Metalloproteinases and Wound Healing

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Significance: Matrix metalloproteinases (MMPs) are present in both acute and chronic wounds. They play a pivotal role, with their inhibitors, in regulating extracellular matrix degradation and deposition that is essential for wound reepithelialization. The excess protease activity can lead to a chronic nonhealing wound. The timed expression and activation of MMPs in response to wounding are vital for successful wound healing. MMPs are grouped into eight families and display extensive homology within these families. This homology leads in part to the initial failure of MMP inhibitors in clinical trials and the development of alternative methods for modulating the MMP activity. MMP-knockout mouse models display altered wound healing responses, but these are often subtle phenotypic changes indicating the overlapping MMP substrate specificity and inter-MMP compensation.

Recent Advances: Recent research has identified several new MMP modulators, including photodynamic therapy, protease-absorbing dressing, microRNA regulation, signaling molecules, and peptides.

Critical Issues: Wound healing requires the controlled activity of MMPs at all stages of the wound healing process. The loss of MMP regulation is a characteristic of chronic wounds and contributes to the failure to heal.

Future Directions: Further research into how MMPs are regulated should allow the development of novel treatments for wound healing.

SCOPE AND SIGNIFICANCE

This review highlights recent advances in understanding the regulation of matrix metalloproteinases (MMPs) in skin and how this knowledge might be applied in patients to improve wound healing. Selected recent advances include microRNA (MiR) regulation, novel peptides, signal transduction, experimental therapies, and novel dressings.

TRANSLATIONAL RELEVANCE

Wound healing is a complex multicellular process involving fibroblasts, keratinocytes, and endothelial cells as well as inflammatory cells. The healing process follows an orderly sequence of events incorporating four distinct, yet overlapping, phases: hemostasis, the inflammatory phase, the proliferation phase, and the remodeling phase. The phases of wound healing are regulated by cross talk between different groups of molecules, including extracellular matrix (ECM), integrins, growth factors, and MMPs. Migration of cells on ECM, and remodeling and degradation of the ECM by MMPs are key elements of wound repair.

CLINICAL RELEVANCE

Chronic wounds, including pressure sores, venous ulcers, and diabetic ulcers, are a major clinical problem with considerable morbidity and associated financial costs. Excessive MMPs are a feature of chronic wounds. Regulation of MMP levels in wounds could lead to improved wound healing.

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OVERVIEW

The MMP family is a group of calcium-dependent zinc-containing enzymes that are involved in the degradation of ECM. Family members share structural (Fig. 1) and sequence similarities, a flexible proline-rich hinge region, and a hemopexin-like C-terminal domain, which functions in recognition of substrates (usually ECM). Exceptions to this rule are MMP-7, MMP-23, and MMP-26, which lack the hemopexin-like domain. Some MMPs have additional insertions, which contribute to the functional differences observed between the MMP types. MMPs can be divided into seven groups based on the substrate preference and domain organization: (1) collagenases, (2) gelatinases, (3) stromelysins, (4) matrilysins, (5) metalloelastases, (6) membrane-type MMPs (MT-MMPs), and (7) other MMPs. Table 1 summarizes the different groups of human MMPs, their substrates, and role in cell migration.[1–3]

