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# Characteristics and cellular mechanism of the wound healing process in the oral mucosa

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## Abstract

Wound healing involves four stages: haemostasis, inflammation, proliferation, and remodelling. Each wound should be considered separately because of the tissue's different environment. The key to successful wound healing is cell signalling and synchronisation between cells and chemical transmitters, which gradient attracts immune cells and prevents pathogens from causing infection.

Both skin and oral mucosa stages of the wound healing process are the same. Nonetheless, some differences affect the outcome of the healing. The most critical factors that impact the process are the time required for wound closure or immune response, the presence of saliva, the level of anti-inflammatory cytokines, and extracellular matrix (ECM) remodelling. Compared to the skin, wounds in the oral mucosa heal much faster and without scarring. Saliva plays a crucial role in healing the oral mucosa – because of higher levels of tissue factor, it reduces the clotting time. Furthermore, it is rich in many growth factors stimulating wound healing. Mesenchymal stem cells are yet another valid matter regarding wound healing in oral mucosa. Outstanding properties of these cells exhibit potential to be applied for therapeutical purposes. Additionally, immune cells' participation and response to tissue damage are more substantial and faster in the oral mucosa than in the skin.

Wound healing is a complex process influenced by many factors, including hyperglycaemia in diabetes, smoking, alcohol, and levels of sex hormones. Some of them, such as smoking, impair all stages of healing, while others only have some elements.

**Running title:** Wound healing process in the oral mucosa

**Keywords:** oral mucosa, wound healing process, cell signalling, stem cells, immunomodulation

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## Introduction

The skin is the body's biggest organ and has many different functions. It takes part in various processes, such as thermoregulation and prevention of electrolyte loss. However, the primary function of the skin, like other barrier tissues (intestine, lung, and oral cavity), is to serve as the first line of defence against physical, chemical, and biological damage [1] that may disrupt homeostasis. They continuously come into contact with the outside world – which requires unique ways to protect the tissues from an invasion of different pathogens, e.g., bacteria, fungi, and air pollution. However, wound healing after an injury is another crucial function of barrier tissues. The wound-healing process begins right after the injury and comprises four different but partially overlapping stages: haemostasis, inflammation, proliferation, and remodelling [1]. In each stage, different cells and chemical mediators are involved. The stages of wound healing are similar in all epithelial tissues. However, there are many factors (both physiological and pathological) that may influence the process. The wound healing process may vary depending on levels of sex hormones, infections, and chronic diseases. Some of the differences derive from the diversity of the tissue environment. For example, the fundamental difference between the skin and oral mucosa is saliva in the oral mucosa, which moistens the environment, and the microbiome, which influences immune reactions. Another critical factor is the function of the oral cavity, e.g., while eating, the oral mucosa is continuously at risk of motion and mechanical abrasion. Still, despite that, oral wounds heal faster than skin and form lesser scars or are even scarless [2,3]. This property cannot be attributed to a single factor but to key extrinsic and intrinsic factors participating in each stage [3].

Understanding the mechanisms of wound healing in the oral mucosa might be applied in future innovative therapies to prevent pathological or impaired wound healing and scar formation in the skin [1]. Interestingly, the ancient Greeks already knew the healing properties of saliva – they used snake saliva to open wounds to enhance cutaneous wound healing [2]. Another example of saliva's wound-healing properties is rats licking burns. Compared to the control group, the investigational group showed better results in healing wounds. Licking (applying saliva to) a wound is a primary human instinct, too. Therefore, it may denote that saliva comprises substances beneficial to wound healing in the oral mucosa and the skin [2]. This review focuses on the characteristics and cellular mechanisms of wound healing in the oral mucosa. Furthermore, the review presents factors determining wound healing and compares the healing process in oral mucosa and skin wounds.

## Phases of the wound healing process

The wound-healing process is a complex set of chemical reactions and cellular activity in every body tissue and organ [4]. The process has been divided into four main stages to understand the physiology and timeline of every molecular shift that occurs in the organism. The four phases are 1 – haemostasis, 2 – inflammation, 3 – proliferation, and 4 – remodelling. Every wound can consist of separate parts in a different phase simultaneously [5]. This requires perfect synchronisation of various cell types in their functions and the factors they secrete. Said synchronisation plays a crucial role in wound healing, determining the efficiency of the process [4].

