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Ovarian cancer: involvement of the matrix metalloproteinases

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Abstract

Ovarian cancer is the leading cause of death from gynecologic malignancies. One of the reasons for the high mortality rate associated with ovarian cancer is its late diagnosis, which often occurs after the cancer has metastasized throughout the peritoneal cavity. Cancer metastasis is facilitated by the remodeling of the extracellular tumor matrix by a family of proteolytic enzymes known as the matrix metalloproteinases (MMPs). There are 23 members of the MMP family, many of which have been reported to be associated with ovarian cancer. In the current paradigm, ovarian tumor cells and the surrounding stromal cells stimulate the synthesis and/or activation of various MMPs to aid in tumor growth, invasion, and eventual metastasis. The present review sheds light on the different MMPs in the various types of ovarian cancer and on their impact on the progression of this gynecologic malignancy.

Ovarian cancer

Ovarian cancer is the fifth leading cause of cancer death in women today according to the National Cancer Institute's (NCI) 2014 statistics. It is diagnosed in ∼22 000 women in the USA and accounts for at least 14 000 deaths each year. Approximately two-thirds of women are diagnosed with stage III or stage IV of the disease, wherein the 5-year survival rate is 25–30% or less, as compared to an 80–95% 5-year survival rate for those with stage I or stage II ovarian cancer (Tingulstad et al. 2003).

There are three main types of ovarian cancer, including epithelial ovarian cancer, sex cord stromal tumors, and germ cell tumors. Of these, epithelial tumors account for about 90% of ovarian cancers (Table 1), and they are the leading cause of death from gynecological malignancies (Zhang et al. 2005, Choi et al. 2007). Sex cord stromal and germ cell tumors account for the remaining ∼10% (Choi et al. 2007). Generally, germ cell tumors present at an earlier age than epithelial ovarian cancer, affecting women in their late teens and early twenties. The average age of women with epithelial ovarian cancer is around 60 years old, and it therefore affects mostly peri- or post-menopausal women. Different epithelial tumors are classified according to the cell types found in the reproductive tract, and they include serous, mucinous, endometrioid, clear cell, and transitional cell types (Table 2).

The risk factors associated with the development of ovarian cancer are based on an increased number of ovulatory cycles, and they include nulliparity, early menarche with late menopause, increasing age, and the use of fertility drugs, although the relationship of the latter to ovarian cancer remains controversial (Rossing et al. 1994, Venn et al. 1999, Dor et al. 2002). Consequently, the incidence of ovarian cancer decreases with multiparity, the use of oral contraceptives, and breastfeeding (Collaborative Group on Epidemiological Studies of Ovarian Cancer 2008, Koshiyama et al. 2014). The observation that ovarian cancer increases with ovulation rate led to the 'incessant ovulation' hypothesis, which was first proposed by Fathalla (1971). According to that hypothesis, follicular rupture results in an inflammatory reaction that damages the ovarian surface epithelial cells in the vicinity of the ovulatory stigma through DNA-altering reactive oxygen species. Such alterations result in potentially mutagenic lesions, such as P53 or BRCA (Fathalla 2013, Koshiyama et al. 2014). Hence, a family history of ovarian cancer is a risk factor mainly because of the genetic mutations of BRCA1 and BRCA2 as well as the presence of Lynch syndrome, which is hereditary (NCI). These mutagenic insults to the ovarian surface epithelial cells then direct the cells toward a malignant fate. Other risk factors may include the use of talc and obesity (NCI).

Histological similarities between serous cancers that arise in the ovaries and those that arise in the fallopian

Table 1 Classification and incidence of the major types of ovarian cancer.

Type of ovarian cancer	Incidence
Epithelial	90%
Germ cell	5%
Sex cord	5%
Primary peritoneal	Rare

tubes have led to the proposal that some ovarian cancers are of fallopian tube origin (Crum *et al.* 2007*a*). Ovulation results in the distal fallopian epithelial cells being bathed with follicular fluid that contains high levels of steroids, inflammatory cytokines, and reactive oxygen species. All of these molecules could lead to mutagenic changes in the tubal epithelial cells, which then give rise to metastasis to the ovary and result in ovarian carcinoma (Crum *et al.* 2007*b*, Fathalla 2013).

