REVIEW

Matrix metalloproteinase-induced cervical extracellular matrix remodelling in pregnancy and cervical cancer

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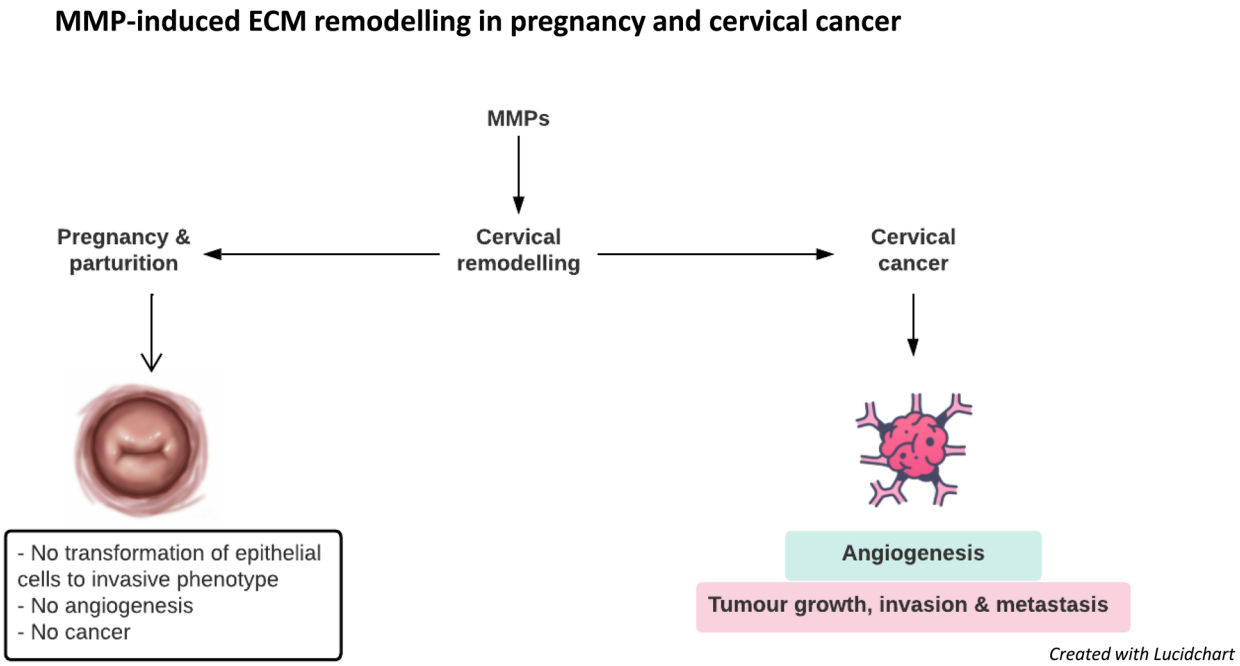
Graphical abstract



- Matrix metalloproteinases (MMPs) are pivotal to the complex extracellular matrix (ECM) modulation, which contribute to cervical remodelling during pregnancy and puerperium.
- However, in cancer of the uterine cervix, this ECM modulation is altered leading to disrupted cell-cell and cell-basement membrane adhesion, abnormal tissue growth, neovascularization and metastasis that disrupt homeostasis.
- Cervical ECM remodelling during pregnancy and puerperium could be a physiological albeit benign neoplasm.

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Abstract

The phenomenal extracellular matrix (ECM) remodelling of the cervix that precedes the myometrial contraction of labour at term or preterm appears to share some common mechanisms with the occurrence, growth, invasion and metastasis of cervical carcinoma. Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that are pivotal to the complex extracellular tissue modulation that includes degradation, remodelling and exchange of ECM components, which contribute to homeostasis under normal physiological conditions such as cervical remodelling during pregnancy and puerperium. However, in cancer such as that of the uterine cervix, this extensive network of extracellular tissue modulation is altered leading to disrupted cell–cell and cell–basement membrane adhesion, abnormal tissue growth, neovascularization and metastasis that disrupt homeostasis. Cervical ECM remodelling during pregnancy and puerperium could be a physiological albeit benign neoplasm. In this review, we examined the pathophysiologic differences and similarities in the role of MMPs in cervical remodelling and cervical carcinoma.

Lay summary

During pregnancy and childbirth, the cervix, which is the barrel-shaped lower portion of the womb that connects to the vagina, gradually softens, shortens and opens to allow birth of the baby. This process requires structural and biochemical changes in the cervix that are stimulated by enzymes known as matrix metalloproteinases. Interestingly, these enzymes also affect the structural and biochemical framework of the cervix during cervical cancer, although cervical cancers usually occur after infection by human papillomavirus. This review is intended to identify and explain the similarities and differences between the structural and chemical changes in the cervix during pregnancy and childbirth and the changes seen in cervical cancer.

Keywords: ▶ cervical remodelling ▶ cervical carcinoma ▶ matrix metalloproteinase ▶ preterm birth ▶ extracellular matrix ▶ tissue inhibitors of metalloproteinases

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Introduction

During normal pregnancy and childbirth, the extracellular matrix (ECM) of the uterine cervix undergoes several histological, catabolic and biomechanical changes collectively termed cervical remodelling. This physiological process involves controlled degradation and remodelling (disorganization) of the ECM collagen framework by matrix metalloproteinases (MMPs) to facilitate cellular proliferation and invasion (Geng *et al.* 2016). Cervical remodelling is crucial for successful pregnancy and delivery both at term or preterm. During pregnancy, the collagenous ECM of fetal membranes and cervix undergo continuous remodelling induced by MMPs in order to adapt to the growing fetus and uterus.

MMPs (matrixins) are zinc-dependent proteolytic enzymes (endopeptidases) that are either constitutively expressed during gestation (e.g. MMP-1, MMP-2 and MMP-3) or induced by active labour (e.g. MMP-9) (Reunanen & Kähäri 2000–2013, Tency *et al.* 2012). The remodelling action of MMPs is balanced by their inhibitors, that is, tissue inhibitors of metalloproteinases (TIMPs, e.g. TIMP-1, TIMP-2, TIMP-3 and TIMP-4) (Arpino *et al.* 2015), which are expressed in fetal membranes, decidua and placenta (Tency *et al.* 2012, Sundrani *et al.* 2017). Successful pregnancy also requires a balanced expression of both MMPs and TIMPs (Heng *et al.* 2012).

There are about 23 MMPs in humans classified based on their amino acid sequences and substrate specificities (Ye 2015). They include collagenases (MMP-1, -8 and -13), gelatinases (MMP-2 and -9), matrilysins (MMP-7 and -26), stromelysins (MMP-3 and -10), MMPs stromelysin-3 type (MMP-11, -19, -21, and -28), membrane-type MMPs (MMP-14, -15, -16, -17, -23, -24 and -25) and others, for example, MMP-12, -20 (enamelysin) and -27 (Zhang & Nothnick 2005, Nagase *et al.* 2006, Ye 2015, Quintero-Fabián *et al.* 2019).