### Haemostasis

Wound healing begins with haemostasis that reduces blood loss from the injured vessels. The three steps during the process are vasoconstriction, primary and secondary haemostasis. The pivotal morphotic elements in haemostasis are the platelets, also called thrombocytes [6]. Once an injury occurs, the vessels constrict, reducing their diameter and limiting the amount of blood flowing out of the wound [7]. This reaction of the body, called vasoconstriction, is triggered by a series of substances referred to as vasoconstrictors, which include: endothelin, epinephrine, norepinephrine, prostaglandins, thromboxane A2 and endoperoxides [6,8]. Physiologically, the platelets are near the vascular walls. However, they are prevented from premature activation by the properties of the endothelium. Endothelial cells secrete inhibitors, including nitric oxide and prostacyclin [9]. Following a rupture of the blood vessels, the blood extravasates into the injury site coming in contact with collagen and another extracellular matrix (ECM) elements leading to the activation of platelets and their release of clotting factors, causing the formation of the blood clot [10]. Fibronectin, fibrin, vitronectin, and thrombospondin comprise the blood clot [5]. Initially, the platelets bind the ECM through the G protein-coupled receptors, activating integrins and amplifying the attachment between the platelets and the ECM components [11].

Further adhesion of the platelets is enabled by interactions between a number of receptors, some of which are tyrosine kinase receptors, glycoprotein receptors, and the von Willebrand Factor (vWF) that connects to the Gp Ib-9 on the platelets [7,8,12]. Activated thrombocytes undergo a morphological transformation, adopting a pseudopodial shape that increases the contact surface between the platelets and ECM [8,9]. They also secrete thromboxane A2 (TXA2), serotonin (5-HT), and adenosine diphosphate (ADP) that promote further platelet aggregation [13]. Secondary haemostasis enables blood coagulation by gradually activating plasma factors,

including intrinsic and extrinsic pathways. The intrinsic pathway consists of factors I, II, IX, X, XI and XII, while the extrinsic pathway of factors I, II, VII and X [14]. Both pathways activate factor X, which converts prothrombin to thrombin, transforming fibrinogen to fibrin. In order to bind the aggregated platelet plug that eventually forms a permanent secondary haemostasis plug, factor XIII covalently crosslinks fibrin. In the succeeding stages of healing, the blood clot also acts as the temporary wound matrix for infiltrating other cells [6,7].

**Inflammation**

The next phase in the process of wound healing is inflammation. Its main task is to prevent microorganisms from entering the injury site and infecting the body. This stage involves three types of cells (neutrophils, macrophages and lymphocytes) that appear in the wound sequentially. The inflammation process consists of two phases: an early inflammatory phase and a late inflammatory phase [5,15]. Common symptoms of inflamed wound sites are pain, redness, and oedema. Neutrophils are the first cells to be attracted to the wound [10]. They appear within 24-36 hours of injury [5], and they immediately begin phagocytosis and secrete proteolytic enzymes to eliminate bacteria and irreversibly destroyed tissue. Proteases are also responsible for the breakdown of ECM. However, several protease inhibitors protect the matrix in unwounded tissue from their activity [4]. Primary proteases are cathepsin G, elastase, and protease 3, released from the azurophilic granules of neutrophils. They are concerned with breaking down elastin, fibronectin, laminin, vitronectin, and collagen IV [6,16]. Neutrophils also produce reactive oxygen species (ROS) [10] that help further sterilise the wound by combining with chlorine [4]. They also initiate NETosis, which is a process of creating neutrophil extracellular traps (NETs), that are chromatin filaments enriched with bactericidal proteins extending into the extracellular space. NETosis efficiently eliminates bacteria, viruses, and fungi [6,17].

After completing their tasks, neutrophils become redundant. Therefore, they must be removed. Neutrophils can undergo necrosis, apoptosis, or autophagy-associated deaths. NETosis may also lead to the destruction of neutrophils [18]. Dead neutrophils are then phagocytosed and replaced by macrophages [4]. Macrophages play a crucial role in the late inflammatory phase, and they appear in the wound 48-72 hours after the injury, where they continue phagocytosis [5]. They live longer than neutrophils and are responsible for activating keratinocytes, fibroblasts, and endothelial cells as well as secreting tissue growth factors, including transforming growth factor alfa and beta (TGF-α and TGF-β), heparin-binding epidermal growth factor, fibroblast growth factor (FGF) and collagenase [5,10]. By performing efferocytosis, macrophages cleanse the wound off of neutrophils, preventing permanent inflammation [6], followed by the migration of lymphocytes, which are attracted to the wound site by interleukin-1 and the breakdown products of immunoglobulin G, 72 hours after the injury [5,15]. The role of lymphocytes is not sufficiently clear. However, the γδ T cells may induce keratinocyte proliferation by secreting keratinocyte growth factors 1 and 2 (KGF-1 and KGF-2), protect from infection and recruit neutrophils to the infection site [19].

