



ROLE OF IMMUNE CELLS IN WOUND HEALING: A MINI-REVIEW

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ABSTRACT:

The skin is the largest anatomical organ in the human body and performs many physiological functions. Protection of the body from harmful environmental influences is among the main functions of the skin. Skin wounds initiate a protective programme to restore tissue integrity and maintain the homeostasis of the body. This process occurs in four consecutive phases: haemostasis, inflammation, proliferation, and tissue remodelling. Different types of cells participate, among which immune cells play a key role. The complex interactions between these cells and the extracellular matrix ensure the physiological course of tissue healing. The purpose of this review is to present the skin as a protective organ and to describe the involvement of immune cells, specifically granulocytes and mononuclear cells, in the distinct stages of wound healing.

Keywords: skin; skin protection; wound healing; immune cells,

INTRODUCTION

The skin is an anatomical organ that covers the entire external surface of the body. With a surface area of about 2 m² and a mass constituting about 15% of the total body mass, it is the largest organ of the human body [1]. Various factors influence the properties and condition of the skin. Among them are the anatomical location (face, limbs, torso), ethnicity, gender, or even lifestyle and body mass index [1].

The physiological functions of the skin are essential for maintaining the homeostasis of the individual and for the survival of the species [2]. Among the most important functions of the skin are protective, thermoregulatory, sensory, water regulation, absorption, and synthesis of vitamin D and melanin [2]. The skin is an organ that is important for the expression of an individual's emotions, especially the skin of the face, and mediates communication between individuals in society [2].

The review aims to summarise the protective strategies of both intact and injured skin, focusing on the involvement of neutrophils, eosinophils, macrophages, lymphocytes, and plasma cells in the physiological course of wound healing.

MATERIALS AND METHODS:

This mini-review includes recent studies on the role of certain immune cells in the physiological process of wound healing. A search of the Medline/PubMed and Google Scholar databases was conducted. The following keywords and phrases were used: „skin“, „skin protection“, „wound healing“, and „immune cells“, combined with the keywords „neutrophils“, „eosinophils“, „macrophages“, „lymphocytes“, and „plasma cells“. Studies were deemed eligible based on the following criteria: peer-reviewed only, published in English, and comprising both research and review articles. Exclusion criteria comprised non-peer reviewed sources, studies lacking sufficient methodological detail, and articles that did not focus on the role of the considered immune cell types in the wound healing process.

THE SKIN AS A PROTECTIVE BARRIER OF THE BODY

The skin is the outermost layer of the body and, unlike other organs, is directly exposed to the influences of the external environment [3]. It serves as a mechanical barrier that protects the organism from external influences—

chemical trauma, microorganisms, radiation [2], sunlight, clothing, and pollution, as well as trauma caused by burns, accidents, or surgeries [3]. In addition, the skin's mobility and elasticity are crucial for normal joint movement, while its strength is essential in areas such as the hands and feet, which are regularly subjected to minor trauma [2]. The physiological characteristics of the skin define it as an extraordinary and vital organ [3].

Strategies for healthy skin protection

The skin is a complex organ that has multiple strategies to protect the body from external threats [4]. First of all, these are its anatomical characteristics related to its organ functions [5]. The skin is anatomically organised into three layers—epidermis, dermis, and hypodermis. The different layers of the skin build a complex and coordinated system of protection for the body.

In uninjured skin, the epidermis serves as the outer protective layer [6]. This layer is impermeable [6] and contains keratinocytes, Langerhans cells, Merkel cells [5], and melanocytes [7]. Epidermal cells are arranged in continuous layers, comprising the basal layer, stratum spinosum, granular layer, and stratum corneum (horny layer). Stratum lucidum is an additional layer represented in some areas of the body (palmoplantar area) [8]. The epidermis also contains sebaceous glands, sweat glands, and hair follicles, which extend into the deeper layers of the skin [5,6]. The epidermis is a physical and biological barrier that prevents pathogens and irritants from entering the body [5].

The middle layer, the dermis, also has two distinct layers: the papillary (superficial) dermis and the reticular (deep) dermis [8]. The dermis consists predominantly of connective tissue, containing blood vessels, lymphatic vessels [5], skin appendages, and mechanoreceptors [7]. Cells found here are fibroblasts, mast cells [5] and immune cells [6]. Also, among the components of the dermis are three types of fibres: collagen, elastic, and reticular. Dermis provides the skin with resilience, strength, and flexibility [5]. The dermis also provides nutrients and immune protection [6].

