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Matrix Metalloproteinase-9 in the Etiopathogenesis of Placenta Accreta Spectrum: A Literature Review

Putri Mirani[1],*, Peby Maulina Lestari[1], Krisna Murti[2], Iche Andriyani Liberty[3], Hana Andrina[4], Cindy Kesty[4], Bella Stevanny[4]

Abstract

The recent increase in placenta accreta spectrum has been correlated with a rise in the rate of cesarean sections. A recent study provides evidence that hampered wound healing results in cesarean scar defects that lead to a failure in the normal process of decidualization and deeper adherence of trophoblasts. Matrix metalloproteinase (MMP) is crucial in every step of wound healing as it alters the wound matrix, facilitating cell migration, as well as tissue remodeling. MMP-9 expression is higher in placental and decidual tissue in cases of placenta accreta. Based on these findings, assessment of MMP-9 expression can shed new light on the etiopathology of placenta accreta spectrum disorder and can be a potential diagnostic marker.

Keywords: Biomarker; Etiopathogenesis; Matrix metalloproteinase; MMP-9; Placenta accreta spectrum disorder

Introduction

Placenta accreta spectrum (PAS) disorder is characterized by abnormal placental attachment to the uterine wall.[1] The recent rise in PAS incidence has been linked to an increase in cesarean section rates. Placental villi detachment from scarred myometrium, due to accumulation of thick fibrinoid material at the Rohr layer level, occurs both inside and around cesarean scars. Deep extravillous trophoblast invasion, distinct from tumor metastasis, correlates with rapid maternal blood flow entering the intervillous space directly from the radial artery.[2] Impaired wound healing leads to cesarean scar defects, hindering decidualization and promoting deeper trophoblast adherence. Consequently, any uterine intervention causing injury and hindering healing may elevate PAS incidence, including curettage,[3] suboptimal healing due to short birth intervals,[4] and in vitro fertilization.[5,6]

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Cell migration on the extracellular matrix (ECM), together with the modification and destruction of the ECM by matrix metalloproteinases (MMPs), are crucial components of the wound healing process. MMPs are a group of zinc (Zn)-containing and calcium-dependent enzymes involved in ECM degradation. Expression of MMP-9 was found in the injured epithelium. MMP-9 is produced by keratinocytes at the forefront of the wound to enhance cell movement and the formation of new epithelial tissue.[7] MMP is believed to be a key enzyme in trophoblast cell penetration during the early period of pregnancy and appears to also play a role in trophoblast invasion. Chen *et al*.[8] reported that the rate of MMP-9 expression in the PAS group was significantly higher compared with the control group. This study aims to review the literature regarding the role of MMP-9 in the etiopathogenesis of PAS.

Regulation of MMP expression and activity

MMP is a class of enzymes that include Zn and are involved in the breakdown of the ECM, with their activity influenced by calcium levels. All MMP variants, with the exception of MMP-7, MMP-23, and MMP-26, possess a structure in their C-terminal domain known as hemopexin. This structure is responsible for substrate recognition, typically of the ECM. Certain MMPs possess supplementary insertions that lead to variations in the functionality of each MMP category. MMPs can be categorized into seven distinct classes according to their substrate choice and domain organization: collagenases, gelatinases, stromelysins, matrilysins, metalloelastases, membrane-type MMPs, and other MMPs.[7]

MMPs are expressed at low levels in normal tissues. MMPs can be swiftly synthesized and triggered in response to the need for tissue remodeling, such as during wound healing. MMPs are expressed in various cell types in the skin, including fibroblasts, keratinocytes, and endothelial cells, as well as inflammatory cells, ie, macrophages, lymphocytes, and monocytes. The expression of MMP can be stimulated by several signals, such as cytokines, hormones, and interaction with other cell types or the ECM.[7]

The MMP is activated by a variety of cytokines and growth factors, including hepatocyte growth factor, fibroblast growth factor, epidermal growth factor (EGF), platelet-derived growth factor, vascular endothelial growth factor (VEGF), tumor necrosis factor α (TNF-α), transforming growth factor β, and keratinocyte growth factor, as well as interleukins and interferons. Several signaling mechanisms regulate the production of MMP, including the nuclear factor kappa-light-chain-enhancer of activated B cells pathway, mitogen-activated protein kinase, activation of focal adhesion kinase through integrin activation, or activation of Wnt signaling. Additional factors that control MMP expression are the alteration of chromatin through epigenetic processes and the regulation of mRNA stability/instability at the post-transcriptional level.[9,10]

