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Review

Regulation of matrix metalloproteinases activity studied in human endometrium as a paradigm of cyclic tissue breakdown and regeneration ☆

Héloïse P. Gaide Chevronnay [a], Charlotte Selvais [a], Hervé Emonard [b], Christine Galant [a], Etienne Marbaix [a,*], Patrick Henriet [a]

[a] Cell Biology Unit, de Duve Institute, Université catholique de Louvain, avenue Hippocrate, 75, B1.75.05, B-1200 Bruxelles, Belgium
[b] CNRS UMR 6237 and Faculté de Médecine, Université de Reims Champagne-Ardenne, F-51100 Reims, France

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ABSTRACT

When abundant and activated, matrix metalloproteinases (MMPs, or matrixins) degrade most, if not all, constituents of the extracellular matrix (ECM). The resulting massive tissue breakdown is best exemplified in humans by the menstrual lysis and shedding of the endometrium, the mucosa lining the uterus. After menstruation, MMP activity needs to be tightly controlled as the endometrium regenerates and differentiates to avoid abnormal tissue breakdown while allowing tissue repair and fine remodelling to accommodate implantation of a blastocyst. This paper reviews how MMPs are massively present and activated in the endometrium at menstruation, and how their activity is tightly controlled at other phases of the cycle. Progesterone represses expression of many but not all MMPs. Its withdrawal triggers focal expression of MMPs specifically in the areas undergoing lysis, an effect mediated by local cytokines such as interleukin-1α, LEFTY-2, tumour necrosis factor-α and others. MMP-3 is selectively expressed at that time and activates proMMP-9, otherwise present in latent form throughout the cycle. In addition, a large number of neutrophils loaded with MMPs are recruited at menstruation through induction of chemokines, such as interleukin-8. At the secretory phase, progesterone repression of MMPs is mediated by transforming growth factor-β. Tissue inhibitors of metalloproteinases (TIMPs) are abundant at all phases of the cycle to prevent any undue MMP activity, but are likely overwhelmed at menstruation. At other phases of the cycle, MMPs can elude TIMP inhibition as exemplified by recruitment of active MMP-7 to the plasma membrane of epithelial cells, allowing processing of membrane-associated growth factors needed for epithelial repair and proliferation. Finally, receptor-mediated endocytosis through low density lipoprotein receptor-related protein-1 (LRP-1) efficiently clears MMP-2 and -9 at the proliferative and secretory phases. This mechanism is probably essential to prevent any excessive ECM degradation by the active form of MMP-2 that is permanently present. However, shedding of the ectodomain of LRP-1 specifically at menstruation prevents endocytosis of MMPs allowing full degradation of the ECM. Thus endometrial MMPs are regulated at the levels of transcription, release from infiltrating neutrophils, activation, binding to the cell membrane, inhibition by TIMPs and endocytic clearance by LRP-1. This allows tight control during endometrial growth and differentiation but results in a burst of activity for menstrual tissue breakdown. This article is part of a Special Issue entitled: Proteolysis 50 years after the discovery of lysosome.

1. Introduction

The endometrium, the mucosa lining the uterine cavity, is a remarkable tissue that undergoes cyclic remodelling in response to ovarian steroids throughout the reproductive life of women. Oestradiol stimulates tissue growth during the proliferative phase of each cycle, whereas progesterone acts on oestradiol-primed endometrium to induce glandular secretion and differentiation of stromal cells into decidual cells. Decidualization is accompanied by the production and assembly of a distinct pericellular basement lamina, containing laminin, type IV collagen, heparan sulfate proteoglycans (HSPGs) and osteonectin, by the secretion of fibronectin and type V collagen, and by an increased number of uterine Natural Killer (uNK) cells [1, 2].

