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Review Paper

Biophysical approach to studying protein interactions in skin wound healing

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ABSTRACT

Cutaneous wounds are a significant health problem worldwide. That is why wound healing and biological factors, including proteins, are substantial. This complicated and dynamic process consists of five overlapping phases: Hemostasis, Inflammation, Granulation tissue formation, Re-epithelialization, and Remodeling. Cells and proteins shared in these phases can trigger myriad activities that eventually complement each other. This paper aims to provide an understanding of the key proteins' functions and signaling involved in the wound healing process, based on data available on bioinformatics websites. These proteins include the interleukin-1 family, tight junction proteins (occludin and claudin), platelet-derived growth factor (PDGF), and extracellular matrix components such as matrix metalloproteinases (MMPs), fibronectin, and laminins. In addition, by examining the significant role of inflammatory cytokines, proteases, and members of the large family of metalloproteinases, we can take novel measures to accelerate the healing of chronic wounds that are stuck in theinflammatory phase. Additionally, it is notable that mediator proteins are vital, as they exhibit co-expression and share molecular interactions with key proteins. Therefore, their absence or impaired functioning can disrupt the normal healing process of skin wounds.

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1. Introduction

According to a 2018 study, the total spending on wound care was estimated to be between $28.1 billion and $98.8 billion. The first place belonged to surgical wounds, followed by diabetic infections and ulcers [1]. It has been projected that wound care costs for chronic ulcers and surgical wounds will exceed $22 billion by 2024 [2]. With a global average of 6.4%, foot ulcers have shown a higher prevalence in North America compared to other regions, such as Europe. Besides, statistical data have shown that males are more prone to such wounds compared to females [3].

On the other hand, reports indicate an annual growth rate of 6.6% for Diabetic Foot Ulcers (DFUs) between 2016 and 2024. Regarding the Coronavirus Infection Disease 2019 (COVID-19) pandemic, it is worth noting that individuals who regularly visit wound clinics utilize 30% fewer acute care services. Data suggest that visits to these centers decreased by 40% in 2020 compared to 2019 during the pandemic [3,4].

2. Skin structure

The skin, the largest organ in the human body, serves as an interface between the integumentary system and the environment, preventing pathogen penetration and physical damage to tissues by forming a defense barrier. It is also a primary site for vitamin D synthesis, playing a role in thermal regulation and excretion, which ultimately leads to the maintenance of homeostasis [5,6]. Epidermis, dermis, and hypodermis are the three main layers of the skin that make up skin tissue, along with skin appendages such as sweat glands, sebaceous glands, and hair follicles [7]. The dermis is the mesenchymal layer of the skin, comprising two structural layers: papillary and reticular. Fibroblasts are the most abundant cells in this layer, capable of extracellular matrix (ECM) synthesis and remodeling during wound healing. Collagen bundles form an ordered network in conjunction with elastin strands [8]. As the papillary dermis ages, its thickness decreases, and it becomes steadily thinner until it is replaced by reticular fibers [9].

3. Wound healing phases

Wound healing consists of five integrated phases: Hemostasis, Inflammation, Granulation tissue formation, re-epithelialization, and remodeling, which overlap (Figure 1). Due to the fact that the activity of the transcription machine in response to a wound is a time-consuming process, pathways independent from transcription initiate their activity immediately after tissue injury. One of these pathways is dependent on Ca^{2+}. From the very first moments of tissue injury, the amount of intracellular Ca^{2+} increases in the margin of the wound, and then it propagates in the form of a Ca^{2+} wave to the central areas [10]. Damage-associated molecular pattern (DAMP) molecules, including fibronectin in the ECM, uric acid, and Adenosine triphosphate (ATP) in the cytosol, and mitochondrial reactive oxygen species (ROS), along with lipid mediators and hydrogen peroxide, induce signals required for the recruitment of inflammatory cells [11,12]. Studies have shown that hydrogen peroxide reduces infection, promotes angiogenesis, and acts as an activator in keratinocyte regeneration [13]. Figure 2 illustrates the early inflammatory response and vascular microenvironment changes during the initial phase of wound healing.

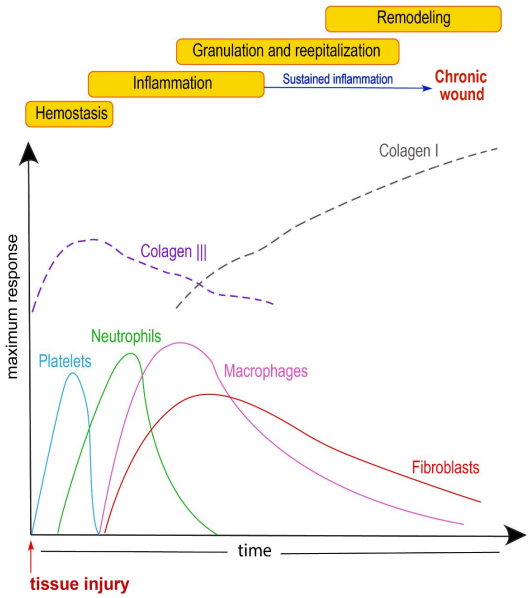

Figure 1. Wound healing phases and the involvement of key cells and components. This complicated and dynamic process consists of five overlapping phases: Hemostasis, Inflammation, Granulation tissue formation, Re-epithelialization, and Remodeling. Platelets are the first group of key cells that stop bleeding. This process is then followed by the contribution of inflammatory factors and the maximum activity of fibroblasts necessary for the synthesis of ECM components.