The activity of MMPs is tightly regulated through gene expression and the precise activation and inhibition of specific enzymes. MMPs are initially present in an inactive form known as pro-MMP and are subsequently activated. Zinc ions (Zn^{++}) are essential for the catalytic activity of all MMPs, as they are required at the active site. MMP activation entails the dissociation of the link between the PRCGVPD prodomain and Zn^{++} located on the active site.[11] Pro-MMP is triggered by serine proteinases and other MMPs. The activation of MMPs can be regulated through the inhibition of proteinases by plasma proteinase inhibitors (such as α_1-proteinase and α_2-macroglobulin) or by MMP-binding proteins like thrombospondin. Tissue inhibitors of metalloproteinases (TIMPs) are the primary regulator of MMP, acting as a selective inhibitor of MMP.[12]

MMPs not only participate in the degradation and restructuring of the ECM but also regulate cell-to-cell and cell-to-matrix signaling by releasing cytokines and growth factors that have accumulated in the ECM. They modify the structure of cell surface receptors and junction proteins to regulate inflammation and apoptosis. Additionally, MMPs significantly influence cellular activity by facilitating the release of physiologically active fragments from damaged proteins.[13–15] For instance, in the context of wound healing, membrane-type 1 matrix metalloproteinase (MT1-MMP) enzymatically cleaves a segment of the c-2 chain of laminin 332, particularly targeting the c-2 domain III located in the basement membrane of the skin. This process subsequently promotes the migration of keratinocytes.[16]

Relationship between MMP and wound healing

Wound healing is an intricate process involving multiple cell types, including fibroblasts, keratinocytes, endothelial cells, and inflammatory cells. The healing process adheres to a systematic progression through four interconnected phases: hemostasis, inflammation, proliferation, and remodeling. Regulation of wound healing involves factors such as ECM, integrins, growth hormones, and MMPs. Cell migration within the ECM, together with the ECM restructuring and breakdown by MMPs, is a crucial component in wound healing. Chronic wounds, such as pressure ulcers, venous ulcers, and diabetic ulcers, pose significant clinical challenges, leading to considerable morbidity and financial burden. These chronic wounds are characterized by an excessive presence of MMPs. Regulating MMP levels in wounds can potentially enhance the process of wound healing.[7]

MMP plays a significant role in all stages of wound healing by modulating the wound matrix, facilitating cell migration and also tissue remodeling. During wound healing, keratinocyte migration requires the hemidesmosomes' disruption of basal epidermal keratinocyte, which allows keratinocytes to detach from the basement membrane and move within the wound matrix. Keratinocytes can migrate by traversing a transient wound matrix composed of fibronectin (FN) and fibrin or by directly contacting the underlying dermis. The interaction between the ECM components and keratinocytes triggers the activation of specific integrins. Upon encountering FN, integrins α5β1 and αvβ6 are activated, while integrins α3β1 and α6β4 bind to laminin-332. Lastly, integrin α2β1 functions as a receptor for collagen.[17] The expression and activity of MMPs are precisely regulated during the process of wound healing, with each MMP localized to a specific area within the wound and present at certain phases of the wound repair process.[7]

The regulation of inflammation in the wound region involves chemokine activity and the expression of MMPs by epithelial, stromal, or inflammatory cells. MMP-1, MMP-3, and MMP-9 play crucial roles in modulating chemokines during wound healing by proteolytically breaking them down, either completely removing them or generating receptor antagonists.[18] The depletion of ECM during the process of wound healing stimulates the activation of MMP-1 in the basal keratinocytes located at the leading edge of the migrating epithelium. The expression of MMP-1 is controlled by the interaction between type I collagen and integrin α2β1. Stimulation of MMP-1 expression occurs when cells encounter type I collagen, promoting cell migration. Sustained MMP-1 expression necessitates communication between integrin α2β1 and the EGF receptor.[19]

