

The bimodal role of matrix metalloproteinases and their inhibitors in etiology and pathogenesis of endometriosis (Review)

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Abstract. Aberrant regulation of matrix metalloproteinases (MMPs) may be the primary cause of endometrial lesion formation in a group of predisposed women. Prospect for the genuine origin of endometriosis is ongoing, since retrograde menstruation leads to presence of endometrial debris in peritoneal cavity of many women, which do not experience endometriosis. Tissue remodeling is regulated precisely by a balance of MMPs and their inhibitors. Interplay between factors enhancing and suppressing matrix turnover is crucial for cyclic preparation of endometrium for embryo implantation, and endometrial shedding and renewal in physiology of primates. Disorders of the regulation of matrix remodeling leads to augmentation of implantation and invasive growth of ectopic endometrial tissue. Moreover, endometriosis-induced changes in the matrix balance leads to adhesion formation, ovulatory dysfunction and fertility impairment. The review summarizes the current knowledge regarding the regulation of extracellular matrix turnover in the physiology of the endometrial cycle and in the development of endometriosis, as well as the pathophysiology of ovulatory dysfunction in endometriotic women. Therapeutic modalities utilizing modulation of tissue remodeling were discussed.

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1. Introduction

Endometriosis is a condition defined as presence of endometrium outside of uterine cavity. It is very common, with an incidence of 5-20% among women in reproductive age, however, its causes still remain obscure. Numerous theories were proposed to explain etiology of endometriosis, reviewed well by Burney and Giudice (1). Unfortunately, a single, sufficient explanation of disease causes is missing, since the origin seems to be connected with miscellaneous factors. It is widely accepted that underlying process leading to endometriosis development is retrograde menstruation, which is an antiperistaltic passage of menstrual debris through Fallopian tubes (2). It has been proven though, that retrograde menstruation is a quite frequent phenomenon that occurs also in women without endometriosis (3), therefore other factors must influence the stages of endometriosis development. The essential process in the disease onset is implantation of endometrial cells into peritoneal surface. Interestingly, during this process endometrial cells demonstrate some features of malignancy, as they are able to attach and to invade structure of peritoneum or ovary, in the similar way as cancer cells cause metastasis. This invasion is effectuated with matrix metalloproteinases (MMPs)-group of enzymes involved in tissue remodeling. This review is dedicated to the role of that group of enzymes and their inhibitors in development and pathogenesis of endometriosis.

2. Matrix metalloproteinases and inhibitors of MMP

Group of MMPs is a large family of endopeptidases, that are essential in degradation of extracellular matrix (ECM) and basal membrane (BM). Several subtypes of MMPs are

distinguished, depending on their substrate-specificity and localization: Collagenases, gelatinases, stromelysins, matrilysins and membrane-type metalloproteinases. We summarize classification and substrate specificity of MMPs in Table I, that was based on BRENDA-The Comprehensive Enzyme Information System database (www.brenda-enzymes.org) (4).

MMPs play a crucial role in numerous physiological processes, for instance: bone remodeling, angiogenesis, inflammation, ovulation and embryogenesis (5). What is more, MMPs are involved in cyclic changes of endometrium structure and thickness in the course of endometrial cycle, feature that is caused by changes in steroid hormones concentration levels. MMPs are expressed in both epithelial and stromal cells, with the exception of MMP-7 that is detected selectively in epithelial compartment (6). Furthermore, metalloproteinases present variable activity during the cycle, what was summarized in Table II (7,8).

Numerous MMPs are additionally involved in many pathological processes (9), such as: fibrosis, weakening of matrix (e.g., in aortic aneurysm or dilated cardiomyopathy) or tissue destruction [e.g., cancer invasiveness, also endometrial carcinoma invasiveness and ability to metastasize (10)]. Therefore, the balance between activation and inhibition of MMPs is crucial for maintaining homeostasis. Their increased activity can cause excessive ECM degradation, while their deactivation-insufficient ECM remodeling. Both can lead to development of versatile medical conditions. Development of novel therapies, that would influence MMPs activity, seems to be promising but unreachable in short order.

The balance in MMPs activity is regulated by a very wide range of factors, which prevents accidental overactivation or suppression of MMPs and therefore help maintaining homeostasis. What is more, the number of known interactions is still growing.

3. Regulation of MMP activity

One of the most important means of regulating MMPs activity are interactions with proteins, that inhibit final MMPs activity: Reversion-inducing-cysteine-rich protein with Kazal motifs (RECK) (11) and a group of soluble tissue inhibitor of metalloproteinases (TIMPs) (12). These proteins significantly contribute in ECM remodeling, regulating angiogenesis and inflammatory reactions.

The mechanism of actions of TIMPs and RECK include formation of a stoichiometric complexes between inhibitor and a catalytic region of MMP. Binding blocks MMPs enzymatic activity. MMPs inhibitors are proteins, that have highly conservative sequence among species. Human genome encodes 4 genes coding TIMPs: TIMP1-TIMP4, that vary in substrate specificity (13) (Table III).

Interestingly, TIMPs suppress the activity of not only MMPs, but also proteins from different family of endopeptidases, namely A Disintegrin And Metalloprotease family (ADAM) (14-17). ADAMs also fulfill similar functions in regulating inflammatory responses, cell migration and other aspects of matrix turnover (18). The most active TIMP against ADAMs proteins is TIMP-3, while some other members of this family have only limited regulatory activity; for example, TIMP-1 inhibits ADAM-10 selectively (17).

As summarized by Alexius-Lindgren (19), RECK is membrane-bound MMPs inhibitor, especially active against MMP-9 (11). RECK, similarly to soluble TIMPs, plays a crucial role in ECM remodeling and is involved with metastases and invasiveness of cancer (20). Considering the common features between cancer metastases and endometriosis implants, RECK may be an interesting candidate gene to study in endometriosis development.

