



Research Progress on the Relationship between Matrix Metalloproteinases and Preterm Birth

Qianmei Yu, Hongbin Xu

Chongqing Medical University, Chongqing 400016, China

DOI: 10.32629/jcmr.v5i1.1788

Abstract: Premature birth is the main cause of death in children under the age of 5, and exploring the causes of premature birth has always been a hot research topic. Among them, matrix metalloproteinases (MMPs) have been confirmed to have a certain correlation with premature birth. This article summarizes the correlation between matrix metalloproteinases and preterm birth both domestically and internationally, in order to provide reference for subsequent research.

Keywords: matrix metalloproteinases, premature birth, premature rupture of membranes at term

1. Introduction

On a global scale, one in ten babies is born prematurely, and the premature birth rate is gradually increasing. According to reports, China has the second highest number of premature births in the world, with over one million premature babies born each year [1]. Most premature births are spontaneous and idiopathic, with many causes unclear. Preterm birth is the main cause of death of children under 5 years old, accounting for 70% of neonatal deaths and 75% of neonatal incidence rate [2,3]. Studies have shown that premature infants, compared to full-term infants, have immature physiological development, limited compensatory responses to the extrauterine environment, and are at risk of delayed language development, delayed motor development, and poor academic performance [4-6]. The occurrence of premature birth is multifactorial, such as infection factors, immune factors, uterine factors, genetic variations, and so on. The correlation between MMPs and preterm birth is currently a hot research topic. The overexpression of MMPs leads to premature remodeling of Extracellular matrix (ECM) and plays a major role in preterm birth, but its exact mechanism is still unclear [7].

1.1 The definition of premature birth

The upper limit of the definition of premature birth is globally unified, that is, delivery under 37 weeks of pregnancy; The lower limit setting varies in different countries and is related to the level of newborn treatment. Many developed countries and regions use pregnancy at 20 weeks, while some use pregnancy at 24 weeks. Currently, China uses pregnancy at 28 weeks. Based on the improvement of newborn treatment level in China, we also call on China to change it to pregnancy at 24 weeks [1]. Premature birth can be divided into spontaneous premature birth and therapeutic premature birth, with spontaneous premature birth accounting for the majority, approximately 60% [1]. Spontaneous preterm birth includes preterm birth with intact membranes and preterm birth after premature rupture of membranes. Therapeutic premature birth can prolong gestational age and avoid partial premature birth, such as preeclampsia and intrahepatic cholestasis during pregnancy, by actively managing the primary disease. Due to the unclear pathogenesis of spontaneous premature birth, the treatment effect of spontaneous premature birth is often unsatisfactory.

1.2 High risk factors and etiology of premature birth

The high-risk factors for premature birth include age, race, genetic factors, uterine factors, psychological factors, infection, smoking [8], history of premature birth, maternal nutrition, socio-economic background [1], etc. The main causes of premature birth include: reproductive tract infections [9-11], immune factors [8,12], and uterine factors [13]. Scholars such as Green and ES [9] have proposed that preterm birth is related to reproductive tract infections, but the use of antibiotics cannot improve outcomes, which may be related to early pregnancy infections. Denney, J M, and other scholars [8] proposed that T-helper type 1 cytokine (IL-1 β), multi potent pro-inflammatory cytokines (IL-6) and counter regulatory cytokines (IL-10) are associated with preterm birth and can be reflected in mid pregnancy. Premature birth caused by cervical incompetence is an important component of spontaneous premature birth. Cervical cerclage at 16-18 weeks of pregnancy can effectively prevent the occurrence of premature birth [14]. There are also studies suggesting that premature birth may be related to placental disorders [15, 16]. These studies all suggest that the occurrence of premature birth outcomes may be related to early pregnancy.

