Am J Transl Res 2022;14(7):4391-4405
www.ajtr.org /ISSN:1943-8141/AJTR0137517

Review Article

Role of matrix metalloproteinase in wound healing

Mimansa Kandhwal[1*], Tapan Behl[1*], Sukhbir Singh[1], Neelam Sharma[1], Sandeep Arora[1], Saurabh Bhatia[2,3], Ahmed Al-Harrasi[2], Monika Sachdeva[4], Simona Bungau[5]

[1]Chitkara College of Pharmacy, Chitkara University, Punjab 140401, India; [2]Natural & Medical Sciences Research Centre, University of Nizwa, Nizwa 342001, Oman; [3]School of Health Science, University of Petroleum and Energy Studies, Dehradun 248007, Uttarakhand, India; [4]Fatima College of Health Sciences, Al Ain 50, United Arab Emirates; [5]Department of Pharmacy, Faculty of Medicine and Pharmacy, University of Oradea, Oradea 410028, Romania. [*]Equal contributors.

Received July 20, 2021; Accepted May 27, 2022; Epub July 15, 2022; Published July 30, 2022

Abstract: Matrix metalloproteinases (MMPs) are a group of endopeptidases that play a vital role in the restoration of damaged skin. Through mediating various cellular events such as angiogenesis and vasodilation, MMPs are very crucial for the mechanism of wound healing. These enzymes are endopeptidases that are reliant on zinc which are concealed through the extracellular matrix (ECM). MMPs have different targets in different phases of wound healing through which they are capable of promoting timely healing in the body. This review discusses all the possible role of MMPs and their inhibitors that are involved during every step of the wound healing process. This review highlights the latest advances in the respective field about the regulation and mediation of MMPs in human skin and how these studies can be applied to other branches of medical sciences as well. Published papers were searched via MEDLINE, PubMed and MDPI from the available peer reviewed journals. Research done in the past suggests that active MMPs are involved in the healing progression of the wounds or they have a positive effect towards healing of wounds. Present studies in the relative field will further enhance the knowledge about enzymes working along with their inhibitors. These studies will help in a way to resolve some of the parameters that are necessary for modulating them either positively or negatively.

Keywords: MMPs, chronic wounds, wound healing, TIMPs, inflammation, chemokines, extracellular matrix

Introduction

Matrix metalloproteins, are endopeptidases that help in regeneration of skin, and these are calcium dependent zinc containing endopeptidases also known as metallopeptidases or matrixins. Skin, the largest organ of human body is responsible for protecting the body from outer infection or damage, apart from that it is also responsible for sustaining the fluid balance and thermo regulation [1]. Primary functions of this protective organ include regulation of the body temperature, which permits sensations like heat, cold and touch and importantly it provides protection from the outer environment. Each layer of skin has its own distinctive feature. The layers have their own separate roles and functions to perform [2-4]. It provides a water proof barrier, sweat glands to maintain body temperature and cushioning effect to the skeleton. The dermis layer is responsible for the tensile potency of the skin along with the ECM [5]. This cushioning effect is more pronounced in the presence of the ECM. It is an absolute 3D structure made up of connective tissue and fat cells including collagen, proteoglycans, and glycoproteins (almost 300 different types of protein) [6]. Proper functioning of the skin is very important for the body as it is the first line defensive organ of the human body. Any damage to any of the layer of human skin may alter the proper functioning of the skin which may result in instability. Breakdown in the protective or defensive function of the skin may be considered as a wound which has to be healed in a well-planned manner. The skin itself is directly involved in the healing of cutaneous wounds while it also plays an indirect role in the healing of internal or chronic wounds as well. The integrity of skin is supremely important while main-

taining physiological hemostatis and feasibility of the internal tissues as well. Any damage to the epithelial cells which are present in the epidermal layer of the skin may infringe upon the integrity of the skin [7-10]. This may lead to bacterial infiltration into the skin as the mechanical strength of the skin is compromised. These bacterial infringements through the skin from the external environment may reach up to the dermis layer and the ECM and cause further damage. In order to protect the affected part from further infection the wound has to be healed efficiently. Categorically, wounds can be differentiated into various types that are: Superficial wounds (loss of epidermis layer only), partial wound (loss of epidermis and dermis layer) and full thickness wounds which involve the loss of the dermis subcutaneous fat and sometimes even bone. Apart from these categories, wounds are to be differentiated on the basis of the time taken to heal properly and there are two sub categories which are acute wounds and chronic wounds [11]. Wounds that heal in a synchronized manner of the healing cascade are generally known as acute wounds. While on the other hand noncompliance of some wounds to the healing pattern may lead to delay in their healing. This may occur because of the prolonged residency of one or the other healing phases [12, 13]. For normal functioning of the skin, the damage has to be repaired immediately in order to prevent the further impairment due to infections. Superficial wounds do not possess any threatening damage, whereas partial and full thickness wounds may involve the loss of dermal layer and subcutaneous layer as well. The normal healing process entails a systematic and organized sequence of four dissimilar yet overlapping stages that are hemostatis, inflammatory phase, proliferation phase and remodeling phase [14, 15]. However, interruption in any phase of this dynamic process may eventually lead to the onset of chronic skin ulcers. A functional co-ordination among all the four partially overlapping phases is mandatory in order to commence the progression of tissue restoration. For the healthy progression of wound healing the ECM has to be remodeled efficiently as it is responsible for the tensile strength of the skin and in this process endopeptidases such as matrix metalloproteinases (MMPs) are thoroughly involved. The prominence of this review article is to emphasize the role of MMPs that are systematically involved the wound healing process. At present there are 24 known MMPs that are likely to be present in the human body [16]. MMPs are generally endopeptidases that are competent at eliminating all the damaged components of ECM. The ECM generally promotes all the cellular responses in the process of wound healing including cell adhesion, cell migration and tissue remodeling. Removal of all the damaged proteins and cells within the ECM is the main line of action of the MMPs. Their engagement is seen in all the four phases of the wound healing. During the inflammatory phase they are capable of removing the damaged proteins and forming a temporary ECM [17-21]. While during the second phase that is the proliferation phase, they help in degrading the capillary basement membrane. MMPs also promote angiogenesis during the wound healing cascade. The respective role of MMPs in wound healing can be studied by carefully evaluating all the events that participate in this sequential process. First, the initial phase (hemostasis) is tissue injury which involves epidermal layer, platelets and TGF-β. Immediately after hemostasis the inflammatory phase begins and this involves neutrophils, macrophages, ROS, TNF, VEGF, and PDGF. Granulation and angiogenesis are also two of the most crucial events in the wound healing process [22]. Involvement of fibroblasts, macrophages, endothelial cells are there in these events. Keratinocytes and collagen fiber crosslinking are typically involved in the process of re-epithelialization and tissue remodeling. All of the stages must be completed in a timely way and in a sequential manner in order for the wound to be fully healed [23]. Here, MMPs play a critical role in each and every phase of wound healing. This review discusses the role of MMPs and their inhibitors in different phases of wound healing. This review discusses the entire possible role of MMPs and their inhibitors that are involved during every step of the wound healing process. This review highlights the latest advances in the respective field about the regulation and mediation of MMPs in the human skin and how these studies can be applied to other branches of medical science as well.