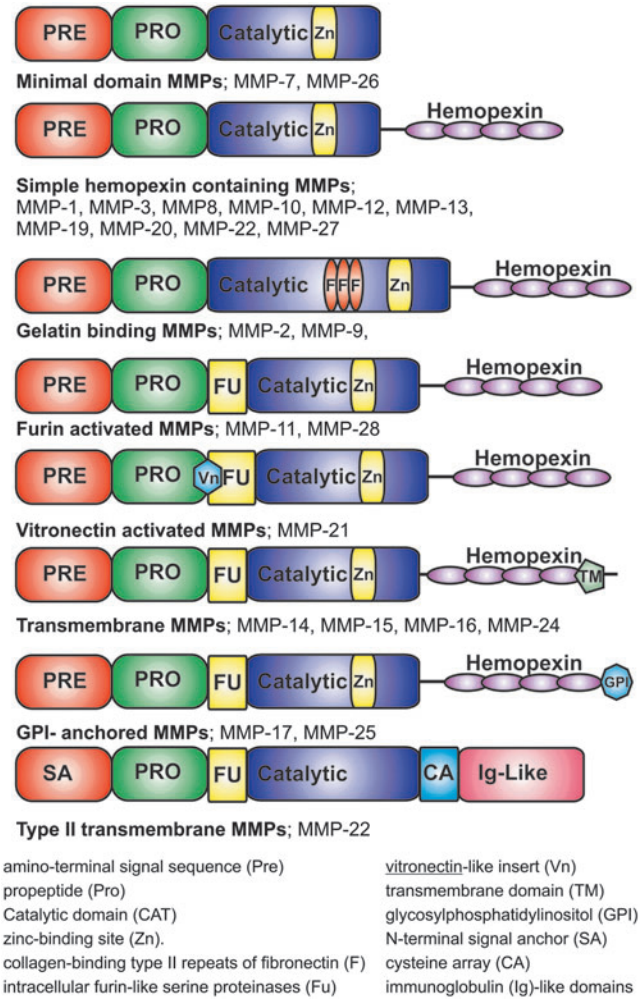

Figure 1. MMP family. MMPs can be divided into eight groups based on structural similarities and shared function. Minimal domain MMPs include MMP-7 and MMP-26. Simple hemopexin containing MMPs: MMP-1, MMP-3, MMP-8, MMP-10, MMP-12, MMP-13, MMP-19, MMP-20, MMP-22, and MMP-27. Gelatin binding MMPs: MMP-2 and MMP-9. Furin-activated MMPs: MMP-11 and MMP-28. Vitronectin-activated MMPs: MMP-21. Transmembrane MMPs: MMP-14, MMP-15, MMP-16, and MMP-24. GPI-anchored MMPs: MMP-17 and MMP-25. Type II transmembrane MMPs: MMP-22. MMP, matrix metalloproteinase.

Regulation of MMP expression and activity

Metalloproteinase secretion and activity are highly regulated. In the normal tissue, MMPs are expressed at basal levels, if at all. When tissue remodeling is required (as in wound healing), MMPs can be rapidly expressed and activated. Multiple different cell types express MMPs within the skin (keratinocytes, fibroblasts, endothelial cells, and inflammatory cells such as monocytes, lymphocytes, and macrophages). MMP expression can be induced in response to a range of signals, including cytokines, hormones, and contact with other cell types or the ECM.

A wide range of cytokines and growth factors transcriptionally activate MMPs; these include epidermal growth factor (EGF), hepatocyte growth factor (HGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor, tumor necrosis factor-α (TNF-α), keratinocyte growth factor (KGF), transforming growth factor-β (TGF-β), as well as interleukins and interferons.[4] A number of signaling pathways have been implicated in the control of MMP expression; these include activation of NF-κB, mitogen-activated protein kinase, or Smad-dependent pathways by growth factors/cytokines; activation of focal adhesion kinase (FAK) by integrin activation, or activation of Wnt signaling. Further regulators of MMP expression include epigenetic modifications of chromatin and post-transcriptional regulation through mRNA stabilization/destabilization.[4,5]

Metalloproteinase activity is tightly regulated by gene expression as well as by controlled enzymatic activation and specific inhibition. MMPs are not initially expressed as catalytically active proteins, but in a latent form (pro-MMP). The catalytic activity of all MMPs requires a zinc ion (Zn^{++}) in the active site. Activation involves the disruption of the bond between the prodomain PRCGVPD (this sequence is highly conserved between MMPs) and the Zn^{++} ion in the active site.[6] Pro-MMPs are activated by serine proteinases as well as by other MMPs. MMP activation can be controlled by inhibition of proteinase activity by plasma proteinase inhibitors, such as α1-proteinase and α2-macroglobulin, or by MMP binding proteins, such

Table 1. *Mammalian matrix metalloproteinases: substrate specificities and role in wound healing*