In addition to MMPs direct binding by inhibitors, their proteolytic activity is regulated also by cytokines, hormones, growth factors and many other biologically active agents (21-23). Steroid hormones were described as main agents, that have an influence on MMPs activity, especially in endometriosis and endometrial tissue turnover. Progestins are widely used in therapy of the disease, decreasing endometrial growth and endometriosis-associated pelvic pain (24). They were proven to inhibit MMPs secretion by eutopic endometrial cells from uterine cavity (25-27) and ectopic lesions (28), and to enhance TIMP-2 activity (29). Similar effect was achieved by non-steroid progesterone receptor (PR) agonist (30). Meanwhile, estrogenic stimulation was proven to induce MMP-2 and MMP-9 expression (31). Moreover, there is a positive correlation between 17 β -estradiol and MMP-2 serum levels in proliferative phase and a negative correlation between progesterone and MMP-2 serum levels in secretory phase of the cycle (32).

Recent studies focus on non-steroid hormones, that could affect MMPs activity. It was shown, that numerous endocrine factors reduced ectopic lesions development in animal models of endometriosis. MMPs activity and endometrial fragment implantation can be regulated by: Leptin (33), somatostatin (34) and melatonin (35). Discovery of such interactions is very promising, as alternative hormonal therapy in endometriosis would probably be less troublesome than hormonal suppression for patients in reproductive age. However, there are no clinical trials on their effectiveness in humans.

Other factors, that impact ECM remodeling by changing MMPs activity are immune system cells. Their role of uterine leukocyte population in endometriosis development was reviewed by Parkin and Fazleabas (36).

Soluble agents, i.e., cytokines, such as TGF- β 1, TNF- α and IFN- γ , IL-1, IL-4 and IL-8 regulate MMPs and TIMPs expression (37-39). IL-8, also known as neutrophil chemo-tactic factor, stimulates MMP-2 and MMP-9 expression in endometrium (40). IL-1 α enhances MMP-1 activity in human endometrial fibroblasts and endometrial cells (27,41). Administration of IL-1 α natural decoy-soluble form of IL-1 receptor type 2 (sIL-1R2), influences MMP-2, MMP-9 and TIMP-1, -2 and -3 activity in murine model of endometriosis, simultaneously affecting endometrial ability to invade and grow in ectopic locations (42). On the other hand, administration of IL-4, an anti-inflammatory cytokine, inhibits MMP-3 and MMP-4 expression and reduces number and volume of ectopic lesions in murine model of endometriosis (43). Besides cytokines, other immunological agents: eicosanoides, such as lipoxin A4 and prostaglandin E2, were also proven to alter MMP activity (44,45).

Other regulators of MMPs and TIMPs activity are growth factors: EGF and FGF, that increase MMP-1, MMP-3, MMP-11 and TIMP-1 expression (39,46). Retinoic acid inhibits MMP-3

Table I. Classification of MMPs.

Enzyme	Aliases	Substrates in human
MMP-1	Interstitial collagenase, collagenase 1	Collagen I, II, III, casein, gelatin, α 2-macroglobulin
MMP-2	Gelatinase A, 72 kDa gelatinase, 72 kDa type IV collagenase	Collagen I, IV, V, elastin, fibrilline, fibrinogen, fibronectin, galectin-3, gelatin, laminin, vitronectin
MMP-3	Stromelysin 1, progelatinase	Collagen I, IV, V, IX, X, α 1-antitrypsin, α 1-proteinase inhibitor, antithrombin III, casein, decorin, elastine, fibrillin, fibrin, fibronectin, gelatin, interleukin (IL)-1b, laminin, osteopontin, pro-MMP-1, tumor necrosis factor- α (TNF- α) precursor, Apaf-1, pro-caspase-9
MMP-7	Matrilysin, PUMP-1, uterine metalloproteinase	Collagen IV, aggrecan, annexin II, β -casein, β 4 integrin, connexin, E-cadherin, defensin, elastin, fibronectin, Fas-ligand, gelatin, insulin-like growth factor-binding protein-3 (IGFBP-3), laminin, nidogen, osteopontin, perlecan, plasminogen, tumor necrosis factor (TNF- α) precursor, syndecan, tenascin-C, tumor-associated antigen 90 K
MMP-8	Neutrophil collagenase, PMNL collagenase	Collagen I, II, III, estrogen receptor α and β , TNF- α ; serpins, bradykinin, angiotensin I, substance P
MMP-9	Gelatinase B, 92 kDa gelatinase, 92 kDa type IV collagenase	Collagen I, III, IV, V, XI, actin, α -enolase, annexin I, crystallin, epidermal growth factor, ezrin, filamin B, galectin-3, gelatin, gelsollin, heat shock proteins, laminin, moesin, nucleolin, stathmin, stromelysin 1, tubulin, vitronectin
MMP-10	Stromelysin-2, transin-2	Collagen IV, V, IX, X, casein, elastin, fibrillin, fibronectin, gelatin, laminin, procollagenase (pro-MMP1)
MMP-11	Stromelysin-3	Collagen IV, VI, IX, α 1-antitrypsin, α 1-protease inhibitor, casein, elastin, fibronectin, insulin-like growth factor-binding protein-1 (IGFBP-1), laminin
MMP-12	Metalloelastase, macrophage metalloelastase, macrophage elastase	Collagen I, III, IV, α 1-antitrypsin, β -casein, elastin, enactin, fibronectin, gelatin, laminin, plasminogen, TNF- α , vitronectin
MMP-13	Collagenase 3	Collagen I, II, III, IV, VI, IX, 'X, XIV, α 2-macroglobulin, antichymotrypsin, β -casein, decorin, factor XII, fibrillin, fibrinogen, fibronectin, gelatin, laminin, plasminogen activator inhibitor, serglycin, TIMP1, transforming growth factor β (TGF- β), xylosyltransferase 1
MMP-14	Membrane type-1-matrix metalloproteinase (MT1-MMP)	Collagen I, II, III, α -1 microglobulin, α -2 macroglobulin, α -2-HS-glycoprotein, α 1-antitrypsin, α 1-proteinase inhibitor, α 5 integrin, apolipoprotein A, apolipoprotein E and apolipoprotein J, brain-specific angiogenesis inhibitor 1, casein, CD44, fibrin II, E-cadherin, elastin, endoglin, entactin, epidermal growth factor receptor, extracellular matrix metalloproteinase inducer, gelatin, fibrillin, fibrin, fibrinogen, fibroblast growth factor receter (FGFR) 1 and 4, fibronectin, galectin-3, gelsolin, growth differentiation factor-1, heparin-binding epidermal growth factor, hepatocyte growth factor activator inhibitor-1, inter- α inhibitor H4, intercellular cell adhesion molecule-1, kidney injury molecule-1, Kisspeptin/metastin, laminin, mannose-binding lectin, mucin 1, N-cadherin, Notch1, pro-MMP-2, -8 and -13, pro-transforming growth factor β , progelatinase A, receptor-activator of NF- κ B ligand, stromal cell-derived factor 1, testican-1, transforming growth factor- β , transglutaminase, vitronectin