Wound healing cascade

Wound healing undergoes mainly three phases namely the inflammatory phase, the prolifera-

tive phase and maturation phase. The inflammatory phase forms clots and is followed by inflammation cell build up in the wound or injury site. This phase lasts up to 2-5 days and includes vasoconstriction, platelet aggregation and clot formation followed by vasodilation and phagocytosis. The second phase lasts for about 2-3 weeks which consists of granulation, contraction and epithealization. Thereafter comes the maturation phase in which new tissue is formed and this phase last for approximately 3 weeks. The superficial wound quickly crosses the threshold of the primary stage of the healing process, which is hemostatis, upon injury to the skin. Excessive bleeding is protected by the onset of clotting in the blood vessels that is further accomplished by accumulation of platelets around the ruptured endothelium region resulting in the formation of the plug. A blood clot is formed upon further cascade of events. The serine proteinase thrombin cleaves fibrinogen into fibrin threads, which bind with platelets to create a clot. Not only does the development of a blood clot halt bleeding, but it also functions as a temporary matrix for cell migration [24, 25]. The cells surrounding the clot release various inflammatory cytokines and growth factors which further signal attraction of various cells such as neutrophils, lymphocytes, monocytes and macrophages and initiate the phase of inflammation. Neutrophils arrive at the site of injury only within a few hours. They are highly responsible for the release of fibronectin which has multiple roles [25, 26]. Fibronectin and fibrin create a provisional matrix which initiates migration of cells and helps them stick together. Their adhesion power is totally dependent on the intensity of the injury that has occurred [23]. Growth factors cause macrophage activation, which results in the production of reactive oxygen species (ROS), multiple growth factors such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), MMPs, transforming growth factor-beta (TGF-beta), and fibroblast growth factor (FGF). Angiotensin II is an important factor that can induce the stimulation of macrophages. It is mainly regulated upon reaction of the renin-angiotensin system (RAS) pathway. It generally co exists in the fibroblasts, macrophages and endothelial cells present in human skin. Secretion of MMPs and ROS is usually initiated by the activation of AngII along with the trigger of inflammatory cells. Stimulation of these factors initiates the further intensification of keratinocytes. They are also responsible for their migration through the injured cells as well. TGF-βs plays crucial part in regulation and development of the ECM. Humans have 3 isoforms (TGF-β1-3), each presenting distinct function in regulation of components of the ECM, and proliferation of cells and even cell death [27-29]. The most well-known is TGF-1, which regulates the generation and destruction of numerous elements involved in the healing process of wounds [25]. Upon binding of TGF-1 to its corresponding receptor, synthesis and manufacturing of ECM components such as collagen, fibronectin, and hyaluronic acid are triggered in several cell types, including fibroblasts [30]. Collagen is mainly synthesized by fibroblastic cells and other constituents which are accumulated within the ECM [16]. Fibroblasts are also accountable for the stimulation of ROS which further secrete defensive factors of the body against any kind of microbial attack in the body that are peroxide ions and superoxide ions [31]. The synthesized ROS generate various cytokines which further increase the proteinase production and alter the fragments of the ECM [31]. The main characteristic of ROS is that it has twofold functions that are associated with it. The antimicrobial function is of great advantage to the human body as it protects the body from foreign particles. However, excessive levels of ROS may damage the constituents of ECM [31, 32]. This moderate equilibrium between the secretions of ROS may activate the intricate pathways in the body which activates the MMPs secreted in the wounded area. The elevated levels of ROS could harm the tissues and in turn may alter the wound healing process [33-35]. Dealings that are involved in the next event of the cascade are of great importance and the events are angiogenesis and granulation. In this phase the granulated tissue is supported by the blood supply. Vascular support is increased in the affected tissue and the site surrounding it as well. This process is a reciprocating way that the human body has to deal with excessive blood loss which occurs during wounds. The vascular supply also allows the continuous supply of oxygen to the wounded area. Granulation tissue is generally soft pink to red in appearance which marks the presence continuous vascular supply to the wounds [31]. Around the wounded area the presence of

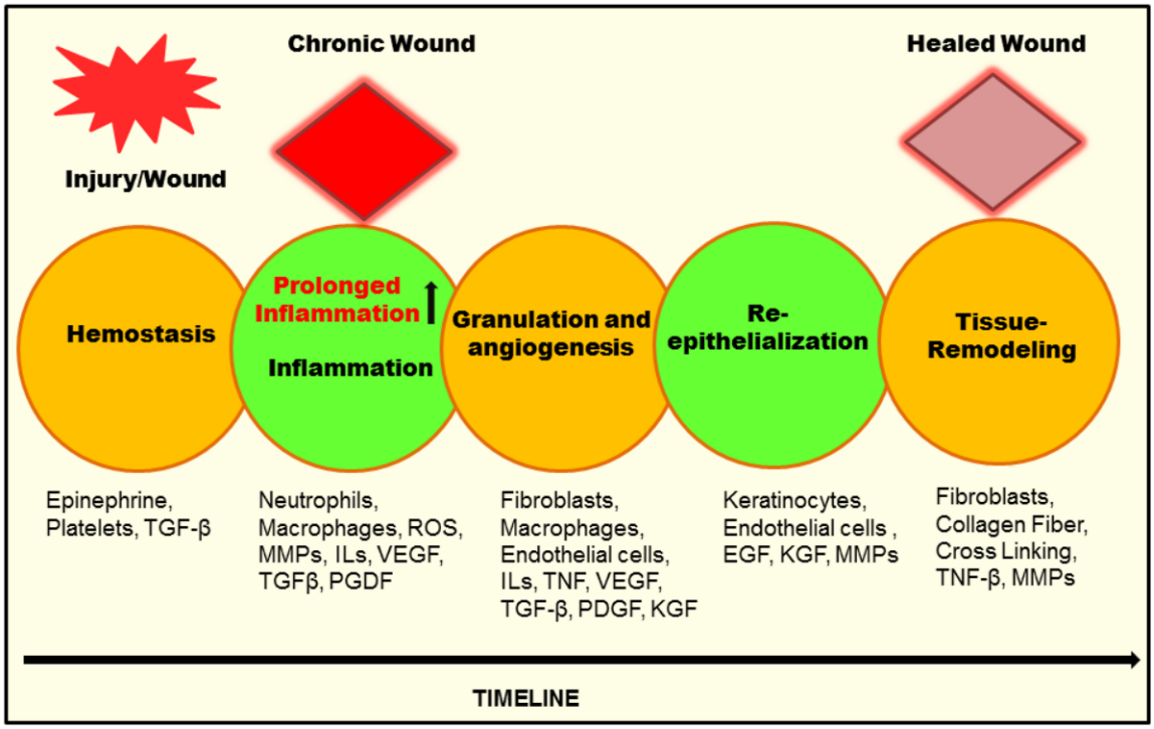

Figure 1. Diagrammatic representation of well-orchestrated events involved in the wound healing cascade.

fibroblasts markedly start increasing through the process of migration [36]. Proliferation of the fibroblasts is also a distinctive feature of this phase in the wound healing as it interacts with the growth factors and the ECM which initiates the process of fibroblasts proliferation. Integrins also play a vital role in the mediation of the whole proliferation process as they are the respective receptors for the fibroblasts. They are also responsible for the biochemical signaling of the earlier mentioned process. The extracellular sphere of influence of intergrins bind with the ECM portion and the internal surface of the receptor and are accountable for several signaling procedures [37]. Exposure of the integrins and other fibroblast receptors like discoidin to collagen is responsible for the processing of MMP 2 in the wounded tissue. MMP2 allows the migration of the fibroblast during angiogenesis and ECM remodeling. The interaction of integrins with collagen is responsible for the strength of the ECM and in turn encourages the secretion of supplementary growth factors. In a mouse model, Rossiter et al. confirmed that the absence of keratinocyte-specific VEGF is responsible for aberrant angiogenesis and delayed wound healing [38]. Final support given by the granulation tissue to the epithelial cells is the re-epithelialization phase of the wound healing. Keratinocytes are generally involved during this phase and they are the main mediators that can positively influence the healing phase. Likewise to the other cells in the earlier phases of wound healing keratinocytes also undergo the same process of migration, differentiation and proliferation. Migration of keratinocytes occurs toward the centre of the wound in order to close the wounded site completely. In order to do that keratinocytes must not lose their grip with the adjacent tissue. Keratinocytes also have a distinct feature of changing their shape and size before migration in order to accelerate the process of wound closure [39-41]. Here again integrins are involved as keratinocytes and move towards the newly molded ECM. During this process MMPs are continuously activated through macrophages and keratinocytes in order to degrade the matrix components to achieve healthy healing of the tissue [42-44]. After all the complexity of the events, the wounded tissue enters the last phase which is tissue remodeling [31]. In this phase type 3 collagen is replaced by type 1 collagen in order to give more tensile strength to the tissues. Different phases of wound healing are explained in **Figure 1**.