Beneath the dermis is the hypodermis (also known as subcutaneous adipose tissue), the bottom layer of the skin. The hypodermis has many functions: it acts as the main structural support of the skin, a shock absorber to protect from harm, and has an important role in body temperature control [5]. It is rich in adipocytes [7], well vascularised [5], provides growth factors to the dermis, and acts as an energy reservoir [7].

In addition to acting as a physical barrier, the skin also provides protection by releasing various biomolecules [9]. The lipids of the stratum corneum (free fatty acids, sphingosine), as well as genetically encoded primary peptides (defensins, cathelicidins, dermicidins), synthesised in the stratum corneum and present in sebum and sweat, exhibit antibacterial activity and contribute to the protection of the body [10]. Some chemokines and neuropeptides also possess antimicrobial activity as an alternative function [11].

The skin exhibits an antimicrobial barrier function by maintaining an acidic pH, which reduces the colonisa-

tion of pathogenic bacteria and yeast colonisation [10].

Enzymatic and non-enzymatic antioxidant systems that counteract oxidative stress are included in the network of the skin's defence mechanisms. Ascorbic acid (vitamin C), uric acid, and alpha-tocopherol (vitamin E) are the non-enzymatic antioxidants. Antioxidant enzymes include catalase, superoxide dismutase, glutathione peroxidase, and antioxidant-reducing enzymes (e.g., methionine sulfoxide reductase) [10].

Importantly, the skin contains both resident and recruited immune cells, including mast cells [9], plasmacytoid dendritic cells, myeloid dendritic cells, Langerhans cells [11], lymphocytes, macrophages [9], and Toll-like receptors [11]. These constitute the skin immune system, which acts as an integrated sensory device, continuously monitoring the skin and contributing to the maintenance of homeostasis [9].

The physiological properties of the skin, its role as a mechanical barrier, the secretion of protective biomolecules, and the presence of immune-protective components, determine the skin as the first line of defence and a barrier of the body against harmful environmental agents [9,11]. Maintaining the protective functions of the skin depends primarily on the strength of this barrier. Therefore, any functional or structural defect can cause various skin diseases [9].

Strategies to protect wounded skin

The skin is the interface between the individual and the environment [2], making it a critical structure that is highly vulnerable to injury [6,12]. Alterations in the form of trauma or wounds can have a negative effect on the patient's overall health [3]. In addition, prolonged healthcare can also have a significant impact on the healthcare economy [6]. Therefore, the skin plays an important role in preserving health and maintaining the well-being of the individual [3].

Wounds are one of the most common skin injuries. Early and late complications are common causes of morbidity and mortality, which is why wounds remain a serious clinical problem in everyday pathology [13].

Wounds result from injuries that break the surface of the skin, body tissues, or organs [14]. Injuries can range from disruption of the skin's epithelial integrity to deeper damage involving subcutaneous tissue, with injury to structures such as tendons, muscles, vessels, nerves, parenchymal organs, and even bones [15].

Injuries can result from everyday activities: at work, accidents during indoor or outdoor activities, or simply while walking or playing [14]. In addition, they may result from extreme situations and environmental impacts—vehicle accidents or those caused by weapons and other subjects [14]. Wounds can occur accidentally or be caused intentionally [15]. Injuries can also be minor or life-threatening [14].

