

Matrix metalloproteinases and their roles in poor wound healing in diabetes

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Abstract

The prevalence of diabetes is increasing worldwide and has been forecasted to double in the next 20 years. The major increase in morbidity and mortality of diabetes is due to the development of complications, including failure of the wound healing process. Foot ulcers occur in 25% of all patients with diabetes and failure of healing eventually leads to deep-seated infection and amputation. Impaired wound healing is therefore the pivotal event responsible for most of the morbidity (and mortality) of diabetic foot disease. Consequently, a detailed understanding of the wound healing process in diabetes and how it can be improved is of great importance. However, efforts to develop new therapies are hampered by a lack of knowledge of the molecular mechanisms responsible for the poor wound healing.

Our laboratory is examining the role of matrix metalloproteinases (MMPs) in this regard. These proteolytic enzymes are important in normal wound repair and have been shown to be abnormally expressed in diabetic wounds. Our studies focus on evaluating MMPs as both markers and mediators of impaired wound healing in diabetes. Information will lead to a better understanding of poor wound healing in diabetes and ultimately more optimal therapeutic interventions.

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Introduction

Amongst the many other chronic complications, diabetes can cause impaired wound healing and, with it, increased morbidity. Up to 25% of all patients with diabetes will develop a foot ulcer and, each year in Australia, approximately 3000 persons with diabetes require amputation secondary to foot ulceration¹. The essential components of diabetic foot ulcer treatment include increasing blood supply (in the case of ischaemic ulcer) and reduction of foot bearing pressure (in the case of neuropathic ulcer). Despite concerted treatment, for reasons not completely understood, many ulcers do not heal and it is this failure to heal which eventually leads to deep-seated infection and amputation. Therefore impaired wound healing is the pivotal event responsible for most of the morbidity (and mortality) in diabetic foot disease. A detailed understanding of the wound healing process in diabetes and how it can be improved is of great importance.

Wound healing in diabetes

Normal wound healing involves a highly complex and orderly series of events^{2,3}. The initial step in this process is the formation of a clot composed mainly of fibronectin and fibrin. A transient inflammatory phase with neutrophil and macrophage infiltration then occurs, followed by re-epithelialisation and granulation tissue formation. The granulation tissue is then further remodelled and subsequently replaced by more mature connective tissue, a process predominantly involving fibroblasts.