MMPs and its inhibitors

There are currently 28 known MMPs out of which 24 are human enzymes. MMPs generally exist in three different categories that are inactive, active and complex MMPs. These enzymes are endopeptidases which are reliant on zinc and are concealed through the ECM. The primary structure of MMPs comprises a single arrangement of the N-terminus, a pro-domain which is capable of capping the active binding site and a catalytic sphere of influence [45, 46]. The activities of MMPs are synchronized by a group of endogenous tissue inhibitors of metalloproteinase (TIMPs). These inhibitors are further divided into 4 subtypes (TIMPS 1, 2, 3, 4). The inhibitors bind specifically to block the functioning of MMPs. MMP 7 and MMP 26 are also classified as matrix-lysins that exhibit the very basic structure comprising the minimal domain which is discussed above. The catalytic domain is exemplified by the zinc-binding HExxHxxGxxH motif, consisting of three conserved histidines [47, 48]. Numerous MMPs have an additional domain known as the hemopexin-like domain, which is located at the C-terminus of the previously stated basic arrangement and functions in conjunction with it. According to the current hypothesis, the hemopexin-like domain has a role in substrate identification. These domains are shown to be associated with MMP-3 and MMP-10 (also known as stromelysin-1 and-2), MMP-1, 8, and -13 (also known as collagenases), MMP-12 (metalloelastase), MMP-20 (enamelysin), and MMP-22 and -27 (also known as stromelysin) [49].

MMPs and wound healing

Role in inflammation

The inflammatory phase is generally associated with incursion and commencement of the leukocytes. There are several factors which are involved directly or indirectly in order to manipulate this inflammatory stage of wound healing. Many of those factors include chemokines, cytokines, ECM splinters and lipid mediators. Antimicrobial peptides are also among one of those influencing factors as well. Metalloproteinases are a group of proteins which are held responsible for the secretion and pursuit of these factors. Studies from different labs revealed that MMPs that originated or developed from epithelial cells normalize various events in the inflammatory stage which is also the initial stage of the wound healing. The events which are to be regulated through MMPs in this phase are transepithelial migration of leukocytes and partition of signaling proteins such as chemokines. It has been validated through the work done by Parks et al. that MMPs are prominently expressed in the inflammatory cells [50]. While on the other hand stromal and epithelial cells at the wounded site have also corroborated to express multiple MMPs including MMP 1, 2, 3, 7, 9, 10 and 28. All these respective MMPs could possibly mediate the activity of chemokines. This regulation could occur through distressing the production of the chemokine slope or via direct proteolysis [51-54].

These signaling proteins or chemokines are subcategorized into small families like CC chemokines and CXC chemokines. This subdivision occurs on the basis of their discrete function of magnetizing the leukocytes resulting in their influx. Apart from this their N-terminal cysteine residues are also a major factor which is taken into consideration while dividing these subfamilies [55, 56]. The first family which is the CC chemokines plays a considerable role in the chemotaxis of monocytes. However CXC chemokines are generally held responsible for the regulation of neutrophil chemotaxis. If the other dividing factor is also taken into consideration while comparing these two closely related chemokine subfamily varies. The respective function or activity of these signaling proteins is downgraded by MMPs by their division or severance. CC chemokines are responsible for downstream signaling through the formation of receptor antagonist in the presence of MMPs. While on the other hand CXC chemokines variably respond to the MMPs. It has been noted that some of the CXC chemokines are totally impervious to the presence of MMPs while some others are promptly affected by MMP presence. This dissimilarity elaborates on a major operative variation of humans and mice [57, 58]. MMP 8 and 9 are accountable for the processing of Human CXCL8. This process is responsible for the significant amplification in the activity of CXCL8. Functional responses of MMP such as modulations in the migration of inflammatory cells at

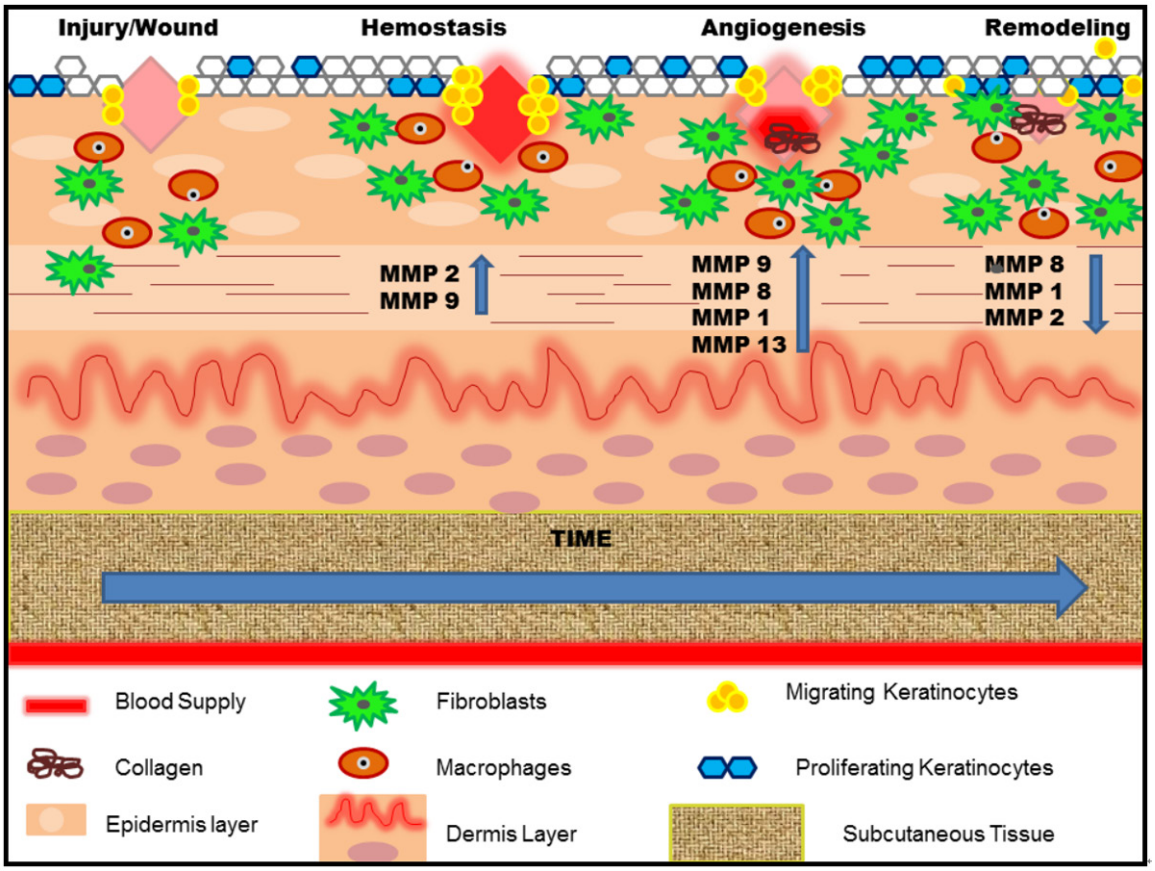

Figure 2. Diagrammatic illustration of the events during the complex wound healing process and the role of specific MMPs during each well-orchestrated event.

the wound site are totally different in humans and mice. This discrepancy is the core reason needed research in this field. There is another CXC chemokine which is found to be handled or processed by several MMPs, which is CXCL5 (LIX). The MMPs which are thoroughly involved in the operation of this chemokine are 1, 2, 8, 9 and 13. These are validated by the studies of Tester et al. as well. This phase of chemokine processing is ultimately responsible for the enhancement of more inflammatory cells to be involved in the wound healing process. Furthermore the processing of CXCL12 and several MMPs such as 1, 2, 3, 9, 13 and 14 are thoroughly involved in the process [58, 59]. Results of CXCL 12 processing via MMPs are totally different than the previous CXCL5 processing which consequentially alleviates the efficiency of chemokines. Out of all the known MMPs, MMP1, 3 and 9 are validated to possess extensive capability of supervising the signaling of chemokines. MMPs are generally involved in absolute chemokine breakdown and generate antagonist for chemokine receptors in order to enhance the performance of chemokines. In addition to MMPs, ADAM 10 is capable of sorting chemokines. ADAM10 is capable of cleaving CXCL16 off the cell surface, therefore allowing it to bind to its particular receptor and influence T-cell initiation at the injured region [60]. This shows that both the metalloproteinases that are MMPs and ADAMs, are thoroughly involved in the mediation of chemokines. Positive and negative regulations are carried out by these metalloproteinases. MMP expression and regulation in the wound healing cascade is diagrammatically represented in **Figure 2**.