**Proliferation**

Following haemostasis and inflammation is the proliferation phase, characterised by the formation of granulation tissue, angiogenesis, and re-epithelialisation [4,10]. The proliferative phase begins three days (72 hours) after an injury and lasts up to two weeks [5]. Fibroblasts migrate, attracted to the wound by platelet-derived growth factor (PDGF) released from platelets, where they synthesise new ECM. On top of that, secreted by various cells, TGF-β1 further induces collagen synthesis by fibroblasts [20]. Epidermal stem cells then signal fibroblasts to transform into myofibroblasts [6]. They are mesenchymal cells that resemble both fibroblasts and smooth muscle cells. They contract the wound by bringing its edges closer to each other, facilitating epithelialisation [21]. Myofibroblasts achieve it by extending their cytoskeleton and attaching it to fibronectin and collagen fibrils that form the ECM, and as those extensions retract, the wound contraction ensues [22]. Angiogenesis is a crucial process in wound healing, as newly formed capillaries transport oxygen and nutrients necessary to support all cells that form the new tissue. The essential cells concerned with neovascularisation are endothelial cells (ECs) that reside on the inner surface of blood vessels. They begin angiogenesis by sprouting and proliferating in response to cytokines that exhibit pro-angiogenic properties [6]. Those cytokines are FGF, vascular endothelial growth factor (VEGF), TGF-β, angiopoietin, and mast cell tryptase. ECs invade the ECM stroma and form cylinder structures that go on to expand and branch off, forming networks [23]. Re-epithelialisation lasts up to three weeks, during which keratinocytes migrate to the edge of the wound, where they proliferate and restore the epidermal barrier. Failure of keratinocytes may result in wound recurrence and ultimately cause abnormalities in the healing process [20,24,25]. Interfollicular stem cells enable re--epithelialisation by generating keratinocytes that migrate to the wound [6].

**Remodelling**

Wound healing ends with the remodelling phase, which can last for months or even years, during which the wound site undergoes structural chan-

ges. The capillaries formed previously during angiogenesis begin to decline and regress, the ECM reorganises, and the granulation tissue transforms into scar tissue [6]. Endothelial cells, macrophages, and fibroblasts continue to secrete metalloproteinases responsible for the breakdown of collagen type III, one of the main components of the granulation tissue. Collagen type I replaces it, allowing for wound reinforcement. A series of inhibitors that eventually terminate the reactions carried out by metalloproteinases regulate the activity of those enzymes. The cells and the processes activated by them during earlier phases begin to subside. Apoptosis, or the exit of those cells from the site, decreases the number of endothelial cells, macrophages, and myofibroblasts in the wound. Due to the decline of the neovasculature, the blood flow to the injured area is limited, resulting in a slower metabolic rate [5,26]. All the processes mentioned above result in scar tissue formation, which marks the end of wound healing. In adults, every wound turns into a collagenous scar, meaning that once damaged, tissue cannot return to its previous structure and properties.

In contrast, a different situation occurs in the fetal skin and the oral mucosa. Early-gestation fetal wound healing restores the typical architecture of the epidermis and dermis and the preservation of collagen, hair follicle, and sweat gland patterns. However, the phenomenon still needs to be thoroughly elucidated [20].

## Differences between the wound healing in the oral mucosa and the skin

Although there are differences in the wound healing process between the skin and oral mucosa, there are also many common features. The stages of wound healing are the same in both the skin and oral mucosa (namely: haemostasis, inflammation, proliferation, and remodelling) [27]. However, there are individual differences between them in terms of factors such as the time required for wound closure or immune response, the presence of saliva, level of anti-inflammatory cytokines, and ECM remodelling [3].

### Haemostasis

During the haemostasis phase, there is a higher expression of PDGF in oral wounds compared to skin wounds in rats. This observation suggests that oral wounds may have a greater level of platelet activation than skin wounds [28]. Moreover, adding saliva to blood samples has been observed to reduce clotting time. This phenomenon is thought to be linked to the high level of tissue factor (TF) found in extracellular vesicles present in saliva [29].

### Inflammation

The inflammation phase showed the following differences between the skin and oral mucosa: the peak of the neutrophil influx in the oral mucosa appeared 3 days after wounding, while in the skin the number of neutrophils showed a consistent increase for up to 6 days after the initial wound suggesting that neutrophils are recruited more quickly to oral wounds compared to other types of wounds [30]. Moreover, in oral keratinocytes, there is a faster increase in Intercellular Adhesion Molecule-1 (ICAM-1 also known as a cluster of differentiation – CD54), expression compared to skin keratinocytes that may result in a faster influx of immune cells and thus faster wound healing. In addition, when stimulated with interleukins: IL-1α and IL-1β, oral keratinocytes exhibit upregulation of ICAM-1 expression, while skin keratinocytes do not demonstrate the same response [31]. The oral mucosa experiences a significant increase in T cells on day 3, which then decreases by day 6.

Conversely, skin wounds demonstrated a consistent but insignificant increase in T cells for up to 6 days following the injury. These observations indicate that the influx of T cells is delayed in skin wounds compared to oral mucosa [30]. Furthermore, the analysis of the oral mucosa transcriptome has shown that gene networks associated with cellular movement and migration are greatly stimulated in the uninjured oral mucosa [30]. Overall, the participation of immune cells in the process of wound healing is more prolonged in skin wounds compared to oral wounds [3].