Table I. Continued.

Enzyme	Aliases	Substrates in human
MMP-15	Membrane type-2 matrix metalloproteinase (MT2-MMP, MTMMP2)	Weak collagenase activity; cell surface tissue transglutaminase, fibronectin, laminin, pro-MMP-2 and -13, tenascin
MMP-16	MT3-MMP, MTMM3	Collagen III, casein, fibronectin, gelatin, pro-MMP-2
MMP-17	MT4-MMP, MTMM4	MT4-MMP acts as a TNF- α -converting enzyme, and as a glycosylphosphatidylinositol-anchored enzyme
MMP-19	RASI-1 MMP-18 (precursor of MMP-19)	Very limited activity versus gelatin; tenascin C
MMP-20	Enamelysin, enamel metalloproteinase	Collagen V, amelogenin, enamel protein, endostatin
MMP-21	HTX7	α 1-proteinase inhibitor
MMP-23B	Femalysin, matrix metalloproteinase in the female reproductive tract, MIFR, MIFR-1	
MMP-24	MT5-MMP-5, MTMMP5	Gelatin, fibronectin, pro-MMP-2
MMP-25	MT6-MMP, MMP-20, MMPL1	Collagen IV, α 1-proteinase inhibitor, fibrin, fibronectin, gelatin, pro-MMP-2
MMP-26	Matrilysin-2, endometase	Collagen IV, α 1-antitrypsin, α 2-macroglobulin, fibronectin, fibrinogen, insulin-like growth factor-binding protein 1 (IGFBP-1), plasminogen, pro-MMP-9, vitronectin
MMP-27	-	Casein, gelatin
MMP-28	Epilysin	Casein, NCAM

Examples of their substrates. Source: BRENDA-The Comprehensive Enzyme Information System (4).

and MMP-7 secretion (47), and expression of extracellular matrix metalloproteinase inducer (EMMPRIN), a glycoprotein that was first discovered in tumor cells, which increases MMP-1 and MMP-2 expression (48).

Factors presented above act simultaneously and affect each other. For example, Bruner *et al* reported, that progesterone requires TGF- β for its action and that progesterone and TGF- β cooperate in MMPs secretion inhibition (49). Moreover, immunological impact on endometriosis development can be prevented by both steroid hormones or retinoic acid (41,47). Those findings among others are an evidence, that no single factor is a master switch in MMPs and TIMPs regulations and subsequently in endometriosis etiology.

4. MMP in menstrual effluent

As mentioned above, assumption of the pivotal role of retrograde menstruation is the most widely accepted theory explaining etiology of endometriosis. Studies performed *in vitro* showed, that endometrial cells can attach to intact peritoneum and invade through the mesothelium within 18-24 h (50), concomitantly causing changes in morphology of the surface (51). Those initial steps of ectopic lesions development require MMPs activity for basement membrane and ECM breakdown and subsequent invasion into the stroma. High levels of numerous MMPs in endometrium during menstruation (7,52) and blockage of ectopic lesions formation in murine model of endometriosis after TIMP-1 intraperitoneal treatment (53) are solid arguments for MMPs crucial role in endometriosis onset.

Noteworthy, the retrograde menstruation does not seem to be anomaly, as it is quite common and is observed both in women with and without endometriosis (3). What is more,

no difference was found in menstrual effluent volume and MMP-2 and MMP-9 levels in menstrual blood of women with endometriosis and in healthy control (54). In conclusion, retrograde menstruation itself could be considered more as a condition and not as the only or main cause of ectopic endometrial lesions occurrence. Other molecular, genetic, hormonal and immunological factors could have significant contribution to disease development.

5. MMP in peritoneal fluid

As retrograde menstruation is not sufficient to initiate ectopic lesions in peritoneum, the peritoneum has to provide a micro-environment for implant invasion. Numerous studies show altered cytokine levels and balance in peritoneal fluid collected from patients with endometriosis (55-57), and, as mentioned above, cytokines are potent regulators of MMPs activity. It remains undetermined, whether the imbalance is a cause and not a secondary result of ectopic lesions presence. Anyway, the immunological reactions ongoing in peritoneum may influence balance between MMPs and their inhibitors in endometriotic early implants and therefore augment endometriosis onset or further development. This theory is supported by the finding, that uterine endometrial cells cultivated in medium containing peritoneal fluid collected from women with endometriosis are characterized by MMP-2 overexpression (58).