Role in epithelial repair

Re-epithelialization is one of the most important and necessary phases of the sequential process of wound healing. Progression of building healthy tissue all over again at the denuded area is generally categorized as re-epithelializa-

tion [21]. In this tricky process the wounded cells have to lose their grip on the ECM fragments so that they can freely move across the ECM in order to heal completely. Involvement of numerous MMPs can be seen in this phase of wound healing such as 1, 3, 7, 9, 10, 14 and 28 [61-63]. MMP1 which is also known as collagenase 1 is expressed at the wounded site during this particular phase of wound healing but its activity is valid till the closure of the wound after that it automatically gets turned off [64, 65]. Keratinocytes usually are transferred from the basal lamina at the wounded stage and then they bump into a matrix present in the dermal layer of the skin which is highly rich in type 1 collagen. MMP expression was initiated via ligation of keratinocytes to this particular ECM component with the help of α2β1 integrins. Findings from the labs of Gill et al. suggested that Keratinocyte migration was assisted by MMP1 above the dermal layer matrix. This procedure was carried out through alleviating the effectiveness of collagen and integrin fragments [66-68]. Reduced contact between the two results in the migration of keratinocyte. MMP 10 (stromelysin-2) is confined with MMP1 however MMP 3 (stromelysin-10) is restricted only to the cells following the migrating overlook. The non-overlapping location of MMP3 and 10, two very similar proteinases, suggests that these two MMPs have separate roles in re-epithelialization. In addition to all of these favorable functions, MMPs participate in the development of airway epithelial cells [69, 70]. There is certain evidence from nude mice which uses human tracheal xenografts to confirm the presence of MMP 7 and MMP 9. Their expression and activity were found maximum during the later phases of the wound healing progression. Specific inhibition of these respective MMPs contributes to the impairment in the differentiation of the epithelial cells. This evidence collectively proves that MMPs are necessary in wound healing for proper differentiation of epithelial cells [71]. MMP 10 is also produced by the epithelial layer during the cell migration process revealing that these MMPs are mandatory during cell migration. Tampa et al. corroborated that MMP 10 enhances the process of cell migration. This phase that is the repairing phase of wound healing which includes various cellular responses such as migration, proliferation and differentiation and even cell death [72, 73]. Now, it is quite evident that these events or responses either separately or collectively are able to generate MMPs due to the line of action of these proteinases that have been deciphered up until now. All this evidence corroborates the idea that practically all the MMPs have been confirmed as positive influencers of the wound healing process apart from MMP 2 and MMP 9 that may have the negative or inhibitory effects on the cell proliferation [74].

Role in wound contraction

Specifically, MMP 3 is required for the last step of the wound healing process, which is the resolution phase. It is very evident from the studies of Bullard et al. that the contraction of wound was slowed down in mice lacking MMP3 [75-77]. Slowdown in the pace of contraction of wound healing ultimately increases the size of the wound, which may slow down the whole process of wound healing. In this situation the epithelial cells might also take longer to migrate during the migration phase, which is also a negative sign in the healing process. There is one other role of MMPs which was originally thought of as its main function which is the elimination of the ECM fragments. ECM degradation is a very vital and necessary step in the process of healthy wound healing. Currently, it has been shown that the primary function of most of the MMPs is to activate several cellular factors such as growth factors, cytokines and chemokines. They are certainly capable of activating their respective receptors as well. Reframing of the collagen generally consists of the mortification of the present collagen fibers in order to build the new ones. This is the most important event in the resolution phase of the wound healing. Because MMPs are capable of this process, it seems plausible that they would have a key role in collagen remodeling during wound resolution. Different types of mammalian MMPs and their possible role in wound healing are mentioned in **Table 1**.

MMP inhibitors during the wound healing cascade

Since the activity of metalloproteinase in wound healing is controlled by endogenous tissue inhibitors of metalloproteinases, it is important to understand how they work. These inhibitors have the ability to attach to particular locations in the body's immune system, resulting in

Table 1. Mammalian MMPs and their respective roles in wound healing cascade and several other diseases

MMPs (Synonym)	Possible Role in Wound Healing	Favorable Substrates	Possible Role in Other Diseases	Ref.
MMP 1 (Collagenase-1)	It elevates the degree of migration of the keratinocytes resting on fibrillar collagen Its level in drastically increased in diabetic patients also suffering from diabetic foot ulcer Excessive production in the keratinocytes may delay the repair process	Collagen I, II, III, VII and X	Release growth factors and have negative impact in cancer	[68, 78]
MMP-8 (Collagenase-2)	Produced by neutrophils Positively stimulates the cutaneous healing Increased levels can be seen in diabetic patient (Diabetic foot ulcers)	Collagen I, II, III	Act as biological markers in respiratory disorders such as asthma and chronic obstructive pulmonary disease	[79, 80]
MMP-13 (Collagenase-3)	Initiates Re-epithelialization through contracting the wound	Collagen I, II,III, IV, IX, X	Involved in the pathogenesis of osteoarthritis	[81, 82]
MMP-2 (Gelatinase A)	Hasten up the process of Wound healing Stimulate the activation of MMP 9 Keratinocyte immigration or relocation	Gelatin; collagen I, IV, V, VII, and X	Their levels significantly rise in colorectal cancer tissues	[83, 84]
MMP-9 (Gelatinase B)	Advances Cell Migration in whole body except Cornea	Elastin, Fibrillin, Collagen I, III, IV, V	Regulates pathological remodeling processes that involve inflammation and fibrosis in cardiovascular disease	[85, 86]
MMP-3 (Stromelysin 1)	Stimulates the activation of MMP-9 and positively influence the wound retrenchment and impaired healing	Collagen IV, V, IX, and X; fibronectin; Elastin; gelatin	Involved in the pathology of rheumatoid arthritis (RA) and ankylosing spondylitis (AS)	[74, 87]
MMP-10 (Stromelysin 2)	Expressed at Keratinocytes at the exposed side of the wound	Collagen IV, V, IX and X; fibronectin; Elastin	Involved in skeletal development	[88, 89]
MMP-7 (Matrilysin)	Obligatory role in re epithelialization process	Elastin; fibronectin; laminin; nidogen; collagen IV; Tumor necrosis factor	Their levels significantly rise in patients suffering from carotid atherosclerosis	[90, 91]
MMP-12 (Metalloelastase)	Promising monitoring ofangiogenesis due its capability ofproducing angiostatin	Collagen IV; gelatin; fibronectin; laminin	It degrades extracellular matrix elastin and enables infiltration of immune cells responsible for inflammation and granuloma formation	[92, 93]

