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Chapter 2

Regulatory Mechanisms and Chemical Signaling of Mediators Involved in the Inflammatory Phase of Cutaneous Wound Healing

Fernando Pereira Beserra,
Lucas Fernando Sérgio Gushiken,
Maria Fernanda Hussni and
Cláudia Helena Pellizzon

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Abstract

Wound healing is a highly complex biological process composed of three overlapping phases: inflammatory, proliferative, and remodeling. The acute inflammatory response has being an integral role in tissue healing and fundamental for the homeostasis and reestablishment. This phase depends on the interaction of cytokines, growth factors, chemokines, and chemical mediators from cells to perform regulatory events and complex interactions of the extracellular matrix, extracellular molecules, soluble mediators, various resident cells such as fibroblasts and keratinocytes, and infiltrated leukocyte subtypes that act to restore or replace the integrity of the skin. If this well-orchestrated response becomes deregulated, the wound can become chronic or progressively fibrotic, with both outcomes impairing tissue function, which can ultimately lead to organ failure and death. In this chapter, we will review the pathway in the skin healing cascade, relating the major chemical inflammatory mediators, cellular and molecular, as well as demonstrating the local and systemic factors that interfere in healing and disorders associated with tissue repair deficiency in chronic inflammations, burns and hypertrophy.

Keywords: wound healing, inflammation, cytokines, growth factors, chemokines

1. Introduction

1.1. Skin wound healing

Skin is the largest organ of all vertebrates, and it is very important to protect the organism against external damage [1]. When the loss of structural integrity of the skin occurs, the organism starts the wound healing process, involving some coordinated, interdependent, and overlapping mechanisms—such as inflammation, cell proliferation, reepithelialization of wounded area, and extracellular matrix remodeling—to restructure the skin homeostasis [2, 3]. The initial mechanism of wound healing is the fibrin clot synthesis to avoid bleeding and to keep the local hemostasis, leading to the platelet retention and activation of local vascular mediators [4, 5]. From now on, there is the dilatation of the local vessels due to the release of histamine and serotonin, as well as the increase of vessel permeability, improving the leukocyte migration to the wounded area and starting the inflammatory process. In the first 5 days after the lesion, neutrophils are attracted to the region, removing pathogenic antigens and dead tissue through phagocytosis and protease secretion. After 3 days, there is the macrophage migration to the wounded area, with the maintenance of inflammatory response [5]. Due to the tissue destruction, the local keratinocytes release interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), essential cytokines in the inflammatory mechanism, through recruitment and activation of leukocytes in the region and with important roles coordinating other wound healing mechanisms. With these facts, keratinocytes, macrophages, platelets, and endothelial cells of wounded area release some mediators such as growth factors (EGF, FGF, PDGF, TGF-β), cytokines (IL-1β, IL-6, IL-8, IL-10, TNF-α, IFN-γ), and chemokines, which will control other subsequent mechanisms in skin wound healing [6, 7].

Therefore, the inflammatory mechanism is an important step to the correct and well-coordinated wound healing, modulating the subsequent mechanisms of healing. Furthermore, the comprehension of inflammatory response can lead to new treatments to wound repair and decrease of healing disorders like hypertrophic scars, keloids, chronic inflammation, skin infections, and unwounded lesions [8].

2. Materials and methods

The search for this chapter was carried out on PubMed, Scopus, and Web of Science until June 2018, using “inflammation”, “inflammatory process”, “skin wound healing”, “cytokines”, “chemokines”

Model	Mediator	Target/signaling protein	Biologic effect	References
In vivo BALB/c mice	CD4 cells	IL1β, IL-6, IL-17, IFN-γ, and CXCL-1 IL-4	The absence of CD4 and CD8 lymphocytes changes in cytokine expression and inflammatory cell infiltrate, but does not influence wound breaking strength, collagen content, or angiogenesis	Chen et al. [50]
	CD8 cells	IL1β, IL-6, TNF-α, CXCL-1 and CCL-2, IL-4		