### Proliferation

Observation during the proliferation phase indicated that oral keratinocytes exhibited faster scratch closure in laboratory tests due to their higher proliferation and migration rates than skin keratinocytes, with oral keratinocytes already expressing more genes related to migration and proliferation in unwounded epithelial sheets, indicating inherent differences between the two cell types [32] being the leading cause. In addition, oral fibroblasts produce more hepatocyte growth factor (HGF) and KGF than skin fibroblasts. HGF and KGF induce keratinocyte migration and proliferation, which could help explain why oral wounds tend to re-epithelialize faster than skin wounds in vivo [33].

### Remodelling

In the remodelling phase there is characteristic increased collagen hydrogel contraction in oral fibroblasts, as indicated by several studies [34–38]. Moreover, it was noted that the oral mucosa has more myofibroblasts compared to the skin during wound healing stages of varying duration [39,40].

### Scar formation

Rapid wound closure and reduced scar formation are common in the superior healing phenotype of the oral cavity [3]. The unique healing environment of the oral cavity is attributed to several fac-

tors. During healing, over-activation of the immune system can have negative effects, leading to delayed wound closure and increased scarring [41]. Furthermore, it has been observed that the ratio of TGF-β1/TGF-β3, a factor suggested to be a predictor of scar formation, is reduced in oral mucosa [42] such as expression of cytokines and fibrosis mediators, including annexin A1 (ANXA1) and secretory leukocyte peptidase inhibitor (SLPI) [30].

In both pig and mouse studies, the number of vessels increased after wounding in both oral and skin wounds. However, the number of newly formed blood vessels was significantly higher in skin wounds compared to oral wounds [39,43]. Interestingly, the number of blood vessels returned to normal in the oral mucosa, while the vascular density remained elevated in skin wounds up to 60 days after injury in pigs or 7 days in mice [39,43]. This increased vascular density in skin wounds relates to hypertrophic scar formation, which may explain the greater scarring observed in skin wounds compared to oral mucosal wounds [44].

### The impact of saliva and other factors on the wound healing process

Saliva provides better conditions for wound healing as it contains various peptides and proteins, including growth factors such as EGF, VEGF, and FGFs, as well as histatins [45–47]. In addition, both histatin 1 (Hst1) and histatin 2 (Hst2) have demonstrated the ability to promote the migration of oral and skin keratinocytes in vitro, making them essential components of the remarkable healing properties of saliva [48–50].

Salivary microbes can be beneficial for maintaining homeostasis and promoting wound healing. However, the overgrowth and colonization of pathogenic microorganisms can occur in certain conditions, such as large burn wounds, oral ulcers, or gingivitis, which can negatively impact wound healing [51,52]. Recent literature suggests that certain types of microbes may exert a beneficial effect by training or stimulating the immune system, which in turn influences the wound-healing cascade [53–55]. In addition, the oral mucosa is constantly mechanically stimulated during mastication, which increases immune responsiveness [56].

## Cell signalling during the wound healing process in oral mucosa

The advantages of regeneration of the oral mucosa arise from the seemingly unfavourable conditions it endures. Factors such as rich oral microbiome, which at the surface level seem like a hurdle in wound healing process, contribute to a more potent immune response and faster wound closure and remodelling [57,58].

Continuous bacterial exposure primes towards a more rapid and intense immune response, ultimately leading to faster wound closure [30,39,57,59–61]. Compared to skin wounds, quicker resolution of inflammation in oral wounds results primarily from both rapid proinflammatory response and faster and increased anti-inflammatory cytokine release [39]. Unremarkable cytokine secretion differences between sterile gingiva and human skin cultures support the thesis [62]. The state, however, changes with exposure to a commensal biofilm resulting in an expected increase of interleukin production in gingiva cells [57,59,63].

Innumerable factors influencing the superiority of wound healing in oral mucosa, though the common denominator is the intense cell signalling during the regenerative process. Therefore, it is imperative to briefly go through the above phases of wound healing to specify the processes underlying each of them.

### Haemostasis

Haemostasis phase in the wound healing of oral mucosa is brief. Keratinocytes, fibrocytes and platelets release vast amounts of chemokines such as chemokines (C-C motif) ligand 4 and 8 (CCL4 or CCL8). In doing so, they rapidly initiate the process of inflammation through chemoattraction of immune cells [64].

Cell molecular patterns are also released in the site of wounding in the haemostasis phase. Pathogen-associated molecular patterns (PAMPs) located exclusively in microorganism and damage-associated molecular patterns (DAMPs), endogenous molecules released by the destroyed cells of the organism, are bound by toll-like receptors (TLRs) capable of pattern recognition, most notably receptors for advanced glycation endproducts (RAGEs), and trigger cascade of cell signalling – further amplifying the sudden onset of inflammation [65].