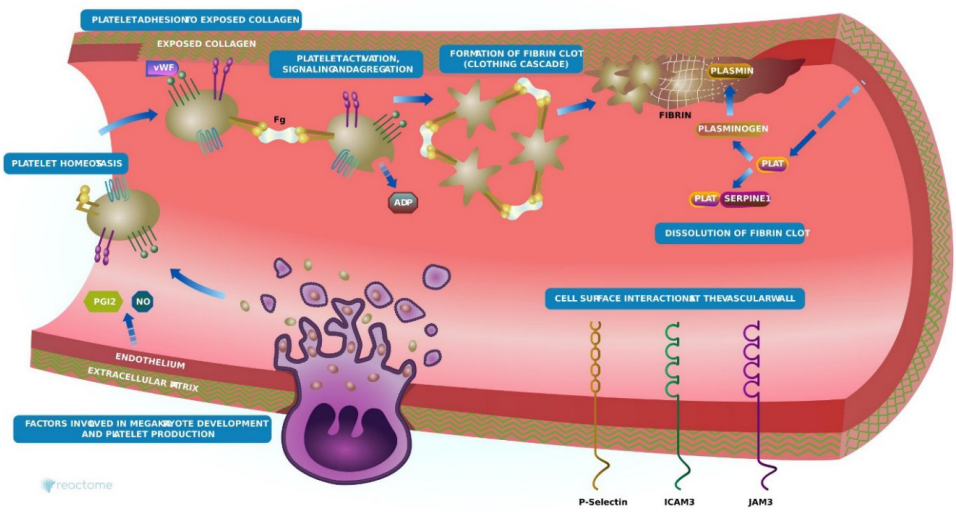

Figure 2. Early phase of wound healing. The reaction of inflammatory factors in response to skin wounds in the microenvironment of the vessel

3.1 *Hemostasis*

Hemostasis is the immediate response to a wound injury that stops bleeding. This process itself consists of three phases: vasoconstriction, primary hemostasis, and secondary hemostasis [11]. Platelets activate the smooth muscles in the vessel walls and cause temporary contraction by producing PDGF [11,14]. After platelet aggregation in primary hemostasis, they activate themselves by interacting with ECM components. Platelets do not interact with endothelial cells of vessels under normal physiological conditions [15]. However, at the time of wounding and in the first stage of skin repair, they bind to ECM proteins such as fibronectin, collagen, thrombospondin, and von Willebrand factor through their glycoprotein receptors associated with G proteins [16]. Then, inside-out signaling is activated, leading to integrin activation on the platelet surface and increased platelet binding with each other, as well as with ECM components. Specific integrins adhere to collagen type 1, causing platelets to release adhesive components and soluble mediators, such as cyclic AMP, which makes platelets sticky [17]. Subsequently, the amount of actin filaments in the cytoskeleton increases via outside-in signaling, and these filaments account for 70% of the entire protein amount. These changes in actin filaments lead to significant alterations in platelet conformation as they transform from rounded to a fried-egg shape, thereby building stronger interactions with the ECM [11,18]. Secondary homeostasis begins after platelet plug formation and maximum adhesion between platelets and the ECM.

In this phase, soluble fibrinogen converts into insoluble fibrin along with the activation of the coagulation cascade [11,19]. Then, the combination of platelet plugs and fibrin strands forms a thrombus, which prevents bleeding [20]. Platelets show heterogeneity based on their location in the growing thrombus. For instance, platelets situated in the center of the thrombus contain more p-selectin, while marginal platelets show less expression of p-selectin [21]. This provisional fibrin matrix formed for blood coagulation is later degraded by a serine protease named Plasmin [22]. Platelets, the most essential cells in hemostasis, release several growth factors and cytokines including transforming growth factor beta (TGF-β), transforming growth factor alpha (TGF- α), platelet-derived growth factor (PDGF), fibroblast growth factors (FGF), insulin-like growth factor (IGF) and vascular endothelial growth factor (VEGF). Monocytes and neutrophils are recruited to the wound site by PDGF and TGF-β. In addition, platelets play a crucial role in the initial inhibition of bacterial infection during the healing process, as they regulate the production of antimicrobial peptides by expressing specific toll-like receptors on their surface [23].

3.2 *Inflammation*

The inherent inflammation of a wound hinders the invasion of pathogens [16]. However, if this inflammation becomes uncontrolled, it can lead to an impaired healing process. The hemostasis and neurogenic inflammation phases begin from the very first moments of injury and continue for approximately an hour. Then the neutrophil population increases instantly [24]. Neutrophil recruitment to the wound site initially increases, driven by Interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α). However, their population begins to decline after approximately four days [16]. Neutrophils, the first group of leukocytes present at the wound site, remove pathogens through phagocytosis and clear the site of injury from cell debris and necrosis [25,26]. Apart from this, they are responsible for the production of proteolytic enzymes, antimicrobial peptides, and ROS [27]. One of the

proteases released by neutrophils is elastase, which facilitates cell movement and migration within the ECM. Elastase activity, however, is later inhibited by α-1 protease, which is released by macrophages [25]. Neutrophils act as chemoattractants, recruiting other inflammatory cells to the wound site and inducing a greater cellular response by producing pro-inflammatory cytokines [28]. Blood monocytes infiltrate the injured tissue and differentiate into macrophages. Therefore, the phagocytosis function of neutrophils is replaced with that of macrophages approximately after the fourth day of inflammation [22]. Macrophages release several growth factors and chemokines, which lead to the proliferation phase of healing and promote the production of new components in the ECM. During the inflammation phase, fibronectin plays a crucial role in activating macrophages to facilitate wound site clearance [29].

Additionally, mast cells induce swelling, redness, and pain at the wound site by releasing granules that contain histamine, enzymes, and active amines [17]. Secreted histamine increases vascular permeability, which causes more neutrophils to enter the site of injury [30]. It is also a stimulator for keratinocyte proliferation in the next phase of wound healing [31]. With the uncontrollable and long-term persistence of this phase, which can result from infections caused by microbial agents, wounds tend to become chronic because inflammatory factors prevent the normal process of wound healing, thereby stopping the process in this phase [32,33].