1.3 Prediction methods for premature birth

At present, the main methods for predicting premature birth include measuring the length of the cervical canal and detecting fetal fibronectin (fFN) in vaginal secretions. Scholars such as Lu Xun [17] have proposed that the cervical length of premature delivery women is indeed significantly shorter than that of full-term pregnant women, but the measurement of cervical canal length is related to the level of the measurer. The fFN detection of vaginal secretions has a higher negative predictive value [12,18]. At present, research hotspots include MMPs and interleukin-related factors (IL), such as MMP9, MMP8, IL-27 [19], IL-6 [20,21], IL-2 [19], IL-17 [18], and other inflammatory mediators for predicting premature birth.

2. MMPs

The first MMP was discovered in 1962. It is a protease responsible for the degradation of fibrous collagen during tadpole tail metamorphosis, and is therefore called interstitial collagenase [7, 22]. MMPs belong to the metzincins superfamily and are a class of zinc dependent endopeptidases that can degrade various protein components of ECM.

2.1 Structure composition of MMPs

In vertebrates, the MMPs family consists of 28 members, with at least 23 expressed in human tissues, including 14 expressed in the vascular system. According to their degradation substrates and structural characteristics, MMPs can be divided into: Gelatinase, including MMP2 and MMP9, capable of degrading type IV, V, VII, X, XI, and X IV collagen, gelatin, elastin, proteoglycans, and fibronectin; collagenases, including MMP1, MMP8, MMP13, and MMP18, with substrates including type I, II, III, V, and IX collagen, tendon derived proteins, and fibronectin [23]; stromelysins, including MMP3, MMP10, MMP11, substrates including III, IV, V, VII, IX, and X type collagen, elastin, and fibronectin; matrilysins, including MMP7 and MMP26, have substrates such as type IV collagen, elastin, fibronectin, and tendon derived proteins; model MMPs (Membrane type (MT) MMPs) include MMP14, MMP15, MMP16, MMP17, MMP24, and MMP25, with substrates including type I and IV collagen, gelatin, elastin, fibronectin, and laminin. Other MMPs include MMP12, MMP19, MMP20, MMP21, MMP22, MMP23, MMP27, and MMP28, with substrates including IV and V collagen, gelatin, and elastic fibers [24].

2.2 Cell sources and functions of MMPs

MMPs are produced by various tissues and cells, mainly secreted by pro-inflammatory cells and uterine placental cells, including fibroblasts, osteoblasts, endothelial cells, vascular smooth muscles, macrophages, neutrophils, lymphocytes, and cytotrophoblasts [22]. MMPs are usually secreted in the form of inactive matrix metalloproteinase precursors, which are cleaved into active forms by various proteases, including other MMPs [26]. MMPs promote cell proliferation, migration, and differentiation, playing a role in embryo implantation, placental formation, neovascularization and tumor transformation, cell apoptosis, and tissue repair [22]. MMPs affect the function of endothelial cells and the migration, proliferation, Ca²⁺ signaling, and contraction of vascular smooth muscle cells. MMPs can also affect the bioactive molecules on the cell surface, regulate various cells and signaling pathways.

2.3 Biological functions of MMPs

MMPs play a role in many biological processes, such as tissue remodeling and growth, wound repair, tissue defense mechanisms, and immune responses. The morphogenesis of different tissues and organs, including the lungs, bones, and blood vessels, from embryo implantation, was detected to increase the expression of MMPs [24]. MMPs participate in the growth, proliferation, migration, and relaxation of vascular smooth muscle; Participate in processes such as endothelial cell function, angiogenesis, cell apoptosis, tissue repair, wound healing, embryo implantation during pregnancy, and invasion of trophoblast cells [22]. MMPs are involved in such pathological processes as hypertension, eclampsia, vascular inflammation, atherosclerosis, coronary syndrome, myocardial infarction, cerebral ischemia and ischemic stroke, peripheral arterial disease, aneurysm, chronic venous disease [24]. Many MMPs also act on non matrix proteins, such as cytokines, chemokines, receptors, antimicrobial peptides, etc. So MMPs should not be seen as a single extracellular matrix proteolytic enzyme, but as enzymes involved in signal transduction between cells and between cells and matrix, a protein with potential signal amplification effects.