Peritoneal fluid collected from women with endometriosis shows elevated levels of MMPs and decreased levels of its inhibitors. MMP-2 (32), MMP-3 (59) and MMP-9 (60,61) levels were significantly higher in peritoneal fluid of women with endometriosis than in healthy control, while TIMP-1 levels were lower (61). However, no differences were found

Table II. Relative expression of various MMPs and TIMPs through the menstrual cycle.

Protein	Menstrual cycle phase						
	Menstrual		Proliferative		Secretory		
	Early	Late	Early	Late	Early	Mid	Late
MMP-1	++++	++++	+	+	+	+	+
MMP-2	+++	+++	++	++	++	++	++
MMP-3	++++	++++	+	+	+	+	+
MMP-7	++++	++++	++++	++++	+	+	+
MMP-8	++++	++	+	+	+	+	+
MMP-9	++	++	+	+	+	+	+
MMP-10	++++	++++	++	++	+	++	++
MMP-11	++++	++++	++++	++++	+	+	+
MMP-12	++++	+	+	+	+	+	+
MMP-14	+++	+++	++	++	++	++	++
MMP-15	++	++	++	++	++	++	++
MMP-16	+	+	++	++	++	+	+
MMP-19	++	++	++	++	++	++	++
MMP-26	+	+	++	++	++++	++	+
TIMP-1	++	++	++	++	++	++	++
TIMP-2	++	++	++	++	++	++	++
TIMP-3	++++	++	++	++	++	++	++++
TIMP-4	+	+	+	++	++++	++	+

Minimal expression, +; Strong expression, ++++; and Moderate expression, ++ and +++. MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase.

Table III. Characterization of substrate specificity of TIMPs.

Variable	TIMP-1	TIMP-2	TIMP-3	TIMP-4
Activity against MMPs	Membrane-type MMPs (MT1-, MT3-, MT5-MMP) MMP-19	Very wide activity (weaker inhibition of MMP-3 and MMP-7 in comparison to TIMP-1)	Very wide activity (weaker inhibition of MMP-3 and MMP-7 in comparison to TIMP-1)	Active against most MMPs
Activity against ADAMs	ADAM-10	ADAM-12	ADAM-10, -12, -17, -28 -33, ADAMTSs	ADAM-17, -28
Other functions	EPA-erythroid-potentiating activity Anti-apoptotic	EPA-erythroid-potentiating activity Anti-apoptotic	Inhibits angiogenesis Pro-apoptotic	
Interaction with pro-MMP	Pro-MMP-9	Pro-MMP-2	Pro-MMP-2 Pro-MMP-9	Pro-MMP-2

MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases.

between the groups in TIMP-2 levels, and MMP-13 levels in peritoneal fluid were lower in women with endometriosis than in healthy control (62).

Interestingly, although sex hormones are one of the most significant regulators of MMPs activity, no correlations between steroid hormones levels and MMP-9 (61) and TIMP-1 (63) activity in peritoneal fluid was found. This supports the theory,

that there are the additional factors, that play a role in endometriosis early formation. However, once lesion appear, hormonal factors affect its growth and activity, causing cyclic changes and bleeding. Therefore hormonal treatment, that reduces the cyclic pattern and the level on endogenous hormones, is usually the first step in endometriosis management. Those relations have been proven by many studies. Among first

findings on the issue is good to mention studies from 1990s, that showed reduction of hormone level in peritoneal fluid by gonadotropin-releasing hormone agonist (GnRH-a) in rat endometriosis model (64). Moreover, in women with endometriosis treated with weak androgen danazol, TIMP-1 level in peritoneal fluid returned to normal (63). Therefore, although hormonal factors have a questionable role in endometriosis onset, they clearly participate in its development.

6. Changes of MMPs and TIMPs activity in eutopic endometrium

Studies revealing differences in MMPs and TIMPs activity in uterine endometrium collected from women with endometriosis and from healthy subjects, largely contributed to research on endometriosis. However, they do not fully clarify, whether MMPs or their inhibitors deregulation in eutopic endometrium is a primary pathology, that lead to disease development, or secondary reaction to ectopic lesions. Those abnormalities may also be secondary to occurrence of peritoneal lesions, which subsequently cause immunological or hormonal deregulation, that eventually influence uterine endometrium. Similar activity of MMPs in menstrual effluent of healthy and affected women militate for the first theory. Despite of the origins of the imbalance, although uterine endometrium from healthy women and women with endometriosis are structurally similar, wide range of biochemical and molecular differences are found between them (65). Endometrium derived from women with endometriosis shows higher proteolytic activity than from healthy controls (66). However, when comes to activity of specific MMPs and TIMPs in those two clinical groups, numerous opposing results were published. This may be caused by variability of MMPs activity during menstrual cycle or usage of different research methods, that present variable sensitivity and specificity for tested issues. For example, Colette *et al* found no statistically significant changes in MMP-9 level in uterine endometrium from study and control group, when tested by quantitative polymerase chain reaction (qPCR); however, the differences were significant, when using enzyme-linked immunosorbent assay (ELISA) or zymography (67). Reports on these conflicting results are summarized in Table IV (58,59,66-78).