### Inflammation

Inflammation in oral mucosa, similarly to haemostasis, proceeds rapidly but no less strongly than in skin wounds, ultimately leading to quicker wound closure and the beginning of remodelling phase [66]. Although 'low' inflammation is typically suggestive of scarless healing process, and oppositely 'high' inflammation is considered to be responsible for hypertrophic scar formation, impairment of immune response in early stages of regeneration may paradoxically serve as a biomarker for hypertrophic scar formation [3], leading to not only excessive tissue destruction and scarring, but also resulting in wound infection, which in itself is tightly related to prolonged healing process [58,67]. This information suggests efforts to resolve the inflammatory stage as quickly as possible, while maintaining its functional purpose.

CCL2 and CCL3 can serve as examples of this, as they are secreted in more significant amounts in

skin wounds (compared to their oral counterparts [68,69]) upon stimulation with tumour necrosis factor α (TNF-α) and gamma interferon (IFN-γ). This by itself is not necessarily harmful, but this trend persists even at the latter stages of skin and wound healing [30,68], leading to prolonged macrophage invasion and inflammation.

This tendency is present across the board when comparing oral and skin wound healing, with the latter one presenting a slower influx of immune cells, which contribute towards inflammation for a longer period of time [30].

All immune cells enter the wound in response to chemokine gradient. The main factor responsible for the speed of this process is the influx of neutrophiles to the wound site. They release proinflammatory cytokines and chemokines such as CCL2 and CCL3 [64,68] secondarily attracting immune cells like macrophages who further contribute to the inflammation-stimulative processes. IL-8 also known as chemokine (C-X-C motif) ligand 8 (CXCL8) can serve as an example of such a potent chemoattractant; in fact, the most potent one in the human body [70]. Secreted by M1 macrophages (pro-inflammatory phenotype stimulated by IFN-γ) it is produced in higher amounts by oral keratinocytes and fibrocytes, than those of the skin origin [71]. Among others, M1 cells are also responsible for IL-6 and TNF-α secretion [72].

Cytokines such as TNF-α affect keratinocytes that subsequently increase expression of CD54 – an adhesion molecule used by neutrophils to facilitate extravasation – a crucial process in remodelling (sped up by IFN-γ and exacerbated by TNF-α) [31]. The increase in CD54 expression is higher in oral keratinocytes [31].

T-cell secreted chemokines such as CCL5 and CXCL10 contribute to a more significant influx of T helper cells 1 (Th1) cells in oral wounds [30]. In contrast, the concentration of CCL227, responsible for Th22 chemoattraction, is higher in skin wounds and remains elevated over a prolonged period of time [30,68].

Overall, we can observe a more 'diffused' proinflammatory cytokine profile in skin wounds, reflected in the presence of T-cells, monocytes, and mast cells in wounds at a later stages of healing [30,39]. Besides, an increased expression of IL-6, IL-18, IL-23 and IFNs can be noted, compared to oral wounds [30,68], with some of the mentioned interleukins being associated with poor wound healing [73,74]. Contrarily, IL-1α, IL-1β and TNF-α expression is higher in oral wounds, which however, doesn't seem to largely affect the tendency of immune cells' contribution towards weaker wound healing that has been stated above [30,68].

**Proliferation**

The process of re-epithelialization in the oral mucosa progresses with the wound remaining open for its entire duration, being exposed to oral microbiome and saliva. This leads to quicker wound closure without scab formation [30,39,57,59–61]. Oral fibroblasts, which produce more inducers of keratinocyte migration and proliferation than their skin counterparts: HGF and KGF, are attributed to the process [34].

Another crucial part of the proliferation phase is angiogenesis, leading to increased vascular density – a state intrinsically linked to hypertrophic scar formation [44]. Because of this, the 'objective' of the oral mucosa is to limit the formation of new blood vessels and normalise their amount quickly after healing, as close as possible to the initial quantity.

Stagnation of blood flow after interruption of vessel continuity leads to hypoxia and angiogenic response. Many growth factors are released to stimulate cell proliferation and migration, most notably hypoxia-inducible factor 1α (HIF-1α). The result is creation of numerous, underdeveloped vessels, that 'leak' immune cells and nutrients to the wound site [75,76]. Another growth factor essential in the angiogenic process is VEGF, which high concentration can be found in saliva (which greatly exceeds the concentration of VEGF in plasma) [3].

Although higher levels of both of those substances are found in oral wounds, ultimately the amount of newly created vessels is higher in skin wounds [76]. Moreover, the normalization of their number happens quickly in oral wounds, whereas in skin wounds it remains elevated even after the wound is healed [3,39,43].