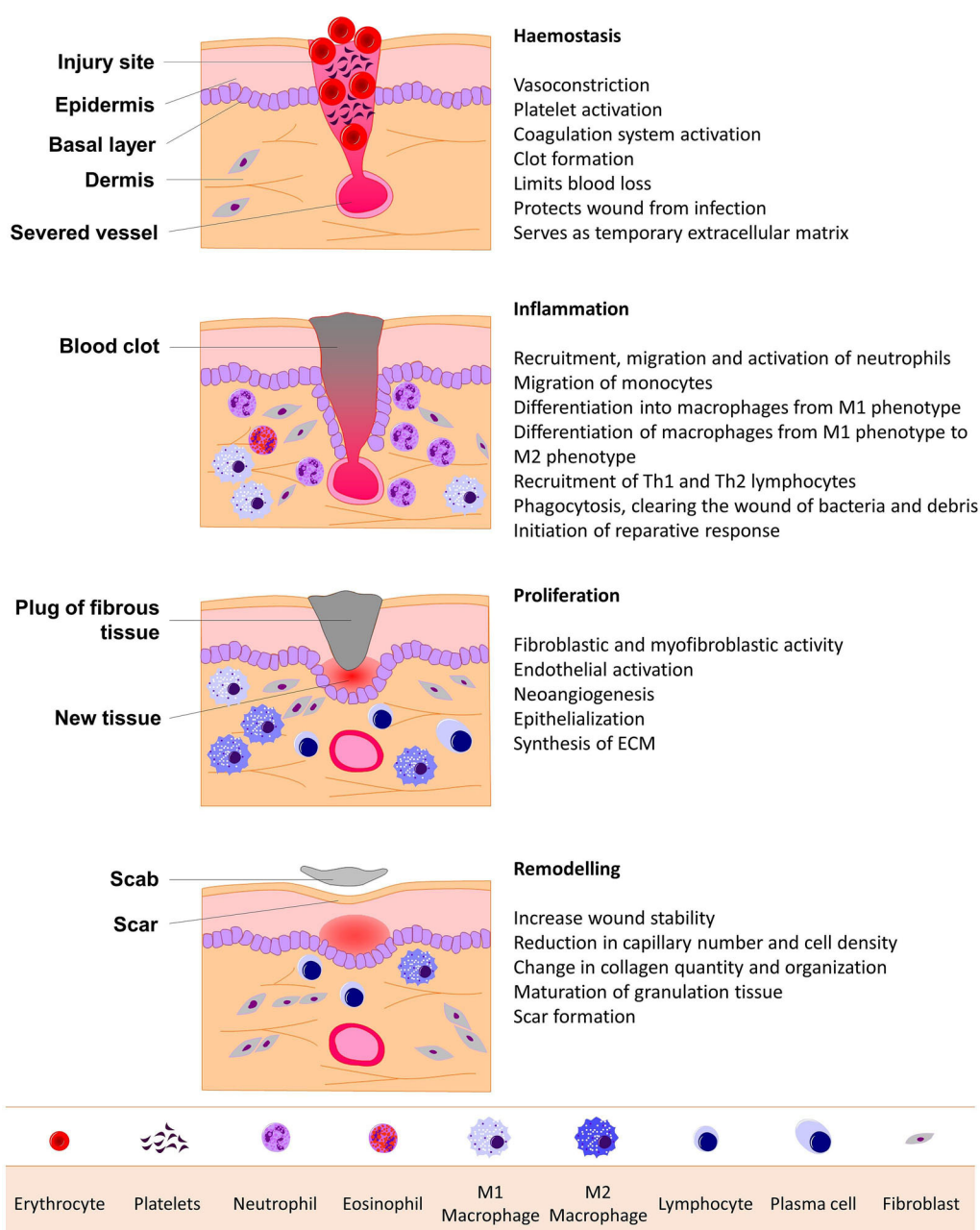
Agents causing injury are of different origins—chemicals, sharp objects (surgery, cuts), heat, cold, pressure, animal bites or insect stings, as well as diseases such as vascular pathology, connective tissue diseases, nutritional deficiencies, and malignancy [14].

Wounds form regularly throughout life and can pose a threat to the individual [16]. In response to this threat, an evolutionarily developed rapid response is initiated with a programme for tissue and homeostasis repair. In this way, the organism counteracts changes in order to maintain a stable and relatively constant internal environment [16]. Wound healing is a complex process that seeks to restore tissue integrity and functional capacity after injury [13].

Regardless of the aetiological factor and the severity of tissue damage, the healing of every wound is associated with dynamic changes in the wound microenvironment, occurring in four consecutive and overlapping phases: haemostasis, inflammation, proliferation, and remodelling [13, 16]. These involve multiple mechanisms, such as the secretion of inflammatory mediators and growth factors; cell-cell and cell-extracellular matrix (ECM) inter-

actions that drive cell proliferation, migration, and differentiation; processes related to epithelialisation, fibroplasia, and angiogenesis; wound contraction; and remodelling. These mechanisms begin at the moment of physical injury and continue throughout the wound repair process [15]. In healthy individuals, restoration of the functional epidermal barrier is highly effective, while restoration of the deeper dermal layer results in scar formation with significant loss of original tissue structure and function [17]. The disrupted normal repair reaction has two main manifestations: ulcerative skin defect (chronic wound) or excessive scar formation (hypertrophic scar or keloid) [17]. Therefore, although there is an overlap of the phases of this dynamic process, each phase is necessary for the next to be completed [18]. The wound healing process is represented schematically in Figure 1.