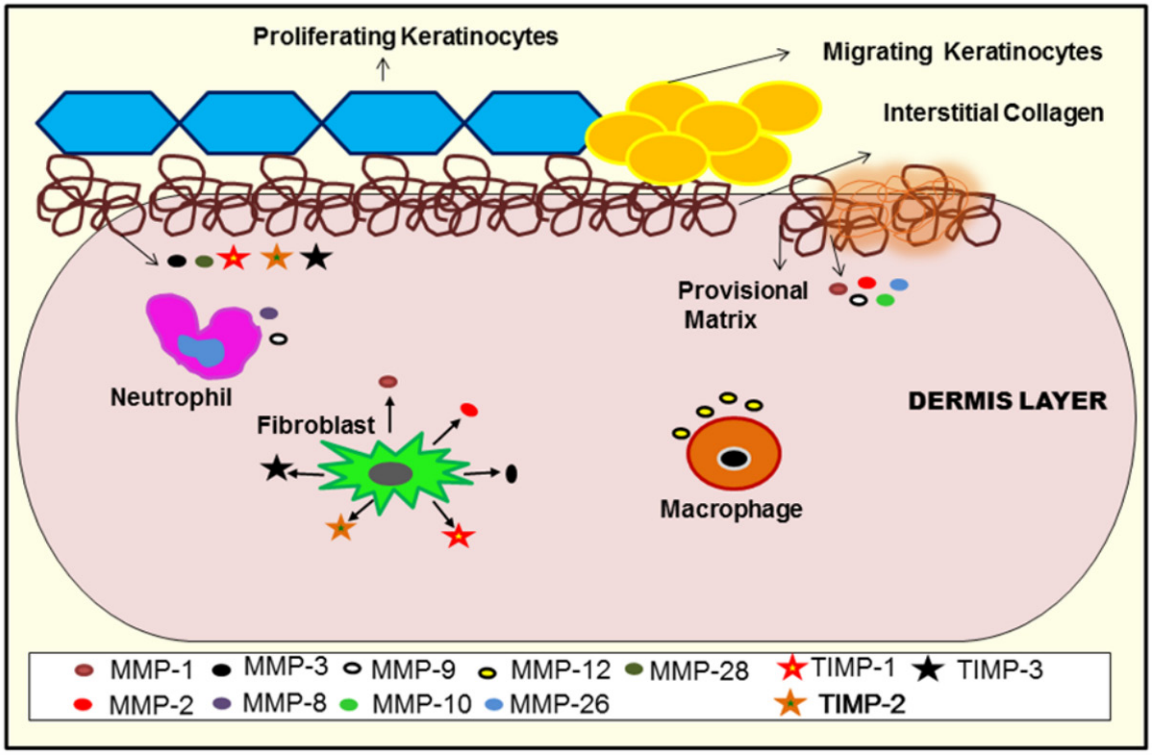

Figure 3. Pictorial illustration of the dermis layer and the role of MMPs and their respective inhibitors in wound healing.

inflammation suppression. The variables that are involved in the process of inflammation include several cytokines and chemokines, with TNF being the most prominent. TNF is a cytokine that induces acute inflammation and is activated by ADAM 17 or TACE (TNF converting enzyme). TNF-, in a manner similar to that of monocytes, increases the production of MMP9 by activating the transcription factors NFxB and NFxE [94]. MAP kinase pathways in inflammatory cells further regulates or alters many aspects of wound healing. Another inhibitor of MMP in wound healing is TIMP3 and in its absence ADAM17 is enhanced which leads to constitutively increase TNFα release [95-97]. This release further triggers the inflammatory cell infiltration into the liver. Also increased levels of TNFα are responsible for increased IL6 (interleukin 6) release. This behavior causes increased susceptibility to LPS (lipopolysaccharide) induced mortality [98]. TIMP 3 is the sole inhibitor that is capable of functioning during an inflammatory response. During a lung infection or damage, the release of TIMP1 is enhanced [98]. It has been shown that the loss of TIMP1 results in an increase in vascular permeability and neutrophil diapedesis into pulmonary tissue. TIMP1 is also crucial for limiting leukocyte extravasation and vascular permeability via the mechanism of endothelial cell apoptosis, which is a process that occurs in the absence of TIMP1 [97]. TIMP1, on the other hand, has an anti-apoptosis impact on cytokine-simulated endothelial cells via the phosphatidylino-sitd-3-kinase pathway, which is a novel discovery (**Figure 3**).

TIMP 3, which functions as a metalloproteinase inhibitor, is required for the regulation of the inflammatory response by modulating cytokine signaling and inflammatory cell adhesion, among other things. On the basis of these findings, it may be inferred that MMP inhibitors play an extremely important role in all areas of wound healing [73, 97]. Apart from that, the TIMP3 and TIMP1 proteins are also capable of controlling cell migration by inhibiting the activity of particular MMPs. The specific function of TIMPs in the control of cell migration has not yet been determined, but some research has shown that TIMP2 increases the migration of keratinocytes into cell culture when *in vivo*

techniques are used. According to the findings of recent research, TIMPs are capable of performing MMP-independent tasks in addition to their capacity to block MMP activity. As evidenced, TIMP3 is a potent inhibitor of the angiogenesis process in wound healing. It also has the capability to directly bind to the vascular endothelial growth factor receptor and prevent the direct binding of VEGF [73]. The angiogenesis phase is of great importance during the cascade of healing wounds as it aids the formation of granulation tissue in order to enhance the vascular supply in and around the affected area. This crucial phase is regulated by TIMP3 and this particular inhibitor of MMPS can dramatically impact the wound healing process. After all the granulation and angiogenic phase, the final stage of the wound healing is the closure of the wound and the contraction of the wound is an important event towards the success of this closure. In the process of re-epithelialization, cutaneous wounds are treated with GM 6001 but it also responsible for the decrease in the pace of wound contraction as well [24, 99, 100]. One more adverse effect of this treatment is the inability to differentiate between the granulation tissue and healthy tissue which leads to impairment in the wound restoration phase. On the other hand the role of the ECM in the wound resolution phase is an important aspect which can be carefully examined and monitored. Collagen is the key requirement for converting the granulation tissue into scar tissue and this process is thoroughly regulated by TIMP3. Fibronectin along with collagen are inhibited and their release is further decreased in the absence of TIMP3.

Conclusion

It has been found that MMPs exist in basically in three distinct forms, which are pro MMPs, active MMPs and TIMPs (complex) MMPs. According to research, it has been confirmed and verified by different scientists that active MMPs are involved in the healing progression of wounds or they have a positive effect towards the healing of wounds. At present there are no such methods or mechanisms which can evenly classify between these three forms of MMPs which confirms that the activity of MMPs in wound healing is still challengeable. However quantitative profiling of a few active MMPs is crucial in examining every possible role of MMPs during wound healing progression, specifically during the ECM reframing phase. Medical research is a tool through which new therapeutic involvement for specific disorders can be identified and examined through various phases. In the case of wound healing, all the respective enzymes and receptors must be carefully examined and studied before introducing any kind of novel drug or molecule. This same principal should be considered in the case of MMPs and wound healing as well. Future experimental work that may include animal models to study MMPs, ADAMs or TIMPs, must be done in order to further explore the field. These studies will further enhance the knowledge on how exactly these enzymes work. Studies of their respective inhibitors are also equally important. These studies will help in a way to resolve all the parameters that are necessary for modulating them either positively or negatively.

Future perspectives

In recent years it has been verified by scientists that MMPs possess several beneficial properties which are the underlying principles of pathologies of different diseases. They have a characteristic role in the degradation of the ECM which ultimately releases numerous biological factors that further act as activators in the wound healing process. They are generally involved in the activation of various growth factors and also in detachment of the membrane. These are the predominant functions of MMPs, and substrates of MMPs are basically non matrix molecules. Currently many novel techniques are being used in order to study the substrates of MMPs in detail. This could be the ground of future research of meta-analysis which would be able to differentiate downstream effects and profile substrates precise to each protease. For studying or analyzing the enhanced role of MMPs in different physiologies and pathologies, efficient analysis of protease substrate is very important. Almost all the variants of the MMP family are actively involved in several biological events in the body. However, few of them are restricted or specified to certain cells only like MMP 20 (specified for dental tissue). Their constitutive physiological expression is normally low, with transiently higher rates due to homeostatic matrix remodeling or specific developmental

events. These short expression peaks underline their stringent regulation under physiological conditions and highlight their important role in tissue homeostasis and development. Uneven regulation of the functions of MMP specifically in the pre-chemo phase of cancer is a matter of conflict for MMPs as promising therapeutic targets. Although the first clinical trial failed in which broad spectrum MMP inhibitors were involved. The main ground on which future research will rely is the blueprint or draft of the desired therapeutic agents in inhibition of selective MMP variants. Management of wound healing is still a very challengeable issue which has to be supervised with more efficacy and persistence in order to prevent acute wounds from becoming chronic. Thorough experimentation and study in this relative field is very important so that this can be addressed more efficiently. Careful examination of MMPs, their regulation and specific roles with respect to the ECM and its components may provide a new basis for further research in this respective field of wound healing. Research is still underway for framing innovative methods regarding MMPs in treating wounds. This promising field is capable of recognizing novel inhibitors to deal with this problem.

Acknowledgements

The authors express gratitude to Chitkara College of Pharmacy, Chitkara University, Punjab, India, for providing basic facilities for completion of the article. This research did not receive any specific grant support from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Tapan Behl, Chitkara College of Pharmacy, Chitkara University, Punjab 140401, India. Tel: +91-8527517931; E-mail: tapanbehl31@gmail.com

References

[1] Baldassarro VA, Lorenzini L, Giuliani A, Cescatti M, Alastra G, Pannella M, Imbimbo BP, Villetti G, Calzà L and Giardino L. Molecular mechanisms of skin wound healing in non-diabetic and diabetic mice in excision and pressure experimental wounds. Cell Tissue Res 2022; 388: 595-613.