Member	*Substrates*	*Role in wound healing*	*Determined in*	
			Cell culture	In vivo, ex vivo
Collagenases				
MMP-1 (collagenase-1)	Collagen I, II, III, VII, and X; aggrecan; serpins; alpha2-macroglobulin; kallikrein; chymase	Promotes human keratinocyte migration on fibrillar collagen Expressed by keratinocytes at their trailing membrane edge during wound healing Overexpression in keratinocytes delays reepithelialization	X	X
MMP-8 (collagenase-2)	Collagen I, II, and III; aggrecan; serpins; 2-MG	Cleaves collagens, predominant collagenase in healing wounds		X
MMP-13 (collagenase-3)	Collagen I, II, III, IV, IX, X, and XIV; gelatin; fibronectin; laminin; tenascin; aggrecan; fibrillin; serpins	Promotes reepithelialization indirectly by affecting wound contraction		X
Gelatinases				
MMP-2 (gelatinase A)	Gelatin; collagen I, IV, V, VII, and X; laminin; aggrecan; fibronectin; tenascin	Accelerates cell migration	X	
MMP-9 (gelatinase B)	Gelatin; collagen I, III, IV, V and VII; aggrecan; elastin; fibrillin	Expressed by keratinocytes at the leading edge of the wound Promotes cell migration and reepithelialization except in cornea	X	X
Stromelysins				
MMP-3 (stromelysin −1)	Collagen IV, V, IX, and X; fibronectin; elastin; gelatin; aggrecan; nidogen; fibrillin; E-cadherin	Expressed by keratinocytes at the proximal proliferating population that supplies the leading edge during wound healing Affects wound contraction	X	X
MMP-10 (stromelysin-2)	Collagen IV, V, IX, and X; fibronectin; elastin; gelatin; laminin; aggrecan, nidogen; E-cadherin	Expressed by keratinocytes at the leading edge of the wound		X
MMP-11 (stromelysin-3)	Serine protease inhibitors; 1-proteinase inhibitor	Unknown		
Matrilysins				
MMP-7 (matrilysin)	Elastin; fibronectin; laminin; nidogen; collagen IV; tenascin; versican; 1-proteinase inhibitor; E-cadherin; tumor necrosis factor	Required for reepithelialization of mucosal wounds	X	X
Metalloelastases				
MMP-12 (metalloeslastase)	Collagen IV; gelatin; fibronectin; laminin; vitronectin; elastin; fibrillin; 1-proteinase inhibitor; apolipoprotein A	Macrophage specific (not expressed by epithelial cells)		
Membrane-type MMPs				
MMP-14 (MT1-MMP)	Collagen I, II, and III; gelatin; fibronectin; laminin; vitronectin; aggrecan; tenascin; nidogen; perlecan; fibrillin; 1-proteinase inhibitor; alpha2-macroglobulin; fibrin	Promotes keratinocyte outgrowth, airway reepithelialization and cell migration	X	X
MMP-15 (MT2-MMP)	Fibronectin; laminin; aggrecan; tenascin; nidogen; perlecan	Unknown		
MMP-16 (MT3-MMP)	Collagen III; fibronectin; gelatin; casein; laminin; alpha2-macroglobulin	Unknown		
MMP-17 (MT4-MMP)	Fibrin; fibrinogen; tumor necrosis factor precursor	Unknown		
MMP-24 (MT5-MMP)	Progelatinase A	Unknown		
MMP-25 (MT6-MMP; leukolysin)	Gelatin	Unknown		
Other MMPs				
MMP-19 (RASI-1)	Gelatin; aggrecan; cartilage oligomeric matrix protein; collagen IV; laminin; nidogen; large tenascin	Unknown		
MMP-20 (enamelysin)	Amelogenin; aggrecan; cartilage oligomeric matrix protein	Expressed in developing teeth		
MMP-21		Unknown		
MMP-22		Unknown		
MMP-23 (CA-MMP)		Unknown		
MMP-26 (endometase)		Expressed by migrating keratinocytes during cutaneous wound healing		
MMP-27		Unknown		
MMP-28 (epilysin)	Casein	Expressed by a distal intact population of keratinocytes during wound healing		

Adapted from Chen and Parks[1] and Zhang and Nothnick.[2]
MMP, matrix metalloproteinase; MT, membrane type.

as thrombospondin-1 and −2.[7] The major regulators of MMP are the tissue inhibitors of metalloproteinases (TIMPs), which are specific inhibitors of the MMPs.[8]

MMPs are now known to carry out a range of diverse functions in addition to degrading or remodeling the ECM. MMPs have been shown to regulate cell–cell and cell–matrix signaling through the release of cytokines and growth factors sequestered in the ECM. MMPs modify cell surface receptors and junctional proteins, regulating processes, including cell death and inflammation. MMPs also play an important role in the release of biologically active fragments of degraded proteins, indirectly modifying cellular behavior.[1,9–13] For example, within the wound environment, MT1-MMP releases a fragment from the γ-2 chain of laminin 332 (γ-2 III domain) found within the skin basement membrane; this fragment contains multiple EGF-like repeats and promotes keratinocyte migration.[14,15]