Fig. 1. Schematic representation of the four phases of wound healing: haemostasis, inflammation, proliferation, and remodelling.



IMMUNE CELLS INVOLVEMENT IN WOUND HEALING

Wound healing after skin injury involves a complex interaction between many cellular players of the skin, primarily keratinocytes, fibroblasts, vascular endothelial cells, and recruited immune cells, and their associated extracellular matrix [17]. The immune response involves various participants in a complex and stepwise manner - neutrophils, eosinophils, macrophages, and cells of adaptive immunity - lymphocytes and plasma cells. Immune cells and factors are key regulators and participants in wound healing, and their local accumulation is an important part of the protective programme of the wounded tissue [16]. They participate from the beginning, immediately after tissue injury, and mediate the processes in the following phases of tissue repair [19, 20].

Neutrophils

As immune cells, neutrophils, are usually not observed in normal skin [6]. After wounding, neutrophils are the main players in the early inflammatory phase and are the dominant cells in the first 24 hours, constituting nearly 50% of all cells at the wound site [22]. The recruitment peaks around day 2 post-wound onset [18].

The neutrophil's role is multifactorial. As important effector cells in the innate immune system, neutrophils constantly patrol the organism for signs of microbial infections [23]. Firstly, because of blood vessel disruption, neutrophils are collected passively at the wound site. Afterwards, they move from the circulation into the tissue (diapedesis) [24] to form a dense barrier against invading pathogens [22].

Neutrophils are highly efficient in bacterial eradication by producing reactive oxygen species, releasing cytotoxic granular contents, forming neutrophil extracellular traps (NETs), and phagocytosing invaders [16]. In addition, the proinflammatory cytokines tumour necrosis factor α (TNF- α) and interleukin-1 (IL-1) are expressed initially and predominantly by neutrophils within a few hours after wounding and appear to act as main inducers of chemokines [19, 22]. After executing their antimicrobial functions, they are quietly cleared by tissue-resident macrophages [23].

The successful transition from the inflammatory to the proliferative phase of healing is the key to efficient healing and tissue normalisation following injury. Neutrophils contribute to this process not only indirectly—as targets for macrophage efferocytosis following apoptosis—but also actively by regulating cell proliferation and angiogenesis [16]. It is an important fact that they are able to modulate the activities of neighbouring cells and contribute to the resolution of inflammation, as well as regulate macrophages for long-term immune responses [23].

Furthermore, neutrophils can direct an adaptive immune response by presenting antigen to T cells [19]. They also play roles in preparing the wound tissues for the following proliferative phase through the release of vascular endothelial growth factor (VEGF) and proteolytic enzymes [25]. Taken together, neutrophils play a pivotal role in the response to skin injury and in leading proper wound healing [19].

Eosinophils

Eosinophils represent a minor component of circulating leucocytes and are generally considered to be terminally differentiated as post-mitotic cells [26]. Eosinophils infiltrate primary and secondary lymphoid organs. Besides immunomodulatory functions, eosinophils also support the functional integrity of non-lymphoid organs. In addition, other tissues, including the skin, are targets for eosinophilic infiltration during inflammation [27].

Classically, eosinophils are viewed as being involved in host defence against parasites and promoting allergic reactions. However, new regulatory functions of eosinophils have also been identified [26]. Eosinophils express a wide variety of surface receptors, molecular surface markers, cytokines, lipid mediators, and other major molecules. Stored in eosinophil granules, they can be released in response to specific stimuli and affect the microenvironment and various cellular functions. Thus, from passive cells, they take the shape of powerful effector cells [28].

It is known that eosinophils interact with other cells (B cells and T cells). Furthermore, they can indirectly activate mast cells, neutrophils, basophils, and macrophages in adipose tissue. These multifunctional cells can process antigens and act as antigen-presenting cells, contributing to the adaptive immune response by producing chemoattractants [28]. On the other hand, the reciprocal interactions between platelets and eosinophils favour the development of tissue inflammation and remodelling. Phagocytosis and cell killing are other important functions of eosinophil granulocytes [27].

Eosinophils also exhibit antimicrobial activity towards viral and bacterial pathogens [28]. They execute bacterial killing through several intra- and extracellular mechanisms, which may vary according to the involved pathogens. Intracellular killing mechanisms have been demonstrated for *Staphylococcus aureus*, *Escherichia coli*, and *Listeria monocytogenes* [27].