3.3 Granulation tissue formation

The formation of the granulation tissue as a new connective tissue on the surfaces of a wound is a key phase in cutaneous wound healing [34]. This phase does not occur in a discrete time but continues persistently in the background of healing [20]. Granulation tissue formation simultaneously commences the regenerative polarization of M2 macrophages, proliferation and differentiation of fibroblasts, matrix deposition, and angiogenesis [35,36]. In this case, the AKT (v-Akt murine thymoma viral oncogene homolog) signaling pathway is essential for regulating macrophage survival and coordinating their responses to metabolic and inflammatory signals. This serine/threonine-specific protein kinase is a key component in PI3K signaling [37]. Hypoxic adipose stem cell exosomes (HypADSCs-Exo) stimulate the proliferation and migration of fibroblasts by activating the PI3K/Akt pathway, thereby increasing the expression of vascular growth factors.

Additionally, the activation of AKT signaling pathways by extracellular vesicles from mesenchymal stem cells (MSCs) facilitates endothelial cell proliferation and stimulates the formation of new vessels [38]. Immigration of fibroblasts to granulation tissue and their differentiation into myofibroblasts initiates new collagen and glycosaminoglycans synthesis on days 5 to 7 of healing, which is accompanied by local contraction of the wound [20,39]. Apart from this, actin and vimentin play a vital role in wound contraction [36]. Adipose tissue-derived stem cells (ADSCs) and dermal fibroblasts also play a role in this phase of healing. Finally, proteoglycans stabilize the wound by forming the core of the wound. Then, re-epithelialization begins with cell migration from the wound margin [20].

3.4 Re-epithelialization

Re-epithelialization of the wound begins with keratinocyte activity located in the epidermis, followed by new vessel formation and peripheral nerve repair [40,41]. Keratinocytes are activated by being exposed to cytokines, growth factors, pathogens, and hydrogen peroxide [39]. Then they move to the center of the wound bed from the verge [42]. Re-epithelialization commences after 16 to 24 hours in normal wounds but after 5 to 7 days in chronic wounds [20,43].

Several mechanisms are involved in the entire re-epithelialization process, which is necessary for successful wound closure. In this phase, microRNAs are vital, as are other factors, including cell receptors, matrix metalloproteinases, and cytokines [43,44]. Re-epithelialization of superficial wounds in humans primarily occurs in precursor cells of eccrine sweat glands. In contrast, the re-epithelialization phase of deep wounds occurs in the interfollicular epidermis due to the damage inflicted on the sweat gland's structure [43]. Next, new vessels are formed by angiogenesis and vasculogenesis. Angiogenesis refers to the formation of new vessels from pre-existing vessels.

In contrast to vasculogenesis, in which new blood vessels are formed from endothelial progenitor cells (EPCs) [20,27]. During the proliferation phase, M2 macrophages, which possess anti-inflammatory properties, regulate interactions among various cells, including fibroblasts, keratinocytes, and endothelial cells. Hypoxic conditions in the wound are a primary driver of angiogenesis, stimulating the synthesis of hypoxia-inducible factor-1 (HIF-1) in endothelial cells, macrophages, fibroblasts, and keratinocytes. Then, endothelial cells undergo metabolic changes in response to the influence of proangiogenic factors, ultimately leading to the budding of new blood vessels [15]. After new vessels become stable, laminins, the most abundant glycoproteins of the basal lamina, have a vital role in providing stability and strength to repaired tissue [45]. In addition, tight junction proteins, including occludin and claudin, as well as adherens junction proteins, such as cadherin, must be stable enough to maintain tissue integrity during re-epithelialization [46,47].

3.5 Remodeling

In the final phase of wound healing, granulation tissue gradually degrades. The epidermis, dermal vessels, and muscle fibers are regenerated and eventually form a functional tissue. Remodeling begins three weeks after

the injury and may last for over a year [27]. In this phase, there must be a balance between ECM components synthesis and degradation. It is especially essential for collagens. Since collagen type I predominates over collagen type III in undamaged normal skin, specific metalloproteinases must degrade a substantial amount of collagen type III, allowing collagen type I to dominate the tissue [48]. Fibroblasts, as the primary cells in this phase, replace the initial fibrin clot with extracellular components, including proteoglycans, fibronectin, and hyaluronan, in addition to collagen synthesis [49]. Elastin is also produced through its monomeric subunit, named tropoelastin, in order to make up elastic fibers [50]. Elastin is crucial for maintaining tissue integrity and elasticity after an injury occurs, as it provides durability and resilience to the tissue [51,52]. The immune system plays an active role in tissue repair and regeneration. In the early and late stages of wound healing, damaged skin triggers an extensive response from the immune system, characterized by the broad recruitment of immune cells. Among all immune cells responsible for wound healing, macrophages, especially those with the M2 phenotype, play a vital role in tissue regeneration due to their great potential in ECM regeneration [37,53]. Ultimately, the remaining cells from the preceding phases undergo apoptosis. Although the process underlying wound healing has not been fully understood, it is essential for fibroblasts, as their high activity can lead to fibrosis and scar formation (Figure 2) [54].

4. Key proteins involved in wound healing

4.1 Matrix metalloproteinases (MMPs)

MMPs are a class of zinc-dependent endopeptidases that are able to degrade collagens and proteoglycans present in the ECM. The activity of these proteases contributes to tissue development, a process necessary for wound healing [55]. Endogenous specific tissue inhibitors of MMPs (TIMPs) control the degenerative potential of MMPs at gene activation and transcription levels [56]. MMP-9 and MMP-1 are crucial for keratinocyte migration during the proliferation phase. Since keratinocytes interact with ECM proteins through their transmembrane receptors (integrins), MMPs cut off integrins from ECM components and thus help keratinocytes to move easily in the ECM. Macrophages degrade the dense network of fibrin in angiogenesis by releasing several proteases, such as the MMP family [23]. Apart from this, after wounding, MMPs, particularly MMP-9, with the help of Nitric Oxide (NO), cause EPCs to move from the bone marrow, where they are typically found, to the bloodstream to carry out vasculogenesis [57]. Fibroblasts release several proteolytic enzymes that facilitate their movement in the ECM. These enzymes are collagenase (MMP-1), gelatinase (MMP-2 and MMP-9), and stromelysin (MMP-3) [17]. Among MMPs, collagenases and gelatinases cleave intact fibrillar collagen and damaged ones, respectively. Collagen I and collagen III are often cleaved by MMP-1 and MMP-8.