The two main inhibitors of MMPs are TIMPs and serum-borne inhibitor (e.g. alpha 2-macroglobulin). TIMP is the main inhibitor of distinct MMPs produced locally (Gomez *et al.* 1997). Four identical TIMPs have been described (TIMP 1–4). TIMP-1 selectively binds to MMP-1, -2, -3

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and -9 (Zhang & Nothnick 2005). TIMP-2 inhibits MMP-2 (Howard *et al.* 1991), while TIMP-3, which is exclusively found in the ECM, has strong affinity for MMP-9 compared to other MMPs (Geng *et al.* 2016). TIMP-1 and TIMP-2 inhibit the activities of all known MMPs; hence, they are crucial in maintaining the balance between ECM deposition and degradation in several physiological processes (Gomez *et al.* 1997). TIMP-4 may have no significant preferential inhibitory action against MMPs (Curry & Osteen 2003), but it is involved in ECM homeostasis in a tissue-specific manner (Gomez *et al.* 1997).

An imbalance in the MMPs:TIMPs ratio, such as an increase in MMPs over TIMPs, results in aberrant ECM degradation and preterm rupture of membranes and preterm birth (PTB) (Athayde *et al.* 1999, Sundrani *et al.* 2017). Intrauterine (intraamniotic) infection, often ascending from the vagina through the cervix, is a major inducer of MMP production by immune cells and causes spontaneous PTB (sPTB) (Maymon *et al.* 2000*b*, 2001, Park *et al.* 2003, Becher *et al.* 2010). Consequently, MMPs and TIMPs have been employed as markers of PTB (Tency *et al.* 2012).

Similarly, MMPs perform critical roles in malignant tumour growth and cancer cell survival, for example, cervical carcinoma cells may utilize stromal MMPs to develop an invasive phenotype (Reunanen & Kähäri 2000–2013, Fullár *et al.* 2015). MMPs are not only implicated in the physiological process of cervical remodelling during gestation but are also involved in malignant tumour growth, invasion and metastasis (Kugler 1999, Gonzalez *et al.* 2013, Geng *et al.* 2016). A distorted MMP:TIMP ratio has been implicated in various human disease conditions including cancers, endometriosis, osteoarthritis, rheumatoid arthritis, amyotrophic lateral sclerosis, systemic sclerosis, sepsis, vasculopathies, preeclampsia, spontaneous and recurrent pregnancy loss, diabetes, chronic obstructive pulmonary disease, acute respiratory distress syndrome, glaucoma, HIV-1-associated neurocognitive disorders, periodontitis, etc. (Tayebjee *et al.* 2005, Amălinei *et al.* 2007, Montagnana *et al.* 2007, Rysz *et al.* 2007, Kubota *et al.* 2008, Raffetto & Khalil 2008, Anumba *et al.* 2010, Brew & Nagase 2010, Niebroj-Dobosz *et al.* 2010, Stojanovic *et al.* 2010, Mühl *et al.* 2011, Navratilova *et al.* 2012, Nissi *et al.* 2013, Nga *et al.* 2014, Xing *et al.* 2017).

Due to the pleiotropic effect of MMPs, it can be hypothesized that cervical remodelling may be akin to a physiological albeit benign neoplastic process. Furthermore, the physiological limit of MMP expression and/or other possible regulatory mechanisms that induce degradation of the ECM of the cervix, cell growth and invasion without stimulating overt malignant transformation of the cervical tissue during gestation is yet to be elucidated. Therefore, this review seeks to examine the pathophysiologic differences in the role of MMPs in cervical remodelling and carcinoma. The similarities and differences between MMP-induced cervical ECM remodelling in pregnancy and childbirth vs cervical carcinoma were highlighted.

Cervical architecture and remodelling during gestation

The normal human cervical tissue is the barrel-shaped lower portion of the uterus. It has a central (cervical) canal that connects the uterine cavity at the internal os and vaginal lumen at the external os (Vink & Mourad 2017). Although its shape depends on the age, parity and menstrual status of the woman, it measures 3–4 cm in length and 2.5 cm in diameter (Vink & Mourad 2017).

The cervix comprises an epithelium and a stromal region (Yoshida *et al.* 2019). The stromal region is predominately a homogenous, hydrated collagenous structure containing relatively fewer cells. The ECM constitutes 85–90% of the cervix and contains collagen fibrils (types I and III), proteoglycans, glycosaminoglycans (hyaluronan), elastin and matricellular proteins (thrombospondin 2, tenascin C, and secreted protein acidic and rich in cysteine protein), while immune cells, smooth muscle cells, fibroblasts and glandular/vascular cells make up ~10–15% (Fig. 1).

The mechanical (tensile) strength of the cervix is attributed to the fibrillar collagen orientation and degree of cross-links in the ECM, which is secreted by fibroblast and epithelial cells within the tissue (Danforth *et al.* 1974, Akins *et al.* 2011, Vink & Mourad 2017). The other components of the ECM also influence its global tensile

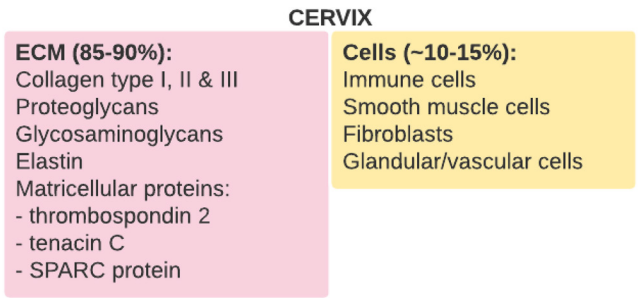

Figure 1 Composition of the uterine cervical stroma. Glycosaminoglycans (e.g. hyaluronan). ECM, extracellular matrix; SPARC protein, secreted protein acidic and rich in cysteine (basement-membrane protein 40 or osteonectin).

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strength. The proteoglycans organize collagen fibrils, while hyaluronan enhances tissue hydration and redistribution of collagen fibres. Hyaluronan also impairs the interaction of fibronectin and collagen (Word *et al.* 2007) and promotes cervical ripening by stimulating macrophages, which produce cytokines that attract other inflammatory cells into the cervical stroma (Word *et al.* 2007, House *et al.* 2009). The matricellular proteins regulate matrix formation and cell--matrix interactions and undergo increased turnover during remodelling (Danforth *et al.* 1974, Leppert 1995, Akins *et al.* 2011, Vink & Mourad 2017).

The normal cervical tissue structure also comprises an endocervix and ectocervix. The endocervical canal is lined by a mucus-secreting simple columnar epithelium, which forms numerous tubular mucous glands. The vaginal portion of the cervix (ectocervix) is lined by non-keratinized stratified squamous epithelium. The junction between the endo- and ectocervical cells is the squamocolumnar junction. Both the endo- and ectocervical cells confer some degree of protection against ascending vaginal infection (Vink & Mourad 2017).