These cellular changes set in motion the events that change the phenotype in ovarian or fallopian tube cells from benign to malignant and allow the tumor to grow, acquire vascularization, and gain the characteristics that lead to metastasis. Chief among these changes in the tumor cell is the ability to modify the surrounding extracellular matrix (ECM). The ECM is a key regulatory component in cellular physiology that provides an environment for cell migration, allows differentiation, and, in some cases, decides the ultimate fate of cell survival or cell death (Birkedal-Hansen *et al.* 1993). In order for tumor cells to grow, invade, and metastasize, it is crucial for the cells to be able to disrupt the surrounding ECM. This matrix degradation allows tumor cells to proliferate, easily detach from their primary site, extravasate, and invade other tissues (Schropfer *et al.* 2010). Matrix metalloproteinases (MMPs) are known to be important players in the physiological process of cancer progression (John & Tuszynski 2001, Kessenbrock *et al.* 2010). The present review focuses on the recent literature on the involvement of the MMPs in ovarian cancer.

The MMP system

The MMP family in humans encompasses 23 related proteolytic enzymes that share common structural and functional similarities (Kleiner & Stetler-Stevenson 1993, Murphy *et al.* 1999). These functional similarities include: i) the presence of zinc in the active site of the catalytic domain, ii) the synthesis of the enzyme in an inactive or latent form, iii) the activation of the latent zymogen, and iv) the inhibition of enzyme action by both serum-borne and tissue-derived metalloproteinase inhibitors in the extracellular environment. Based on their structural similarities, the MMPs are classified into four broad categories: collagenases, gelatinases, stromelysins, and membrane type enzymes (MT-MMPs), as illustrated in Fig. 1. However, a few MMPs exhibit different characteristics and are classified outside of these four broad classes, as discussed later in the present review.

Studies have shown that the MMPs act on a diverse group of ECM components, including the collagens, gelatins, fibronectins, and laminins (Murphy *et al.* 1999, Nagase & Woessner 1999, Curry & Osteen 2003, Berchuck *et al.* 2009). Yet the MMPs also exhibit activity toward other MMPs, growth factors, and cytokines, such as insulin-like growth factor (IGF) binding proteins (IGFBP), epidermal growth factor, tumor necrosis factor α, and substance P (Sternlicht & Werb 2001). The ability of these enzymes to cleave binding proteins as well as growth factors has expanded the repertoire of MMP actions to include the modulation of cell growth. In the tumor microenvironment, MMPs may be the key regulatory point in disrupting the balance between growth and antigrowth signals, and they may thereby influence the bioavailability of growth factors to stimulate tumor cell growth, as reviewed by Kessenbrock *et al.* (2010). For example, one of the main pathways that is typically altered in cancer cells is the transforming growth factor-beta (TGF-β) receptor system, which leads to increased invasion and the metastatic potential of cancer cells (Massague 2008). TGF-β is activated via proteolytic conversion by MMPs, such as MMP2, MMP9, and MMP14 (Mu *et al.* 2002). The ability of the MMPs to turn on TGF-β activity suggests that MMPs have indirect tumor-promoting effects (Kessenbrock *et al.* 2010).

The regulation of ECM turnover and cell growth by MMPs is rigorously controlled by MMP inhibitors. There are two major classes of inhibitors, the serum-borne and the tissue-derived inhibitors (Curry & Osteen 2003). The serum-borne inhibitors include the macroglobulins, which have a potent ability to inhibit a broad range of proteinases. The tissue inhibitors of metalloproteinases, or TIMPs, are a family of four inhibitors that are locally produced, and they specifically inhibit MMPs. The TIMPs differ in their selectivity for different MMPs. For example, TIMP2 has a high affinity for MMP2, whereas

Table 2 Major cellular subtypes of ovarian epithelial cancer.