2.4 MMP9

The MMP9 gene is located at the 20q13.12 locus, with a total length of 7.7 Kb. It consists of 13 exons and 12 introns [25, 27]. MMP9 is activated in the form of proenzyme from the intracellular endocrine system to the extracellular system through a series of proteases hydrolysis in the body [25]. MMP9 is mainly involved in processes such as angiogenesis, cell apoptosis, cell proliferation, embryo implantation during pregnancy, invasion of trophoblast cells, and remodeling of

placental and uterine arteries [22]. The MMP9 domain can be cleaved by MMP3, MMP2, or hypochlorous acid, and MMP3 may be the most effective activator of MMP9. The main circulating inhibitors of MMP9 are α 2 macroglobulin, activated MMP9 is α 2 macroglobulins are captured and cleared from the circulatory system by clearing receptors. As an inhibitor of MMP9, TIMP1 specifically binds to the carboxyl end of the enzyme precursor or activated catalytic region of MMP9, forming a complex that specifically inhibits the activity of MMP9.

3. MMPs and premature birth

3.1 The role of MMPs in preterm birth

MMPs are involved in processes such as blastocyst implantation, spiral artery pregnancy transformation, and placental formation [22]. The expression of these proteases increases during pregnancy and reaches its highest level during delivery, but in some cases, the expression of proteases occurs earlier than expected, leading to premature birth [7]. MMPs are produced in the form of inactive proenzymes, which, upon activation, degrade the chorionic villi, amniotic membrane, and cervical ECM, leading to weakened softening of the membranes and cervix, rupture of the membranes, cervical dilation, contraction of the uterine muscle layer, and placental abruption [23,26]. Scholars such as Nold and C [28] have learned through mouse animal experiments that increasing the ratio of MMPs to TIMPs plays an important role in amniotic membrane rupture and premature birth. Its mechanism of action is that it participates in immune/inflammatory responses [29, 30].

3.2 MMPs related to premature birth

In the study by Dymanowska Dyjak, I et al. [31], it was found that the concentration of MMP8 in serum and cervical secretions was significantly increased in preterm delivery. Timokhina, E et al. [22] proposed that MMP2 and MMP9 are involved in the invasion of maternal blood vessels by cytotrophoblasts and the remodeling process of placental and uterine arteries. In the report by Duran Ch á vez, J et al. [23], it was found that an increase in plasma MMP9 levels and a decrease in MMP2 levels were positively correlated with preterm birth, with plasma MMP9 levels increasing the risk of preterm birth by nearly three times. Pandey, M et al. [32] analyzed the roles of MMP1, MMP8, and MMP9 genes in preterm birth, and concluded that MMP9 plays a crucial role in preterm birth. MMP9 is significantly overexpressed in the membranes of preterm premature rupture of membranes [33, 34]. Litwiniuk, Ma ł The Gorzata [26] controlled trial showed that the cervical region of premature amniotic membrane showed a decrease in TIMP-1 levels and an increase in MMP9 levels. Pandey, M et al. [32] have proposed that MMP9 plays an important role in promoting preterm birth, which can be used as a diagnostic tool during pregnancy. But there are also studies indicating low expression of MMP9 on the membranes of preterm infants with intact membranes [33]. Pereza, N et al. [29] did not find a relationship between MMP1 and MMP9 and preterm delivery with intact membranes, while Dymanowska Dyjak, I et al. [31] found no differences in the serum and cervical secretion levels of MMP9 between preterm delivery and full-term delivery.

4. Summary

The incidence rate of preterm birth is relatively high around the world, and the prognosis of preterm infants is poor. With the improvement of medical environment, the survival rate of preterm infants is gradually increasing, but the quality of life is not improved significantly, which needs to consume a lot of medical resources and social attention. Therefore, reducing the occurrence of premature infants is very important. The treatment effect of spontaneous premature birth is not satisfactory, so predicting premature birth is more important. Most research results show that MMP9 is highly expressed in preeclampsia and in preterm delivery after premature rupture of membranes, but there is some controversy regarding preterm delivery with intact membranes. Further research is needed to determine whether MMPs can predict premature birth.