Blood is supplied to the cervix via the descending branch of the uterine artery and drained via the uterine vein. Oxygen, hormones, immune cells, cytokines/chemokines, etc. reach the cervix via the blood supply. Like other pelvic organs, it is innervated mainly by autonomic nerves from the inferior hypogastric plexus (pelvic plexus) that is a combination of hypogastric (sympathetic, T10–L2) and pelvic splanchnic (parasympathetic, S2–S4) nerves. Painful stimuli is transmitted via afferent sensory nerve fibres through the pelvic splanchnic nerves to the S2--S4 sacral nerves (Vink & Mourad 2017).

Cervical remodelling

Parturition in mammals involves transformation of the myometrium from a quiescent to a contractile state. The cervix also remodels from a closed rigid structure to a distensible and elastic ring that opens sufficiently to allow the delivery of the fetus (Timmons *et al.* 2010, Gonzalez *et al.* 2013). Cervical remodelling is essential for safe birth. It is a nonlinear, time-dependent and anisotropic process determined by structural changes in the ECM (Myers *et al.* 2008).

Because it is quite challenging to obtain whole cervical tissue or biopsies during pregnancy in humans, most of the understanding of the molecular mechanisms and biochemical changes associated with cervical remodelling emanate from rodent studies (Timmons *et al.* 2010, Mahendroo 2012, Vink & Mourad 2017, Yellon 2017, Yoshida *et al.* 2019). Cervical remodelling involves reorganization of collagen fibril network with a gradual loss of tensile strength (Akins *et al.* 2011). It is an active dynamic process that begins from the subepithelial stroma long before uterine contraction (labour) and involves four overlapping phases, that is, softening, ripening, dilatation and postpartum repair (Read *et al.* 2007, Word *et al.* 2007, Timmons *et al.* 2010). These phases involve progressive loss of tensile strength, tissue compliance and integrity. The ripened cervix dilates sufficiently to allow passage of a term fetus. The process of cervical remodelling occurs as a continuum during gestation and may not be distinctly differentiated in relation to time (Word *et al.* 2007). Cervical ripening may also be described as involving increased tissue softening, effacement, dilation (Yellon 2019) and shortening, and it is clinically identified by an elevated Bishop's score (House *et al.* 2009).

Cervical remodelling affects the composition and structure of the ECM, as well as epithelial, stromal, immune and endothelial cell function in a closely regulated endocrine environment. After initiation of the remodelling (softening) process by the cervical stromal tissues, the cervical epithelial cells provide an immunomucosal barrier that protects the stromal compartment from inappropriate access of invading microorganisms during ECM remodelling (Read *et al.* 2007). This is achieved by epithelial proliferation, differentiation and secretion of large amounts of mucus (Timmons *et al.* 2010, Mahendroo 2012). After birth, tissue integrity and competency are rapidly recovered (postpartum repair) to prevent ascending intrauterine infection (Gonzalez *et al.* 2013).

Role of matrix metalloproteinases in cervical remodelling associated with term and preterm delivery

Activation of MMPs and collagen degradation are involved in the common pathway to cervical remodelling in both term and preterm birth (Fig. 2). MMPs are ECM remodelling proteinases and their activities are tightly regulated during pregnancy. For instance, MMPs are temporally expressed in the cervix and cervicovaginal fluid during the final ripening processes. Though MMP-2 is constitutively expressed during pregnancy, it increases gradually as cervical ripening approaches in order to enhance collagen denaturation. In contrast, MMP-1 and -9 are selectively expressed and are only activated during the final cervical ripening process. Upregulation of MMP-1, -3, -7 and -8 has

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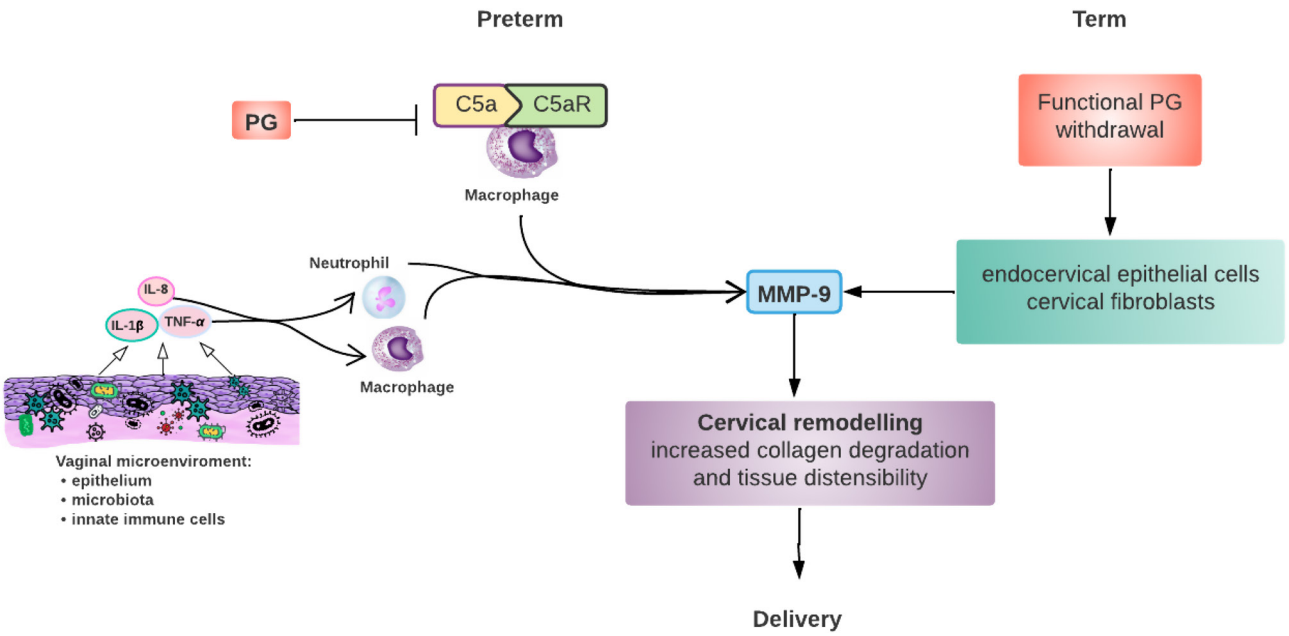

Figure 2 Matrix metalloproteinase-9 (MMP-9) induced cervical remodelling in term and preterm birth. At term, functional progesterone (PG) withdrawal (not mere reduction) stimulates endocervical epithelial cells and cervical fibroblasts to produce MMP-9, whereas MMP-9 is released by macrophages after the binding of complement component 5a (C5a) to its receptor (C5aR) during preterm labour. MMP-9 can also be released by both neutrophils and macrophages stimulated by pro-inflammatory cytokines and chemokines induced by host immune response to vaginal dysbiosis. The released MMP-9 stimulates increased cervical collagen degradation and tissue distensibility leading to remodelling and delivery eventually. Progesterone inhibits MMP-9 release by inhibiting C5aR expression on macrophages.

also been reported in cervical tissues around labour (Geng *et al.* 2016).