As presented in the Table IV, wide range of studies focused on MMP-2, -3, -9 and TIMP-1. Nevertheless, obtained results are unsettling, as even samples collected in one specific phase of the cycle and choosing the same method of measurement, gave totally non-reproducible outcomes. Partial explanation to this phenomenon could be various processes taking place in ectopic lesions, that would influence eutopic endometrium in a paracrine way. Newly formed lesions, with implantation process in progress, show different MMPs and TIMPs activity and cytokines levels than mature lesions with fibrosis and immune reaction on site. Therefore, uterine endometrium derived from women with endometriosis may show different MMPs and TIMPs activity, depending on ongoing processes in ectopic lesions and the disease stage.

7. Activity of MMP in ectopic lesions

Numerous studies were performed to explain the relationships between MMPs levels in ectopic lesions and eutopic

endometrium; similarly to results for uterine endometrium, it is quite common, that conflicting observations are reported. Those differences may be caused by wide range of reasons and could occur at any step of the study: choice of study group (e.g., different endometriosis stages or different phase of menstrual cycle), various types of ectopic lesions (e.g., peritoneal lesions, ovarian endometrioma wall fragments, endometrial tumors, pigmented or non-pigmented lesions), usage of different techniques (qPCR, western blotting and immunohistochemistry) or even different method of statistical analysis.

Endometriosis stage may affect results of MMPs assessment, as they are most active in early changes. Lu *et al* showed, that implantation of endometrium fragments in peritoneum in mouse model of endometriosis significantly increases MMP-2 level on site (79). Similarly, in murine model of endometriosis performed by Sotnikova *et al*, MMP-2 levels were also the highest in early ectopic changes and decreased in time, while TIMP-2 levels were acting the opposite way-decreased after transplantation and gradually increased (58). Moreover, in rat model of endometriosis, ectopic endometrial tissue showed higher expression of MMP-3 than uterine endometrium, and this relation was also the strongest in early lesions (80). Ueda *et al* spotlighted, that MMPs levels may also differ in pigmented and non-pigmented ectopic lesions (81). What is more, MMPs activity also differs in different types of ectopic lesions: retrovaginal, peritoneal or ovarian (71). For example, MMP-1 is active in red peritoneal and ovarian lesions, and inactive in black peritoneal and retrovaginal lesions (82) and MMP-27 is present in ovarian and peritoneal, but absent in retrovaginal lesions (83).

As mentioned before, MMPs levels in uterine endometrium vary significantly throughout menstrual cycle; Mizumoto *et al* showed, that it also applies to ectopic changes (84). All that lead to a conclusion, that studies on MMPs especially on humans are very hard to conduct and to analyze, as high number of unrecognized factors may affect analysis of their outcomes.

All papers known to the authors, that compare MMPs and TIMPs levels in ectopic lesions and homologues eutopic endometrium are summarized in Table V (68,70,72-78,85-88). The results of previous studies are quite consistent when it comes to MMP-2 activity. Most of the studies spotlight higher activity of MMP-2 in ectopic lesions in comparison to uterine endometrium.

However, some studies use different type of control and investigate differences between MMPs and TIMPs activity in endometriotic lesions and uterine endometrium from healthy control [summarized in Table VI (58,73,75,76,81,83,89,90)]. This kind of analysis also seems to be informative in endometriosis research, since it compares 'most pathologic' with totally healthy tissue. In ectopic changes vs. homologous uterine endometrium analysis, the deregulation of MMPs-TIMPs balance is hard to see in ectopic lesions, as eutopic endometrium is also affected by the disease. What is more, in majority of those studies, no attention has been paid to phase of menstrual cycle during samples collection, which makes the results quite unreliable and straitened to analyze.

8. Levels of MMP in serum

Endometriosis firm diagnosis requires laparoscopic surgery, which is an invasive procedure performed in general anesthesia. This is why numerous studies are conducted in order

Table IV. Alterations in MMP's/TIMP's expression in eutopic endometrium in endometriosis vs. control endometrium.^a

First author, year	MMP-no.	Obtained result	Method used and phase of menstrual cycle	(Refs.)
Di Carlo, 2009	MMP-1	Increased in women with endometriosis	qPCR, IHC, secretory	(68)
Collette, 2004	MMP-2	No difference	Zymography, ELISA; in cell culture	(66)
Di Carlo, 2009			IHC, secretory	(68)
Szymanowski, 2016			qPCR, secretory	(69)
Wenzl, 1998			IHC, results evaluated irrespective of the phase	(70)
Uzan, 2004			IHC, whole cycle	(71)
Sotnikova, 2010		Increased in women with endometriosis	qPCR, PNS	(58)
Di Carlo, 2009			qPCR, secretory	(68)
Chung, 2002			qPCR and zymography, whole cycle	(72)
Gilabert-Estellés, 2007	MMP-3	No difference	qPCR and ELISA, proliferative	(59)
Gilabert-Estellés, 2007		Increased in women with endometriosis	qPCR and ELISA, secretory	(59)
Gilabert-Estellés, 2003			qPCR, whole cycle	(73)
Ramón, 2005			qPCR, ELISA, PNS	(74)
Uzan, 2004		Decreased in women with endometriosis	IHC, whole cycle	(71)
Collette, 2006	MMP-9	No difference	qPCR, PNS	(67)
Szymanowski, 2016			qPCR, secretory	(69)
Chung, 2001			qPCR, whole cycle	(75)
Collette, 2004		Increased in women with endometriosis	Zymography, ELISA; in cell culture	(66)
Collette, 2006			Zymography, ELISA, PNS	(67)
Di Carlo, 2009			qPCR, IHC, secretory	(68)
Pan, 2008			Western blotting, whole cycle	(76)
Uzan, 2004	MMP-11	Decreased in women with endometriosis	IHC, whole cycle	(71)
Chung, 2002	MT1-MMP	Increased in women with endometriosis	qPCR, secretory phase	(72)
Gaetje, 2007	MT5-MMP	Increased in women with endometriosis	qPCR, PNS	(77)
Gilabert-Estellés, 2007	TIMP-1	No difference	qPCR and ELISA, proliferative; qPCR secretory	(59)
Collette, 2004			ELISA, proliferative	(66)
Collette, 2006			qPCR and ELISA, PNS	(67)
Szymanowski, 2016			qPCR, secretory	(69)
Gilabert-Estellés, 2003			ELISA, whole cycle	(73)
Laudanski, 2014			Western blotting, ELISA, proliferative	(78)
Gilabert-Estellés, 2007		Increased in women with endometriosis	ELISA, secretory	(59)
Laudanski, 2014			qPCR, proliferative	(78)
Collette, 2004		Decreased in women with endometriosis	ELISA, secretory	(66)
Sotnikova, 2004	TIMP-2	Increased in women with endometriosis	qPCR, PNS	(58)
Chung, 2002		Decreased in women with endometriosis	qPCR, proliferative	(72)
Chung, 2001	TIMP-3	No difference	qPCR, proliferative	(75)