Model	Mediator	Target/signaling protein	Biologic effect	References
In vivo BALB/c mice	Neutrophil	MPO, macrophages, and collagens	Neutrophil depletion exhibited significantly accelerated re-epithelialization, without altering the macrophage infiltration or the collagen content in the wound bed	Dovi et al. [51]
In vivo C57BL/6 mice	Epinephrine	IL-6, IL-1β, TNF-α, IL-1α, and GM-CSF and PMN	Epinephrine altered the neutrophil (PMN)-dependent inflammatory response to a cutaneous wound through an IL-6 mediated mechanism via β2 adrenergic receptor-dependent	Kim et al. [52]
In vivo C57Bl/wild-type mice	IL-1β	Human recombinant IL-1β, occludin, claudin-1, claudin2, claudin-3, and claudin-5	IL -1β induced increased claudin -1 expression in cell culture	Rozlomiy and Markov [53]
In vivo BALB/C mice	IL-12	Recombinant murine IL-12-rMuIL-12/collagen structure and alignment	IL-12 induced a rapid onset and higher metabolic activity in wounded skin at early time	Li et al. [54]
In vivo BALB/C mice	EFG	EGFR/vaccination extracellular domain (ECD)	Not change the wound healing and inflammatory speed	Fuentes et al. [55]
In vivo BALB/C mice and IL-6 KO mice	IL-6	IL-6/ICAM-1 VCAM-1 IL-1α Il-1β MIP-1α	Delayed angiogenesis and collagen deposition, by the reduced expression of angiogenic and fibrogenic growth factors Reduced inflammatory response	Lin et al. [56]
In vitro Keratinocytes	IL-1β and TGF-β1	IL-1β TGF-β1/tissue type plasminogen activator (tPa)	IL-1 β interacts com PA by tPA TGF-β1inibits functional tPA	Lian et al. [57]
In vitro Human and mice fibroblasts	Platelet-derived growth factor (PDGF)	IL-8	Fetal fibroblasts produced less IL-8. Much less IL-8 in stimulated fetal fibroblasts than in adults	Liechty et al. [58]
In vivo C57/Bl6 mice and Mgl2DTR/GFP mice	CD301b macrophage	IL-10, platelet-derived growth factor–β and TGF-β1	CD301b-expressing subpopulation of macrophages is critical for activation of reparative process	Shook et al. [59]
In vivo Levels and role of chemokine CX3CL1 (fractalkine) and its receptor CX3CR1 in mouse model	CX3CL1 and CX3CR1	MPO, Hydroxyproline (collagen accumulation at the wound sites), TGF-1, VEGF	Inflammation, fibrosis, neovascularization, and regeneration of parenchymal cells were affected by the receptor	Ishida et al. [31]

Model	Mediator	Target/signaling protein	Biologic effect	References
In vivo db/db mice as a diabetic skin wound model.	Peptide inhibitor of complement C1 (PIC1)	complement system (CS), Signal transducer, activator of transcription 4 (STAT4), Leukocyte infiltration, C5a, C3, C3a	PIC1 loaded into the derma CELL did reduce the number of inflammatory cells in the wound bed	Cunnion et al. [60]
In vivo kCYC/mice	IL-10	Mast cells migrating, Macrophages, IL-10, IL-6, aFGF, bFGF, TGF-1, PDGF, TNF-α mRNA	kCYC/mice mast cell increased. IL-10: increased, bFGF decreased in kCYC/mice. IL-10 plays an important role in delayed wound healing	Kimura et al. [61]
In vivo C57BL/6J mice	IL-1β	p38, MAPK, ERK	IL-1β stimulates PTGS2 in fibroblast and p38-MAPK in other cells. PGE2 activates INHBA	Arai et al. [62]
In vivo Sprague Dawley Rats	IL-4, IL-12, IL-6, IGF-1 and IFN-α e γ	—	IGF-1, IL-4, IL-6, and IL-3 important in inflammatory phase	Lania et al. [63]
In vivo Mouse model with conditional depletion of macrophages	Inducible diphtheria toxin receptor + diphtheria toxin injections + mice lacking the TGF-b receptor type II (TbRII), Depletion of macrophages	Number of macrophages, neutrophils, and cells positive for activated caspase-3, VEGF-A, or TGF-β1	Inflammatory phase: reduced formation of vascularized granulation tissue, leading to minimized scar formation. Phase of tissue formation: severe hemorrhage in the wound. Wound closure did not occur. No significant impact in tissue maturation phases.	Lucas et al. [64]
In vivo C57Bl/6J mice	Ly6cloMHCIIhi macrophage	IL-17	Ly6cloMHCIIhi macrophages had a non-inflammatory transcriptomic profile and demonstrated that inhibition of IL-17 in mice accelerated normal and delayed healing.	Rodero et al. [65]
In vivo C57BL/6mice	γδ T Cell	FGF-7, FGF-10, IGF-1, JAML	γδT Lymphocytes stimulate the gene and protein expression of important mediators in acute healing model	Xu et al. [66]
Mutant mice ICOS −/− ICOSL -?-	IL-6 and IL-4	—	IL6 and ICOS-ICOSL signaling the skin wound healing in mutant mice	Maeda et al. [67]
In vivo C57BL/6 mice and human acute wounds	Macrophage M1 and M2	IRF-8	IRF-8 is an inflammatory mediator. Inhibition of IRF-8 impairs wound healing.	Guo et al. [68]