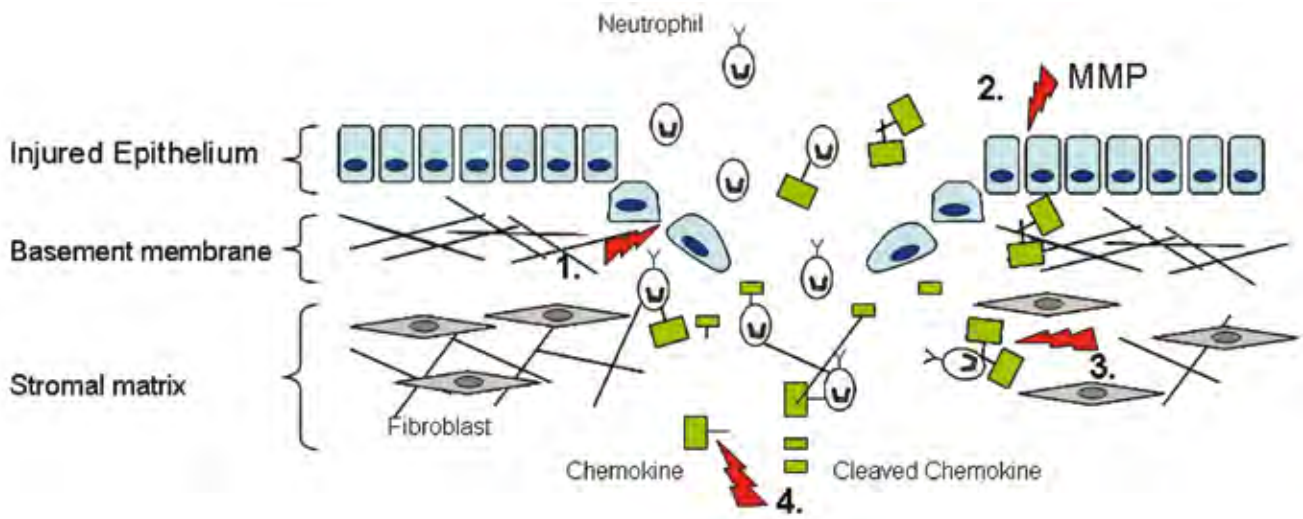


Figure 1. Schematic representation of the varied functions of MMPs in wound healing. During tissue repair, MMPs are involved in:

- 1 Cell migration – by direct proteolysis of the ECM or by processing of cell-ECM adhesion molecules.
- 2 Re-epithelialisation – by cleavage or shedding of junctional proteins.
- 3 Leukocyte influx – by establishment of a chemotactic gradient that guides migration of neutrophils.
- 4 Inflammation – by processing of multiple cytokines which can lead to receptor activation or inhibition depending on the cytokine and the wound environment.

In diabetic wounds, a persistence of inflammatory cells, in particular neutrophils and macrophages, is seen. This is associated with delayed formation of mature granulation tissue⁴ and a parallel reduction in wound tensile strength⁵. Why this aberration occurs is unclear, although bacterial infection⁶, abnormal concentrations of cytokines, increased advanced glycation end-products (AGEs) and low concentrations of some growth factors may play a role⁷⁻¹¹. One other potentially important finding in diabetes is a disturbance in the expression and activation of matrix metalloproteinases (MMPs), a group of enzymes responsible for extracellular matrix (ECM) degradation¹²⁻¹⁴.

The MMP system and wound healing

For wounds to heal, the ECM needs to be laid down and then progressively remodelled to reach maturity. The enzymes primarily involved in the degradative arm of this turnover process are the MMPs. They comprise a family of some 24 distinct but structurally related enzymes that, when acting together, can degrade almost all ECM components^{15, 16}.

MMPs can be divided into four subgroups based on substrate specificity – interstitial collagenases, stromelysins, type IV collagenases and membrane type-MMPs (MT-MMPs). They are secreted in latent forms which are cleaved to become



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biologically active. Their activities are also tightly regulated by their inhibitors, the tissue inhibitors of metalloproteinases (TIMPs), which bind to the active MMP enzyme with high affinity. Four TIMPs (TIMP 1-4) have been identified; each has the ability to bind and inhibit MMP activities to a varying extent. MMPs are produced by many cell types involved in wound healing including fibroblasts, keratinocytes and inflammatory cells. Their expression is modulated in response to signals from cytokines, growth factors, cell-matrix interactions and altered cell-cell contacts¹⁶⁻¹⁸.

The pattern of MMP expression in normal wound healing is complex, with the concentration of the various MMPs changing according to the phase of healing^{3,19-21}. For example, in the inflammatory phase, neutrophils and macrophages infiltrate the wound to phagocytose bacteria and there is an increase in expression of MMP-9^{3, 19-21}. In the proliferative phase, fibroblasts predominate and the level of MMP-9 decreases, whilst the expression of other MMPs, particularly MMP-2 and MMP-1 begin to increase^{3, 19-21}.

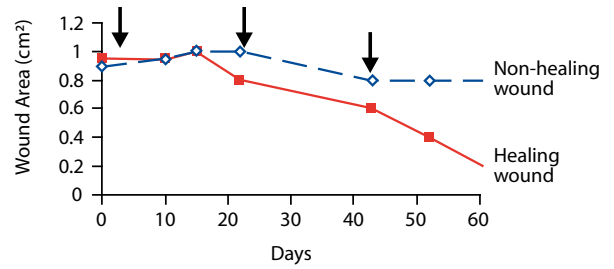
Apart from their role in ECM remodelling, MMPs have other important functions, including regulation of cell growth and differentiation. Specifically with regard to wound healing, they can alter cell motility, affect cell-cell interactions, and release growth factors and cytokines to affect cellular proliferation and growth (Figure 1)^{17, 18, 22, 23}. These many functions of MMPs further reinforce the concept that they are key players in wound repair.