The expression of MMP-1 reaches its highest level on the first day post-injury in migrating basal keratinocytes located at the edge of the wound. It then gradually declines until the process of re-epithelialization is complete. The expression of specific laminin isoforms in keratinocytes, during the later phases of tissue remodeling, serves as a signal for the reduction of MMP-1 activity. The decline in MMP-1 expression appears to play a crucial role in the process of normal tissue remodeling, as chronic nonhealing wounds exhibit elevated MMP-1 levels. MMP-8, also referred to as interstitial collagenase, is generated and secreted by wound fibroblasts, neutrophils, and macrophages. Increased MMP-8 levels in persistent wounds hinder the healing process, leading to detrimental effects on type I collagen.[20] MMP-13, a collagenase produced by fibroblasts deep within the chronic wound bed, has a significant impact on the maturation of granulation tissue. It modulates various processes, including myofibroblast activity regulation, inflammation, angiogenesis, and extracellular matrix degradation.[21]

Gelatinase refers to MMPs capable of binding to gelatin. MMP-2, also known as gelatinase A, has specificity towards various substrates, including gelatin, collagen types I, IV, V, VII, and X, laminin, aggrecan, FN, and tenacin. MMP-2 plays a critical role in wound healing by facilitating cellular migration. MMP-9, or gelatinase B, targets several substrates, including gelatin, collagen types I, III, IV, V, and VII, aggrecan, elastin, and fibrillin. Keratinocytes, at the forefront of the wound, express MMP-9 to enhance cell migration and re-epithelialization. The initial detection of active MMP-2 and MMP-9 in wound fluid indicates their involvement in the process of wound healing. The presence of MMP-2 at the periphery of fresh wounds is linked to the expression of laminin-332 and an

enhanced movement of keratinocytes.[22] Laminin-332 demonstrates dual migratory activities, dependent on protein processing. The enzymes MMP-2 and MT1-MMP degrade the c-2 chain of laminin-332, resulting in the formation of a promigration fragment stimulating the movement of cells. This fragmented portion, rich in EGF-like repeats, acts as a concealed binding molecule, exclusively found in tissues undergoing remodeling and malignancies.[16]

MMP9 is present in various damaged epithelial tissues, including the eye, skin, gut, and lung. It contributes to the process of wound healing and cellular communication. Specifically, MMP-9 has a significant function in the movement of keratinocytes being prominently produced by migrating keratinocytes at the leading edge of wound closure. Studies with MMP-9 knockout mice have demonstrated a delay in wound closure, highlighting the pivotal role of MMP-9 in the healing of wounds.[23] Chronic wounds, characterized by hypoxia, exhibit increased keratinocyte migration and MMP-9 activity.[24,25] Additionally, the absence of MMP-9 in mice results in hindered cell proliferation through the activation of Smad2 signaling, leading to delayed healing of corneal wounds.[26]

Angiogenesis is a crucial process in wound healing, facilitating the formation of vascular-rich granulation tissue essential for tissue regeneration. MMP-2 and MMP-9 are key regulators of angiogenesis during wound healing. They accomplish this by activating proangiogenic cytokines such as TNF-α and VEGF, as well as producing antiangiogenic peptides such as endostatin, derived from type XVII collagen found in the basement membrane. In-vitro studies have demonstrated that other members of the MMP protein family, including MMP-3, -7, -9, -13, and -20, can generate antiangiogenic fragments such as endostatin from type XVII collagen. Similarly, MMP-2, -3, -7, -9, and -12 form angiostatin from plasminogen.[27,28]

TIMPs are natural regulators of MMP activity and have a crucial function in controlling cell migration throughout the process of wound healing by modifying the activity of MMPs. TIMP-1, which inhibits the activity of MMPs, is present in epithelial cells involved in the healing process of excisions and burns, particularly those located near blood vessels in humans.[29] TIMP-2 has been demonstrated to impair and expedite cell migration in vitro by inhibiting MMPs.[30,31] TIMP-3, acting as an inhibitor for MMPs, is involved in regulating the process of ECM remodeling during wound healing. Aberrant remodeling of collagen and FN was evident in TIMP-3 knockout mice.[32] The role of MMP-9 in wound healing was depicted in Figure 1.