In comparison, collagen IV is degraded by MMP-9 [58]. During the remodeling phase, MMPs play a crucial role in collagen degradation. During this phase, an appropriate balance between ECM component formation and degradation is necessary. Consequently, macrophages generate MMPs to cleave collagen III [49]. In chronic wounds, however, a link has been established between MMP-9 levels and the bacterial population at the site of injury [59].

4.2 Platelet-derived growth factor (PDGF)

PDGF is a dimeric molecule comprising a disulfide bridge and polypeptide chains of A, B, C, and D. These chains are able to make homodimer structures (PDGF-DD, PDGF-CC, PDGF-BB, PDGF-AA) or heterodimer (PDGF-AB) ones [60]. Their receptors, which contain α and β chains, are found in one of these isoforms: αα, αβ, or ββ. This transmembrane receptor exhibits tyrosine kinase properties in its cytoplasmic domain, and it contains immunoglobulin-like chains in its extracellular domain [61]. Platelet-derived growth factors play a crucial role in the homeostasis and proliferation phases of wound healing; they are also essential for mesenchymal cells, as they are involved in various processes, including cell growth, survival, and apoptosis [62]. Smooth muscles of the vessel wall are the primary receptors for PDGF, which cause temporary contraction to stop bleeding as the primary response to the injury [63]. During the initial hours of platelet activity, growth factors originating from platelets, such as PDGF, are released intensely. Activated platelets continue to release these factors for approximately 7 days, which has a paracrine effect on other cells [64]. Inflammation causes endothelial cells to alter their gene expression pattern and phenotype in response to the influence of cytokines, such as PDGF, on these cells. The mentioned changes ultimately lead to advancements in wound healing [27].

Additionally, PDGF is one of the cytokines that participate in the recruitment of neutrophils and monocytes to the wound site, thereby preventing infection. PDGF is also involved in the migration of fibroblasts to the wound core and serves as a regulator of fibroblast activity, with the help of TGF-β [17]. Angiogenesis is also considered a key phase during proliferation, which begins with the involvement of VEGF and PDGF [27,57].

4.3 Fibronectin

Fibronectin is a glycoprotein in the extracellular matrix, with a molecular weight of 230 to 270 kDa, that plays several roles in enhancing tissue healing, cell movement, and attachment within the ECM [65,66]. Each fibronectin molecule comprises three types of repetitive subunits, designated as subunits I, II, and III, which provide specific domains for the attachment of

various components, including collagen, heparin, heparan sulfate, gelatin, metalloproteinases, and growth factors, within the ECM [67,68]. Fibronectin can connect ECM components to actin filaments present in the cytoskeleton by interacting with integrins on cell surfaces [29]. This glycoprotein has been identified in two different forms: plasma fibronectin (pFN) and cellular fibronectin (cFN) [69]. Hepatocytes in the liver synthesize plasma fibronectin, and then it enters the bloodstream in a soluble form that is inactive.

In contrast, cellular fibronectin is released locally by several cells, including fibroblasts, chondrocytes, monocytes, and endothelial cells, at the site of inflammation [68]. Even though cellular fibronectin is highly potent in hemagglutination and fibroblast alignment, plasma fibronectin is much more essential in the initial phases of wound healing [29,68]. Soluble fibronectin forms a fibrin clot when it reaches the site of inflammation by binding to fibrin filaments. Platelet aggregation is also mediated by fibronectin attachment to the surface integrins of platelets, which eventually stops bleeding by forming a platelet plug [70]. The role of fibronectin is not limited to the homeostasis phase, but it is active in all stages of wound healing [29]. Platelets have a role in the formation of matrix fibrils from plasma fibronectin by increasing the expression of fibronectin attachment sites [68]. During early inflammation, fibronectin is cleaved into 110-120 kDa fragments by proteolytic enzymes, facilitating cellular interactions with monocytes [71]. In this phase, fibronectin participates in the clearance of the wound site from pathogens as it can have a role in phagocytosis by expressing opsonic properties [72]. Transforming growth factor beta (TGF-β) is also one of the cytokines that induce cellular fibronectin expression in cutaneous wounds, thereby stimulating the healing process [73]. The signaling pathway of Fibronectin expression is highly mediated by cellular communication network factor 2 (CCN2) in human fibroblasts. CCN2 is as essential as it can hinder fibronectin expression in its absence, even if TGF-β signaling is entirely conducted [73].

Additionally, it has been suggested that different isoforms of cellular fibronectin play a role in the re-epithelialization phase [66]. Fibronectin interacts with collagen type I and gelatin via the I6–9 and II1–2 domains, respectively [74]. Direct interaction between collagen and fibronectin is done by proteins named Periostin and Thrombospondin-2. Periostin acts as an intracellular scaffold for collagen fibers by localizing in the cytoplasmic reticulum of fibroblasts [75]. Thrombospondin-2 also contains domains with a high affinity for fibronectin, which therefore play a helpful role in the assembly of ECM components in the remodeling phase [76]. Fibronectin can interact with several members of the integrin family, such as α5β1 and αIIbβ3, through the Arg-Gly-Asp (RGD) motif in FNIII10 subunit [77]. In addition to an RGD motif, the PHSRN synergy sequence of fibronectin is required for full integrin-binding activity [78]. Fibronectin can also bind directly to growth factors, relaying soluble signals crucial for wound healing. These growth factor binding sites have been shown to occur at the heparin-binding domains (HBDs) of fibronectin [79]. Members of significant growth factors, such as PDGF, TGF-β, and FGF, contain multiple binding sites in fibronectin molecules; however, most of them have a high affinity for FN III12–14 [65]. Syndecan, a member of the small family of transmembrane proteoglycans, is another molecule that plays a role in fibronectin interactions. Members of this family enhance cell-fibronectin interactions with the help of their sulfate side chains [80,81]. Eventually, it is important to note that, apart from the vital role that different isoforms of fibronectin have, fibrils derived from plasma fibronectin are shorter in length compared to those derived from cellular fibronectin [82].