Eosinophils are not often examined in the cellular infiltrate of wound tissue. Wong DT, et al. report that the dynamic nature of eosinophil infiltration occurs during the course of wound healing [29] and that it depends on the type of wounds [30]. A peak level of eosinophils is reached after 3 days, as the increase reverts to normal levels after 6 days in scalpel wounds. For laser wounds, the time points are after 6 days and 10 days, respectively. In addition, when re-epithelialisation is complete, eosinophils slowly disappear from the regenerating connective tissue [30]. Other studies show the presence of eosinophil infiltration for a longer period. Eosinophils infiltrated into the clot and base of the wound disappear by day 21, but in the granulation layer of the wound, their numbers continue to increase up to day 21 in the rabbit cutaneous open wound model [31]. The sustained level of eosinophils found in the wound proper, even after surface re-epithelialisation, suggests that these granulocytes may play an important “architectural” role in the post-acute phase of the wound healing process [31].

The eosinophil may express complex roles during wound healing. There is evidence for the participation of

these granulocytes in the general cellular orchestra involved in the different stages of wound repair. Studies demonstrate the relationship between eosinophil infiltration and growth factor secretion, which actively participates in the process of tissue repair under experimental conditions [29, 32]. Healing cutaneous wounds in hamsters contained prominent infiltrates of eosinophils, and TGF- α and TGF- β 1 proteins were detectable both within eosinophils and extracellularly. Furthermore, there is a temporal order of expression of these two cytokines, as the eosinophil expression of TGF- α precedes that of TGF- β 1 [29]. It is also important that eosinophils contain a metalloprotein that degrades types I and III collagens, which is why they have a role in the alterations in connective-tissue matrices [33].

Another study demonstrates that eosinophils negatively affect wound re-epithelialisation, as effective reduction of eosinophil infiltration leads to faster wound closure [34]. Overexpression of IL-5, a cytokine produced by T helper 2 cells and an eosinophil regulator, leads to wider wounds, impaired re-epithelialisation, delayed collagen deposition, and significantly increased inflammatory cell infiltration, particularly eosinophils and CD4(+) cells, which delay healing [35].

Macrophages

Macrophages are key regulators of the wound healing process. They are the most important cells present in the later stages of the inflammatory process (48-72 hours) [36].

Skin-resident macrophages are among the first cells to respond when acute injury occurs. But the resident cells' response is only short-term. They recognise damage-associated molecular patterns and secrete chemokines that recruit other cells from the blood [19]. Basically, macrophage infiltration is derived from circulating monocytes that are recruited to areas of injury and differentiate into macrophages [37], after exposure to alarmins [18].

Macrophages exhibit phenotypic plasticity manifested as a phase response during wound healing—initial dominance of the M1 phenotype and switching to anti-inflammatory M2 macrophages by days 5–7 [18].

Following activation, M1 proinflammatory macrophages produce a multitude of mediators and cytokines, including interleukin-1, interleukin-6, interleukin-12, TNF α , and inducible nitric oxide synthase. Furthermore, they also produce chemoattractants, including chemokines, which recruit additional leucocytes [38].

Initially, the infiltrated proinflammatory macrophages clean the wound of bacteria, foreign debris, and dead cells [37]. In this way, they act in synchrony with the other players—the neutrophils. Macrophages also secrete matrix metalloproteases (MMPs), which are critical in the autolytic debridement of necrotic tissue [36, 37].

In a normally healing wound, neutrophils undergo apoptosis after performing their function at the wound site. Macrophages can induce apoptosis and clear apoptotic neutrophils (efferocytosis) [18, 21], and represent the single most effective means of neutrophil removal [38].

On the other hand, successful efferocytosis by macrophages may be requisite for the generation of a mac-

rophage phenotype (M2 phenotype, “alternatively activated” or reparative phenotype) [38]. The M2 phenotype is characterised by the expression of anti-inflammatory mediators, such as IL-1R antagonist, decoy IL-1 receptor type II, and IL-10, and by the production of growth factors (TGF- β 1, VEGF, insulin-like growth factor-1), and supports the proliferative process of repair [18, 38].

Macrophage activity is associated with wound angiogenesis. Inflammatory macrophages interact with endothelial cells and positively influence wound angiogenesis. Afterwards, macrophages participate in blood vessel regression during the resolution phase of wound repair [39].