The role of specific MMPs in wound repair

MMPs play a crucial role in all stages of wound healing by modifying the wound matrix, allowing for cell migration and tissue remodeling. Keratinocyte migration during wound healing requires the dissolution of the basal epidermal keratinocytes hemidesmosomes; this disrupts their contact with the basement membrane and allows migration through the wound matrix. Keratinocytes either migrate through the provisional wound matrix (consisting of fibronectin and fibrin) or migrate in contact with the dermis underlying this matrix. The ECM that the keratinocyte interacts with determines the integrins that are activated; $\alpha_5\beta_1$ and $\alpha_v\beta_6$ integrins are activated on contact with fibronectin, $\alpha_3\beta_1$ and $\alpha_6\beta_4$ integrins bind to laminin-332, and $\alpha_2\beta_1$ integrin is a collagen receptor.[16,17] MMP expression and activity are tightly controlled during wound healing; specific MMPs are confined to particular locations in the wound and to specific stages of wound repair (Fig. 2).

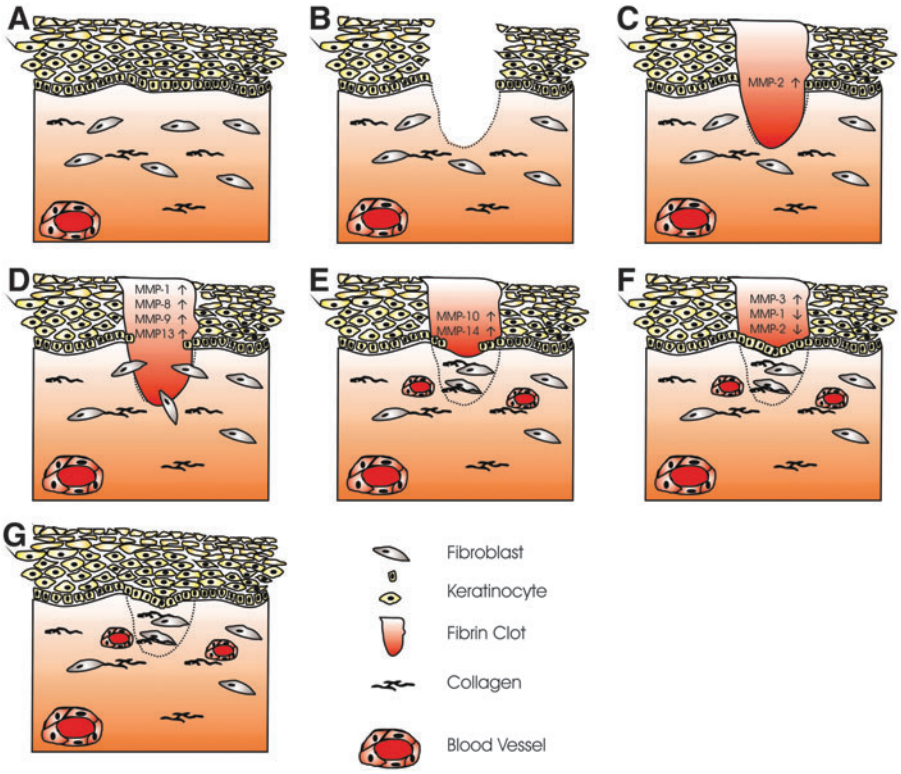

Figure 2. Wound healing. Healthy skin consists of a stratified squamous epithelium, basement membrane, and dermis **(A).** The epithelium is made up of basal keratinocytes (proliferative) and stratified suprabasal keratinocytes (differentiating), which eventually lose their nuclear material. The dermis is made up of extracellular matrix, predominantly collagen, is populated by fibroblasts, and contains the blood vessels that supply the skin. **(B)** A full-thickness wound of the skin damaging both epidermis and dermis. **(C)** Inflammatory phase, the wound is filled with a fibrin clot sealing the wound, MMP-2 expression is increased. **(D)** Fibroblasts migrate into the wound area; using MMPs, they remodel the fibrin clot replacing it with new extracellular matrix. Epithelial cells upregulate MMP expression and migrate into the wound area **(E).** Failure to remodel the extracellular matrix due to increased MMP expression or inflammation is seen in chronic wounds and plays a part in their failure to heal. **(F)** Reepithelialization: epithelial cells migrate from the surrounding epithelium, proliferating and closing the wound. Expression of promigratory MMPs is decreased and tissue remodeling MMP expression is increased. **(G)** Wound maturation: epithelial cells proliferate and differentiate reforming the stratified squamous epithelium. Fibroblasts continue to remodel the underlying dermis over a period of several months.