4.4 *Tight junction proteins*

The formation of new tight junctions between cells is an essential aspect of the wound healing process and must occur in a tightly regulated manner. The main transmembrane proteins involved in tight junctions are occludin and claudins, which are connected to the cytoskeleton via scaffolding proteins, including zona occludens-1 (ZO-1), ZO-2, and ZO-3 [46]. It is also important to note that the expression of these two proteins decreases in chronic wounds that remain in the inflammatory phase, while other proteins, such as the fibroblast growth factor family, exhibit a trend in expression over sustained inflammation [83].

4.4.1 *Occludin*

Occludin contains four transmembrane domains forming two extracellular loops and three cytoplasmic domains [84]. The two intracellular terminals of occludin, especially the carboxylic terminal (COOH), are phosphorylation sites rich in serine, threonine, and tyrosine residues where occludin can interact with other proteins such as ZO-1 [85]. Occludin, with a molecular weight of 59 kDa, belongs to the TAMPS proteins, which contain the MARVEL domain (MAL and Related proteins for Vesicle trafficking and membrane Link) [86]. The Occludin gene is on the long arm of chromosome 5 in humans (5q13.2), which encodes a 522-amino acid sequence [87]. The last 150 amino acids of the C-terminal domain in occludin can interact with F-actin directly. This direct interaction between the C-terminal domain of occludin and F-actin is a unique feature, as other tight junction proteins lack this ability and instead require additional mediators, such as scaffolding proteins, to facilitate protein-protein interactions. [88]. Phosphorylation induces two negative charges at physiological pH, which can alter the strength of protein-protein interactions in binding sites [89]. A study of occludin phosphorylation sites is highly recommended as it is considered necessary in

wound remodeling and tissue repair [90]. One of the essential sites of phosphorylation is serine 490 (S490). When serine 490 is phosphorylated in response to VEGF, the interactions of occludin with ZO-1 are attenuated. This data suggests that the regulation of occludin phosphorylation at this site plays a crucial role in the development of proliferative responses following endothelial damage [90,91]. Additionally, Inhibition of serine 408 (S408) phosphorylation by mediating the CK2 enzyme leads to more protein interactions in the lateral plasma membranes. So, dephosphorylated occludin at this site can interact with Claudin 2 (cldn2) through interaction with ZO-1 [92].

4.4.2 *Claudins*

Claudin, similar to occludin, is a transmembrane protein that plays a vital role in the formation of cell tight junctions and regulating cell permeability. Among 27 members of the claudin family in mammals, claudin 1 (cldn1) has the most interactions with scaffolding proteins, which modulate tight junction stability [93]. Unlike occludin, the two extracellular domains of claudin are different in size, and the two C-terminal and N-terminal intracellular domains are shorter in length [85,94]. The Claudin 1 (cldn1) gene is on the long arm of chromosome 3 in humans (3q28), which encodes a 211-amino acid sequence [95]. Interactions of Claudin 1 with scaffolding proteins such as zona occludens (ZO) and multi-PDZ domain protein 1 (MUPP1) are mediated through short linear motifs that bind to PDZ domains—named after PSD95, Dlg1, and ZO-1—which are commonly found in junctional adaptor proteins [96]. PDZ domains are small globular structures containing 80 to 90 amino acids that bind to the C-terminal residues of the intracellular domain. After inserting the hydrophobic motif of claudin one into the PDZ domains of proteins, 1 to 5 amino acids on the upstream binding site form an antiparallel beta strand that aligns with a beta strand in the PDZ domain [90]. Since the C-terminal of claudin 1 is rich in threonine, serine, and tyrosine, phosphorylation is also abundant in this area [83].

Contrary to the effect of phosphorylated S490 on occludin, which attenuates the interactions, it has been shown that phosphorylation of tyrosine residues in claudin 1 has no effect on the intensity and extent of interactions of this protein with ZO-1. Syndecan, a single-transmembrane proteoglycan, exhibits a striking resemblance to claudin 1 in terms of binding to PDZ domains in proteins [90,97]. Phosphorylation of PDZ binding motifs in syndecan does not affect the binding affinity to Tiam1. Syndecan can bind to Tiam1, whether it is phosphorylated or dephosphorylated, in this area. At the same time, it must be dephosphorylated to interact with the two PDZ1 and PDZ2 domains required for binding in the syntenin protein [98,99]. Apart from this, the binding of phosphorylated syndecan to Tiam-1 can make some shifts in the dynamics of PDZ domains in Tiam-1 [90].

4.5 *Interleukin 1*

The Interleukin-1 family comprises 11 pro-inflammatory and anti-inflammatory cytokines that play a significant role in regulating immune and inflammatory responses through their specific receptors. Some members of this family, such as IL-1β, are produced in the form of propeptides that require caspase proteins for biological activation [100]. IL-1β and other precursor ligands belonging to the IL-1 family, such as IL-33 and IL-1α, have long propeptides containing approximately 110 amino acid residues at the N-terminus [101].

The full-length IL-1α is cleaved by a calcium-dependent protease, calpain, to become mature [102,103]. In comparison, neutrophil Elastase and Cathepsin G take part in the activation process of IL-33 [104]. IL-1β is also activated by caspase-1, along with the involvement of cytosolic multiprotein complexes, known as inflammasomes [101,105]. The binding of IL-1 cytokines to their receptors leads to the recruitment of specific coreceptors, which ultimately triggers the intracellular signaling pathway [100].