MMPs and abnormal wound healing in diabetes

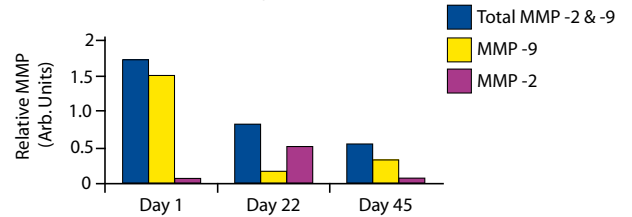
Increased circulating and tissue glucose level can alter wound healing by a complex interplay of metabolic signals leading to the activation of the pathways that increase inflammation²⁴. In some cells, hyperglycaemia activates the mitogen-activated protein kinase or protein kinase C pathways to stimulate cytokine production and promote inflammation. High glucose levels may also indirectly affect MMPs by formation AGEs which accumulate during prolonged hyperglycaemia and which are also pro-inflammatory^{24, 25}. These pathways can collectively affect wound healing by enhancing inflammation and thereby affecting remodelling of ECM²⁶⁻²⁸.

Studies from our laboratory have shown that high glucose affects differently various MMPs²⁹⁻³². In some cells, high glucose concentration decreased MMP-2, MT1-MMP³², but increased MMP-9, a pattern consistent with what is seen in diabetic wounds. Studies by others have shown in chronic wounds, including some diabetic wounds, elevated expression and activation of MMPs -2,-9 and -1 and decreased expression of TIMPs^{13, 33-36}. Whether these effects are cell type

A. Fluid sampling days analysed



B. Representative healing wound



C. Representative non-healing wound

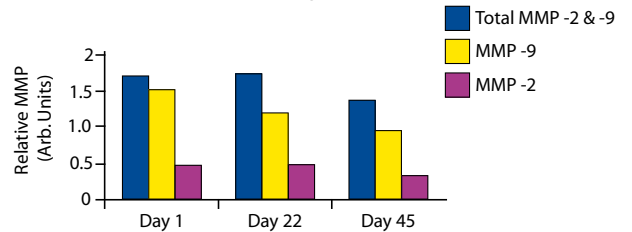


Figure 2. MMPs -2 and -9 in representative diabetic foot ulcer wound fluid.

A) Wound healing rate and collection times for a representative healing (solid line) and non-healing (broken line) diabetic foot ulcer. Zymographic analysis of wound fluid total MMPs -2 and -9 (solid bars), MMP-9 (hatched bar) and MMP-2 (open bar) obtained from a B) healing wound or C) poorly healing wound.

specific and how they change as the diabetic wound heals has not been studied in detail. There is also a relative paucity of data regarding the pattern of expression of MMPs in human diabetic foot ulcers^{13, 33, 35, 37, 38}, a problem partly due to the difficulty in obtaining tissue samples. To overcome this, we have recently developed a simple and non-invasive technique to study wound fluids. We have shown that wound fluid MMP levels reflect what occurs in the tissue and can be used to predict future wound healing in diabetic foot ulcers³⁹.

Regulation of MMPs by inflammation

The expression and activity of some MMPs are regulated by growth factors⁴⁰⁻⁴¹, whilst others, especially MMP-9, are regulated by inflammatory mediators, including cytokines such as TNF- α , IL-1 β , IL-6 or bacterial endotoxins⁴². In turn, MMPs can also activate specific cytokines and chemokines⁴³⁻⁴⁵ and have a number of potential key proinflammatory actions in wound healing. Together these data suggest a link between diabetes induced inflammation and MMP expression and activation.