| Type of epithelial cancer	Subtypes	Incidence
Serous	Cystomas, benign cystadenomas, cystadenomas, cystadenocarcinomas	7/10
Mucinous	Cystomas, benign cystadenomas, cystadenomas, cystadenocarcinomas	1/10
Endometrioid	Benign cysts, adenocarcinomas, endometrioid tumors, adenocarcinomas	1/20
Clear cell	Cystomas, benign cystadenomas, cystadenomas, cystadenocarcinomas	3/100
Undifferentiated/unclassified	Tumors that do not fall into any of the other groups	1/10
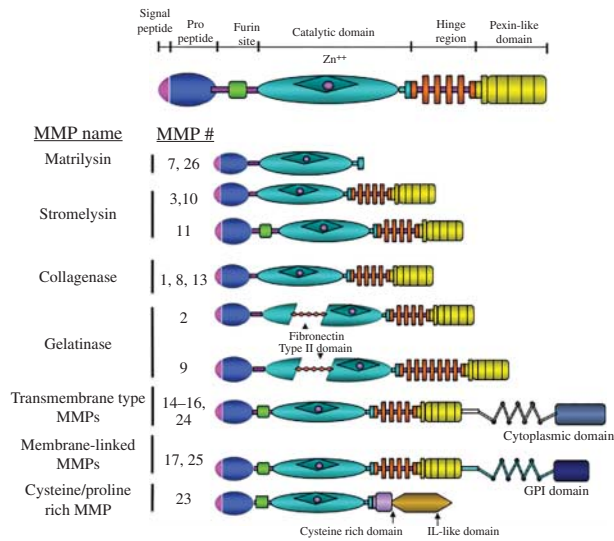
Figure 1 Schematic of the different classes of MMPs. The overall structure of the MMPs contains a signal peptide, a pro-peptide, a furin site, a catalytic domain, a hinge region, and a pexin-like domain. The gelatinases differ insofar as they also contain a fibronectin type II domain. Matrilysins lack the pexin-like domain, and the membrane types contain a cytoplasmic or GPI domain. Figure modified from Nagase & Woessner (1999) and Curry & Osteen (2003).

TIMP1 preferentially binds to MMP9 (Gomez *et al.* 1997). TIMP3 is able to inhibit the membrane type 1 MMP (MT1-MMP or MMP14), unlike TIMP1, which cannot act on MT1-MMP. However, unlike TIMP1 or TIMP2, TIMP3 is secreted and then bound to the ECM, and it has been suggested that the ECM allows TIMP3 to act as an additional regulatory stop point by working at the site of MMP action (Gomez *et al.* 1997).

MMPs and ovarian cancer

The collagenases: MMP1, MMP8, MMP13

The three collagenases share structural similarities and have the ability to act on a broad variety of substrates. Although all of the collagenases cleave fibrillar collagen, these proteases have different affinities toward type I, type II, and type III collagen. MMP14, which is a membrane type MMP, also acts on collagens and will be discussed in the membrane type MMP section later in the present review. The collagenases also have different mechanisms for reaching the extracellular environment (Nagase & Woessner 1999, Borkakoti 2000). For example, MMP8 is predominately found in neutrophils, where it is synthesized and stored in granules until it is needed. Unlike MMP8, MMP1 and MMP13 are produced and secreted in a wide range of cell types in response to specific stimuli without being stored. The collagenases have been implicated in ovarian cancer because of their expression patterns, which are dependent on the stage and tumor type (Behrens *et al.* 2001, Hantke *et al.* 2003, Stadlmann *et al.* 2003). For example,

MMP1 and the gelatinase MMP9 were shown to be strongly expressed in both stromal and epithelial tumor cells of serous invasive carcinomas and to be up-regulated in the fibroblastic stroma of borderline tumors, but they were shown to be expressed at very low levels in serous benign cystadenomas (Behrens *et al.* 2001).