Interleukin-1 family causes neutrophil recruitment with the help of lipopolysaccharide (LPS) from damaged vessels to the wound site [106]. Apart from this, macrophages and neutrophils, key cells in the inflammatory phase of wound healing, participate in fibroblast activation by releasing cytokines, including IL-1, IL-6, and IL-8 [17]. During the healing process, Schwann cells (SCs) belonging to the peripheral nervous system differentiate into progenitor-like cells for axon regrowth. This process leads to the induction of several factors, including IL-1α, IL-1β, Prostatic Acid Phosphatase-III (PAP-III), and Monocyte Chemoattractant Protein-1 (MCP-1), which attract blood-circulating monocytes to the site of injury [107,108].

In chronic wounds, the pro-inflammatory cascade induced by IL-1β and TNF-α activity persists for a prolonged period until the protease level increases. This process prolongs the inflammatory phase, which might lead to biofilm formation and microbial infection [109,110].

4.6 *Laminin*

Laminins are a family of ECM glycoproteins located in the basal lamina, which separates epithelial cells from the underlying stroma [111]. Laminin is a heteromeric protein with a molecular weight of 900 kDa comprising three subunits: α, β, and γ chains. This protein has roles in angiogenesis and the re-epithelialization phases of cutaneous wound healing [111,112]. Laminin-8 (α4β1γ1), laminin-10 (α5β1γ1) and laminin-5 (α3β3γ2) are the main laminins involving in wound healing actively [45,113,114]. Laminins-1, 5, and 6 are expressed in the skin basement membrane zone, where dermal/epidermal junctions are found [115]. Over angiogenesis, laminin-8 enhances endothelial cell

attachment, migration, and tubule formation in the dermal area, while the expression of laminin-10 is in blood vessels, in the vicinity of skin injury [45]. A5G81, a laminin-derived dodecapeptide, is used in wound closure [114]. Laminins can directly bind to several growth factors through their heparin-binding domains (HBDs), which are typically located in the laminin-type G domain (LG), specifically in the five globular domains of the C-terminus of the α3 subunit in laminin.[79]. In the epidermal basement membrane, α3β1 integrin is the primary receptor for laminin-332, made up of three distinct polypeptide chains (α3, β3, and γ2) which undergo proteolytic processing necessary for keratinocytes' adhesion, resulting in wound repair [116, 117]. Additionally, it has been demonstrated that the α3 G45 domain in laminin-332 influences the expression of MMP-9 and MMP-1 in primary keratinocytes. These proteins exert their proteolytic activities along the keratinocyte's path as it migrates [118].

4.7 Elastin

Elastin is a highly durable protein in the extracellular matrix that plays a predominant role in the elastic properties of various tissues and organs, including skin, lungs, tendons, cartilage, and blood vessels [119,120]. Tropoelastin, the soluble monomeric precursor of Elastin, is produced in fibroblasts and smooth muscle cells [121]. When tropoelastin leaves the cell membrane, it undergoes coacervation to form elastin fibers within the ECM [122]. Elastin is composed of both hydrophobic and hydrophilic domains. Nonpolar amino acids, typically valine, proline, and glycine, have been observed in hydrophobic domains, while hydrophilic domains of Elastin are mostly rich in alanine and lysine [119]. This long-lived protein, with a lifespan of approximately 70 years, provides resilience and elasticity to vertebrate tissues [123]. Both Elastin and tropoelastin can promote cellular responses such as proliferation and cell adhesion, which are important during wound healing [124].

Kappa-elastin, an elastin-derived peptide, has been shown to be chemotactic to monocytes during the inflammatory phase. In addition, matricryptins, bioactive ECM fragments formed by the proteolytic process of enzymes, are capable of regulating various physiological processes such as tissue repair and angiogenesis. For instance, elastin matricryptin VGVAPG, a six-amino acid fragment produced by the proteolytic cleavage of the MMPs family, is also chemotactic for both monocytes and fibroblasts [125]. The elastin receptor complex (ERC) is the primary receptor for elastin-derived peptides to interact with cells. ERC is a heterodimeric receptor comprising a peripheral protein named EBP serving as a binding site for elastin-derived peptides [126]. Intracellular signaling pathways follow this binding. In human dermal fibroblasts, pro-MMP-1 induction by these peptides contributes to the activation of the MEK1/2–ERK1/2 (Mitogen-Activated Protein Kinase Kinase 1/2 – Extracellular Signal-Regulated Kinase 1/2) signaling pathway via a mechanism dependent on Protein Kinase A (PKA) and Phosphoinositide 3-Kinase (PI3K) [127]. Cell surface heterodimeric transmembrane receptor, integrin α_v β_3, is also involved in the cell interaction of tropoelastin. This receptor binds to the RKRK sequence of tropoelastin located in its C-terminal domain [78]. Fibroblast migration and proliferation, which are necessary for later phases of wound healing, are induced by Elastin. Additionally, Elastin can enhance keratinocyte migration and terminal differentiation, which play a role in re-epithelialization and restoring the epidermal framework [52].

5. Material and methods

In this study, we introduced and examined the interactions of proteins involved in the cutaneous wound healing process. The online databases and websites we have used as references are: UniProt, SIGNAL, SIGNOR 2.0, PubMed, Reactome, GeneMania, MINT, MethA, QuickGO (GOA), and IntAct. Although there are some exceptions, we attempted to export data from articles published over the last 12 years. Data collection and finally processing lasted from the beginning of December 2021 to the end of June 2022.