Model	Mediator	Target/signaling protein	Biologic effect	References
			IRF8 coordinates M1 macrophage population (decrease of M1 mediators IL-1 β, IL-6, TNF-α, iNOS), with no interference in M2 macrophage mediators (arg-1, mrc-1, IL-10)	
In vitro Human skin fibroblasts CCD966-SK and HaCaT keratinocytes In vivo BALB/C mice	Fibroblasts and keratinocytes IL-19	IL-19	IL-19 upregulates KGF expression in fibroblasts and KGF induces IL-19 expression in keratinocytes KGF promotes keratinocyte proliferation. IL-19 induces keratinocyte migration	Sun et al. [69]
In vivo SKH-1 mice	COX-2	COX-1 and COX-2	Selective inhibition of COX-2 and nonselective inhibition of COX-1 and COX-2 did not affect the healing of sutured surgical incisions in mouse skin.	Blomme et al. [70]
In vivo BALB/c mice	IFN-γ and TGF-β1	MPO, TGF-β, Stat1, P-Stat1, Smad2, P-Smad2, Smad3, Smad7, α-Tubulin, VEGF, CD3, IL-12p35, IL-12p40, IL-18, COLIAI	Crosstalk between the IFN-γ/Stat1 and TGF-β1/Smad signaling pathways in the skin wound healing.	Ishida et al. [71]
In vivo Wistar rats	—	EGF, VEGF, IGF and FGF	Growth factors accelerated the healing process promoting greater angiogenic activity and accelerated fibroplasia and the deposition of type I collagen	de Masi et al. [72]
In vivo C3H/Hej TLR4-deficient and wild-type C3H/HeOuj mice In vitro NHEK and THP1 cell line	TLR4	CD3+, T cells, Ki67, NF-κB, p-p38, and p-JNK	TLR4 is activated in early skin wound healing, with a functional mutation of TLR4 results in altered inflammatory cell infiltration, differential cytokine production, and impaired wound closure, besides IL-1β production by injured keratinocytes is induced through the TLR4-p38/JNK pathway	Chen et al. [73]
In vivo C57BL/6 mice	Vγ4 T cells	IL-17A, IGF-1, CCL20, NF-κB p65, p-NF-κB p6, STAT3, p-STAT3, IL-1β, IL-23p19	Mechanistic link between Vγ4 T cell-derived IL-17A, epidermal IL-1β/IL-23, DETC-derived IGF-1, and wound healing responses in the skin	Li et al. [74]

Model	Mediator	Target/signaling protein	Biologic effect	References
In vitro Primary keratinocytes and fibroblasts of IL-6 KO or C57BL/6 mice	IL-6 from keratinocytes and fibroblasts	IL-6, STAT3	IL-6 induces keratinocyte migration indirectly, through the STAT3 activation cascade in fibroblasts, with the synthesis of a fibroblast-derived factor	Gallucci et al. [75]
In vivo Ja18KO (iNKT cell-deficient) mice and C57BL/6 mice	Invariant natural killer T cells (iNKT) and neutrophils	MIP-2, KC, IL-17A, MCP-1, RANTES	MIP-2, KC, IL-17A (neutrophil attractors) were increased in JA18KO mice. MCP-1 and RANTES (macrophage and lymphocyte attractors) were decreased in Ja18KO mice. Decrease of neutrophil apoptosis in Ja18KO mice. iNKT ciNKT cells promote skin wound healing by regulating neutrophil apoptosis	Tanno et al. [76]
In vivo PPAR-γ KO mice and C57BL/6 J male mice	PPAR-γ from macrophages	PPAR-γ, TNF-α, VEGF, collagen 1	Increase of TNF-α in PPAR-γ KO mice and delay in wound healing	Chen et al. [77]
In vivo Human incision model	IL-4 from mast cells	IL-4, MCP-1	Increased MCP-1 chemoattractant activity in mast cell migration. Increase of IL-4 synthesis by mast cells IL-4 stimulates fibroblast activation	Trautmann et al. [78]
In vivo WBB6F1/J-KitW/KitW–v mast cell KO female mice and WBB6F1 female mice	Mast cells	TNF-α, MIP-2, VEGF, FGF-2	Decrease of neutrophil infiltration in KO mice. Increase of FGF-2 in KO mice. Mast cells modulate neutrophil infiltration in wound site, with unlikely influence in proliferative phase of wound healing	Egozi et al. [79]
In vivo miR-31 loss-of-function mice	miR-31	NF-kB, STAT3, RAS/MAPK	Increase of miR-31 in wound edge keratinocytes during inflammation through NF-kB and STAT3 pathways miR-31 regulates keratinocyte migration through RAS/MAPK pathway	Shi et al. [80]
In vitro Primary normal human	IL-6, IL-8, TNF-α	STAT3, p38, JNK, EGFR	STAT3, p38, JNK, and NF-kB activation lead to IL-6, IL-8, and TNF-a increase in	Han et al. [81]