In a herculean effort, Stadlmann *et al.* (2003) examined MMP expression in 302 patients using immunohistochemistry on tissue cylinder specimens. In their study, they collected 119 serous, 40 mucinous, 68 endometrioid, 16 undifferentiated, 16 mullerian, 24 clear cell, five malignant Brenner, ten sex cord, and four yolk sac tumors. The tumors were graded and correlated with prognosis and also processed for microarrays and immunohistochemistry. Numerous MMPs were expressed in all of the ovarian cancers as discussed in detail within each MMP class in the following sections. Interestingly, only MMP8 expression levels correlated with tumor grade, tumor stage, and a poor prognosis. MMP8 was up-regulated by interleukin-1β, which suggests that that pro-inflammatory cytokines may promote the invasive potential of ovarian cancer by stimulating MMP8 expression.

Because MMP13 has been associated with ovarian cancer, it has been studied as a potential prognostic indicator. Hantke *et al.* (2003) investigated the protein levels of MMP13 in ascitic fluids of 30 patients with advanced ovarian cancer. Using an ELISA, they stratified MMP13 values into two subpopulations, one population with short survival (median 16 months) and one with long overall survival (median 36 months). MMP13 was shown to be associated with shorter survival. Thus, the levels of MMP13 in ascitic fluid may identify a patient's risk and potential survival outcome.

Overexpression of the MMPs may transduce the signals for tumor cell migration and invasion through a cell surface receptor that is coupled to G proteins, protease-activated receptor 1 (PAR1). PAR1 is cleaved by MMP1, which promotes breast cancer migration and invasion (Boire *et al.* 2005). PAR1 has also been identified in ovarian cancer. Agarwal *et al.* (2008) identified a metalloprotease cascade, wherein pro-MMP1 was activated to MMP1, which in turn directly activated PAR1. This activation of MMP1–PAR1 induced the secretion of several angiogenic factors from ovarian carcinoma cells, which caused endothelial cell proliferation, endothelial tube formation, and migration (Agarwal *et al.* 2010) as well as epithelial ovarian cancer cell invasion (Wang *et al.* 2011*a*). Further investigation of PAR1 has demonstrated that serum levels of PAR1 are elevated in patients with epithelial ovarian cancer, but serum levels were not of predictive nor of prognostic value in that group of patients (Karabulut *et al.* 2014).

Polymorphisms in the MMP promoter may lead to the overexpression of MMPs in ovarian cancer. For example, Kanamori *et al.* (1999) reported that a guanine (G) insertion/deletion polymorphism within the promoter

region of MMP1 possesses greater transcriptional activity, that the proportion of patients who contained the polymorphism was elevated in patients with ovarian cancer, and that MMP1 expression was elevated in ovarian cancer tissue. Subsequent investigation into the association between promoter polymorphisms and cancer risk has questioned the role of promoter mutations in the expression of MMP1 (Wenham *et al*. 2003, Li *et al*. 2006), but it has also indicated a possible association between polymorphisms in the MMP7, MMP8, MMP12, or MMP13 promoters and the susceptibility to epithelium ovarian cancer in various populations (Li *et al*. 2006, 2009, Arechavaleta-Velasco *et al*. 2014).

The gelatinases: MMP2 and MMP9

MMP2 and MMP9 have been extensively studied in cancer, and there is a plethora of literature that documents their expression in ovarian cancer and cancer progression. Hence, the overview in the present review highlights some of these findings and emphasizes their similarities and controversies. Brun *et al*. (2008, 2012) have extensively characterized the localization and expression levels of MMP2, MMP7, MMP9, and MT1 in different types and stages of ovarian cancer. They report that serous tumors express higher levels of MMP2, MMP7, and MMP9 as compared to mucinous tumors. However, in the surrounding stromal tissue, the expression of MMP2 and MMP9 did not differ between tumor types. When classified into benign, borderline, and malignant tumors, the expression levels of these MMPs were different across the tumor subtypes. For example, MMP2 expression was higher in benign tumors than it was in borderline and malignant tumors, whereas MMP9 was higher in malignant tumors as compared to borderline tumors. In the stroma of serous tumors, the expression of MMP2 was highest in benign and border-line tumors as compared to malignant tumors. As for MMP9, it was highest in malignant tumors. In mucinous tumors, both MMP2 and MMP9 expression was highest in malignant tumors (Brun *et al*. 2008).