Epithelial, stromal, or inflammatory cell expression of MMPs can control inflammation in the wound area through the regulation of chemokine activity.[18] MMP-1, MMP-3, and MMP-9 are the major chemokine regulators during wound healing, degrading chemokines by proteolysis to remove them entirely or to generate receptor antagonists (reviewed by Gill and Parks[19]).

MMP-1, MMP-8, and MMP-13 (interstitial collagenases). The loss of ECM during wound healing triggers the rapid expression of MMP-1 in basal keratinocytes at the migrating epithelial front in wounds.[20] MMP-1 expression is controlled by the binding of type I collagen to $\alpha_2\beta_1$ integrin. The MMP-1 expression is induced when cells are in contact with type I collagen promoting migration.[21]

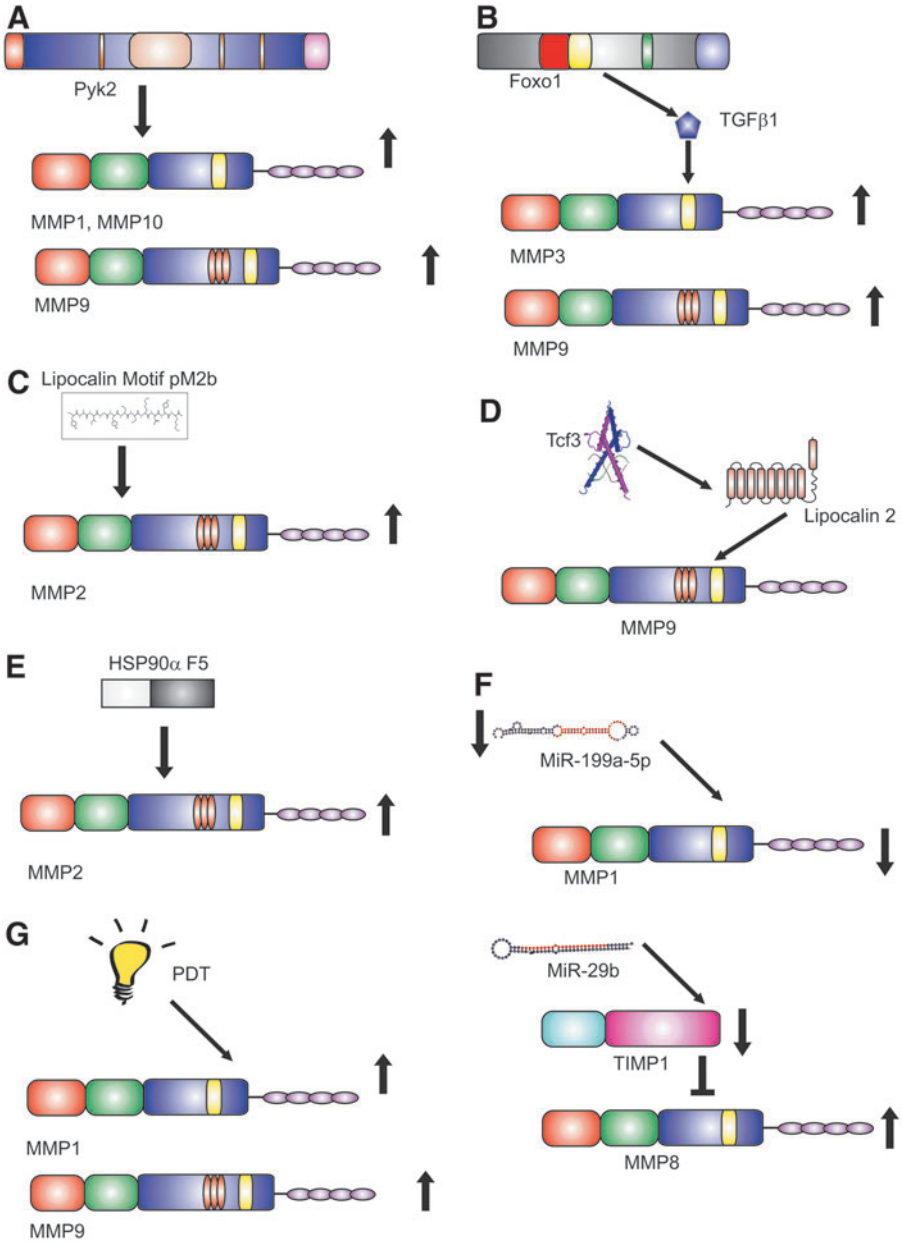

Figure 3. Novel regulation of MMPs. Recent advances in the regulation of MMP expression and activity have used a variety of mechanisms. **(A)** Pyk2 has been shown to increase the expression of MMP-1, −9, and −10 in mouse models. **(B)** FOX01, a member of the forkhead family of transcription factors, upregulates TGFβ1 leading to an increase in MMP-3 and MMP-9. **(C)** The 12 peptide fragment comprising the lipocalin conserved motif pM2b have been shown to increase MMP-2 in rat models of wounding. **(D)** Tcf3 increases secretion of lipocalin 2, which stabilizes MMP-9 increasing activity. **(E)** A 115 amino acid fragment (F5) of Hsp90α increases the secretion of MMP-2. **(F)** MiR, small hairpin loops of noncoding RNA, have been shown to regulate the MMP activity in wound models. **(G)** PDT has been shown to increase the expression of MMP-1 and MMP-9. MiR, microRNA; PDT, photodynamic therapy; Pyk2, proline-rich protein tyrosine kinase 2; Tcf3, transcription factor 3; TGF-β, transforming growth factor-β.

For sustained MMP-1 expression, cross talk between $\alpha_2\beta_1$ integrin and the EGF receptor is required.[22] The MMP-1 expression peaks at day 1 after wounding in migrating basal keratinocytes at the wound edge followed by a gradual decrease until re-epithelialization is complete. Laminin isoforms expressed during the final stage of tissue remodeling in keratinocytes act as a signal for the downregulation of MMP-1.[23] Downregulation of MMP-1 seems to be important for normal tissue remodeling as there are high levels of MMP-1 in chronic nonhealing wounds. MMP-8 is another interstitial collagenase that is secreted by wound fibroblasts, neutrophils, and macrophages. An increased expression of MMP-8 in chronic wounds is detrimental to wound repair causing breakdown of type I collagen.