[2] Li D, Cheng S, Pei Y, Sommar P, Kärner J, Herter EK, Toma MA, Zhang L, Pham K, Cheung YT, Liu Z, Chen X, Eidsmo L, Deng Q and Xu Landén N. Single-cell analysis reveals major histocompatibility complex II-expressing keratinocytes in pressure ulcers with worse healing outcomes. J Invest Dermatol 2022; 142: 705-716.

[3] Zhang KY, McQuibban GA, Silva C, Butler GS, Johnston JB, Holden J, Clark-Lewis I, Overall CM and Power C. HIV-induced metalloproteinase processing of the chemokine stromal cell derived factor-1 causes neurodegeneration. Nat Neurosci 2003; 6: 1064-1071.

[4] Zhou M, Zhang YH, Ardans JA and Wahl LM. Interferon-γ differentially regulates monocyte matrix metalloproteinase-1 and-9 through tumor necrosis factor-α and caspase 8. J Biol Chem 2003; 278: 45406-45413.

[5] Kirby GT, Mills SJ, Cowin AJ and Smith LE. Stem cells for cutaneous wound healing. Biomed Res Int 2015; 2015: 285869.

[6] Bonnans C, Chou J and Werb Z. Remodelling the extracellular matrix in development and disease. Nat Rev Mol Cell Biol 2014; 15: 786-801.

[7] Caley MP, Martins VL and O'Toole EA. Metalloproteinases and wound healing. Adv Wound Care (New Rochelle) 2015; 4: 225-234.

[8] Martins VL, Caley M and O'Toole EA. Matrix metalloproteinases and epidermal wound repair. Cell Tissue Res 2013; 351: 255-268.

[9] Rohani MG and Parks WC. Matrix remodeling by MMPs during wound repair. Matrix Biol 2015; 44: 113-121.

[10] Salazar JJ, Ennis WJ and Koh TJ. Diabetes medications: impact on inflammation and wound healing. J Diabetes Complications 2016; 30: 746-752.

[11] Croasdell Lucchini A, Gachanja NN, Rossi AG, Dorward DA and Lucas CD. Epithelial cells and inflammation in pulmonary wound repair. Cells 2021; 10: 339.

[12] Shaw TJ and Martin P. Wound repair at a glance. J Cell Sci 2009; 122: 3209-3213.

[13] Yamaguchi Y and Yoshikawa K. Cutaneous wound healing: an update. J Dermatol 2001; 28: 521-534.

[14] Martin P. Wound healing--aiming for perfect skin regeneration. Science 1997; 276: 75-81.

[15] Schultz GS, Davidson JM, Kirsner RS, Bornstein P and Herman IM. Dynamic reciprocity in the wound microenvironment. Wound Repair Regen 2011; 19: 134-148.

[16] Abou-El-Hassan H, Bsat S, Sukhon F, Assaf EJ, Mondello S, Kobeissy F, Wang KKW, Weiner HL and Omeis I. Protein degradome of spinal cord injury: biomarkers and potential therapeutic targets. Mol Neurobiol 2020; 57: 2702-2726.

[17] Levi E, Fridman R, Miao HQ, Ma YS, Yayon A and Vlodavsky I. Matrix metalloproteinase 2 releases active soluble ectodomain of fibroblast growth factor receptor 1. Proc Natl Acad Sci U S A 1996; 93: 7069-7074.
[18] Preece G, Murphy G and Ager A. Metalloproteinase-mediated regulation of L-selectin levels on leucocytes. J Biol Chem 1996; 271: 11634-11640.
[19] Suzuki M, Raab G, Moses MA, Fernandez CA and Klagsbrun M. Matrix metalloproteinase-3 releases active heparin-binding EGF-like growth factor by cleavage at a specific juxtamembrane site. J Biol Chem 1997; 272: 31730-31737.
[20] Rundhaug JE. Matrix metalloproteinases and angiogenesis. J Cell Mol Med 2005; 9: 267-285.
[21] Solomonov I, Zehorai E, Talmi-Frank D, Wolf SG, Shainskaya A, Zhuravlev A, Kartvelishvily E, Visse R, Levin Y, Kampf N, Jaitin DA, David E, Amit I, Nagase H and Sagi I. Distinct biological events generated by ECM proteolysis by two homologous collagenases. Proc Natl Acad Sci U S A 2016; 113: 10884-10889.
[22] Ong HT and Dilley RJ. Novel non-angiogenic role for mesenchymal stem cell-derived vascular endothelial growth factor on keratinocytes during wound healing. Cytokine Growth Factor Rev 2018; 44: 69-79.
[23] Singer AJ and Clark RA. Cutaneous wound healing. N Engl J Med 1999; 341: 738-746.
[24] Toriseva M and Kähäri VM. Proteinases in cutaneous wound healing. Cell Mol Life Sci 2009; 66: 203-224.
[25] Schultz GS and Wysocki A. Interactions between extracellular matrix and growth factors in wound healing. Wound Repair Regen 2009; 17: 153-162.
[26] Hartono SP, Bedell VM, Alam SK, O'Gorman M, Serres M, Hall SR, Pal K, Kudgus RA, Mukherjee P, Seelig DM, Meves A, Mukhopadhyay D, Ekker SC and Hoeppner LH. Vascular endothelial growth factor as an immediate-early activator of ultraviolet-induced skin injury. Mayo Clin Proc 2022 97: 154-164.
[27] Macri L, Silverstein D and Clark RA. Growth factor binding to the pericellular matrix and its importance in tissue engineering. Adv Drug Deliv Rev 2007; 59: 1366-1381.
[28] George AJ, Thomas WG and Hannan RD. The renin-angiotensin system and cancer: old dog, new tricks. Nat Rev Cancer 2010; 10: 745-759.
[29] Hyytiäinen M, Penttinen C and Keski-Oja J. Latent TGF-β binding proteins: extracellular matrix association and roles in TGF-β activation. Crit Rev Clin Lab Sci 2004; 41: 233-264.
[30] Roberts AB, Heine UI, Flanders KC and Sporn MB. Transforming growth factor-β: major role in regulation of extracellular matrix. Ann N Y Acad Sci 1990; 580: 225-232.
[31] Kandhwal M, Behl T, Kumar A and Arora S. Understanding the potential role and delivery approaches of nitric oxide in chronic wound healing management. Curr Pharm Des 2021; 27: 1999-2014.
[32] Alexander CM, Howard EW, Bissell MJ and Werb Z. Rescue of mammary epithelial cell apoptosis and entactin degradation by a tissue inhibitor of metalloproteinases-1 transgene. J Cell Biol 1996; 135: 1669-1677.
[33] Gary Sibbald R and Woo KY. The biology of chronic foot ulcers in persons with diabetes. Diabetes Metab Res Rev 2008; 24 Suppl 1: S25-S30.
[34] Kümin A, Schäfer M, Epp N, Bugnon P, Born-Berclaz C, Oxenius A, Klippel A, Bloch W and Werner S. Peroxiredoxin 6 is required for blood vessel integrity in wounded skin. J Cell Biol 2007; 179: 747-760.
[35] Guo S and DiPietro LA. Factors affecting wound healing. J Dent Res 2010; 89: 219-229.
[36] Boudreau NJ and Jones PL. Extracellular matrix and integrin signalling: the shape of things to come. Biochem J 1999; 339: 481-488.
[37] Olaso E, Labrador JP, Wang L, Ikeda K, Eng FJ, Klein R, Lovett DH, Lin HC and Friedman SL. Discoidin domain receptor 2 regulates fibroblast proliferation and migration through the extracellular matrix in association with transcriptional activation of matrix metalloproteinase-2. J Biol Chem 2002; 277: 3606-3613.
[38] Rossiter H, Barresi C, Pammer J, Rendl M, Haigh J, Wagner EF and Tschachler E. Loss of vascular endothelial growth factor a activity in murine epidermal keratinocytes delays wound healing and inhibits tumor formation. Cancer Res 2004; 64: 3508-3516.
[39] Hong Y, Lange-Asschenfeldt B, Velasco P, Hirakawa S, Kunstfeld R, Brown LF, Bohlen P, Senger DR and Detmar M. VEGF-A promotes tissue repair-associated lymphatic vessel formation via VEGFR-2 and the α1β1 and α2β1 integrins. FASEB J 2004; 18: 1111-1113.
[40] Tran KT, Lamb P and Deng JS. Matrikines and matricryptins: implications for cutaneous cancers and skin repair. J Dermatol Sci 2005; 40: 11-20.
[41] Wilson SE. Defective perlecan-associated basement membrane regeneration and altered modulation of transforming growth factor beta in corneal fibrosis. Cell Mol Life Sci 2022; 79: 144.
[42] Birkedal-Hansen H, Moore WG, Bodden MK, Windsor LJ, Birkedal-Hansen B, DeCarlo A and