Although MMP2 staining was present in 76% of malignant tumors and 54% of benign tumors on immunohistochemical analysis, other studies have indicated that high levels of epithelial MMPs are not necessarily specific to malignant tumors. In fact, MMP2 is more frequently expressed in benign tumors than it is in carcinomas (Brun *et al*. 2012). These discrepancies may be a result of the different methods that the investigators used to analyze the samples as well as the arbitrary thresholds that were put in place by the different groups to determine staining intensity upon immunohistochemistry analysis (Brun *et al*. 2012).

Both MMP2 and MMP9 have been extensively studied in relation to their role in the migration and invasion of ovarian cancer. MMP2 and MMP9 have been shown to be secreted and activated in ovarian cancer, to be closely correlated with the invasion and metastasis of cancer cells, and to correlate with poor survival (Davidson *et al*. 1999).

When MMP9 was silenced using siRNA, the invasive ability of cancer cells decreased, which suggests a role for MMP9 in invasiveness (Hu *et al*. 2012). MMP9 has also been shown to be involved in the release of vascular endothelial growth factor from tumor cells and to cause ascites in ovarian cancer (Belotti *et al*. 2003). MMP9 was also suggested to play two potential roles in tumor development, where it acts as a tumor promoter when it is present in ovarian tumor stroma but prevents tumor advancement when it is expressed in the epithelium (Sillanpaa *et al*. 2007).

MMP2 has been previously shown to control the attachment and adhesion of metastatic ovarian cancer cells to peritoneal surfaces by cleaving ECM proteins and enhancing their binding to integrins (Kenny *et al*. 2008). Similarly, Kenny & Lengyel (2009) showed that the presence of MMP2 in ovarian cancer regulates the ability of the ovarian cancer to metastasize. MMP2, like MMP7, was measured in the serum of ovarian cancer patients, and serum levels of MMP2 in those patients were lower than those of healthy controls (Acar *et al*. 2008).

Both MMP2 and MMP9 levels have been investigated in the urine of patients in combination with CA125. Coticchia *et al*. (2011) showed that MMP2 and MMP9 levels in the urine may be clinically helpful for diagnosing ovarian cancer, and their results were independent of CA125 levels. Platelet-derived growth factor-D (PDGF-D) has been also shown to promote ovarian cancer invasion, and this increase in invasion is caused by PDGF-D increasing the expression of MMP2 and MMP9 (Wang *et al*. 2011*b*). Finally, in a meta-analysis of 30 published studies on MMP9 and its prognostic use in ovarian cancer, the expression of MMP9 was shown to be generally positively correlated with poor prognosis (Li *et al*. 2013).

The stromelysins: MMP3, MMP10, and MMP11

MMP3 plays a significant role in regulating ECM remodeling as well as activating other MMPs. MMP3 is known to be overexpressed in cancerous hen ovaries as well as other human cancers (Choi *et al*. 2011). The activation of MMP3 in ovarian cancer has been linked to the down-regulation of miRNA200, wherein the induction of MMP3 overexpression caused a decrease in the ability of miR200 to inhibit ovarian cancer invasiveness. Similarly, an increase in the expression of miR200 has been shown to inhibit the expression of MMP3 (Sun *et al*. 2014). In humans, MMP3 expression is present in the cystic fluids of ovarian tumors and appears to be correlated with the activation of MMP7 and MMP9 (Furuya 1999).

MMP10 is known to play a role in vascular remodeling (Rodriguez *et al*. 2008) and other functions, including cancer progression (Nabeshima *et al*. 2002), yet there have been very few studies on its role in ovarian cancer. Davidson *et al*. (2014) observed that when TP53 was mutated in ovarian cancer cell lines and exposed to hypoxic conditions, 40% (five genes) of the genes that were up-regulated were involved in ECM degradation, and one of them was MMP10. Our lab has shown that the activation of the PKC pathway in human ovarian cancer cell lines caused an increase in MMP10 expression, and this increase potentially plays a role in ovarian cancer migration (Al-Alem *et al*. 2013). In chemotherapeutic treatment, MMP10 was highly induced in ovarian cancer cells that became resistant to platinum-based chemotherapy as compared to cells that were non-resistant (Solar & Sytkowski 2011). Furthermore, MMP3 and MMP10 expression was increased in rat ovarian surface epithelia following *Ras* activation (Ulku *et al*. 2003).