Model	Mediator	Target/signaling protein	Biologic effect	References
keratinocytes In vivo BALB/c female mice			infected wounds. Mixidin2 and mixidin3 modulated inflammatory signaling with anti-inflammatory activity	
In vivo B57BL6/J, B57BL6/NJ, CD301bGFP-DTR, and Il27Ra−/− mice	IL-27 (dendritic cells)	Keratin-6 (keratinocytes)	IL-27 is synthesized by dendritic cells and modulates keratinocyte proliferation, migration, and differentiation after skin injury	Yang et al. [82]

Table 1. Chemical mediators involved in the inflammatory response of skin wound healing.

and "growth factors" as keywords. The articles published in the last 20 years were considered (1998–2018). The results are displayed in **Table 1**.

3. Results and discussion

3.1. Mediators involved in the inflammatory phase of wound healing

Wound healing is an extremely dynamic and interactive biological process involving complex interactions of extracellular matrix, extracellular molecules, soluble mediators, multiple resident cells (fibroblasts and keratinocytes), and subtypes of infiltrating leukocytes that together act to restore integrity of the damaged tissue and replace the lost. This process comprises three sequential and overlapping stages, regardless of the amount of injured tissue: hemostasis/inflammation; cell proliferation and matrix repair; and reepithelialization and remodeling of scar tissue, which involve complex biochemical and cellular mechanisms [9].

The inflammatory phase, hemostasis, leukocyte migration, and the beginning of the tissue repair cascade occur. Initially, in response to inflammatory agents, there is reduction of blood flow by vasoconstriction, and with extravasation of blood from the injured vessel, platelets are activated causing the coagulation process to begin [10]. During this process, there is a progressive increase in vascular permeability to migrant cells and biologically active substances. From this process, essential elements for the physiological continuation of healing appear: a fibrin framework, necessary for the migration of the cells that will reach the lesion site, and pro and anti-inflammatory chemo/cytokines that will aid in cell activation and migration [11].

3.2. Neutrophils and macrophages

Neutrophils are the first immune cells recruited into wounded tissue to play a role in reestablishing tissue homeostasis through pathogen phagocytosis and macrophage recruitment as well as excessive neutrophil activity which can contribute to the development of

nonhealing wounds. They play a central role in both killing microbes and promoting wound healing [12]. These cells are extremely important in the inflammatory process, but once recruited into wound sites in such large numbers with exacerbated cytokine secretion, overproduction of reactive oxygen species (ROS), causing extracellular matrix (ECM) and cell membrane damage, and resulting in premature cell senescence [13].

Monocyte-derived macrophages are often considered to be the most important immune cell type in this process. In intact skin, these cells are the most abundant cell types performing sentinel and homeostatic function. The monocytes migrate from vascular circulation to wound. Both infiltrating and resident macrophages on skin are activated by local signals and developed into several subpopulations defined by their different functional phenotypes [14]. Many studies have confirmed that macrophages are critical for proper skin wound healing [15–17]. Upon initial infiltration, proinflammatory macrophages, also called M1, are also responsible for removing cellular debris, damaged matrix, microbes, and neutrophils [17].