References

- [1] Zhang J, Sun K, Zhang Y. The rising preterm birth rate in China: a cause for concern[J]. *Lancet Glob Health*, 2021,9(9):e1179-e1180.
- [2] Couceiro J, Matos I, Mendes J J, et al. Inflammatory factors, genetic variants, and predisposition for preterm birth[J]. *Clin Genet*, 2021,100(4):357-367.
- [3] Frey H A, Klebanoff M A. The epidemiology, etiology, and costs of preterm birth[J]. *Seminars in Fetal and Neonatal Medicine*, 2016,21(2):68-73.
- [4] Pascoe L, Burnett A C, Anderson P J. Cognitive and academic outcomes of children born extremely preterm[J]. *Semin Perinatol*, 2021,45(8):151480.

- [5] Sharma D, Padmavathi I V, Tabatabaii S A, et al. Late preterm: a new high risk group in neonatology[J]. *J Matern Fetal Neonatal Med*, 2021,34(16):2717-2730.
- [6] Care A, Nevitt S J, Medley N, et al. Interventions to prevent spontaneous preterm birth in women with singleton pregnancy who are at high risk: systematic review and network meta-analysis[J]. *BMJ*, 2022,376:e64547.
- [7] N M, Am M, M Z, et al. The Effect of B(9) and B(12) Vitamins Deficiency on Hypomethylation of MMP-9 gene Promoter Among Women With Preterm Parturition[J]. *Biochem Genet*, 2022,60(1):336-350.
- [8] Denney J M, Nelson E, Wadhwa P, et al. Cytokine profiling: variation in immune modulation with preterm birth vs. uncomplicated term birth identifies pivotal signals in pathogenesis of preterm birth[J]. *J Perinat Med*, 2021,49(3):299-309.
- [9] Green E S, Arck P C. Pathogenesis of preterm birth: bidirectional inflammation in mother and fetus[J]. *Semin Immunopathol*, 2020,42(4):413-429.
- [10] Short C S, Quinlan R A, Wang X, et al. Vaginal Microbiota, Genital Inflammation and Extracellular Matrix Remodeling Collagenase: MMP-9 in Pregnant Women With HIV, a Potential Preterm Birth Mechanism Warranting Further Exploration[J]. *Front Cell Infect Microbiol*, 2021,11:750103.
- [11] Lamont R F. Spontaneous preterm labour that leads to preterm birth: An update and personal reflection[J]. *Placenta*, 2019,79:21-29.
- [12] Ronde E, Reiss I, Hankemeier T, et al. The Potential of Metabolomic Analyses as Predictive Biomarkers of Preterm Delivery: A Systematic Review[J]. *Front Endocrinol (Lausanne)*, 2021,12:668417.
- [13] Zhang Xiaojiao, Chen Huiyue. The predictive value of mid-term cervical elastic strain rate combined with anterior cervical angle ultrasound measurement for preterm birth [J] *J Pract Obstet Gynecol*, 2022,38(04):274-277.
- [14] Shennan A, Story L, Jacobsson B, et al. FIGO good practice recommendations on cervical cerclage for prevention of preterm birth[J]. *Int J Gynaecol Obstet*, 2021,155(1):19-22.
- [15] Bhattacharya S, McCall S J, Woolner A. Recurrent pregnancy loss and subsequent preterm birth: association or causation[J]. *Fertil Steril*, 2022,117(4):820-821.
- [16] Wu C Q, Nichols K, Carwana M, et al. Preterm birth after recurrent pregnancy loss: a systematic review and meta-analysis[J]. *Fertility and Sterility*, 2022,117(4):811-819.
- [17] Lu Xun, Wang Jing, Zhang Wenwen, et al. The predictive value of late pregnancy blood NLR combined with fFN and cervical length on the risk of premature birth [J] *Journal of Molecular Diagnosis and Therapy*, 2022,14(03):397-400.