MMP11 is known to be involved in tumor remodeling; however, a study that explored the protein expression of MMP2 and MMP11 in 100 tissue samples from patients with stage III ovarian cancer showed that MMP2, but not MMP11, was correlated with aggressive cancer cells (Perigny *et al*. 2008). In contrast, Mueller *et al*. (2000) showed that there was a higher percentage of low malignant tumors that express MMP11 in the stroma that is adjacent to the tumor. This expression correlated positively with tumor stage.

The membrane type MMPs: MMP14–17, MMP24, and MMP25

The membrane type MMPs are unique among the MMP family because they are not secreted into the extracellular space; rather, they contain a domain that anchors them into or onto the plasma membrane (Fig. 2). An extracellular domain directs the proteolytic component of the enzyme to the exterior surface of the cell. There are six members of this family, and they are divided into type I and type II MT-MMPs (Sounni & Noel 2005). The type I MT-MMPs include MT1 (MMP14), MT2 (MMP15), MT3 (MMP16), and MT5 (MMP24), and they have a transmembrane domain and an intracytoplasmic domain. The type II MT-MMPs, MT4 (MMP17) and MT6 (MMP25), have a glycosylphosphatidylinositol (GPI) link domain that anchors them onto the cell membrane (Curry & Osteen 2003, Sounni & Noel 2005). By virtue of their presence on the surface of the cell, all of the MT-MMPs are thought to participate in pericellular proteolysis to promote cell growth and migration, which are hallmarks of cancer metastasis (Murphy *et al*. 1999). For example, high local concentrations of active MT1 on the cell membrane of metastatic cancer cells have been proposed to play an important role in cell migration (Sabeh *et al*. 2004, Wolf *et al*. 2007, Kessenbrock *et al*.
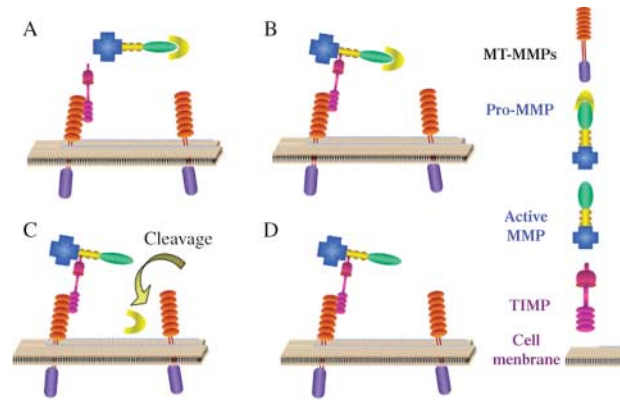

Figure 2 MMP activation. Certain MMPs are activated by the membrane type MMPs. (A) TIMPs attach to the active site of the MT-MMPs. This allows MMPs surrounding the cell in proximity to the MT-MMPs to be bound by TIMPs, thereby forming a MT-MMP:TIMP:ProMMP complex. (B) The complex is in close proximity to other MT-MMPs on the cell surface, which are capable of cleaving the pro-peptide (C) and cause the MMP to become active (D).

2010). MMPs are mostly activated via serine proteinases that cleave pro-domain peptide bonds. In addition, MT-MMPs can cleave pro-forms of other enzymes, including secreted pro-MMPs such as MMP2 and MMP9, as discussed in the earlier section on the gelatinases, which contributes to their involvement in ovarian cancer. MMP14 in particular activates MMP2, whereas MMP15 and MMP24 fail to activate MMP2 (Zucker *et al*. 1998, Miyamori *et al*. 2000). MT-MMPs are inhibited via TIMP2, whose C-terminal acts as a receptor for the pro-MMP2. A nearby uninhibited MT-MMP cleaves the adjacent pro-MMP2, which is further cleaved to the active form of MMP2 (Strongin *et al*. 1995, Deryugina *et al*. 2001) (Fig. 2).