6. Discussion

Angiogenesis, inflammation, and endothelial cell proliferation play a crucial role in cutaneous wound repair. According to studies carried out, proteins involved in the wound healing process create an enormous network of cell interactions and signaling. These proteins are classified into two key protein groups: those that serve as mediators. Firstly, it is essential to note that various proteins and growth factors have distinct and sequential effects on both wound beds and other regulatory factors, resulting in physical interactions and signaling pathways. Among all, co-expression of proteins is significant since it can form a chain of protein activities. PDGF is one of the key proteins necessary for the normal growth of blood vessels as well as cell proliferation and immigration. Figure 3 demonstrates the co-expression and physical interactions between integrins, interleukins, and syndecans involved in these signaling cascades. Signaling is regulated by the formation of PDGFA-PDGFB heterodimer based on their similarity [128]. PDGFs bind to collagens, thrombospondin (an early activator of lymphocytes), and osteopontin (an angiogenic inhibitor) [129]. The C-terminal of thrombospondin, which is named the cell-binding domain, can bind to many cells. For instance, it regulates the activity of some integrin families by binding to CD47 [130]. Complement, Uegf, Bmp1 (CUB) domain of TSG-6 protein increases fibronectin assembly and can form a bridge between fibronectin 1 (FN1) and thrombospondin [131,132]. Physical interactions between different types of thrombospondins and FN1, as well as the co-expression

of FN1 with VEGF, initiate the complex process of wound healing. VEGF exerts its angiogenic effects by binding to its specific receptor (VEGFR-2 or KDR) [133]. VEGFR-2 binds to VEGF-A, VEGF-C, VEGF-E, and VEGF-D homodimers [134]. This binding initiates receptor dimerization, which then activates the intracellular tyrosine kinase domains. VEGFR-2 activation relays downstream signals, including stress-activated protein kinase 2/p38 MAP kinase, phosphatidylinositol 3-kinase, and Focal Adhesion Kinase (FAK), as well as AKT, which lead to endothelial cell migration and vessel formation [135]. VEGFR-2 is a key receptor among the VEGFR proteins. Its activation relays signaling pathways, which can have negative or positive effects by expressing and activating different factors. For instance, it can lead to the expression of other VEGF receptors, such as VEGFR-1 [134]. This factor is the first mediator of the physiological effects of VEGF-A on angiogenesis, endothelial cell proliferation, and migration [134,136,137]. In addition, the signaling pathways involving fibronectin and collagen (particularly col6a5) and fibronectin 1 with HGF at the same site are other essential signaling systems involved in skin repair [138, 139]. These signaling pathways can eventually affect the activity of cell adhesion molecules, Interleukins (especially IL-7), and integrins [140]. Human IL-7 and IL-7Ralpha form a crucial complex when they bind to the γ_c receptor. The following signaling cascades play a fundamental role in ECM remodeling. Unlike other gamma (c) family receptors, IL-7Ralpha ectodomain uses glycosylation to modulate its binding to IL-7 [141]. Co-expression of Integrin beta-2 with the Interleukin family and its physical interaction with P-selectin glycoprotein ligand 1 (PSGL-1) induces another important signaling pathway [142]. Integrin beta-2 (GAL/ITGB2) is also a receptor for intercellular adhesion molecule1 (ICAM1), ICAM2, ICAM3, and ICAM4. Their simultaneous expression leads to precise coordination among them [143]. Physical interactions and signaling pathways induced by ITGA7 lead to the involvement of laminin in the repair process. Additionally, the co-expression of ITGA7 with IL33 and CLDN5 promotes the healing process. Although Claudin 1, 2, and 3 can interact with Claudin 5 and induce strong signaling pathways, they do not interact with each other [144]. Additionally, Claudin-1 can interact with tight junction protein1 (TJP1) and TJP2, also known as ZO-1 and ZO-2, from the tight junction protein group through their PDZ domains [96]. These interactions are further illustrated in Figure 4, highlighting the role of fibronectin and tight junction components in maintaining structural integrity. MMP2 plays a fundamental role by interacting with claudin, collagen, and FGFs. It can affect MMP1 and MMP7 activation, whereas MMP2 activation does not occur through the involvement of MMP1 and MMP7 [133,137,145]. MMP1 initiates its activity by cleaving the Pro33-Ile34 or Asn66-Leu67 bond, which is followed by an autolytic cleavage in Asn109-Tyr110 [136]. It is worth mentioning that MMP14 initially cleaves the Asn66-Leu67 and MMP2 binding sites, which subsequently leads to cleavage of Asn109-Tyr110 [146]. Under the physiologic condition, MMP14 binds to TIMP2 and serves as a receptor for proMMP2 [147]. The activity of proMMP2 is enhanced by its binding with collagen 1 [148]. In this case, the involvement of another Integrin member, integrin Beta 1, facilitates proMMP2 binding to the cell surface [149].

Therefore, key proteins, including matrix metalloproteinases (MMPs), platelet-derived growth factors (PDGFs), fibronectin, occludin, claudin, Interleukin-1 family members, laminin, and Elastin, form an extensive network of proteins that leads to various signaling pathways essential for skin repair. So that the absence of any of these factors might lead to impaired wound healing.

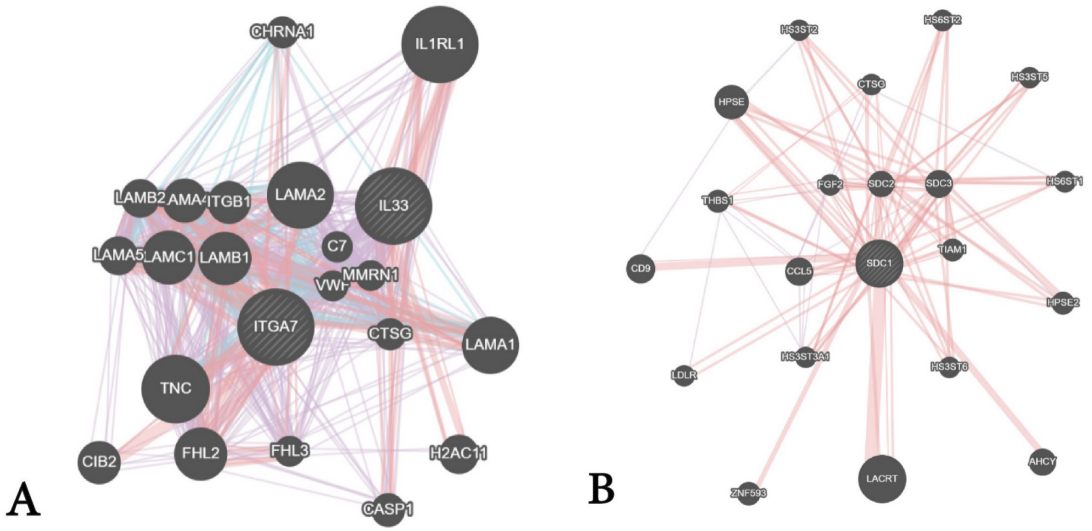

Figure 3. Physical interactions and co-expression of proteins. A) ITGA7: Integrin alpha 7, IL-33: Interleukin 33. B) SDC1: Syndecan 1