MMP-9 appears to be the main collagenase involved in cervical remodelling in term and preterm labour via plausibly different functional mechanisms (Fig. 2). The mechanisms indicate that PTB is not a mere quickening of the normal physiological cervical processes that lead to term delivery (Gonzalez *et al.* 2011*a*). At term, endocervical epithelial cells and cervical fibroblasts produce MMP-9 induced by functional progesterone (PG) withdrawal (not mere reduction) (Gonzalez *et al.* 2011*a*, Yellon 2017). Cytokines released by other gestational tissues, such as the myometrium, placenta and fetal membranes, also augment the release of MMPs in the cervix in the absence of inflammatory cells at term (Thomson *et al.* 1999, Gomez-Lopez *et al.* 2010). By contrast, during preterm labour, MMP-9 is released by macrophages stimulated by binding of complement component 5a (C5a) to its receptor (C5aR) on macrophages (Gonzalez *et al.* 2011*b*). PG prevented PTB in mouse model by decreasing the expression of C5aR on macrophages and inhibiting the release of MMP-9 (Fig. 2) (Gonzalez *et al.* 2011*b*). Therefore, cervical remodelling at term and preterm are essentially the same mechanism triggered by different mediators and effector cells (Fig. 2) (Gonzalez *et al.* 2011*a*,*b*, 2013).

Pathomechanism of MMPs- and TIMPs-induced ECM modulation during pregnancy and delivery

Prior to labour at term, cervicovaginal MMP-9 correlated with cervical ripening (Choi *et al.* 2009). Serum MMP-9 has been shown to be higher in women that deliver preterm compared to term women (Tency *et al.* 2012). The MMP-9:TIMP-1 and MMP-9:TIMP-2 ratios were increased in women who delivered preterm (<34 weeks) compared to gestational age-matched controls (i.e. not in preterm labour) or women in labour at term. These ratios facilitated gelatinolysis and ECM degradation in preterm labour (Tency *et al.* 2012). While TIMP-1 and -2 concentrations were lower in preterm, irrespective of labour, TIMP-4 and MMP-9 concentrations were increased in labour.

Microbial invasion of the amniotic cavity possibly due to cervicovaginal and/or intrauterine infection induces inflammatory responses that lead to preterm prelabour rupture of membranes and sPTB. A crucial part of this process is the increase in MMP-9 and reduction in MMP-2 that induces labour (Maymon *et al.* 2000*a*). Intrauterine infection can also induce an increase in MMP-3 and reduction in TIMP-2 (Maymon *et al.* 2001, Park *et al.* 2003). The inflammatory responses leading to the release of MMPs are mediated by cytokines. For example, tumour necrosis factorTNF-α stimulated the release of MMP-1 and -3 and

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suppressed TIMP in a dose-dependent manner in chorionic cells (So *et al.* 1992). TNF-α also upregulated proMMP-9 in human myometrial smooth muscle cells (Roh *et al.* 2000). TNF-α mediated upregulation of MMPs and subsequent degradation of collagen and other components of the ECM is believed to be dependent on nuclear factor kappa B (NF-κB) signalling. This is because of the correlation between MMP-9 activity and NF-κB in human term myocyte cultures (Choi *et al.* 2007). Various inflammatory cytokines also induce the release of MMPs from cervical tissues and fetal membranes as well as inflammatory cells such as leukocytes (Geng *et al.* 2016).

In addition to mediating cervical ECM remodelling during pregnancy and childbirth, MMPs also induce similar ECM degradation in cervical tissues as part of cancer formation and progression although triggered by a different stimulus. However, MMP-induced cervical ECM degradation in cervical carcinoma appears to be a part in a complex pathological pathway that transforms normal cells to neoplastic phenotype. The subsequent sections of this review shall highlight various molecular mechanisms through which cervical epithelial tissues are transformed to cancer phenotypes and how they gain access to the bloodstream to metastasize to distant tissues.

Role of MMPs in cervical carcinoma

Cervical carcinoma is the fourth most common cancer worldwide (Yuan *et al.* 2017) and the most common gynaecological cancer (Chen *et al.* 2021). It is the second leading cause of cancer death among young women, with persistent human papillomavirus (HPV) infection identified as the main aetiological risk factor (Siegel *et al.* 2018, Chen *et al.* 2021). Cancer-associated high-risk papillomavirus types (hrHPV) immortalize and transform cervical epithelial cells using viral E5, E6 and E7 oncogenes (Kivi *et al.* 2012).

Tumour metastasis is a complex process involving loss of cell–cell and cell–matrix adhesion, degradation of ECM and induction of angiogenesis (Zhang *et al.* 2014). Apart from degrading matrix proteins, MMPs also cleave several non-matrix proteins including cytokines, growth factors, adhesion molecules, lipoproteins and clotting factors, leading to their shedding, activation or inactivation. Although the levels of MMPs in normal adult tissues are typically low, tissues with inflammation or undergoing active remodelling in certain physiological or pathological processes/conditions express increased levels of MMPs (Ye 2015). For instance, elevated expression of MMPs including MMP-2, -9, -11 and -12 has been observed in invasive cervical carcinomas compared with normal tissues (Sheu *et al.* 2003, Vazquez-Ortiz *et al.* 2005). MMPs have been implicated in pathophysiological processes such as cell apoptosis, matrix remodelling, epithelial–mesenchymal transition (EMT) (Rosas *et al.* 2008, Quintero-Fabián *et al.* 2019) and cellular proliferation by which they regulate the microenvironment and behaviours of cancer cells (Chen *et al.* 2021).

EMT, which involves destruction of intercellular junctions and cell–basement membrane adhesion, degradation of ECM and components of basement membrane induced by MMPs, increases infiltration and tumour cell migration ability. The cells become motile and invasive and can metastasize to distance tissues via the bloodstream (Quintero-Fabián *et al.* 2019).

MMPs regulate ECM turnover and facilitate cancer occurrence, invasion and metastasis (Libra *et al.* 2009, Zhu *et al.* 2018). Overexpression of MMPs indicates poor prognosis for cervical cancer (Chen *et al.* 2021). MMP-1 regulates cervical cancer growth and lymph node metastasis via EMT and shows promise as a prognosticator of lymph node metastasis of cervical carcinoma (Tian *et al.* 2018). Knockdown of MMP-1 resulted in decreased proliferation, migration and invasion of cervical cancer cell lines, upregulated expression of the epithelial marker E-cadherin and downregulated expression of the metastasis-associated gene vimentin (Tian *et al.* 2018).