The role of MMP-9 in placenta accreta

Several theories propose explanations for the atypical placentation observed in PAS, primarily attributing it to a malfunction in trophoblast activity, resulting in an excessive infiltration of the myometrium. Another concept suggests that the failure of the normal process of decidualization in the uterine scar area may lead to the formation of aberrant adhesions. MMP enzymes break down and modify the ECM as well

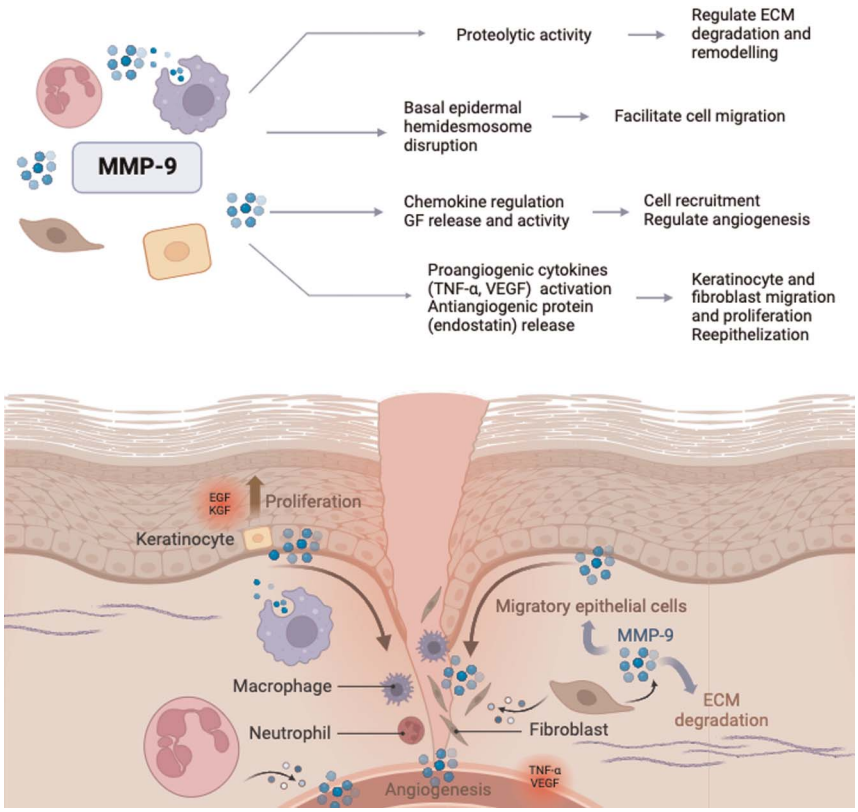

Figure 1. The role of MMP-9 in wound healing. MMP: Matrix matalloproteinase; ECM: Extracellular matrix; GF: Growth factor; TNF-α: tumor necrosis factor alpha; VEGF: Vascular endothelial growth factor; EGF: Epithelial growth factor; KGF: Keratinocyte growth factor.

Table 1

Studies reporting the association between matrix metalloproteinase-9 and placenta accreta.

First Author (Year)	Title	Article type	Findings
Ke *et al.*[34] (2006)	Involvement of MMP-2, -9, and tissue inhibitors of metalloproteinase-1, 2 in occurrence of the placenta accreta	Original research	• MMP-9 mRNA expression in placenta accreta (n = 23) was significantly higher than in normal placenta (n = 28). • MMP-9 transcription in accreta decidua (n = 9) was significantly higher than normal decidua (n = 11). • Upregulation of MMP-9 in the placenta is involved in placenta accreta.
Chen *et al.*[7] (2021)	Persistent hypoxia induced autophagy leading to invasiveness of trophoblasts in placenta accreta	Original research	• MMP-9 was found in the cytoplasm of trophoblasts, appearing as brown or punctate granules. • The placenta accreta group (n = 10) had a significantly greater rate of MMP-9 expression compared with the control group (n = 10).
Wang *et al.*[35] (2023)	Overexpressed LAMC2 promotes trophoblast overinvasion through the PI3K/Akt/MMP2/9 pathway in placenta accreta spectrum	Original research	MMP-9 protein expression was significantly higher in placental tissue with PAS in comparison with pernicious placental tissue without PAS.