3.3. Cytokines

Wound healing is regulated by growth factors and cytokines that are essential not only in the inflammatory process but also in the cell proliferation and maintenance in the repair process by various mechanisms [18].

Cytokines released by neutrophils during apoptosis are chemotactic for monocytes, which start to arrive 5–6 h post injury. IL-1β is a key interleukin of antimicrobial response by inflammatory response amplification; it stimulates leukocyte recruitment, the release of acute phase proteins, and the increase of permeability of blood vessels [19]. Some authors consider this cytokine as part of a proinflammatory positive feedback loop that sustains a persistent proinflammatory wound macrophage phenotype, contributing to impaired healing of diabetic wounds [18].

TNF-α is a second proinflammatory cytokine that contributes to a chronic wound state. It acts on several stages of leukocyte recruitment mechanism, neutrophils and macrophages, inducing molecular adhesion regulation, chemokine production, and metalloproteinase matrix, as well as tissue inhibitors of metalloproteinases [20]. Interleukin IL-6 is a soluble proinflammatory mediator with pleiotropic activities in inflammation, hematopoiesis, and immune responses [21]. Together with TNF-α and IL-1β, IL-6 is present in high concentrations in inflammatory processes. After IL-6 is secreted into the area of injury at the beginning of the inflammatory process, it is directed to the liver through the bloodstream, transmitting the information and inducing the hepatocytes to produce certain inflammatory agents [22]. Another important cytokine in the inflammatory phase is IL-8, which also acts as a chemokine (CXCL8). This cytokine is mainly produced by monocytes and in smaller amounts by fibroblasts, endothelial cells, keratinocytes, melanocytes, hepatocytes, and chondrocytes. It usually receives stimuli from other cytokines, such as IL-1, TNF-α, and IFN-γ [23]. The main action of IL-8 is the migration to cells of the immune system, mainly neutrophils, also determining an increase in the expression of endothelial adhesion molecules cells [13].

Since prolonged presence of proinflammatory cytokines may prevent resolution and both pro and anti-inflammatory cytokines are necessary for wound healing, sequential delivery of pro and anti-inflammatory cytokines could be an interesting strategy for improving chronic wound healing [17]. For example, IL-22, considered a proinflammatory cytokine, helped the wound healing of diabetic mice by inducing keratinocyte proliferator and signal transduction and activation of transcription 3 (STAT3) [24]. In this same context but in other tissues, to improve bone repair, decellularized bone was engineered to sequentially release IL-4 (proinflammatory cytokine) and implanted in mice at the site of injury. The sequential release promoted macrophage polarization to switch from a pro to an anti-inflammatory phenotype, resulting in improved wound healing [25].

IL-10 is a regulatory cytokine, which can be secreted by many kinds of immune cells, including Th1, Th2, Th17, Treg, and CD8+ T cells, B cells, dendritic cells, macrophages, NK cells, eosinophils, neutrophils, basophils, and MCs, as well as nonimmune cells including keratinocytes. This cytokine is considered an anti-inflammatory cytokine because it is capable of inhibiting the production of other proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6 [26]. In addition to its potent anti-inflammatory effects, IL-10 has been shown to regulate fibrogenic cytokines, such as transforming growth factor-β (TGF-β), as a part of its role in the regulation of tissue remodeling [27].

3.4. Chemokines

Chemokines are small molecules that induce chemotaxis and activation of certain subsets of leukocytes. They are classified into four types: CC chemokines, CXC chemokines, C chemokines, and CX3C chemokine. Chemokines play important roles in wound healing and are important for maintaining skin homeostasis, and their disruption can result in skin pathologies [28]. They also play important roles in establishing microenvironment in which migratory immune cells, together with skin-resident cells, cause prolonged inflammation [29].

CX3CL1 is expressed by inflamed endothelial cells and epithelial cells, including macrophage, keratinocytes, and vascular smooth muscle cells, whereas CX3CR1 is mainly expressed by neutrophils, monocytes, mast cells, T cells, and NK cells [30]. In the cutaneous wound healing, CX3CL1 has been shown to be expressed by macrophages and endothelial cells, while CX3CR1 is expressed by macrophages and fibroblasts. Decreased expression of macrophage-related cytokines, such as TGF-β and VEGF, and reduced deposition and α-smooth muscle actin and collagen were shown in the injured skin of CX3CR1−/− mice [31].