An association has been described between ovarian cancer and the MT-MMPs. For example, MT1 and MT2 have been reported to be associated with ovarian carcinoma (Fishman *et al*. 1996, Stack *et al*. 1998). MT1 has been associated with aggressive tumor behavior (Drew *et al*. 2004) and a shorter disease-specific survival in epithelial ovarian cancer (Kamat *et al*. 2006). In contrast to MT1 and MT2, MT3 mRNA was not detected in malignant pleural or peritoneal effusions (Davidson *et al*. 2001).

There are extremely limited reports on the association of MT4, MT5, and MT6 with ovarian cancer. In the normal ovary, we have observed an increase in MT6 around the time of ovulation (Puttabyatappa *et al*. 2014). In ovarian cancer, the data that do exist have been performed in cell lines. For example, Delassus *et al*. (2010) reported that MMP25, along with other MMPs, was differentially regulated in SKOv3 ovarian cells. However, in their provocative study, these investigators reported striking variability in MMP expression in cancer cell lines. A comparison of the MMP signaling pathways

in the ovarian cancer SKOV3 cells with those from lung, brain, prostate, or breast cancer cells revealed that the induction of MMP expression differed so widely that almost 90% of the pathways were different in cells from one cancer to another (Delassus *et al.* 2010). In 18 out of 51 signaling pathways, a known suppressor of cancer progression stimulated, rather than inhibited, MMP expression. Likewise, ten signaling pathways that up-regulated MMP expression in the cells of some cancers resulted in the down-regulation of MMP in other cancer cells. These results highlight that there are pronounced differences in the signaling pathways between cells from different cancers (Delassus *et al.* 2010).

Support for the role of the MT-MMPs in ovarian cancer invasion is forthcoming from cell culture studies. OVCA 433 cells, which express a mutated form of MT1 that resulted in sustained cell surface activity by MT1, caused a cellular phenotypic epithelial–mesenchymal transition characterized by enhanced migration and collagen invasion (Moss *et al.* 2009). Likewise, MT1 increased the invasion of ovarian carcinoma cells through the activation of pro-MMP2 (Fishman *et al.* 1996).

In addition to their role in invasion, the MT-MMPs may play a key role in the vascular changes or vasculogenic mimicry associated with ovarian tumor formation and growth. MT1 is known to activate the pro-form of MMP2 to the active enzyme (Sood *et al.* 2004). Together, MMP2 and MMP14 appear to regulate the development of vasculogenic-like networks and matrix remodeling by aggressive ovarian cancer cells (Sood *et al.* 2004), which may allow further cell growth and proliferation (Fig. 3).

The matrilysins: MMP7 and MMP26

MMP7, also known as matrilysin-1, is the smallest member of the MMP family and acts on a variety of substrates (Wang *et al.* 2005). It is also one of the few MMPs that is secreted by tumor cells rather than stromal cells, and it has been shown to be expressed in almost all organ tumors in the body (Wielockx *et al.* 2004, Ii *et al.* 2006). MMP7 overexpression has been implicated in numerous cancers and is linked to advanced cancer stages and poor prognosis (Ii *et al.* 2006). In particular, MMP7 has been shown to be elevated in 80% of malignant human ovarian cancers as compared to 40% in normal or benign samples. MMP7 has also been shown to be expressed in stromal ovarian cancer tissues, particularly those of serous cancers (Brun *et al.* 2008). Polymorphisms in the MMP7 promoter region have shown that single nucleotide polymorphisms in MMP7 are significantly higher in ovarian cancer patients than they are in controls (Li *et al.* 2006). In addition, the serum levels of MMP7 were higher in patients with ovarian serous (Meinhold-Heerlein *et al.* 2007) and mucinous (Shigemasa *et al.* 2000) cancers as compared to controls. MMP7 serum levels were also higher in preoperative as compared to post-operative patients (Tanimoto *et al.*
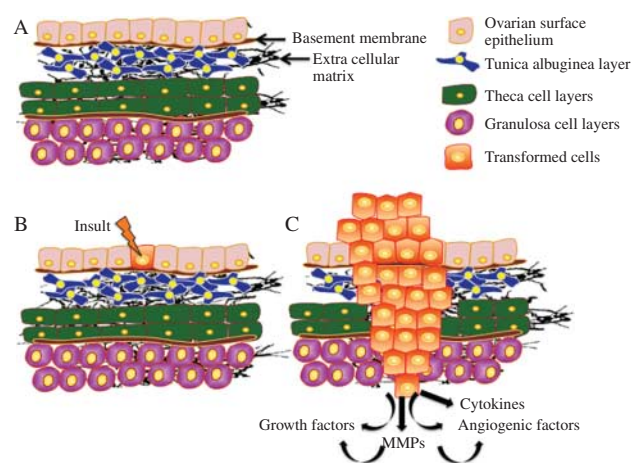