Saliva, which reduces clotting time attributed to higher levels of TF, plays another crucial role [29]. It's rich in many growth factors stimulating wound healing, such as previously mentioned VEGF, but also EGF, FGFs as well as Hst1 and Hst2 [45,46].

Histatins together with cathelicidin (LL-37) are a part of host defence peptides (HDPs) may be considered two main factors in human saliva responsible for both, skin and oral keratinocyte, and fibroblast migration [45,46,48,77]. On infection and injury, both skin and gingiva release a great ton of LL-37 by degranulating neutrophils and keratinocytes [78]. Cathelicidin is a potent chemoattractant for many immune cells, which also suppresses collagen synthesis and possesses anti-fibrotic activity, thus improving wound healing [79].

Mireille A. Boink et al. researched the ability of salivary peptides to stimulate the secretion of antimicrobial chemokines[80][80]. They investigated CCL20 secretion and compared it with other chemokines [80]. CCL20 is a chemokine with natural

antimicrobial properties, attracting T-cells and human $\beta$-defensins 1 and 2 [81,82]. Results from stimulation of keratinocytes and fibroblasts with Hst1 and LL-37 were in all cases more potent with gingival cells, with responsiveness to Hst1 stimulation showing a severe disproportion in CCL20 secretion between skin and gingiva, from whom the second showed a significantly more potent response [80].

Interestingly, keratinocyte-fibroblast cocultures showed a synergistic increase in CCL20 secretion, far more significant than in monocultures of either of the cell types. Those findings suggest the existence of synergistic mediators secreted by either of the cell colonies, which is believed to make keratinocytes more responsive to Hst1 and LL-37 exposure when scultured together with fibroblasts [80].

**Remodelling**

Remodelling begins once the wound is closed and microbial balance is properly restored. Releasing anti-inflammatory cytokines to dampen the immune response characterises the process. Fibroblasts play the primary role in remodelling, depending on cytokines secreted by macrophages [39,43], in this phase – M2 phenotype macrophages.

Factors like TGF-β and IL-4 induce change from M1 to anti-inflammatory M2 macrophages [3]. In addition, they secrete growth factors (mainly TGF--β), matrix metalloproteinases (MMPs) in order to stimulate the transition of fibroblasts to myofibroblasts, as well as induce myofibroblast-regulated remodelling the ECM – a step which is absolutely crucial for the quality of the scar [72].

MMPs and tissue inhibitors of metalloproteinases (TIMPs) are essential to break down the ECM and induce vessel regression. MMPs can inactivate chemokines and growth factors, thus restraining inflammatory and fibrotic responses during remodelling [3]. For example, MMP2 inhibits immune cell chemotaxis, while MMP9 directly rids the site of wounding of proinflammatory CXCL8 [83]. A low concentration of MMPs is generally associated with fibrosis and scar formation, such as seen in skin wounds [84]. Despite that, some of them, like MMP9, are associated with delayed wound healing [85]. Keratinocyte- fibroblast co-cultures secrete higher levels of MMP9 in skin than in oral wounds [86] in similar fashion to the secretion of many chemokines after stimulation with Hst1 and ll-37 [80].

Collagen reorganisation plays a vital role in normalising the wound and its scarring. Therefore, its level is generally higher in oral than skin wounds, exhibiting increased collagen expression [87]. Furthermore, this leads to diminished collagen reorganisation resulting in and explains increased vascularisation of healed skin wounds (or somewhat decreased normalisation of vasculature), as this process is intrinsically reliant on swift and thorough reorganisation [88]. Additionally, thicker collagen fibres have been observed in large amounts in skin with higher fibroblast expression of collagen types 1 and 3, presumably further hindering the ECM-degrading process [87].

## Factors affecting wound healing

**Diabetes**

Examples of disorders that impact wound healing could be diabetic disease and associated hyperglycemia, a development factor of atherosclerosis [89]. On the other hand, atherosclerosis leads to decreased blood flow and a deficit of oxygen and nutrients necessary for healing tissue. Either way, high glucose levels in the blood might be a potential cause of endothelial cell dysfunction, which is critical for healing skin [90]. Hyperglycemia also reduces the activity of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase, which could lead to increased reactive oxygen species levels [91]. Excessive oxidative stress causes a decrease in the ability to heal wounds [92]. In addition, atherosclerosis-triggered hypoxia leads to initial inflammatory reactions and points to increased oxidant free radicals [93,94], which in turn promote advanced glycation endproducts (AGEs) that are involved in contracting vascularisation [95]. Damage to microvascular circulation is a significant factor in impaired wound healing in diabetes [96].

**Age**

On the one hand, some study says there is no evidence that could confirm that age is a factor in poor wound healing [97]. However, on the other, there is a study which denies the earlier thesis and says older people present slower wound healing compared with younger adults, regardless of sex [98], as aging reduces the number of fibroblasts, which is connected with their proliferative activity [99]. Fibroblasts are involved in wound healing by creating a new ECM and collagen structures and breaking apart the fibrin clot [100], which may be the reason why age is the factor that reduces the ability of wound healing.