MMP-7 is involved in cell proliferation, migration and invasion acting as an oncogene in cervical cancer cells. MMP-7 expression in the tissue and serum was significantly higher in cervical cancer patients compared to healthy individuals and correlated with increased pathological grade, clinical stage and lymph metastasis. Therefore, MMP-7 may be a clinically applicable biomarker for cervical carcinoma (Zhu *et al.* 2018). Similarly, MMP-7 mRNA and proteins were reported to be higher in cervical neoplastic tissues than normal tissues and in nodal metastatic group than in no nodal metastatic group. The authors concluded that MMP-7 may be a useful marker in determining the invasive and metastatic potential of cervical squamous cell carcinoma (Wu *et al.* 2006). MMP-7 is primarily produced by neoplastic cells, while most MMPs are expressed by stromal cells, such as fibroblasts, vascular and inflammatory cells (Overall & Kleifeld 2006). MMP-7 may be a specific tumour cell signal that induces stromal cell components required for angiogenesis (Ito *et al.* 2007). For instance, it reactivates inactive vascular endothelial growth factor (VEGF) from stromal fibroblasts, thereby stimulating angiogenesis in pancreatic cancer cells (Ito *et al.* 2007).

Sheu *et al.* reported that while MMP-7 expression was much lower, the expression of MMP-2 and MMP-9

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was significantly higher in squamous cell carcinoma of the uterine cervix, and their gelatinolytic activity was strongly correlated with lymphovascular permeation and subsequent lymph node metastasis. MMP-2 and MMP-9 were related to clinical stage, nodal metastasis and recurrence of the squamous cell carcinoma (Sheu *et al.* 2003). However, MMP-2 and MMP-9 may exhibit different roles in cervical tumour progression. For instance, MMP-2 could be associated with aggressive behaviour and poor/worse prognosis (Sier *et al.* 2006, Noriyuki *et al.* 2007, Azevedo Martins *et al.* 2020), while MMP-9 expression reduces in high-grade tumours (Rauvala *et al.* 2006) and is associated with favourable prognosis (Azevedo Martins *et al.* 2020).

Furthermore, MMP-10 promotes tumour progression in the cervix through regulation of angiogenic and apoptotic pathways. MMP-10 regulates cervical tumour cell migration and invasion, and endothelial cell tube formation with associated resistance to apoptosis. Increasing MMP-10 expression stimulates the expression of pro-angiogenic (hypoxia-inducible factor (HIF)-1α and MMP-2) and pro-metastatic factors (plasminogen activator inhibitor-1 (PAI-1) and CXCR2). Inhibition of MMP-10 action, for example, with siRNA *in vivo*, reduced tumour growth and associated angiogenesis and stimulated apoptosis (Zhang *et al.* 2014).

Pathomechanism of MMPs- and TIMPs-induced cancer invasion, migration, progression and metastasis

The process of tumour invasion commences with the disruption of intercellular junctions of neoplastic epithelial cells *in situ* and their adhesion to the basement membrane (Fig. 3 and Table 1). The collagen fibrils and other proteins of the basement membrane are then degraded by proteolytic enzymes including MMP-2, MMP-9 (collagen IV) and MMP-14 (collagen I) (Zhai *et al.* 2005, Zhang & Nothnick 2005) secreted by the neoplastic epithelial cells. Tumour cell degradation of ECM also involves MMP-1 and -3 (Sato *et al.* 2009). The spaces created by the degraded basement membrane permit tumour cell invasion into the stroma. The stromal fibroblasts cells respond by producing more ECM and reinforce collagen fibres that encourage cell motility (Jodele *et al.* 2006). The invading neoplastic epithelial cells (Azevedo Martins *et al.* 2020) and stromal fibroblast cells (Jodele *et al.* 2006) continue to secrete proteolytic enzymes (MMPs) to degrade the surrounding ECM (remodelling) to facilitate migration and tumour enlargement, while they (tumour cells) interact with the stromal (fibroblasts, vascular, lymphovascular, endothelial and immune) cells and ECM to form the tumour microenvironment (Jodele *et al.* 2006, Azevedo Martins *et al.* 2020).

The tumour–stroma interaction or tumour–stroma ratio appears crucial in the prognosis of certain cancers including cervical cancer (Azevedo Martins *et al.* 2020). For example, cellular interaction between human cervical carcinoma cells and normal cervical fibroblasts transformed the cancer cells to the invasive phenotype by enhancing production and gene expression of proMMP-1, proMMP-3 and MMP-14, as well as activation of proMMP-2 (Sato *et al.* 2004). The interaction between tumour and fibroblast cells also enhances the expression of extracellular matrix metalloproteinase inducer (EMMPRIN)/CD147 on cervical cancer cell surface. The EMMPRIN mainly engages in the improvement of stromal MMP-1 and -3 expressions (Sato *et al.* 2009).

The innermost zone of the growing tumour forms a hypoxic and necrotic core due to oxygen and nutrient deprivation. The tumour cells respond to the decrease in oxygen and nutrient levels by secreting large amounts of VEGF-A that stimulates the formation of new blood vessels (angiogenesis) to promote tumour survival, growth and progression (Rundhaug 2005, Azevedo Martins *et al.* 2020). Angiogenesis is the rate-limiting step in tumour progression (Bielenberg & Zetter 2015). The MMPs also remodel the perivascular ECM to release angiogenic factors (Roy *et al.* 2006).

Subsequently, the basement membrane of adjacent blood vessels is degraded by the proteolytic actions of MMPs (particularly MMP-2 and MMP-9), exposing VEGF-A receptors (e.g. VEGF receptor-1 and 2) (Quintero-Fabián *et al.* 2019) expressed on pericytes and endothelial cells of the blood vessels and encouraging more angiogenesis. Tumour cells gain entrance into the bloodstream through the spaces created by the ruptured basement membrane of the blood vessels and increase their chances of metastasis to distant tissues.

The activities of the MMPs are directly inhibited by TIMP-1 and TIMP-2 which regulate tumour occurrence and progression (Azevedo Martins *et al.* 2020). Both inhibitors inhibit tumour growth, invasion and metastasis by inhibiting MMPs and exhibiting growth factor-like activities by which they inhibit angiogenesis (Gomez *et al.* 1997). The overall survival of women with advanced cervical cancer has been increased by Bevacizumab – a humanized monoclonal anti-VEGF antibody (Tewari *et al.* 2014).