Macrophage products such as proteases and their inhibitors influence ECM content and remodelling, and wound healing [38]. Macrophages are responsible for the breakdown of ECM fragments by the secretion of MMPs, cysteine proteinases (cathepsin B and L), and serine proteases, and for collagen deposition in wound healing [40]. Thus, depending on the phenotype, from proinflammatory (M1-like phenotypes) to anti-inflammatory (M2-like phenotypes), they take on distinct roles to ensure proper healing [37]. Taken together, skin macrophages actively participate in all stages of acute wound healing and are essential for proper wound resolution [19].

Lymphocytes

Wound healing is a well-coordinated process in which the adaptive immune system actively participates. The adaptive immune response is more delayed but specific and unique in its ability to generate and retain memory. Therefore, it is more perfect at providing protection upon subsequent immunological challenges [41]. Active participants in adaptive immunity are B and T cells, which respectively account for humoral and cell-mediated adaptive immunity [42].

The effector cells recognised free antigen or bound antigen via professional antigen-presenting cells, and subsequently are activated [41]. Lymphocytes are the last immune cells to infiltrate the wound tissue. Lymphocytes are recruited early in inflammation and persist in the wound at low levels for weeks following injury [43]. They are also participants in the late inflammatory phase and can influence wound resolution and remodelling [38].

Earlier work demonstrates lymphocyte participation in wound healing as a dynamic and distinctive process [44]. Peak levels of lymphocyte infiltration were found at different time periods. Fishel RS, et al. found the peak of migrated T lymphocytes was on day 7 [44]. Others report their injury causes T cell infiltration in the reticular dermis of wound edges on days 1 and 3, reaching peak levels on day 14, and is significantly decreased on day 30 [42].

Different T lymphocyte subsets have dissimilar time patterns of distribution in the wound. Migration of W3/25 (helper/effector T lymphocytes) and OX8 (suppressor/cytotoxic T lymphocytes) showed that W3/25 cells predominated over OX8 cells in the superficial portions of the wound on days 5, 7, and 10 [44]. While another study determined earlier peak levels of CD4, followed by CD8, spread over 5-10 and 7-10 days, respectively [45]. Deple-

tion of all T-cells impaired wound healing as assessed by wound breaking strength and collagen synthesis [46]. On the other hand, combined depletion of T-helper/effector and T-suppressor/cytotoxic T-cells leads to enhancement of wound healing parameters [46].

Lymphocytes are not required for the initiation of wound healing, but an intact cellular immune response is essential for a normal outcome of tissue repair [47].

In the setting of wound repair, lymphocytes participate in the inflammatory phase and the tissue remodeling phase [22]. For example, deficiency of CD4 and CD8 lymphocytes alters lymphocyte infiltration (respectively of CD8 and CD4 cells) into wounds, affects neutrophil and/or macrophage infiltration into wounds, and alters cytokine expression. On the other hand, significant changes in wound breaking strength, collagen content, and angiogenesis were lacking in CD4 or CD8 deficiency compared to wild-type mice [45].

T cells are detected within 24 hours of injury and then remain present for at least 30 days, with CD4+ T cells representing the most abundant T cell subset involved in the wound healing process. Thus, CD4+ T lymphocytes may represent a regulatory lymphocyte population in the responses to wound injury and repair. The B and T lymphocyte deficiency results in accelerated epithelial wound closure. Both leucocytes and macrophages are significantly increased in the absence of B and T cells. A deficiency of lymphocytes *in vivo* is associated with an accelerated epithelialisation and fibrosis due to the deposition of more but more immature collagen. Also, microvasculature shows a marked decrease. Successful syngeneic lymphocyte transfer of T cell subpopulations leads to a reduction of leucocyte infiltration and significantly reduces macrophage influx in immunodeficient mice. Collagen bundle organisation and neovascularisation are improved after the transfer of total lymphocytes [42]. In this way, B and T cells not only modulate inflammatory responses but also participate in other stages of tissue repair.

Plasma cells

Plasma cells are differentiated B-lymphocyte white blood cells. They secrete immunoglobulins (antibodies), which are responsible for humoral immunity, and play an important role in the adaptive immune response [48].

Antibodies play key roles in maintaining protective skin immunity [49]. Recently, it was found that plasma cells reside in healthy mouse and human skin, and skin plasma cells develop independently of T cells and microbiota [50].