Akt: Protein kinase B; LAMC2: Laminin subunit gamma 2; MMP: Matrix metalloproteinase; PAS: Placenta accreta spectrum; PI3K: Phosphoinositide 3-kinases.

as the cell-ECM connection, leading to the detachment of epithelial cells. MMPs have crucial roles in the development of cancer, the process of tumor invasion, and the spread of cancer cells to distant sites in the body.[33] Cell migration within the ECM, facilitated by MMP-mediated ECM remodeling, is integral to the wound healing process. MMPs, Zn-dependent enzymes requiring calcium for optimal activity, degrade the ECM. MMP-2 has a function in wound healing by speeding up the movement of cells, whereas MMP-9 is produced by keratinocytes at the forefront of the wound to enhance cell movement and the formation of new epithelial tissue. MMP-2 and MMP-9 were detected in the damaged epithelium.[7]

MMPs are considered crucial enzymes in the process of trophoblast cell penetration in the early stages of pregnancy and are thought to be involved in trophoblast invasion. Chen *et al.*[8] obtained samples of PAS and devised a semi-quantitative score value based on staining intensity. The placenta accreta group had a considerably higher positive rate of MMP-9 expression (60%) compared to the control group (10%). MMP-9 was predominantly found in the cytoplasm of trophoblasts, exhibiting brown granules or punctate structures with positive staining.[8] Reduced trophoblast invasion is linked to increased E-cadherin expression and decreased MMP-9 expression in placental trophoblasts in cases of abortion and preeclampsia.[8] Therefore, decreased E-cadherin expression and increased MMP-9 expression in accreta trophoblasts might indicate increased trophoblast invasion in the accreta. Three studies reporting an association between MMP-9 and placenta accreta are summarized in Table 1.

Research by Ke *et al.*[34] reported that placenta accreta has elevated levels of MMP-9 mRNA expression and protein transcription in comparison to a normal placenta. The expression of MMP-9 mRNA in placenta accreta was 3.84 ± 0.24 copies per microgram of total RNA, which was greater compared with normal placenta (3.21 ± 0.76 copies per microgram of total RNA). The transcription of MMP-9 in placenta accreta and normal placenta was measured to be 3.81 ± 0.66 and 2.50 ± 0.49 copies/μg total RNA, respectively. The elevated expression of MMP-9 in the placenta and decidua may underlie the association between MMP-9 and the development of placenta accreta.

In accordance with previous findings, Wang *et al.*[35] discovered that the expression of MMP-9 protein was notably elevated in placental tissue with PAS, as compared with placental tissue without PAS. Laminin subunit gamma 2 (LAMC2) plays a role in the development of PAS by stimulating the PI3K/Akt/MMP2/9 signaling pathway, which leads to an excessive invasion of trophoblast cells. LAMC2 exhibits significant expression in placental villous syncytiotrophoblast and cytotrophoblast. The expression of LAMC2 mRNA and protein was significantly increased in placental tissue with PAS compared with placental tissue without PAS. Overexpression of LAMC2 significantly enhanced the proliferation, invasion, and migration of HTR8/SVneo cells, while suppressing apoptosis. This was followed by an increased protein expression of MMP-2, MMP-9, and phosphorylated Akt (pAkt). The depletion of LAMC2 yielded the contrary outcome. Furthermore, the administration of LY294002 nullified the impact of LAMC2 overexpression on the growth, movement, infiltration, and programmed cell death of HTR8/SVneo cells. At the same time, it also eradicated the rise in pAkt, MMP-2, and MMP-9 proteins induced by LAMC2 overexpression. These findings offer a novel target for the identification of PAS.

Conclusion

Abnormal placentation in PAS occurs arises from the inadequate decidualization of the uterine scar area, resulting in abnormal adhesion. MMP-9 is involved in wound healing processes and exhibits elevated levels in placental and decidual tissues affected by placenta accreta compared to those in normal placenta. These observations suggest that evaluating MMP-9 expression may offer insights into the pathogenesis of PAS disorder and serve as a potential diagnostic marker.

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Conflicts of Interest

None.

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