In addition to remodelling of ECM, MMP-2 and MMP-9 can also act synergistically to establish the angiogenic phenotype and invasiveness of neoplastic

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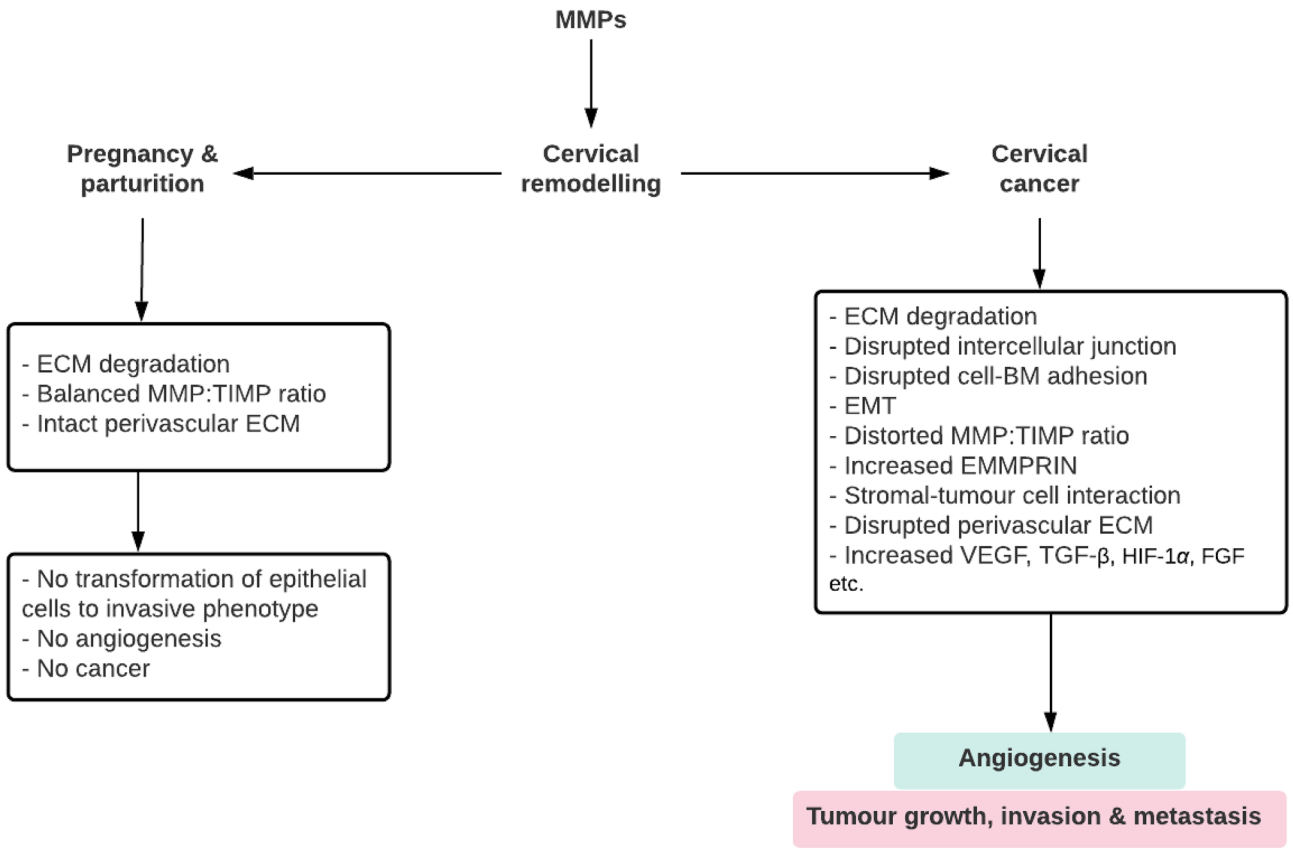

Figure 3 Mechanisms and outcome of matrix metalloproteinase-induced cervical extracellular matrix remodelling in pregnancy and childbirth vs cervical carcinoma. Though the ECM of cervical tissues is degraded in both processes, there is no epithelial cell transformation to invasive phenotype and angiogenesis in pregnancy-associated cervical remodelling, hence, no cancer. Apart from the initial trigger, for example, human papilloma virus infection, the threshold and/or pattern of MMP expression that alter the normal proliferative, invasive and immune tolerance mechanisms of cervical remodelling to cancer growth, invasion and metastasis are yet to be determined and warrant further investigation. BM, basement membrane; ECM, extracellular matrix; EMMPRIN, extracellular matrix metalloproteinase inducer; EMT, epithelial-mesenchymal transformation; FGF, fibroblast growth factor; HIF-1α, hypoxia-inducible factor-1 alpha; MMP, matrix metalloproteinase; TGF-β, transforming growth factor-beta; TIMP, tissue inhibitor of matrix metalloproteinase; VEGF, vascular endothelial growth factor.

keratinocytes (Masson *et al.* 2005). Another mechanism employed by MMP-2, MMP-9 and MMP-14 to induce cancer angiogenesis thereby promoting tumour growth and invasion involves the cleavage of pro-transforming growth factor-β (TGF-β) in a CD44-dependent manner (Yu & Stamenkovic 2000, Quintero-Fabián *et al.* 2019). TGF-β stimulates changes in cancer-associated fibroblasts such as increase in myofibroblasts, fibronectin, laminin and actin alpha 2 that promote tumour invasion (Casey *et al.* 2008). TGF-β also induces EMT that enhances the ability of cancer cells to metastasize. TGF-β can either inhibit or stimulate cell growth. Cells undergo a phenotypic switch during cancer development that activates the growth-promoting/invasive action of TGF-β. The ability of cells to activate this tumour promoter action of TGF-β is attributed to several cellular and nuclear factors, including deficiency of cyclin-dependent kinase inhibitors (Bachman & Park 2005). There is a close correlation in the expression of MMP-2 and MMP-14 in cervical cancer cells (Sheu *et al.* 2003). MMP-14 activates pro-MMP-2 to MMP-2 which determines ECM adhesion and human endothelial cell maturation (Lee *et al.* 2013).

The hypoxic tumour microenvironment also stimulates other growth factors that enhance (in synergy with VEGF) neovascularization that ensures the exchange of oxygen and nutrients with the tumour cells. These growth factors include HIF, endothelial growth factor, basic and acidic fibroblast growth factor (FGF), oestrogen, prostaglandin E_1 and E_2, interleukin-8 (IL-8), TNF and neuropilins (Quintero-Fabián *et al.* 2019). VEGF and FGF-2 also stimulate endothelial cells to secrete MMP-2- and MMP-9-containing vesicles thereby facilitating the proteolytic activity necessary for the angiogenesis-related invasive and morphogenic processes (Taraboletti *et al.*

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Table 1 Similarities and differences between matrix metalloproteinase-induced cervical extracellular matrix remodelling in pregnancy and childbirth vs cervical carcinoma.