Abbreviations: ADAM, a disintegrin and metalloproteinase; ECM, extracellular matrix; EGF, epidermal growth factor; GPI, glycosylphosphatidylinositol; HSPG, heparan sulfate proteoglycan; IGF, insulin-like growth factor; IL, interleukin; LRP, low density lipoprotein receptor-related protein; MMP, matrix metalloproteinase; MT, membrane-type; NGAL, neutrophil gelatinase-associated lipocalin-like; NK, natural killer; PA, plasminogen activator; PAI, plasminogen activator inhibitor; PDGF, platelet-derived growth factor; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinases; TNF, tumour necrosis factor; uPA, urokinase

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* Corresponding author. Tel.: +32 2 764 6755; fax: +32 2 764 6934.
E-mail address: etienne.marbaix@uclouvain.be (E. Marbaix).

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If no pregnancy occurs, the ovarian corpus luteum regresses and secretion of both steroids drops at the late secretory phase, triggering extensive infiltration by neutrophils, proteolytic breakdown and shedding of the endometrium with associated bleeding at menstruation [3–5]. Strikingly, menstrual breakdown of the uterine mucosa is limited to humans, primates and a few other mammalian species such as some bats [6]. Furthermore tissue degradation is restricted to the upper part of the endometrium, the so-called functionalis, despite widespread expression of the oestradiol and progesterone receptors in the deeper basalis as well as in the myometrium and in many other organs such as breast.

A cornerstone in the understanding of menstruation has been provided by the study of Markee [7], based on the examination of endometrial pieces from rhesus monkeys transplanted in the anterior chamber of their own eyes. This work highlighted the alternation of vasodilation and striking vasoconstriction episodes before the onset of bleeding in transplants upon progesterone deprivation. Arteriolar vasospasms are currently attributed to the production of prostaglandins and endothelin, a potent vasoconstrictor [3, 8]. However, one of the most outstanding features observed by Markee was that all transplants severely shrank during the 2–6 days preceding menstruation. It has been assumed that such "tissue regression" was secondary to proteolytic degradation of the endometrium. Indeed, the menstrual effluent is characterized by a high fibrinolytic activity due to the presence of plasmin generated by the plasminogen activators (PAs) produced in the endometrium [9, 10]. In addition to its major substrate fibrin, plasmin can degrade a number of connective tissue proteins, including fibronectin, laminin, proteoglycan core proteins and type IV collagen [11, 12]. It is also a potential activator of the matrix metalloproteinases (MMPs) zymogens and of cytokines such as transforming growth factor-β (TGF-β) [13, 14]. During the secretory phase of the cycle, progesterone stimulates the expression of the PA inhibitor (PAI)-1 by stromal cells of the endometrium, and increases the number of urokinase (uPA) receptors by post-translational mechanisms, thus enhancing internalization of uPA/PAI-1 complexes by stromal cells [15]. Conversely, the diminished concentration of ovarian steroids and of their receptors at the end of the cycle removes the repression of PA activity and enhances the fibrinolytic activity of the menstrual fluid as well as the degradation of the extracellular matrix (ECM). However, neither plasmin nor PAs can degrade type I and type III collagen fibrils that constitute the ECM framework of the endometrium.

Lysosomal enzymes have long been thought to play a prominent role in menstrual stromal breakdown and bleeding after the histochemical observation of acid phosphatase activity in the ECM of late secretory endometrium [16]. Human endometrium possesses a rich lysosomal equipment comparable to that found in the human liver, which is even further increased in conditions associated with abnormal uterine bleeding [17]. Cathepsins are abundant lysosomal enzymes able to degrade ECM components such as collagens, laminin, fibronectin and proteoglycans and to activate other proteinases such as MMPs by cathepsin B, uPA by cathepsins B and L, cathepsins B and L by cathepsin D or inactivate inhibitors such as PAI-1 by cathepsin D [18–20]. However, studies on their expression are controversial and do not support a role in menstruation [21–24]. Furthermore, the activities of N-acetyl-β-hexosaminidase, fucosidase, mannosidase, glucuronidase and acid phosphatase all increase during the proliferative phase, peak at the early secretory phase and decrease at the mid-late secretory phase of the menstrual cycle [25].

