor therapies [23]. Another protein known as stromal-cell derived factor-1 (SDF-1) has been found to control angiogenesis by attracting endothelial progenitor cells (EPC) to the site of the wound and fostering sustained cell proliferation. The local recruitment of monocytes with anti-inflammatory activity has been shown to be promoted by SDF-1, a potent chemotactic agent for monocytes like macrophages. This enhances the growth of the local vasculature. SDF-1 has also been shown to encourage bMSC and EPC chemotaxis to wound sites. The movement of bMSCs and EPCs (Endothelial Progenitor Cells) encourages vascularization, which quickens the healing of wounds. With a three-fold increase in blood vessel formation compared to a control group that did not receive SDF-1, SDF-1 has also been shown to promote angiogenesis in a diabetic mouse model. Full thickness skin wounds that received SDF-1 delivery experienced a markedly faster rate of wound closure and vascularization. Finally, Vgesjö et al., took a novel approach. plasmid-encoded SDF-1-transformed lactobacilli. In mouse models of hyperglycemia and peripheral ischemia, these bacteria were then topically applied to wound sites, hastening wound closure, and improving the effectiveness of bioavailable SDF-1 [23].

Gene and Nucleic Acid-Based Therapies for Wound Angiogenesis

In angiogenesis during wound healing, gene regulation is essential. Non-coding RNAs called microRNAs (miRNAs) are about 21–25 nucleotides long and play a significant role in regulating gene expression by binding to target mRNA and either suppressing or causing mRNA degradation. After inflammation, gene expression is controlled to promote angiogenesis and tissue remodeling. Numerous aspects of wound healing, including cell proliferation and migration, collagen biosynthesis and network maturation, inhibition of neovascularization, and improved blood vessel growth, have been shown to be regulated by miRNAs. MiRNAs are a target of interest in wound healing due to their ability to increase or suppress gene expression. Several miRNAs have been found to specifically control angiogenesis during wound healing. The expression of the pro-angiogenic proteins VEGF, GATA2, Ang-2, and PDGF-B as well as the anti-angiogenic protein TSP-1 is regulated by these miRNAs, which also affect vessel formation and maturity, migration, scar reduction, and

migration regulation. Overall, it is becoming more obvious that miRNAs exert significant control over angiogenesis in the context of wound healing [23].

Methods for Delivering Small Molecules to Promote Angiogenesis and Restore Impaired Wound Healing in Animal Models

Wound healing requires a dynamic angiogenic response. Many researchers have concentrated on the creation of novel strategies for therapeutic angiogenesis to assist in the healing of chronic wounds. Small-molecule treatments that encourage angiogenic activity and can modulate the repair process have been developed in response to recent advancements in our understanding of the biology of chronic wounds. These treatments have exciting potential for clinical use. In the past, diabetic impaired wound healing in animal models was treated with small molecules. One molecule crucial to wound healing has been identified as nitric oxide (NO). Following skin damage, NO levels significantly rise and then gradually fall as the wound heals [13, 23]. It is also has been researched that using other compounds like Adenosine Triphosphate, Statins, Deferoxamine, Hyaluronan Oligosaccharides, can help the healing process in different physiological and pathological ways, as well as Natural compounds which is another objective of wound therapy to encourage adequate healing while minimizing scar complications like unbalanced collagen synthesis, in addition to tissue healing and regeneration. Traditional Chinese Medicine has long used astragaloside IV (AS-IV), one of the main active components in Astragali Radix, which is derived from the root of Astragalus membranaceus, for its curative and anti-scarring properties [23]. Dermatological conditions like skin lesions, eczema, burns, and hypertrophic scars have responded well to herbal treatments [24]. One illustration is the plant Centella asiatica, which contains several active substances found to aid in wound healing, including centelloids, asiaticoside, madecasoside, asiatic acid, and madecassic acid [24]. Previous studies [24,25] demonstrated that ointments containing different doses (0.1%–1%, w/w) of these compounds or a combination improve wound healing. Asiaticoside, which is derived from Centella asiatica, has a variety of pharmacological effects, such as the ability to promote angiogenesis and speed up the healing process after injury [23].

Adipose-Derived Stem Cells (Adscs) and Mesenchymal Stem Cells (Mscs) in Wound Healing

A new and promising method for treating diseases that are not well-suited for conventional therapies is stem cell therapy. To promote angiogenesis and wound healing, various stem cell types have been investigated.

Nearly all adult organs, particularly adipose tissue (AT), have been found to contain multipotent mesenchymal/stromal stem cells (MSCs) as residual stem cells. These cells are isolated within the stromal vascular fraction (SVF) and exhibit the typical mesenchymal cell characteristics in vitro. These cells are more proliferative, have immunosuppressive characteristics that can inactivate T cells, and are commonly known as adipose derived stem cells (ASCs or ADSCs). They can be isolated in a less invasive and more consistent manner. Compared to bone marrow (BM)- and umbilical cord (UC)-MSCs, ADSCs were shown to differentiate into the adipogenic lineage; however, their multipotency is actually more appreciated for ectodermic and endodermic tissue repair [26]. Within subcutaneous tissue, ADSCs have recently been found. We can anticipate that they will be essential to skin regeneration and repair because of their presence. There is proof that ADSCs play a crucial role in preserving the structure of skin tissue, even when acting as a physiologic response to local injury or as mechanisms for skin rejuvenation by seeding younger cells into the epidermis' outer layer. These cells, which were located in the basal layer and self-renewed and differentiated to continuously settle the epidermis with keratinocytes, fibroblasts, and melanocytes, may have an impact on the physiological traits of the injured skin [26]. They also displayed a high capacity for migration and were drawn to the sites of wounding. It has been demonstrated that ADSCs can differentiate into keratinocytes, dermal fibroblasts (DF), and other skin cells [27].

Conclusion

The compound's ability to function in the challenging environment of a poorly healing wound is necessary for the development of effective therapeutics for enhancing wound angiogenesis, particularly for non-healing or complex wounds. Numerous substances have demonstrated great promise in promoting wound healing and angiogenesis in animal models of wound healing, as was covered in this review. In the past, many wound healing therapies that were effective in preclinical models ultimately failed to benefit patients when they were tested in clinical trials. By both replacing, repairing, and regenerating dead or damaged cells and by allowing their turnover to provide continuous recruitment of mature, specialized cells from the basal epidermal layer to its outer layer, resident ADSCs within the skin are thought to be key regulators and play crucial roles in tissue repair and regeneration.

The overall goal of the strategies for treating wound defects are to ensure patient satisfaction in terms of both functionality and aesthetics. Advancements using skin cellular substitutes, biomaterials, and fat graft have been

promising in supporting skin repair due to their excellent capacity to proliferate, differentiate, and migrate along with their immunomodulatory effect. Regarding the makeup of the repaired dermis and epidermis, it remained challenging to ensure complete and functional generation. However, ADSCs are more advantageous in contributing to the biology and function of skin cells the more enriched secretome they can secrete. According to reports, these growth factors autoactivate ADSCs and start the various mechanisms needed for wound healing at different stages [26]. However, effective wound healing is ultimately a temporal process that has several potential vulnerabilities to disease or infection. Although many factors and ways were reviewed in this research for enhancing the healing process, still all of them need more research and experiments especially on humans to be able to increase the speed significantly to benefit the people who are suffering from this problem.

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