Loots MA, et al. found the presence of plasma cells in acute wounds, but regardless of the time point of examination, their number is greater in both types of chronic wounds (diabetic and venous ulcers) [51]. B cells also have beneficial effects on tissue healing. These lymphocytes do normally infiltrate the wound tissue, albeit in low numbers. They were present from day 3 [52] to day 17 after injury [53], and there were no significant differences in B cell counts between different wound sites (epidermal wound margin, edges of panniculus carnosus and wound base) [52].

It has been shown that direct application of mature, naive B cells effectively modifies the balance of mature immune cell populations within the wound microenvironment and accelerates the healing process [53]. The infiltrated B cells produce various cytokines and growth factors that cooperatively promote wound healing [52]. There is also a hypothesis that the B cell immunoglobulins aid in the opsonisation of dead cells at the injury site, facilitating their clearance by macrophages [54, 55].

A study in volunteer patients showed the presence of a small and constant number of plasma cells in the extraction wound. In addition, immunoglobulins IgA, IgG, and IgM were demonstrated in the plasma cells in proportions characteristic of the plasma cells of oral mucous membranes [56]. Plasma cells are present on day 5 after tooth extraction. A proportional dependence is found between the number of plasma cells and the production of antibodies involved in humoral immunity needed in the healing process, as well as the influence of the concentration of the applied treatment with spirulina [57]. In this way, B cells, along with other immune cells, promote the wound repair process [52].

FROM CLASSIC TO INNOVATIONS

Wound treatment, whether acute or chronic, requires a holistic approach that includes assessment of the aetiological factor, the state of the wound and peri wound tissue, the general condition of the patient, and the correct choice of treatment that promotes the wound healing process [58]. Numerous studies on the healing process have led to significant progress in the discovery and understanding of the cellular and molecular mechanisms underlying both physiological development and pathological processes that alter the wound microenvironment or the overall reactivity and resistance of the organism [13]. The immune system is one of the main regulatory systems in the organism, and identifying its response has important clinical significance [59]. This is due to the unique interactions between cells of the innate and adaptive immunity. Immune cells and their products, such as cytokines, chemokines, are essential tools for studying the pathogenesis of pathological processes in the organism, including tissue injury and repair. In addition, they can serve as measurable indicators for identifying the stages of the wound-healing process, monitoring the effectiveness of the applied treatment, or detecting changes that lead to failure of wound healing [59].

The development of medical science has encouraged the application of high-tech approaches and the mastery of new therapeutic interventions. In this regard, nanotechnologies, 3D bio-printing and tissue bio-engineering, regenerative and angiogenic therapies using stem cell treatment, growth factors, therapeutic gases, gene therapy, and others offer great opportunities for improving the healing process of injured tissues [60]. They improve the treatment effects of both traditional, and basic therapeutic agents [61, 62], as well as the development of new agents, capable of changing cellular activity, synthesis and secretion of ac-

tive substances and mediators, which initiate, modulate and regulate the interactions between different types of cells and between cells and extracellular structures at each stage of the wound healing process [63, 64]. In addition, the knowledge gained provides an opportunity for the development of targeted therapies that modulate the ongoing cellular and subcellular events related to the immune response [65, 66].

CONCLUSION

The skin is a mechanical barrier that protects the body from harmful environmental influences. Any damage to the skin's integrity initiates a complex physiological healing process in which immune cells, granulocytes, and mononuclear cells play a key role. The recruited and activated cells secrete various mediators and are actively involved in every stage of the process. They successfully remove pathogens and cell debris, stimulate re-epithelialisation, promote the formation of new blood vessels, and influence the extracellular matrix content.

Cellular cooperation within the immune system

plays a pivotal role in the physiological course of wound repair. Despite numerous clinical observations and experimental studies, conflicting data persist regarding the temporal peak and active involvement of distinct immune cell types and subtypes in suppressing inflammatory changes, as well as promoting angiogenesis, proliferation, and remodelling during physiological wound healing. Consequently, the emerging questions present a challenge to contemporary medicine, requiring a precise investigation into intercellular interactions and the subsequent molecular events. Hence, expanding our knowledge of immune cell dynamics in wound healing is essential to identifying therapeutic targets, effectively modulating specific phases of the process, and ultimately establishing a foundation for advanced wound care management.

Abbreviations:

ECM - Extracellular matrix

TNF - Tumour necrosis factor

IL - Interleukin

VEGF - Vascular endothelial growth factor

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