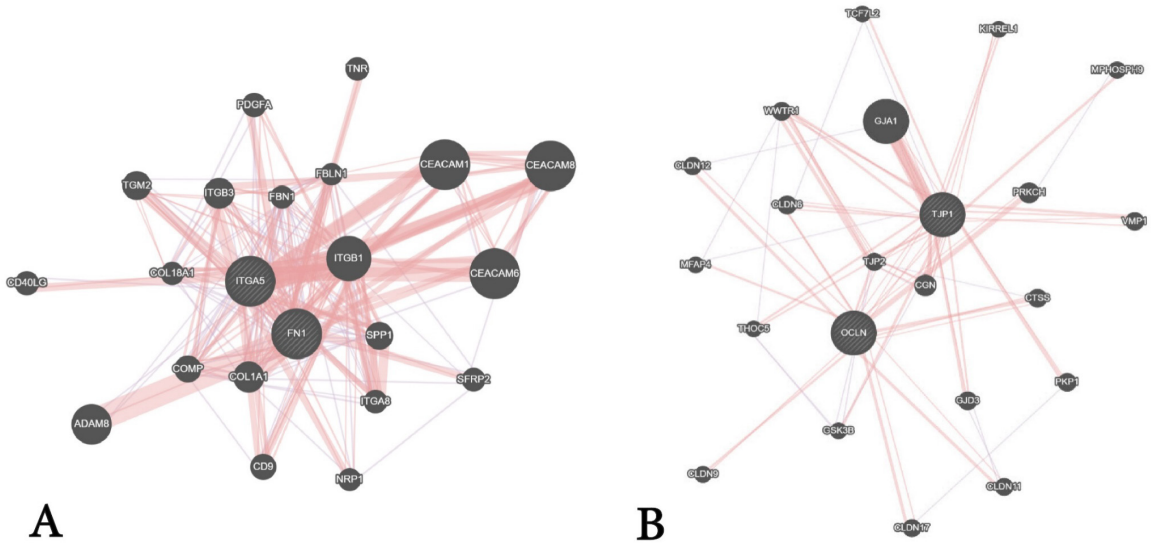

Figure 4. Physical interactions and co-expression of proteins. A) ITGA5: Integrin alpha 5, FN1: fibronectin B) TJP1: ZO-1 (scaffolding protein), OCLN: Occludin

Regarding vascular endothelial growth factor A (VEGFA), which is considered the primary stimulus for the angiogenesis signaling pathway, it is important to note that upon formation of the VEGFA–VEGFR2 heterodimer, several downstream signaling cascades are activated, including the Ras–Raf–MEK–ERK pathway, phospholipase C–protein kinase C (PLC–PKC), Ras homolog family member A (RhoA), signal transducer and activator of transcription (STAT), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), c-Jun N-terminal kinase (JNK), and focal adhesion kinase (FAK). So, any interruption in this signaling might inhibit angiogenesis [150]. In addition, the function of proteins such as von Willebrand Factor (VWF), P-selectin, Granzyme K, and plasminogen, classified as mediator proteins, is essential. For example, GzmK induces IL-6 expression in keratinocytes and dermal fibroblasts, which are activated by protease-activated receptor 1 (PAR-1) [151]. Overall, it is evident that mediator proteins play a crucial role in the wound healing process, as well as key proteins, which are explained in detail. A detailed summary of the main mediator proteins involved in wound healing, including their molecular functions, biological roles, and interaction profiles, is provided in Supplementary Table 1. Thus, our understanding of these complex mechanisms, combined with our knowledge of wound healing, can accelerate the wound healing process and prevent wounds from becoming chronic.

7. Conclusion

Understanding the dynamic and multifaceted nature of protein interactions in cutaneous wound healing is essential for developing effective therapeutic interventions, particularly for chronic wounds. This review highlights the pivotal roles of key proteins—such as MMPs, PDGFs, fibronectin, laminin, interleukins, tight junction proteins (occludin and claudin), and elastin—as well as mediator molecules that modulate signaling cascades and cellular responses. These proteins coordinate a complex network of molecular interactions across all phases of healing, from hemostasis to remodeling. Disruption in the expression or function of any component can impair the healing trajectory and prolong inflammation. Integrating bioinformatics-based protein interaction mapping with experimental data can offer novel insights into targeted therapies for enhancing wound resolution and preventing chronicity.

Supplementary files

Supplementary file 1.

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Authors' contributions

M SN: Conceptualization of the review, primary drafting of the manuscript, and coordination of revisions. S Kh: Contributed to the design and structure of the review, critical revision of content, and interpretation of data from literature sources. H BKhT: Assisted with literature search, data collection, and initial drafting of sections related to biomaterials and

their applications. SM T: Provided input on the technical aspects of wound dressings, assisted in analyzing data, and contributed to manuscript editing. Sh H: Involved in drafting and revising the manuscript, with a focus on the biomedical engineering aspects, and provided critical feedback on the review's final version. All authors read and approved the final version of the manuscript.

Conflict of interest

No potential conflict of interest was reported by the authors.

Ethical declarations

Not applicable.

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