Table IV. Continued.

First author, year	MMP-no.	Obtained result	Method used and phase of menstrual cycle	(Refs.)
Chung, 2001		Decreased in women with endometriosis	qPCR, secretory	(75)

^aSummary of literature comprising used method and phase of menstrual cycle. qPCR, quantitative polymerase chain reaction; IHC, immunohistochemistry; ELISA, enzyme-linked immunosorbent assay. Proliferative/secretory/whole cycle refers to phases of menstrual cycle. PNS, menstrual phase not specified.

Table V. Alterations in MMP's/TIMP's expression in ectopic lesions vs. autologous eutopic endometrium.^a

First author, year	MMP-no.	Obtained result	Method used and phase of menstrual cycle	(Refs.)
Di Carlo, 2009	MMP-1	Higher in ectopic than eutopic	IHC, qPCR, secretory phase	(68)
Shaco-Levy, 2008	MMP-2	No difference	IHC, proliferative	(85)
Di Carlo, 2009		Higher in ectopic than eutopic	IHC, qPCR, secretory	(68)
Wenzl, 1998			IHC, results evaluated irrespective of the phase	(70)
Londero, 2012			IHC, whole cycle	(86)
Chung, 2002		Lower in ectopic than eutopic	qPCR, proliferative	(72)
Gilbert-Estellés, 2003	MMP-3	Lower in ectopic than eutopic	ELISA, PNS	(73)
Meola, 2010			qPCR, proliferative	(87)
Di Carlo, 2009	MMP-9	No difference	IHC, secretory	(68)
Chung, 2001			qPCR, proliferative	(75)
Pan, 2008			Western blotting, whole cycle	(76)
Di Carlo, 2009		Higher in ectopic than eutopic	qPCR, secretory	(68)
Chung, 2001			qPCR, secretory	(75)
Shaco-Levy, 2008			IHC, proliferative	(85)
Liu, 2002			Zymography, PNS	(88)
Chung, 2002	MT1-MMP	No difference	qPCR, proliferative	(72)
Londero, 2012		Higher in ectopic than eutopic	IHC, whole cycle	(86)
Chung, 2002		Lower in ectopic than eutopic	qPCR, secretory	(72)
Gaetje, 2007	MT5-MMP	Higher in ectopic than eutopic	qPCR, PNS	(77)
Gilbert-Estellés, 2003	TIMP-1	Higher in ectopic than eutopic	ELISA, PNS	(73)
Ramón, 2005			qPCR, ELISA, PNS	(74)
Londero, 2012	TIMP-2	Higher in ectopic than eutopic	IHC, whole cycle	(86)
Laudanski, 2014		Lower in ectopic than eutopic	qPCR, proliferative	(78)
Chung, 2001	TIMP-3	No difference	qPCR, whole cycle	(75)

^aSummary of literature comprising used method and phase of menstrual cycle. qPCR, quantitative polymerase chain reaction; IHC, immunohistochemistry; ELISA, enzyme-linked immunosorbent assay. Proliferative/secretory/whole cycle refers to phases of menstrual cycle. PNS, menstrual phase not specified.

to find a sensitive and specific biomarker for endometriosis, that would allow the non-invasive diagnosis. Despite many attempts, no such protein or index based on a group of protein

expression levels has been found so far, that would meet the terms of both: High sensitivity and high specificity (91). MMPs and TIMPs activity in serum was also investigated and showed

Table VI. Alterations in level of MMP's/TIMP's in ectopic lesion in relation to control endometrium.^a

First author, year	MMP-no.	Obtained result	Method used and phase of menstrual cycle	(Refs.)
Gottschalk, 2000	MMP-1	Higher in ectopic lesion than healthy control	IHC, PNS	(89)
Gottschalk, 2000	MMP-2	No difference	IHC, PNS	(89)
Sotnikova, 2010		Higher in ectopic lesion than healthy control:	qPCR, PNS	(58)
Ueda, 2002			qPCR, PNS	(81)
Ria, 2002			<i>In situ</i> hybridization, PNS	(90)
Gottschalk, 2000	MMP-3	No difference	IHC, PNS	(89)
Gilabert-Estellés, 2003			ELISA, PNS	(73)
Gottschalk, 2000	MMP-9	No difference	IHC, PNS	(89)
Pan, 2008		Higher in ectopic lesion than healthy control:	Western blotting, whole cycle	(76)
Ueda, 2002			qPCR, PNS	(81)
Ria, 2002			<i>In situ</i> hybridization, PNS	(90)
Cominelli, 2014	MMP-27	Higher in ectopic lesion than healthy control	qPCR, PNS; one-tailed Wilcoxon signed rank test only	(83)
Ueda, 2002	MT1-MMP	Higher in ectopic lesion than healthy control	qPCR, PNS	(81)
Gilabert-Estellés, 2003	TIMP-1	Higher in ectopic lesion than healthy control	ELISA, PNS	(73)
Sotnikova, 2010	TIMP-2	No difference	qPCR, PNS	(58)
Chung, 2001	TIMP-3	No difference	qPCR, proliferative	(75)
Chung, 2001		Lower in ectopic endometrium than healthy control:	qPCR, secretory	(75)