[24] Another collagenase, MMP-13, which is expressed by fibroblasts deep in the chronic wound bed, plays an important role in the maturation of granulation tissue, including modulating myofibroblast function, inflammation, angiogenesis, and degradation of matrix.[25]

MMP-2 (gelatinase A) and MMP-9 (gelatinase B). The presence of active MMP-2 and MMP-9 in wound fluids initially identified a role for these MMPs in wound healing.[26] The MMP-2 expression at the edge of acute wounds is linked with the expression of laminin-332 and increased keratinocyte migration.[27] Laminin-332 has been shown to have dual functions in migration, dependent on the processing of the protein. MMP-2 and MT1-MMP cleave the γ-2 chain of laminin-332 creating a promigratory fragment that triggers cell migration. The cleaved fragment contains multiple EGF-like repeats and acts as a cryptic ligand. The fragment is only found in tissues undergoing remodeling and tumors.[14,15,28]

Metalloproteinase-9 is expressed in several injured epithelia, including the eye, skin, gut, and lung, playing a role in wound healing and cell signaling.[29–32] MMP-9 plays an important role in keratinocyte migration; it is expressed at the leading edges of migrating keratinocytes during wound closure. MMP-9 knockout (KO) mice display delayed wound closure highlighting the importance of MMP-9 in wound healing.[33] Hypoxia, a feature of chronic wounds, increases keratinocyte migration and MMP-9 activity.[34,35] In MMP-9-deficient mice, MMP-9 has also been shown to inhibit cell proliferation through Smad2 signaling delaying corneal wound healing.[31]

Angiogenesis is an important process during wound healing, with the generation of blood vessel-rich granulation tissue, a critical step in tissue regeneration. Both MMP-2 and MMP-9 play a role in regulating angiogenesis during wound healing through the activation of proangiogenic cytokines, including TNF-α and VEGF, and by generating antiangiogenic peptides (*e.g.*, endostatin from type XVII collagen, expressed in the basement membrane).[36,37] Other members of the MMP family of proteins have also been shown to produce the antiangiogenic fragments, endostatin from type XVII collagen (MMP-3, -7, -9, -13, and -20) and angiostatin from plasminogen (MMP-2, -3, -7, -9, and -12) *in vitro*.[36,38,39]