In our studies we have focused on MMP-9 which is increased in poorly healing wounds in diabetic patients (Figure 2) and is known to be involved in a number of pro-inflammatory actions. These include: cleavage of IL-8 to increase its neutrophil chemoattractant properties⁴⁴; activation of pro-IL-1 β to active IL-1 β (44); alteration of IL-1 α accumulation in wounds to affect its synthesis and degradation²¹; degradation of serine protease inhibitors⁴⁴ and; activation of the latent form of TGF- β to increase its bioactivity and decrease its stability⁴⁶. These actions of MMP-9 can increase cytokine activities and potentiate the inflammatory response. Certainly, roles for MMPs in the formation of chemotactic gradients for responding neutrophils have been described in lung injury models¹². There is thus good reason to believe that alterations in the expression and activities of MMPs in diabetic wounds can affect the timing of the inflammatory response and, by this mechanism, lead to poor wound healing.

Inhibition of MMPs and wound healing

Overall, an imbalance between the MMPs and TIMPs is a consistent finding in non-healing wounds^{8, 33, 35, 39} and correction of the consequent abnormal MMP activities is therefore potentially an attractive therapeutic approach. In our studies in a rodent model of diabetic wound healing,

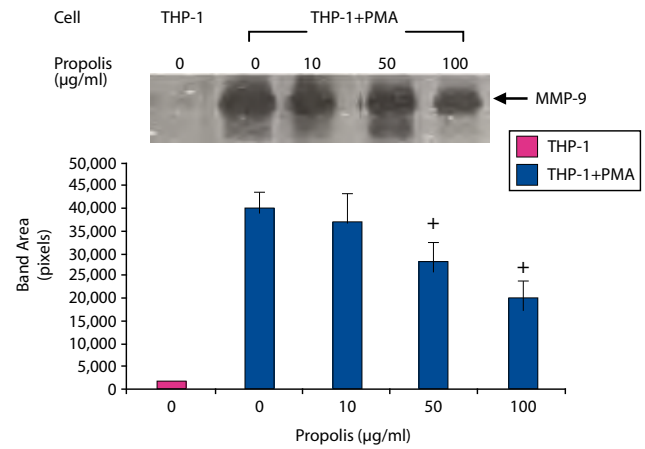



Figure 3. The effect of Propolis on macrophage MMP-9 activity. THP-1 monocytes were differentiated to macrophages by the addition of PMA. Propolis was added to the culture media and 24 hours later the media were collected and MMP activities analysed by zymography. Data represent mean and SD of three individual experiments.

* $p < 0.05$ different from THP-1+PMA alone.

we have successfully used a naturally occurring anti-inflammatory agent called Propolis to improve wound closure and inflammation⁴⁷. Our ongoing studies on Propolis have shown that it can inhibit the expression and activation of



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monocyte/macrophage MMP-9 (Figure 3) and possibly affect wound healing by this mechanism.

Other potentially more direct approaches to alter MMP expression and activities include the use of chemical compounds to inhibit MMP activity, mimicking the effects of TIMPs. The majority of these studies have focused on acute wounds and used broad spectrum MMP inhibitors. Both positive and negative results have been reported. These include ECM deposition and increased wound strength^{48, 49}, decreased macrophage infiltration^{48, 49} and both increased and decreased re-epithelialisation⁴⁸⁻⁵¹. Therefore, whether specific inhibition of MMP-9 can improve healing in chronic wounds is not yet known. However, an MMP-2/-9 inhibitor has been shown to prevent neutrophil recruitment and activation in the presence of hepatic ischaemia reperfusion injury and muscle injury^{52, 53}. In the former study, ablation of MMP-9 activity with a MMP-9 neutralising antibody inhibited neutrophil recruitment^{52, 53}, prevented injury and confirmed the role of MMP-9 in inflammation induction in this model^{52, 53}. Such action, if reproduced in the diabetic wounds, could affect the wound healing process. It is also of interest that in diabetic ulcers, the use of a dressing (Promogran) to absorb MMPs increases wound healing rate¹³, providing further supporting evidence that regulation of wound MMPs can improve wound healing.

Conclusion

Diabetes is known to alter wound healing, although the exact mechanism of this change is poorly understood. Studies in our laboratory suggest a possible role of the MMP system in this regard. The ability of these proteolytic enzymes to regulate inflammatory cytokines, chemokines and growth factors, in concert with their roles in remodelling ECM, may underpin the actions of MMPs in wound healing. Understanding this area better will assist the development of possible therapeutic strategies.

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