^aSummary of literature comprising used method and phase of menstrual cycle. qPCR, quantitative polymerase chain reaction; IHC, immunohistochemistry; ELISA, enzyme-linked immunosorbent assay. Proliferative/secretory/whole cycle refers to phases of menstrual cycle. PNS, menstrual phase not specified.

different levels in women with endometriosis than in healthy controls: MMP-2 and MMP-9 levels were higher (32,60), and TIMP-1 levels lower (63). However, none of them fulfill the requirements of a feasible biomarker for endometriosis diagnosis. Also no correlation was found between stage of endometriosis according to ASRM criteria and MMP-2, MMP-9, TIMP-1 and TIMP-2 levels in serum (92), although the results are dissonant, as Malvezzi *et al* found significantly higher levels of MMP-2 in serum of women with moderate to severe endometriosis compared to milder stages (93).

9. Polymorphism of MMPs genes in endometriosis

Endometriosis seems to have some characteristics of genetic disease, but it certainly does not have a clear Mendelian inheritance pattern. The mechanisms of inheritance and a degree of influence of genetic background in endometriosis development are under discussion from decades (94). Numerous studies were performed in order to find polymorphisms of genes, that are associated with the disease development. For example polymorphisms in the estrogen receptor (95), TP53 (96), or glutathione S-transferase M1 (97) were proven to give predisposition to endometriosis. As MMPs seem to be important players in

endometriosis occurrence and development, their genetics in the disease were also investigated (98-104). Those studies claim a correlation between single-nucleotide polymorphisms (SNPs) and haplotypes of MMP-2, MMP-7, MMP-9, MMP-12 and MMP-13, TIMP2 and endometriosis risk. Recently a few metaanalyses were published, summarizing those results. Two of them emphasize MMP-1 1607 1G/2G polymorphism in predicting endometriosis risk (105,106). Nevertheless, no such correlation was found for MMP-2 15918 T/C (rs243847), MMP-2 -735 C/T (rs2285053), MMP-3 -1171 5A/6A, MMP-7 -181 A/G (rs11568818), MMP-9 -1562 C/T (rs3918242) and MMP-9 R279Q (rs17576) polymorphisms and endometriosis (107). Obtained results require further studies, especially analysis of haplotypes, as they might be more predictive, then single SNPs.

10. Future research and treatment perspectives

Although since decades studies were conducted in order to explain endometriosis etiology, its causes still remain unknown. MMPs together with their inhibitors, as arrangement essential in ECM remodeling, attachment and invasion of endometrium into extrauterine surfaces, are without a doubt important players in the disease development. TIMPs play a protective role in the

disease etiology, as proven by Bruner *et al* (53). The presence and role of MMPs in endometriosis is unquestionable, however the exact sequence of events is unclear. It remains obscure, whether changes in their activity occur primarily in uterine cavity, that due to cellular memory allows endometrium fragments implantation into peritoneum, or whether specific conditions in peritoneal cavity (inflammation or other immunological processes) change MMPs activity in endometrial cells discarded from uterus during retrograde menstruation. Moreover, some balance switches in matrix remodeling in eutopic endometrium can be periodic or temporal and vanish just after lesion constitution on ectopic site. What is more, changes of MMPs and TIMPs activity, demonstrated in uterine endometrium from women with endometriosis may also occur after implantation of ectopic lesions, under the influence of processes taking place in peritoneum. Solution of this riddle seems to be hard to find, as it would require prospective study based on endometriotic biopsies in asymptomatic population of women and long-term observation for endometriosis onset. Taking into consideration the incidence rate of 1/1,000 per year, performance of such study on healthy population would be unfeasible and likely unethical. Furthermore, despite extensive research looking for endometriosis biomarkers, its proper diagnosis or clear exclusion still requires invasive procedure (laparoscopy), since many asymptomatic or conditionally symptomatic (subfertility) cases are present.

Except comparison of uterine endometrium from healthy control and women with endometriosis, numerous studies were also conducted in order to determine activity of MMPs and TIMPs in ectopic lesions (summarized in Tables V and VI). These results are also unsettling, probably because of variable activity of MMPs and their inhibitors depending on numerous factors, such as phase of menstrual cycle or lesion type. In addition, the differences in research outcomes perfectly reflect variable role of MMPs in diverse steps of endometriosis development. Sotnikova *et al* showed, how activity of MMP-2 and TIMP-1 changes in ectopic lesions after their implantation in ectopic lesions in murine model of endometriosis, changing pattern from 'remodeling-favorable' during invasion to 'remodeling-limiting' after lesion formation (58). Change of matrix turnover balance in peritoneal lesion, as well as reactive alteration of the balance in uterus, seems to be promising mechanisms not only for the disease onset but also for the explanation of pathological effects of the disease and symptom occurrence. Therefore, it becomes clear that experiments on human tissue, that are not collected in one, specific point of disease progression, will present unreliable results. As mentioned before, also every lesion type presents diverse results of MMPs and TIMPs activity (71,81). Noteworthy, no correlation was found between American Society of Reproductive Medicine (ASRM) scores and MMPs and TIMPs levels in ovarian endometriomas (108).