3.5. Growth factors

Growth factors are naturally occurring endogenous mediators capable of controlling the control of cell growth, proliferation, migration, and differentiation [32]. Once bound specifically to its receptor, the ligand-receptor interaction is able to activate intracellular signal transduction pathways that regulate different cellular functions [33].

PDGF plays a crucial role in the healing process in both chronic and normal wounds. This growth factor is released from degranulating platelets following an injury into the wound fluid [34]. PDGF stimulates mitogenicity and chemotaxis of cells, such as neutrophils, macrophages, fibroblasts, and smooth muscle cells to the site of the wound, initiating the inflammatory process stage [35]. Its function has already been described during the stage of epithelialization of wound healing by upregulating the production of growth factors, such as insulin-like growth factor (IGF)-1 and thrombospondin-1, in turn IGF-1 increases the motility of keratinocyte cells and thrombospondin-1 inhibits proteolytic and enzymatic degradation of PDGF [36].

Angiogenesis is an extremely important process in normal development and tissue homeostasis and repair, besides contributes directly also to various forms of pathology, such as tumor development and metastasis, psoriasis, rheumatoid arthritis, and wet macular degeneration [37]. One of the most important proangiogenic mediators is vascular endothelial growth factor (VEGF), responsible for stimulating new blood vessels formation, tissue proliferation, migration, differentiation, and survival, which contribute to the angiogenesis process, in addition to influencing the repair and wound closure and granulation tissue formation [38]. The VEGF family has several members, and one of its members such as VEGF-A begins the process of wound healing promoting biological events linked to angiogenesis and migration of endothelial cells [39]. Administration of VEGF-A has been reported to restore impairment of angiogenesis in diabetic ischemic limbs in an animal model as well as to improve the reepithelialization process of diabetic wounds [40].

Epidermal growth factor (EGF) stimulates proliferation and differentiation of various cells, including fibroblasts, endothelial cells, and epithelial cells, and shows mitogenic and migratory activity on the edge keratinocytes of the lesions [41]. EGF participates in this mechanism, which is considered essential in the cutaneous wound healing, which begins a few hours after the injury, but presents a more evident activity in the proliferative phase of wound healing, and continues until the extracellular matrix remodeling phase [42].

Another growth factor that involves healing process activity is the family of fibroblast growth factors (FGF), which have already been reported to play crucial events in the wound healing process [43]. FGFs are secreted by keratinocytes, fibroblasts, endothelial cells, smooth muscle cells, chondrocytes, and mast cells [44]. During an acute cutaneous wound process, it has been reported an increase in the production of FGF-2 and that they are responsible for formation of granulation tissue, reepithelialization, and tissue remodeling [45]. Moreover, functions such as synthesis, deposition of various constituents of the extracellular matrix, and increased motility of keratinocytes are regulated by FGF-2 [46].

Transforming growth factor type-β (TGF-β) activity in the healing process was analyzed by being one of the proteins with the greatest spectrum of activities, with effect on cell proliferation, differentiation and production of extracellular matrix, and immunological modulation [46, 47]. Moreover, TGF-β has many biological activities and is thought to be a particularly important contributor to fibrosis, angiogenesis, and tissue repair. This growth factor can also influence T cells, including Th17 and Treg cells, as well as B cells, dendritic cells, NK cells, neutrophils, and eosinophils [48, 49].

4. Conclusion

Increasing scientific knowledge has contributed to define highly coordinated molecular and cellular events involved in the cutaneous wound healing. Recent findings show that there is a clear correlation between the stage of the wound and its effectiveness in the healing process, and endogenous mediators, such as cytokines, chemokines, and growth factors, indicate important and crucial steps in the normal healing and are useful as prognostic indicators. Although much is known about the cellular and molecular basis of normal skin healing, there are still avenues of research left to unravel that will guide us to better therapies, new therapeutic targets, and strategies for the skin wound treatment, especially chronic wounds.

Conflict of interest

The authors declare no conflict of interests.

Author details

Fernando Pereira Beserra[1], Lucas Fernando Sérgio Gushiken[1], Maria Fernanda Hussni[2] and Cláudia Helena Pellizzon[1]*

*Address all correspondence to: claudia@ibb.unesp.br

1 Department of Morphology, Institute of Biosciences of Botucatu, São Paulo State University (UNESP), São Paulo, Brazil

2 Undergraduate Student School of Veterinary Medicine and Animal Science, São Paulo State University (UNESP), São Paulo, Brazil

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