Engler JA. Matrix metalloproteinases: a review. Crit Rev Oral Biol Med 1993; 4: 197-250.
[43] Black RA and White JM. ADAMs: focus on the protease domain. Curr Opin Cell Biol 1998; 10: 654-659.
[44] Black RA, Rauch CT, Kozlosky CJ, Peschon JJ, Slack JL, Wolfson MF, Castner BJ, Stocking KL, Reddy P, Srinivasan S, Nelson N, Boiani N, Schooley KA, Gerhart M, Davis R, Fitzner JN, Johnson RS, Paxton RJ, March CJ and Cerretti DP. A metalloproteinase disintegrin that releases tumour-necrosis factor-α from cells. Nature 1997; 385: 729-733.
[45] Rosenblum G, Meroueh S, Toth M, Fisher JF, Fridman R, Mobashery S and Sagi I. Molecular structures and dynamics of the stepwise activation mechanism of a matrix metalloproteinase zymogen: challenging the cysteine switch dogma. J Am Chem Soc 2007; 129: 13566-13574.
[46] Lin HL, Xu P and Huang MD. Structure-based molecular insights into matrix metalloproteinase inhibitors in cancer treatments. Future Med Chem 2022; 14: 35-51.
[47] López-Otín C and Overall CM. Protease degradomics: a new challenge for proteomics. Nat Rev Mol Cell Biol 2002; 3: 509-519.
[48] Amour A, Knight CG, Webster A, Slocombe PM, Stephens PE, Knäuper V, Docherty AJ and Murphy G. The in vitro activity of ADAM-10 is inhibited by TIMP-1 and TIMP-3. FEBS Lett 2000; 473: 275-279.
[49] Bajbouj K, Ramakrishnan RK and Hamid Q. Role of matrix metalloproteinases in angiogenesis and its implications in asthma. J Immunol Res 2021; 2021: 6645072.
[50] Parks WC, Wilson CL and López-Boado YS. Matrix metalloproteinases as modulators of inflammation and innate immunity. Nat Rev Immunol 2004; 4: 617-629.
[51] Corry DB, Kiss A, Song LZ, Song L, Xu J, Lee SH, Werb Z and Kheradmand F. Overlapping and independent contributions of MMP2 and MMP9 to lung allergic inflammatory cell egression through decreased CC chemokines. FASEB J 2004; 18: 995-997.
[52] Corry DB, Rishi K, Kanellis J, Kiss A, Song Lz LZ, Xu J, Feng L, Werb Z and Kheradmand F. Decreased allergic lung inflammatory cell egression and increased susceptibility to asphyxiation in MMP2-deficiency. Nat Immunol 2002; 3: 347-353.
[53] Marônek M, Marafini I, Gardlík R, Link R, Troncone E and Monteleone G. Metalloproteinases in inflammatory bowel diseases. J Inflamm Res 2021; 14: 1029-1041.
[54] Saarialho-Kere U, Kerkelä E, Suomela S, Jahkola T, Keski-Oja J and Lohi J. Epilysin (MMP-28) expression is associated with cell proliferation during epithelial repair. J Invest Dermatol 2002; 119: 14-21.
[55] Clark-Lewis I, Kim KS, Rajarathnam K, Gong JH, Dewald B, Moser B, Baggiolini M and Sykes BD. Structure-activity relationships of chemokines. J Leukoc Biol 1995; 57: 703-711.
[56] Zlotnik A, Yoshie O and Nomiyama H. The chemokine and chemokine receptor superfamilies and their molecular evolution. Genome Biol 2006; 7: 243.
[57] Van den Steen PE, Proost P, Wuyts A, Van Damme J and Opdenakker G. Neutrophil gelatinase B potentiates interleukin-8 tenfold by aminoterminal processing, whereas it degrades CTAP-III, PF-4, and GRO-α and leaves RANTES and MCP-2 intact. Blood 2000; 96: 2673-2681.
[58] Tester AM, Cox JH, Connor AR, Starr AE, Dean RA, Puente XS, Lopez-Otin C and Overall CM. LPS responsiveness and neutrophil chemotaxis in vivo require PMN MMP-8 activity. PLoS One 2007; 2: e312.
[59] Van den Steen PE, Wuyts A, Husson SJ, Proost P, Van Damme J and Opdenakker G. Gelatinase B/MMP-9 and neutrophil collagenase/MMP-8 process the chemokines human GCP-2/CXCL6, ENA-78/CXCL5 and mouse GCP-2/LIX and modulate their physiological activities. Eur J Biochem 2003; 270: 3739-3749.
[60] Scholz F, Schulte A, Adamski F, Hundhausen C, Mittag J, Schwarz A, Kruse ML, Proksch E and Ludwig A. Constitutive expression and regulated release of the transmembrane chemokine CXCL16 in human and murine skin. J Invest Dermatol 2007; 127: 1444-1455.
[61] Atkinson JJ, Toennies HM, Holmbeck K and Senior RM. Membrane type 1 matrix metalloproteinase is necessary for distal airway epithelial repair and keratinocyte growth factor receptor expression after acute injury. Am J Physiol Lung Cell Mol Physiol 2007; 293: L600-L610.
[62] Dunsmore SE, Saarialho-Kere UK, Roby JD, Wilson CL, Matrisian LM, Welgus HG and Parks WC. Matrilysin expression and function in airway epithelium. J Clin Invest 1998; 102: 1321-1331.
[63] McCawley LJ, O'Brien P and Hudson LG. Epidermal growth factor (EGF)-and scatter factor/hepatocyte growth factor (SF/HGF)-mediated keratinocyte migration is coincident with induction of matrix metalloproteinase (MMP)-9. J Cell Physiol 1998; 176: 255-265.
[64] Inoue M, Kratz G, Haegerstrand A and Ståhle-Bäckdahl M. Collagenase expression is rapidly induced in wound-edge keratinocytes after acute injury in human skin, persists during healing, and stops at re-epithelialization. J Invest Dermatol 1995; 104: 479-483.