**Levels of sex hormones**

It has been proven in young adults that testosterone negatively impacts healing in the oral mucosa. There is no connection between testosterone level and wound healing in oral mucosa in older men. The relationship is the opposite in postmenopausal women [101]. Some studies say that estrogens have a beneficial impact on dermal healing [102,103]. However, on the other hand, research denies that by demonstrating no relationship between estradiol or progesterone levels on mucosal healing [101]. However, there is also research saying that in women, mucosal wounds heal more slowly than in men, regardless of age [98].

### Alcohol

Alcohol consumption is related to an increase in occurring traumatic wounds. It affects poor wound healing, which is caused by impairing the proliferative response during it and is associated with delays in epithelial coverage, blood vessel regrowth, and collagen synthesis [104]. Cell signalling substances (cytokines and chemokines) are released in response to tissue damage and are essential to wound healing. Alcohol disturbs the process of cell signalisation by cytokine and chemokine production alteration by multiple cell types, which is also a reason for adversely affecting the process of wound healing by alcohol consumption [105].

### Smoking

Nicotine, carbon monoxide, and hydrogen cyanide in cigarette lead to tissue hypoxia, impairing wound healing. Smoking is associated with a decreased proliferation of blood cells such as erythrocytes, white blood cells, and fibroblasts [106]. Decreased red blood cells (RBC) lead to anaemia and hypoxia. Macrophages are concerned with phagocytosis of tissue during the inflammation related to wound healing and produce cytokines essential to healing processes (angiogenesis) [106]. Smoking is associated with reduced fibroblast proliferation during the proliferative stage of wound healing. Therefore, smoking impairs all phases of wound healing [107].

### Tissue oxygenation

Proper tissue oxygenation is necessary for all wound healing processes, such as the oxidative killing of bacteria, epithelial cell migration, collagen synthesis and neovascularisation. Therefore, a chronic deficit of oxygen can stall healing [27,108].

### Infections

Inflammation is a crucial part of wound-healing process as it removes contaminating microorganisms. Prolonged state of wound healing may be caused by the absence of effective decontamination. The absence of effective decontamination may cause a prolonged state of wound healing. Bacteria, as well as endotoxins, are factors that lead to a prolonged increase of proinflammatory cytokines, such as IL-1 and TNF-α, and this is why infections may be a reason for chronic states, which fail to heal [27]. In addition, wound infection may lead to surgical wound dehiscence and psychological stress, harming wound healing [109].

## Mesenchymal stem cells in the process of wound healing in the oral mucosa

### Mesenchymal stem cells

Mesenchymal stem cells (MSCs) play a considerable role in wound healing in the oral mucosa. MSCs are clonogenic, stromal cells that can self-renew, form colonies in vitro, present a fibroblast-like morphology and differentiate into osteocytes, chondrocytes, and adipocytes [110,111]. Furthermore, they have a multilineage differentiation capacity, meaning they differentiate into different cell types from all three germ layers (mesoderm, endoderm, and ectoderm) [112–115]. MSCs, due to their unique properties, make up a valuable resource for exploring therapeutic interventions. The Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy created a list of minimum criteria for counting a cell to human MSC [111]. Firstly, MSCs must be plastic-adherent when maintained under standard culture conditions. The second criterion concerns the expression of clusters of differentiation and other surface molecules, which will be addressed later. The third one says that MSCs must differentiate into osteoblasts, adipocytes and chondroblasts in vitro [110].

### Gingival-derived mesenchymal stem cells

Particular kinds of MSCs are oral MSCs located in the lamina propria of the gingival tissue: Gingival-derived mesenchymal stem cells (GMSCs). According to Xu et al., most (90%) originate in cranial neural crest cells, whereas the rest derive from the mesoderm [115]. Due to their extraordinary properties, GMSCs enable wounds in the oral cavity to heal quicker [1,116,117]. In addition, they display a phenomenal ability to proliferate and migrate, which is better than other MSCs [117,118]. GMSCs need less time to migrate than dermal and adipose MSCs [117]. Some studies even suggest their proliferation occurs without any growth factor [118].

Moreover, they show a superior scar quality, often called scarless [1,116,117]. Several studies have proven their ability to heal without creating scars can be compared to the fetal skin's scarless healing in the first six months of pregnancy [119–121]. Mireille A. Boink et al., in their study, suggest that the scarless healing properties could stem from reduced matrix contraction observed in tissue equivalents with the total thickness [117].