Mechanism	Pregnancy/childbirth	Cervical carcinoma	References
Origin	Subepithelial stroma	Epithelial cells	Read *et al.* (2007), Timmons *et al.* (2010), Mahendroo (2012)
Stimulus	Progesterone withdrawal, complement activation	Altered vaginal microbiota, HPV infection	Gonzalez *et al.* (2011*a*,*b*), Yellon (2017), Siegel *et al.* (2018), Norenhag *et al.* (2020), So *et al.* (2020), Chen *et al.* (2021), Short *et al.* (2021), Kyrgiou & Moscicki (2022), Lin *et al.* (2022)
Epithelial–mesenchymal transformation	No	Yes	Bachman & Park (2005), Tian *et al.* (2018), Quintero-Fabián *et al.* (2019)
Intercellular junction	Intact	Disrupted	Zhai *et al.* (2005), Zhang & Nothnick (2005), Zhang *et al.* (2014), Quintero-Fabián *et al.* (2019)
Cell–BM adhesion	Intact	Disrupted	Zhai *et al.* (2005), Zhang & Nothnick (2005), Zhang *et al.* (2014), Quintero-Fabián *et al.* (2019)
Perivascular ECM	Intact	Disrupted	Roy *et al.* (2006), Quintero-Fabián *et al.* (2019)
Stromal–tumour cell interaction	No	Yes	Sato *et al.* (2004, 2009), Jodele *et al.* (2006), Azevedo Martins *et al.* (2020)
Angiogenesis	No	Yes	Gomez *et al.* (1997), Yu & Stamenkovic (2000), Taraboletti *et al.* (2002), Word *et al.* (2007), Rundhaug (2005), Roy *et al.* (2006), Ito *et al.* (2007), Zhang *et al.* (2014), Bielenberg & Zetter (2015), Quintero-Fabián *et al.* (2019), Azevedo Martins *et al.* (2020), Chen *et al.* (2020)
MMP:TIMP ratio	Balanced	Distorted	Athayde *et al.* (1999), Sundrani *et al.* (2017), Quintero-Fabián *et al.* (2019)
EMMPRIN	No significant change	Increased	Sato *et al.* (2009)
VEGF, TGF-β, HIF-1α, FGF levels	Low or inactive	Increased	Yu & Stamenkovic (2000), Ito *et al.* (2007), Quintero-Fabián *et al.* (2019)
MMP levels	Increased	Increased	Sheu *et al.* (2003), Sato *et al.* (2004), Zhai *et al.* (2005), Sier *et al.* (2006), Wu *et al.* (2006), Noriyuki *et al.* (2007), Sato *et al.* (2009), Zhang *et al.* (2014), Tian *et al.* (2018), Zhu *et al.* (2018), Azevedo Martins *et al.* (2020)
ECM degradation	Yes	Yes	Gomez *et al.* (1997), Athayde *et al.* (1999), Choi *et al.* (2007), Libra *et al.* (2009), Sato *et al.* (2009), Gonzalez *et al.* (2011*a*,*b*), Zhang *et al.* (2014), Geng *et al.* (2016), Sundrani *et al.* (2017), Yellon (2017, 2020), Zhu *et al.* (2018), Quintero-Fabián *et al.* (2019)

BM, basement membrane; ECM, extracellular matrix; EMMPRIN, extracellular matrix metalloproteinase inducer; FGF, fibroblast growth factor; HIF-1α, hypoxia-inducible factor-1 alpha; HPV, human papillomavirus; MMP, matrix metalloproteinase; TGF-β, transforming growth factor-beta; TIMP, tissue inhibitor of matrix metalloproteinase; VEGF, vascular endothelial growth factor.

2002). With the new blood supply and drainage, tumour cells are able to exist as an independent organ (Egeblad *et al.* 2010). Further details on the roles of MMPs and their interactions with growth factors, inhibitor proteins and the EMT process in tumour formation and propagation can be found in the review by Quintero-Fabián and colleagues (Quintero-Fabián *et al.* 2019).

Role of vaginal microbiome in altering MMP activity for both labour and CIN/cancer

The normal vaginal microbiota is dominated by lactobacilli and exhibits low immunostimulatory capacity in pregnant and non-pregnant state (Amabebe & Anumba 2018, 2020). An altered vaginal microbiota with depleted lactobacilli and overgrowth of pathobionts may attract immune cells such as neutrophils and macrophages which release MMPs. The pathway of sub-optimal vaginal microbiota, genital tract inflammation, release of MMP-9 by polymorphonuclear leucocytes, ascending genital tract infection promoted by MMP-induced cervical ECM degradation and subsequent PTB have been suggested in pregnant women living with HIV infection (Short *et al.* 2021). That is, during pregnancy, the trigger for MMP release may be vaginal dysbiosis and resultant host immune response. Though causality is yet to be proven, the mechanism here is somewhat different

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from binding of C5a and C5aR on macrophages (Fig. 2). Instead of complement activation on macrophages, there is an increase in MMP-9/TIMP-1 ratio that correlates with dominance of pathogenic anaerobes, increase in IL-1β, IL-8 and TNF-α, and polymorphonuclear leucocyte counts in a positive feedback fashion. MMP-9 may be released by both neutrophils and macrophages (Short *et al.* 2021) and not macrophages alone.

Similarly, an altered vaginal microbiota deficient in lactobacilli with associated HPV infection and proinflammatory state is also found in women with cervical intra-epithelial neoplasia (CIN) and is associated with disease progression (Mitra *et al.* 2020, 2021). With such dysbiotic vaginal microbiota, there is persistent or slower regression of the disease (Mitra *et al.* 2020). Even surgical excision of the disease may not restore the vaginal microbiota and cytokine levels to optimal levels (Mitra *et al.* 2021). Inability to restore a lactobacilliary microbiota could be responsible for the high susceptibility of such women to pre-invasive and invasive disease recurrence after treatment (Mitra *et al.* 2020). However, in another cohort of non-pregnant women, surgery was associated with decrease in *Atopobium vaginae* and concentrations of IL-1β, TNF-α, MIP-1α and eotaxin (Kawahara *et al.* 2021).

Apart from inhibiting CIN regression, a dysbiotic vaginal microbiota may also stimulate a pro-inflammatory state that enhances proliferation of malignant cells and HPV E6 and E7 oncogene expression (Kyrgiou & Moscicki 2022). By contrast, a lactobacilli-enriched vaginal microbiota is associated with regression of untreated CIN-2 within 12 months (Mitra *et al.* 2020).

Furthermore, a vaginal microbiota dominated by non-lactobacilli species or *Lactobacillus iners* may be a favourable niche for HPV infection. Such dysbiotic microbiota is associated with three- to five-fold greater risk of any prevalent HPV and two to three times higher odds for high-risk HPV infection as well as cervical dysplasia and carcinoma compared with *Lactobacillus crispatus* (Norenhag *et al.* 2020). *L. crispatus* is often decreased in women with CIN/cancer (So *et al.* 2020). CIN or cervical cancer with HPV infection is associated with increased vaginal bacteria diversity predominated by *Gardnerella vaginalis*, *Prevotella* spp., *A. vaginae*, *Dialister invisus*, *Sneathia* spp., *Pseudomonas* spp., and *Finegoldia magna* (So *et al.* 2020, Xie *et al.* 2020, Lin *et al.* 2022). Sialidase secreted by *G. vaginalis* and *Prevotella* spp. (Amabebe & Anumba 2022) may contribute significantly to the progression of HPV infection to CIN/cancer (Lin *et al.* 2022).