Interestingly, changes in MMP-TIMP balance, that occur periodically in menstrual cycle and in endometriosis formation, may not only be technical obstacle in performing studies on endometriosis, but also be an important key to understanding its pathogenesis. As it was described in Table II, bimodal distribution of activity could be observed during physiological menstrual cycle. MMP are activated mainly in menstrual and in lower extend in proliferative phase of the cycle. TIMPs predominate especially

in late secretory phase but TIMP-3 also in early menstrual phase. Similar domination of RECK in second part of the cycle was observed (authors' unpublished data). It is undoubtful, that physiological interplay in regulation of endometrial matrix turnover would be responsible for endometrial growth in proliferative phase, endometrial stabilization in secretory phase, as well as endometrial break-down during menstruation and inhibition of endometrial implant formation in peritoneal cavity after menstruation. TIMP/RECK activation in secretory phase that persist in menstrual debris could be a potent protective mechanism. The inhibitory arm of the system is suppressed in eutopic endometrium in cases with endometriosis, so menstrual debris with lower TIMP expression could augment the implantation and lesion formation. It remains to be determined, which factors downregulate inhibitors of MMPs, because then some therapeutic or prophylactic intervention could be considered.

The role of matrix turnover in endometriosis is not unidirectional. As it was explained above, after the formation of endometrial lesions, the MMP-TIMP balance reverse to matrix stabilization by TIMP predominance (58). On the one hand, the matrix remodeling inhibition can be an important protective reaction that prevents invasive growth of existing lesion and implantation of new endometrial fragments. On the other hand, impairment of normal matrix remodeling in peritoneal cavity is a proposed mechanism of ovulatory dysfunction (luteinized unruptured follicle-LUF syndrome), that could be a main cause of endometriosis related infertility. Overactivated TIMPs could reduce tissue break-down, that is necessary in ovulatory rupture. It was proven on animal model of endometriosis, that rats with endometriosis have increased TIMP-1 and unruptured follicle-like phenotype (LUF syndrome). Moreover, neutralization of TIMP-1 in these animals effectively restored ovulation and fertility (109,110).

Recently an effective stimulation protocol dedicated to LUF syndrome was described for humans. In addition to standard ovarian stimulation, the single injection of G-CSF (granulocyte colony stimulating factor) in preovulatory period was administered, causing a significant reduction of LUF syndrome recurrence in comparison to standard ovarian stimulation alone. It is anticipated, that the most important effect of G-CSF in ovulation is leukocyte recruitment and activation in peritoneal cavity (111). This activation of leukocytes leads to secretion of excessive amounts of MMPs and may overcome stoichiometric inhibition of TIMPs. Although this promising therapy is effective, low-cost and safe example of implementation of drug used before in other fields of medicine, further assessment of clinical effectiveness and clear explanation of molecular mechanism is necessary.

In conclusion, although over-activity of MMPs is one of the key pathologies, that lead to endometriosis occurrence, their excessive inhibition in later stages of the disease may have a deep influence on the endometriosis clinical picture. Implementation of novel treatment modalities that could change the ECM remodeling especially in periovulatory period in humans is promising. Selection between recombinant protein or small-molecule drugs with antagonistic or agonistic properties for MMP-TIMP system of interaction or their regulatory miRNA should be performed on basis of safety and clinical feasibility in practice. Therapeutic intervention has to be personalized and suited to the disease stage to shift the balance into correct direction.

To improve the research in future, every study that includes investigation of MMPs and TIMPs levels should include precise data: A phase of menstruation cycle during sample collection (preferably including sex hormones levels), ectopic lesion localization, its character and morphology. Nevertheless, some studies lack even the most basic information, which is menstrual cycle phase, or even compare the obtained results regardless of the cycle. It seems to distort the results and make collective analysis impossible, since activity of specific agents may differ remarkably between phases of menstrual cycle. On the other hand, certain studies present very complex and extended analysis, comparing obtained results to phase of the cycle and lesions type, such as Londero *et al* (86). Including all the additional information about used samples seems to be essential for correct and conclusive analysis of results, that will later contribute to firmer understanding of MMPs and TIMPs role in endometriosis etiology. Moreover, collecting, processing and storage of the biological material should be performed with unified, standardized approach, such as proposed by World Endometriosis Research Foundation (112).

RECK is an important player in maintaining balance between MMPs and their inhibitors. Although it is very widely investigated in other diseases (i.e., metastases, cancer invasion), research on its role in endometriosis is still sparse. It has been proven to have a pivotal role in many pathological conditions, as being a cellular membrane bound inhibitor closely resembles the activity of TIMPs. Therefore it seems to be necessary to complete previous knowledge of endometriosis and MMPs with studies on RECK.

Although the role of MMPs and their inhibitors in endometriosis etiology is indisputable, clinical usage of this knowledge is still doubtful at the moment. MMPs and their inhibitors regulate enormous number of both physiological and pathological processes. Therefore, any interference in the perfect balance between those agents may have severe consequences. Unfortunately no agents are known, that would work selectively on uterine endometrium or ectopic lesions, but some successful approaches in nonspecific shifting MMP-TIMP balance in periovulatory period were mentioned above (111). Since TIMP, by down regulating MMP activity, also limits development of new ectopic lesions, usage of anti-MMPs agents may have a relevant impact on endometriosis prevention. The adverse effects of the therapy can be limited since the treatment could be periodic and selectively targeted to menstrual cycle. However, further studies are required, in order to clarify if inhibiting metalloproteinases and ECM remodeling would not only arrest occurrence of new lesions, but also limit progression of existing ones.

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Authors' contributions

MB and RBM were involved in the study design, literature analysis, manuscript writing and submission. PKW was involved in the study design, literature analysis, manuscript writing and provided scientific advise. All authors read, review and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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