### GMSCs markers

According to M. Dominici et al., 95% or more of the MSC population must express CD105 (endoglin), ecto-5′nucleotidase (CD73) and CD90 (known as THYmocyte differentiation antigen 1 – THY1) and lack expression (2% or less positive) of CD45, CD34, CD14 or CD11b, CD79a or CD19 and human leukocyte antigen-DR isotype (HLA-DR) surface molecules. Several studies have proved that GMSCs meet these criteria [122,123]. T. I. Mitrano et al., in their study on healthy students' gingival connective tissue, found out that obtained GMSCs were positive for CD13, CD44, CD73, CD90 and CD105 hematopoietic markers and negative for markers CD34, CD38, CD45, and CD54 [122]. In their study, Zhang et al. conducted a cytometry-based assessment of phe-

notypic markers. They proved that human GMSCs are negative for CD45 (100% of cells tested in the study) and express surface markers CD29, CD73, and CD90. However, the presence of markers: stage-specific embryonic antigen 4 (SSEA-4) (36,95%), CD105 (29,9%) and STRO-1 (18,3%) was slightly lower [124]. Many studies prove that along with typical MSC markers, GMSCs express a significant number of other signature molecules. They are capable of expression of CD29 (Integrin beta 1) [124,125] and CD44 [122,125–127]. Moreover, GMSCs produce octamer-binding transcription factor 4 (Oct-4), STRO-1, and SSEA-4 proteins, known as embryonic stem cell markers [128–130].

**Immunomodulatory properties**

Like other MSCs, GMSCs present various immunomodulatory and anti-inflammatory properties. It may occur through cell-to-cell contact or via soluble factors. In their study on GMSCs, Zhang et al. proved that when GMSCs were cocultured with peripheral blood mononuclear cells (PBMCs) in direct cell-to-cell contact, they exhibited greater inhibitory properties on PBMC proliferation compared to when GMSCs were cocultured separately using Transwells [124]. Numerous studies have shown that MSCs enhance their immunosuppressive functions via soluble factors, such as IL- 1, IL-6, IL-10, human leukocyte antigen-G5 (HLA-G5), prostaglandin E2 (PGE2), nitric oxide (NO), indoleamine 2,3-dioxygenase (IDO), transforming growth factor $\beta_1$ (TGF $\beta_1$) [110,131,132]. However, it is significant that the immunoregulatory properties of these soluble factors depend on many factors, such as the level of inflammation in the environment or different experimental conditions [133,134], but neutralising them does not abolish the immunosuppressive properties of MSCs [134]. Some studies suggest that factors like IL-10, HGF and TGF-1 have a low impact on immunosuppression mediated by bone marrow stromal cells (BMSCs) and human adipose-derived stem cells (hASCs) [135–137]. The role of PGE2 in immunosuppression mediated by MSCs is also debatable. Some studies show that by using cyclooxygenase-2 (COX-2) to block PGE2, the immunosuppression caused by BMSCs and hASCs was partly reduced [131,134,135]. Zhang et al., in their study, suggest that TGF-1, PEG2 and NO do not have much influence on a GMSC-mediated suppression of PBMC proliferation, which was done by blocking these factors with specific neutralising antibodies or antagonists for synthetic enzymes [124]. However, Cui et al. claim that PGE2 represents one of the essential soluble factors in the *in vitro* inhibition of allogeneic lymphocyte reaction [137]. Many studies have proven the role of IL-10, and its presence seems important in mediating immunosuppression. In the already mentioned study, Zhang et al. proved that blockage of IL-10 led to a decreased suppression of PBMC proliferation mediated by GMSC [124]. In their study, Jiang et at. claim that stimulating IL-10 production in GMSCs induced by hypoxia may increase the apoptosis of PBMCs [138]. Numerous studies indicate a crucial role of indoleamine 2,3-dioxygenase (IDO) in MSCs-mediated immunosuppression [134,135,139]. IDO is a tryptophan catabolising enzyme, which owes its properties to the reduction of tryptophan or accumulation of the downstream of 3-hydroxy anthranilic acid, 3-hydroxykynurenine and kynurenine [134,135,139]. Although MSCs do not constitutively express IDO, there are a significant number of inflammatory mediators that induce its production [134,135]. IFN-γ stimulation can also upregulate the secretion of IDO [124,140].

## Conclusions

Wound healing in the oral mucosa and other tissues is an exciting topic for further research. The extraordinary characteristics of the oral mucosa, which enable wound healing without scars in a short period of time, could be an inspiration and a potential tool in innovative therapeutic technologies. Furthermore, discovering the mechanisms of wound healing in oral mucosa and applying them to clinical use might prevent impaired or pathological healing and scar formation in the skin. For example, it might be crucial to discover new cell markers or signalling pathways. In addition, deepening the knowledge about cells and chemical transmitters that take part in wound healing processes can be a breakthrough concerning such fields as cell proliferation and stem cells.

**Ethical approval**

This conducted study is not related to either human or animal use.

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**Conflicts of interest**

The authors declare they have no conflict of interest.

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