MMP-3 and MMP-10 (stromelysin-1 and -2). MMP-3 and MMP-10 degrade several collagens (MMP-3 collagen II, III, IV, IX, and X; MMP-10 collagen III, IV, and V) as well as noncollagenous connective tissue macromolecules, including proteoglycans, laminin, and fibronectin.[40] MMP-3 and MMP-10 have distinct expression patterns during wound healing; MMP-3 is expressed adjacent to the wound edge by proliferating cells, whereas MMP-10 colocalizes with MMP-1 at the leading edge of the wound. The distinct patterns of MMP-3 and MMP-10 expression in keratinocytes are thought to be controlled by ECM contact. MMP-3-expressing cells are in contact with an intact basement membrane, whereas MMP-10 expression is seen in cells migrating on type I collagen.[41] Another factor controlling expression are the cytokines EGF, TGF-β1, and TNF-α, which have been shown to regulate the expression of MMP-10 expression.[42] The regulation of MMP-10 expression and activation during wound healing is tightly controlled; uncontrolled MMP-10 expression results in a disorganized migrating epithelium, degradation of newly formed matrix, aberrant cell–cell contacts of the migrating keratinocytes, and an increased rate of cell death of wound edge keratinocytes.[43] MMP-3 regulates the rate of wound healing through its role in wound contraction.[44] It can also activate several pro-MMPs as well as increase bioavailability of many cytokines, such as HB-EGF and basic FGF.[45,46]

MT1-MMP (MMP-14). MT1-MMP plays a pivotal role in cell migration during wound healing.[47] The MT1-MMP expression is localized to keratinocytes in the migrating front of the wound. MT1-MMP activates MMP-2 through degradation of pro-MMP-2, a coordinated process involving two molecules of MT1-MMP and also TIMP-2.[48] The loss of MT1-MMP leads to defective type I collagen turnover and loss of MMP-2 activation.[49,50] MT1-MMP acts to regulate epithelial cell proliferation during wound healing by altering the expression of

the KGF receptor.[51] In addition to controlling proliferation, MT1-MMP also accelerates epithelial cell migration *in vitro* through the cleavage of syndecan-1, CD44, and laminin-332.[14,52,53]

Tissue inhibitors of metalloproteinases. The endogenous regulators of the MMP activity are the TIMPs; they are 20–39 kDa secreted proteins and are able to inhibit a range of MMPs. Through the modulation of the MMP activity, TIMPs play an important role in regulating cell migration in wound healing. TIMP-1 (inhibits MMP-1, −2, −3, −7, −8, −9, −10, −11, −12, −13, and −16) is present in epithelial cells of healing excisional and burn wounds, and it is also expressed in wound fibroblasts, especially in fibroblasts adjacent to blood vessels in humans.[54,55] TIMP-2 (inhibits MMP-1, −2, −3, −7, −8, −9, −10, −13, −14, −15, −16, and −19) has been shown to both impair[53] and accelerate[56] cell migration *in vitro.* TIMP-3 (inhibits MMP-1, −2, −3, −7, −9, −13, −14, and −15) plays a role in controlling ECM remodeling during wound healing. This was clearly demonstrated using *Timp3* knockout mice, which displayed abnormal collagen and fibronectin remodeling.[57]

ADVANCES IN REGULATION OF MMPs

Signal transduction mechanisms regulating MMP expression

There is some evidence to suggest that chronic complications of diabetes mellitus, such as nephropathy and skin lesions, are related to the local expression of components of the renin–angiotensin system. Angiotensin II and its receptors are overexpressed in diabetic skin fibroblasts. Angiotensin II has been shown to stimulate TGF-β secretion through AT1 receptors leading to increased TIMP-1 and type I and III procollagen production in diabetic skin animal models.[58] Losartan, an AT1 receptor inhibitor, can reverse this effect in fibroblasts.

Proline-rich protein tyrosine kinase 2 (Pyk2), an important member of the FAK family, has recently been shown to play an important role in wound healing.[59] Wound closure is delayed in Pyk2-KO mice. Epidermal keratinocytes derived from the KO mouse displayed decreased migration. The overexpression of Pyk2 in human epidermal keratinocytes increased migration and was associated with the increased expression of MMP-1, −9, and −10. These data suggest that Pyk2 is an important regulator of both keratinocyte migration and MMP expression and is worthy of further study in human wounds (Fig. 3A).

The forkhead family member, FOXO1, coordinates the response of keratinocytes to wounding by upregulating TGF-β1 leading to increased MMP-3 and MMP-9 secretion.[60] Moreover, FOXO1 reduces oxidative stress in keratinocytes preventing apoptosis and facilitating wound healing (Fig. 3B).