- [18] Li Xiaoye, Li Dezhong, Liu Yejun. The predictive value of interleukin and fetal fibronectin levels for preterm birth [J] *Chinese Journal of Physicians*, 2022,24(01):101-104.
- [19] Yin N, Wang H, Zhang H, et al. IL-27 induces a pro-inflammatory response in human fetal membranes mediating preterm birth[J]. *Int Immunopharmacol*, 2017,50:361-369.
- [20] Pandey M, Awasthi S, Baranwal S. IL-6: An endogenous activator of MMP-9 in preterm birth[J]. *J Reprod Immunol*, 2020,141:103147.
- [21] Huang Lin, Li Qingrui. Correlation analysis between folate utilization, progesterone induced blockade factor, and serum levels of interleukin-6 with threatened preterm pregnancy outcomes [J] *Chinese Medical Engineering*, 2022,30(05):115-117.
- [22] Timokhina E, Strizhakov A, Ibragimova S, et al. Matrix Metalloproteinases MMP-2 and MMP-9 Occupy a New Role in Severe Preeclampsia[J]. *J Pregnancy*, 2020,2020:8369645.
- [23] Duran-Chávez J, Grandi C, Dos S R L, et al. Relationship between metalloproteinase-2 and -9 levels in plasma and vaginal secretion with preterm birth[J]. *Eur J Obstet Gynecol Reprod Biol*, 2021,261:217-221.
- [24] Wang X, Khalil R A. Matrix Metalloproteinases, Vascular Remodeling, and Vascular Disease[J]. *Adv Pharmacol*, 2018,81:241-330.
- [25] Vafadari B, Salamian A, Kaczmarek L. MMP-9 in translation: from molecule to brain physiology, pathology, and therapy[J]. *J Neurochem*, 2016,139 Suppl 2:91-114.
- [26] Litwiniuk M, Radowicka M, Krejner A, et al. The MMP-9/TIMP-1 imbalance and the reduced level of TGF- β in the cervical area of amniotic membrane is a possible risk factor of PROM and premature labor — proof-of-concept study[J]. *Ginekologia Polska*, 2017,88(7):379-384.
- [27] Jia J P, Wu J H, Hu J R. Correlations of MMP-9 and PPAR γ gene polymorphisms with occurrence of preeclampsia[J]. *Eur Rev Med Pharmacol Sci*, 2022,26(3):771-778.
- [28] Nold C, Esteves K, Jensen T, et al. Granulocyte-macrophage colony-stimulating factor initiates amniotic membrane rupture and preterm birth in a mouse model[J]. *Am J Reprod Immunol*, 2021,86(2):e13424.
- [29] Pereza N, Pleša I, Peterlin A, et al. Functional polymorphisms of matrix metalloproteinases 1 and 9 genes in women with spontaneous preterm birth[J]. *Dis Markers*, 2014,2014:171036.
- [30] Rood K M, Buhimschi I A, Rodewald M K, et al. Evidence for participation of neutrophil gelatinase-associated lipocalin/matrix metalloproteinase-9 (NGAL•MMP-9) complex in the inflammatory response to infection in pregnancies complicated by preterm birth[J]. *Am J Reprod Immunol*, 2016,76(2):108-117.

- [31] Dymanowska-Dyjak I, Stupak A, Kondracka A, et al. Elastography and Metalloproteinases in Patients at High Risk of Preterm Labor[J]. *J Clin Med*, 2021,10(17):3886.
- [32] Pandey M, Awasthi S. Role of MMP-1, MMP-8 and MMP-9 gene polymorphisms in preterm birth[J]. *Journal of Genetics*, 2020,99(1):2.
- [33] Ren Jing The expression and role of matrix metalloproteinase 9 in premature rupture of membranes [D] China Medical University,2004.
- [34] Xie Bin, Sun Zhuohao, Huang Youmin, etc The predictive value of combined detection of multiple inflammatory factors for chorioamnionitis complicated by premature rupture of membranes in parturients [J] *Chinese grassroots medicine*, 2021,28(04):538-542.