Taking together, vaginal dysbiosis is a strong stimulus for the release of MMP-9 which can facilitate the pathway to labour prematurely or progression of cervical neoplasia through several mechanisms including cervical ECM degradation and angiogenesis. The downstream mechanisms and structural and biochemical changes (in pregnancy/labour vs carcinoma) as highlighted in Table 1 may differ. For instance, in normal pregnancy/labour, the MMP/TIMP ratio is usually balanced with no angiogenesis. However, disrupted MMP/TIMP ratios in favour of MMPs and angiogenesis are common in cervical neoplasia (Table 1) and vaginal dysbiosis-induced MMP release during gestation (Short *et al.* 2021). CIN/cancer-associated vaginal microbiota may be useful in predicting the risk of HPV-related diseases and guiding treatment strategies (Norenhag *et al.* 2020). Whether vaginal dysbiosis without clinical infections of HPV or HIV causes CIN or cancer is yet to be fully elucidated and necessitates further investigation. The roles of specific vaginal bacterial community types in the development/progression or prevention/regression of HPV-related diseases (Castanheira *et al.* 2021) need to be unravelled.

Conclusion and future perspectives

MMPs are involved in complex extracellular tissue modulation that includes degradation, remodelling and exchange of ECM, which contribute to homeostasis under normal physiological conditions (Quintero-Fabián *et al.* 2019) such as cervical remodelling during pregnancy and puerperium (Geng *et al.* 2016). However, in cancer such as that of the uterine cervix, this extensive network of extracellular tissue modulation is altered leading to abnormal tissue growth, neovascularization and metastasis that disrupt homeostasis (Quintero-Fabián *et al.* 2019).

Though the initial stimulus may differ, that is, pregnancy hormones or complement activation vs altered vaginal microbiota (dysbiosis) or HPV infection, MMPs induce cervical ECM remodelling during pregnancy and childbirth (Geng *et al.* 2016), as well as in cervical carcinoma. However, the origin, molecular mechanisms and eventual outcome of both MMP-associated processes differ (Table 1). Pregnancy-associated cervical remodelling originates from the subepithelial stroma while the epithelium provides immunomucosal protection against opportunistic infections (Read *et al.* 2007, Timmons *et al.* 2010, Mahendroo 2012). An interesting subject for future investigation is the likelihood of attributing the changes in the stromal compartment to activities of genes and proteins expressed by the overlying epithelium. During pregnancy and parturition-induced cervical remodelling

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which is a physiological (normal) process, there is a balance in the MMP:TIMP ratio. MMPs do not stimulate the perivascular ECM to release pro-angiogenic factors such as VEGF. VEGF is usually present in low inactive form (Ito *et al.* 2007). Hence, angiogenesis, the hallmark of cancer growth and development, is absent, though there may be increased vascular permeability due to increased inducible nitric oxide synthase (Word *et al.* 2007). The MMPs do not degrade basement membrane of blood vessels, so there is no entry of epithelial cells into the bloodstream and metastasis. The MMP-induced EMT and stromal fibroblast-neoplastic epithelial cell interaction characteristic of tumour formation and progression are also absent (Fig. 3 and Table 1). MMP-9 appears to be the primary proteolytic enzyme involved, although its release is triggered by different pathways depending on the gestational age at birth, that is, term or preterm (Fig. 2) (Gonzalez *et al.* 2011*a*,*b*, 2013).

By contrast, besides the presence of HPV infection, cancer-associated cervical remodelling commences with disruption of cell–cell and cell–basement membrane adhesion, EMT (Zhai *et al.* 2005, Zhang & Nothnick 2005, Zhang *et al.* 2014, Quintero-Fabián *et al.* 2019) and tumour cell–stromal interaction (Sato *et al.* 2004, 2009, Jodele *et al.* 2006, Azevedo Martins *et al.* 2020) (Fig. 3 and Table 1). During cervical carcinoma, more MMPs and TIMPs are involved including MMP-1, -2, -3, -7, -9, -10 and -14 (Sheu *et al.* 2003, Sato *et al.* 2004, 2009, Zhai *et al.* 2005, Sier *et al.* 2006, Wu *et al.* 2006, Noriyuki *et al.* 2007, Zhang *et al.* 2014, Tian *et al.* 2018, Zhu *et al.* 2018, Azevedo Martins *et al.* 2020), TIMP-1 and -2 (Sheu *et al.* 2003, Azevedo Martins *et al.* 2020) and EMMPRIN (Sato *et al.* 2009). The MMP:TIMP ratio is dysregulated leading to unregulated degradation of ECM components of cervical tissue and surrounding blood vessels (Quintero-Fabián *et al.* 2019). Through the degradation of ECM components and activation of pro-angiogenic factors such as VEGF and TGF-β, MMPs promote angiogenesis, invasion and metastasis in diverse cancer tissues including cervical cancer (Quintero-Fabián *et al.* 2019) (Fig. 3 and Table 1). As demonstrated with pancreatic tumour cells, inactive VEGF released by fibroblast is reactivated by tumour cells in the tumour microenvironment, thereby stimulating angiogenesis (Ito *et al.* 2007). Connective tissue growth factor that sequesters VEGF *in vivo* and *in vitro* (Chen *et al.* 2020) inactivates VEGF from fibroblasts and inhibits angiogenesis, whereas MMPs such as MMP-7 from tumour cells reactivates it and promotes angiogenesis (Ito *et al.* 2007). Therefore, MMPs are regarded as angiomodulators that may modulate cancer-related angiogenesis in a cell context-dependent manner (Quintero-Fabián *et al.* 2019). The absence or perhaps insufficiency of this angiomodulatory role in pregnancy and puerperium is intriguing and necessitates further investigation.

Regardless of the initial stimulus, although elevated MMP expression is observed in both cervical remodelling during pregnancy and birth, and cervical carcinoma, the point (threshold) at which such expression of MMP becomes metabolically problematic is still unresolved. It is believed that high MMP expression induced erroneous metabolic cascades that stimulate the development of complex abnormal cell pathways that eventually alter cell architecture to a cancerous phenotype. MMPs do not cause cancer *per se*, but they induce cancer progression by increasing growth, invasiveness and metastasis through angiogenesis. Therefore, they are targets for regulation of tumour development (Quintero-Fabián *et al.* 2019). To the best of our knowledge, whether high levels of MMPs can stimulate cervical ECM remodelling and lead to cervical cancer in non-pregnant HPV negative women is yet to be extensively demonstrated.

Furthermore, the trigger of MMP-induced angiogenesis in cervical carcinoma that is absent in physiological pregnancy-associated cervical remodelling is yet to be elucidated, or is cervical remodelling at pregnancy and puerperium a physiological (benign) neoplasm? Perhaps, the action of MMPs in cervical carcinoma is another mechanism whereby tumour cells exploit the physiological proliferative, invasive and immune tolerance mechanisms that promote normal human pregnancy and childbirth to establish a nutrient supply and circumvent or alter the host immune response (Holtan *et al.* 2009). Further investigations are required to determine the threshold signal(s), the determinant factors and the molecular mechanisms of microenvironmental tissue-specific alteration of cell metabolism and phenotype leading to cancer such as cervical carcinoma. The prognosis of pregnant women with positive diagnosis of CIN and cervical carcinoma also requires further evaluation.

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Author contribution statement

E A conceived the idea and created the figures, while E A, H O and D A drafted, revised the manuscript and approved it for submission.

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