Peptide modulation of MMP expression

Lipocalins are multifunctional proteins that have been shown to play a role in response to injury. Lipocalins are abundant in the venom of the *Lonomia obliqua* caterpillar. A peptide comprising the sequence of a lipocalin conserved motif (pM2b) promoted wound healing in a full-thickness rat skin wound model with an increase in collagen and MMP-2 activity. Reduced scarring was also observed (Fig. 3C).[61]

Lipocalin-2 is known to bind to and stabilize MMP-9[62] and was identified as a key secreted factor promoting cell migration *in vitro* and wound healing *in vivo*.[63] Lipocalin-2 secretion is regulated by the transcription factor, Tcf3, which also regulates embryonic and adult skin stem cell functions. Tcf3 is upregulated in skin wounds, and Tcf3 overexpression increases keratinocyte migration and skin wound healing. The transcription factor, Stat3, is an upstream regulator of Tcf3.[63] Lipocalin-derived peptides may be promising tools to develop new formulations to aid wound healing (Fig. 3D).

Normal keratinocytes secrete heat shock protein 90 (Hsp90) in response to tissue injury; Hsp90α in cancer increases MMP-2 secretion. Extracellular Hsp90 is able to promote cell migration in the presence of the inhibitory effect of TGF-β. It is a common promigratory factor for keratinocytes, dermal fibroblasts, and dermal endothelial cells. A 115 amino acid fragment of Hsp90α, F5, promoted healing of murine diabetic wounds far more effectively than conventional growth factors, suggesting promise in human wound healing (Fig. 3E).[64]

MiR regulation of MMPs

MiR are a recently discovered class of noncoding RNAs that play a key role in regulation of gene expression. At the post-transcriptional level, they are thought to regulate the expression of 30% of all human protein-coding genes. They are short single molecules about 22 nucleotides in length. Downregulation of MiR-199a-5p induces wound angiogenesis by derepressing the MMP-1 expression through the transcription factor V-ets erythroblastosis virus E26 oncogene homolog 1 (Ets-1).[65] MiR 29b is a known regulator of TGF-β-mediated fibrosis. Delivery of MiR-29b through a collagen scaffold to full-thickness wounds *in vivo* reduced wound contraction, improved the ratio of collagen type III/I,

and increased the ratio of MMP-8:TIMP-1 resulting in improved ECM remodeling[66] showing the potential of MiR therapy in wound healing (Fig. 3F).

Regulation of MMPs using photodynamic therapy

Topical photodynamic therapy (PDT) is widely used for nonmelanoma skin cancer. It uses a photosensitizing agent and light source to cause altered cell signaling, cell damage, and death. A controlled study of methyl aminolevulinate-PDT in excisional wounds showed that PDT-treated wounds had increased MMP-1, MMP-9, and TGF-β3 production during matrix remodeling with better organization of collagen and smaller scars compared to control wounds from the same patient (Fig. 3G).[67]

Regulation of MMPs using dressings

Wound dressings containing superabsorbent polymers have been devised. They are generated from acrylic acid and a cross-linker by polymerization. Dressings incorporating polyacrylate have a high density of ionic charges and absorb wound exudate. These dressings can bind MMPs and reduce their activity *in vitro*.[68] These dressings also have the potential to inhibit the activity of bacterial proteases, such as those secreted by *Pseudomonas aeruginosa*.[69]

TAKE-HOME MESSAGES

- MMPs play a vital role in wound healing; however, excessive expression of MMPs seen in chronic wounds may inhibit wound closure.
- MMPs are substrate specific; however, one growth factor may regulate multiple different MMPs making them hard to target.
- Novel mechanisms for regulating MMPs are being investigated using signal transduction, peptides, and MiRs to modulate MMP expression and activity.
- Existing treatments like PDT may have a role in controlling the MMP activity.

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Abbreviations and Acronyms

ECM = extracellular matrix
EGF = epidermal growth factor
FAK = focal adhesion kinase
FGF = fibroblast growth factor
Hsp90 = heat shock protein 90
KGF = keratinocyte growth factor
KO = knockout
MiR = microRNAs
MMP = matrix metalloproteinase
MT = membrane-type
PDT = photodynamic therapy
Pyk2 = proline-rich protein tyrosine kinase 2
Tcf3 = transcription factor 3
TGF-β = transforming growth factor-β
TIMP = tissue inhibitors of metalloproteinases
TNF-α = tumor necrosis factor-α
VEGF = vascular endothelial growth factor