In contrast to lysosomal enzymes, MMPs appear to play a pivotal role in menstrual tissue breakdown. Involvement of MMPs in this process has been demonstrated *in vitro*, using explants of human endometrium cultured for 3–4 days either in presence or in absence of physiological concentrations of oestradiol and progesterone [26]. Hormone withdrawal induces a menstrual-like breakdown of cultured tissue and disappearance of the argyrophilic collagen-rich fibrils of their ECM that is fully prevented by synthetic inhibitors of MMPs but not by inhibitors of serine, cysteine or aspartate proteinases. Most MMPs were found to be expressed in human endometrium where their activity was also demonstrated *in vivo*, being most prominent at menstruation [27]. This paper reviews the different mechanisms regulating their activity throughout the menstrual cycle, so as to limit tissue lysis to the menstrual phase, while accommodating tissue remodelling during the other phases of the cycle.

2. Matrix metalloproteinases and their inhibitors

The 23 human MMPs, also called matrixins, are Zn-dependent endopeptidases, members of the metzincin family. They are able to degrade most, if not all, components of the ECM at neutral pH, and to activate or degrade a diverse array of cytokines, chemokines and growth factors [28, 29]. MMPs share structural similarities, possessing a highly conserved Zn-binding site in a deep cleft within the catalytic domain and an N-terminal propeptide domain which masks the active site through a conserved "cysteine switch" motif (Fig. 1). Variations in their structure and in substrate preferences have been proposed to distinguish subgroups: (i) the matrilysins, (ii) the "classical" MMPs including the collagenases, the stromelysins and the metalloelastase, (iii) the gelatinases, (iv) the membrane-type (MT) MMPs, and (v) the more recently discovered "non-conformist" MMPs (Table 1). However, bioinformatics methods now propose a different association of the various MMPs based on six evolutionary subgroups [30]. The non-catalytic domains determine the substrate specificity of MMPs. In particular, the fibronectin type II domains of gelatinases are important for cleaving type IV collagen, elastin and gelatines, whereas MMP-1 cannot cleave the triple helix of collagen without its hemopexin domain [31].

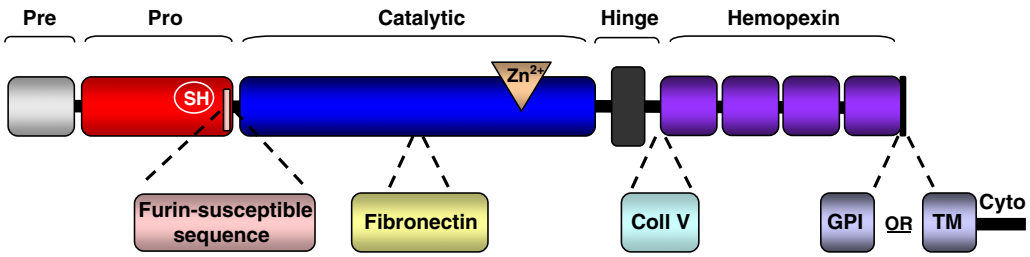

Fig. 1. Matrix metalloproteinase structure. All MMPs share common structural features. The pre-peptide (20 residues) targets MMP to the endoplasmic reticulum and is followed by the prodomain (about 80 residues), which is involved in enzyme latency. Inhibition of the catalytic domain (160 to 170 residues) in the zymogen form results from its partial coverage by the propeptide mediated through binding of the cysteine switch motif (represented by the sulfhydryl; SH) with the zinc ion (Zn^{2+}) of the active site (represented by the orange triangle). Four domains similar to hemopexin (about 200 residues), involved in substrate recognition, are bound to the catalytic domain through the hinge region, except for matrilysins, MMP-7 and -26, which lack these domains, and for the peculiar MMP-23, which possesses a different domain. Membrane-bound MMPs (MT-MMP) possess either additional glycosylphosphatidylinositol (GPI) anchoring-domain or transmembrane (TM) and cytosolic (Cyto) domains. Gelatinases, MMP-2 and -9, are characterized by the insertion of 3 fibronectin type II motifs into the catalytic domain. Several MMPs are also characterized by the presence into the prodomain of a sequence for cleavage by furin.