[65] Hosseini M and Shafiee A. Engineering bioactive scaffolds for skin regeneration. Small 2021; 17: e2101384.
[66] Pilcher BK, Sudbeck BD, Dumin JA, Welgus HG and Parks WC. Collagenase-1 and collagen in epidermal repair. Arch Dermatol Res 1998; 290 Suppl: S37-S46.
[67] Spradling KD, McDaniel AE, Lohi J and Pilcher BK. Epsin 3 is a novel extracellular matrix-induced transcript specific to wounded epithelia. J Biol Chem 2001; 276: 29257-29267.
[68] Pilcher BK, Dumin JA, Sudbeck BD, Krane SM, Welgus HG and Parks WC. The activity of collagenase-1 is required for keratinocyte migration on a type I collagen matrix. J Cell Biol 1997; 137: 1445-1457.
[69] Mulholland B, Tuft SJ and Khaw PT. Matrix metalloproteinase distribution during early corneal wound healing. Eye (Lond) 2005; 19: 584-588.
[70] Salmela MT, Pender SL, Karjalainen-Lindsberg ML, Puolakkainen P, Macdonald TT and Saarialho-Kere U. Collagenase-1 (MMP-1), matrilysin-1 (MMP-7), and stromelysin-2 (MMP-10) are expressed by migrating enterocytes during intestinal wound healing. Scand J Gastroenterol 2004; 39: 1095-1104.
[71] Coraux C, Martinella-Catusse C, Nawrocki-Raby B, Hajj R, Burlet H, Escotte S, Laplace V, Birembaut P and Puchelle E. Differential expression of matrix metalloproteinases and interleukin-8 during regeneration of human airway epithelium in vivo. J Pathol 2005; 206: 160-169.
[72] Tampa M, Georgescu SR, Mitran MI, Mitran CI, Matei C, Caruntu A, Scheau C, Nicolae I, Matei A, Caruntu C, Constantin C and Neagu M. Current perspectives on the role of matrix metalloproteinases in the pathogenesis of basal cell carcinoma. Biomolecules 2021; 11: 903.
[73] Sigurdson L, Sen T, Hall L 3rd, Rubenfeld A, Hard R, Gardella J, Bright F and Hicks WL. Possible impedance of luminal reepithelialization by tracheal cartilage metalloproteinases. Arch Otolaryngol Head Neck Surg 2003; 129: 197-200.
[74] Bullard KM, Lund L, Mudgett JS, Mellin TN, Hunt TK, Murphy B, Ronan J, Werb Z and Banda MJ. Impaired wound contraction in stromelysin-1-deficient mice. Ann Surg 1999; 230: 260-265.
[75] McCawley LJ and Matrisian LM. Matrix metalloproteinases: they're not just for matrix anymore! Curr Opin Cell Biol 2001; 13: 534-540.
[76] Rousselle P, Montmasson M and Garnier C. Extracellular matrix contribution to skin wound re-epithelialization. Matrix Biol 2019; 75-76: 12-26.
[77] Khokha R, Murthy A and Weiss A. Metalloproteinases and their natural inhibitors in inflammation and immunity. Nat Rev Immunol 2013; 13: 649-665.
[78] Sunami E, Tsuno N, Osada T, Saito S, Kitayama J, Tomozawa S, Tsuruo T, Shibata Y, Muto T and Nagawa H. MMP-1 is a prognostic marker for hematogenous metastasis of colorectal cancer. Oncologist 2000; 5: 108-114.
[79] Lobmann R, Ambrosch A, Schultz G, Waldmann K, Schiweck S and Lehnert H. Expression of matrix-metalloproteinases and their inhibitors in the wounds of diabetic and non-diabetic patients. Diabetologia 2002; 45: 1011-1016.
[80] Prikk K, Maisi P, Pirilä E, Reintam MA, Salo T, Sorsa T and Sepper R. Airway obstruction correlates with collagenase-2 (MMP-8) expression and activation in bronchial asthma. Lab Invest 2002; 82: 1535-1545.
[81] Toriseva MJ, Ala-aho R, Karvinen J, Baker AH, Marjomäki VS, Heino J and Kähäri VM. Collagenase-3 (MMP-13) enhances remodeling of three-dimensional collagen and promotes survival of human skin fibroblasts. J Invest Dermatol 2007; 127: 49-59.
[82] Li NG, Shi ZH, Tang YP, Wang ZJ, Song SL, Qian LH, Qian DW and Duan JA. New hope for the treatment of osteoarthritis through selective inhibition of MMP-13. Curr Med Chem 2011; 18: 977-1001.
[83] Ratzinger G, Stoitzner P, Ebner S, Lutz MB, Layton GT, Rainer C, Senior RM, Shipley JM, Fritsch P and Schuler G. Matrix metalloproteinases 9 and 2 are necessary for the migration of Langerhans cells and dermal dendritic cells from human and murine skin. J Immunol 2002; 168: 4361-4371.
[84] Groblewska M, Mroczko B, Gryko M, Pryczynicz A, Guzińska-Ustymowicz K, Kędra B, Kemona A and Szmitkowski M. Serum levels and tissue expression of matrix metalloproteinase 2 (MMP-2) and tissue inhibitor of metalloproteinases 2 (TIMP-2) in colorectal cancer patients. Tumour Biol 2014; 35: 3793-3802.
[85] Ogata Y, Enghild JJ and Nagase H. Matrix metalloproteinase 3 (stromelysin) activates the precursor for the human matrix metalloproteinase 9. J Biol Chem 1992; 267: 3581-3584.
[86] Yabluchanskiy A, Ma Y, Iyer RP, Hall ME and Lindsey ML. Matrix metalloproteinase-9: many shades of function in cardiovascular disease. Physiology (Bethesda) 2013; 28: 391-403.
[87] Green MJ, Gough AK, Devlin J, Smith J, Astin P, Taylor D and Emery P. Serum MMP-3 and MMP-1 and progression of joint damage in early rheumatoid arthritis. Rheumatology (Oxford) 2003; 42: 83-88.
[88] Vaalamo M, Karjalainen-Lindsberg ML, Puolakkainen P, Kere J and Saarialho-Kere U. Distinct expression profiles of stromelysin-2 (MMP-10), collagenase-3 (MMP-13), macrophage metal-

loelastase (MMP-12), and tissue inhibitor of metalloproteinases-3 (TIMP-3) in intestinal ulcerations. Am J Pathol 1998; 152: 1005-1014.
[89] Bord S, Horner A, Hembry RM and Compston JE. Stromelysin-1 (MMP-3) and stromelysin-2 (MMP-10) expression in developing human bone: potential roles in skeletal development. Bone 1998; 23: 7-12.
[90] Chen P, McGuire JK, Hackman RC, Kim KH, Black RA, Poindexter K, Yan W, Liu P, Chen AJ, Parks WC and Madtes DK. Tissue inhibitor of metalloproteinase-1 moderates airway re-epithelialization by regulating matrilysin activity. Am J Pathol 2008; 172: 1256-1270.
[91] Abbas A, Aukrust P, Russell D, Krohg-Sørensen K, Almås T, Bundgaard D, Bjerkeli V, Sagen EL, Michelsen AE, Dahl TB, Holm S, Ueland T, Skjelland M and Halvorsen B. Matrix metalloproteinase 7 is associated with symptomatic lesions and adverse events in patients with carotid atherosclerosis. PLoS One 2014; 9: e84935.
[92] Mohan A, Neequaye N, Malur A, Soliman E, McPeek M, Leffler N, Ogburn D, Tokarz DA, Knudson W, Gharib SA, Schnapp LM, Barna BP and Thomassen MJ. Matrix metalloproteinase-12 is required for granuloma progression. Front Immunol 2020; 11: 553949.
[93] Krstic J and Santibanez JF. Transforming growth factor-beta and matrix metalloproteinases: functional interactions in tumor stroma-infiltrating myeloid cells. ScientificWorldJournal 2014; 2014: 521754.
[94] Kim KH, Burkhart K, Chen P, Frevert CW, Randolph-Habecker J, Hackman RC, Soloway PD and Madtes DK. Tissue inhibitor of metalloproteinase-1 deficiency amplifies acute lung injury in bleomycin-exposed mice. Am J Respir Cell Mol Biol 2005; 33: 271-279.
[95] Smookler DS, Mohammed FF, Kassiri Z, Duncan GS, Mak TW and Khokha R. Cutting edge: tissue inhibitor of metalloproteinase 3 regulates TNF-dependent systemic inflammation. J Immunol 2006; 176: 721-725.
[96] Madtes DK, Elston AL, Kaback LA and Clark JG. Selective induction of tissue inhibitor of metalloproteinase-1 in bleomycin-induced pulmonary fibrosis. Am J Respir Cell Mol Biol 2001; 24: 599-607.
[97] Boulday G, Fitau J, Coupel S, Soulillou JP and Charreau B. Exogenous tissue inhibitor of metalloproteinase-1 promotes endothelial cell survival through activation of the phosphatidylinositol 3-kinase/Akt pathway. Ann N Y Acad Sci 2004; 1030: 28-36.
[98] Qi JH, Ebrahem Q, Moore N, Murphy G, Claesson-Welsh L, Bond M, Baker A and Anand-Apte B. A novel function for tissue inhibitor of metalloproteinases-3 (TIMP3): inhibition of angiogenesis by blockage of VEGF binding to VEGF receptor-2. Nat Med 2003; 9: 407-415.
[99] Velnar T, Bailey T and Smrkolj V. The wound healing process: an overview of the cellular and molecular mechanisms. J Int Med Res 2009; 37: 1528-1542.
[100] Chang M. Restructuring of the extracellular matrix in diabetic wounds and healing: a perspective. Pharmacol Res 2016; 107: 243-248.