Figure 3 Schematic of ovarian cancer formation. The ovary is comprised of several cell layers, including the surface epithelium and the underlying tunica aluginea, which are separated from each other by a basement membrane. The theca layer lies under the tunica albuginea and is separated from the granulosa cell layer by a basement membrane (A). The presence of an insult or a spontaneous mutation to the cells of the surface epithelium causes cells to transform (B). This transformation leads to an uncontrolled growth of cells and the increased expression of growth factors, immune factors, MMPs, and others. More importantly, for continuous cell growth, cells need to degrade the surrounding matrices; hence, ovarian cancer cells utilize an increased expression of specific MMPs to destroy the type of matrix adjacent to the tumor cells (C).

1999) and were also higher before chemotherapy (Gershtein *et al.* 2010), which indicates that MMP7 may be useful as a biomarker. In contrast, Sillanpaa *et al.* (2006) showed that the 10-year disease-related survival was better when the tumor expression of MMP7 cells was elevated.

MMP7 secretion has been shown to correlate with metastasis (Shiomi & Okada 2003, Wang *et al.* 2005). One potential mechanism for the increased invasiveness seen with MMP7 is its activation of MMP2 and MMP9 (Ii *et al.* 2006). MMP2 has been previously shown to control the attachment and adhesion of metastatic ovarian cancer cells to peritoneal surfaces by cleaving ECM proteins and enhancing their binding to integrins (Kenny *et al.* 2008). Another mechanism for MMP7 action is the degradation of IGFBP, which thus increases the bioavailability of IGF and increases the growth of cancer cells (Ii *et al.* 2006).

Very few reports have examined MMP26 (matrilysin-2) expression in ovarian cancer. MMP26 was not detected in ovarian cancer cell lines, such as BG-1 and OAW-42 (Schropfer *et al.* 2010), nor was it significantly elevated in tissues from ovarian cancer patients (Zhao *et al.* 2009). In contrast, Ripley *et al.* (2006) reported that immunostaining of MMP26 was increased with ovarian carcinoma tumor stage III/IV, which indicates that the invading tumor cells possess the strongest staining for MMP26.

The metalloelastase: MMP12

MMP12 shares homology with the other MMPs in that it has a similar domain structure with both the collagenases and stromelysins 1 and 2. However, MMP12 is distinct from the other MMPs insofar as it only shares a 33–48% amino acid homology with the other members of this family (Shapiro *et al.* 1993). MMP12 is produced by macrophages, degrades elastin, and has been shown to be associated with inflammatory skin diseases, atherosclerosis, angiogenesis, and cancer (Nenan *et al.* 2005, Chen *et al.* 2013). Very few studies have explored the role of MMP12 in ovarian cancer. Polymorphism studies indicate that an 82A/G polymorphism of MMP12 may be a risk factor for the development of epithelial ovarian cancer progression (Li *et al.* 2009).

Conclusion

There is an extensive body of literature to suggest that MMP overexpression is associated with an increased metastatic potential of ovarian tumors, which leads to poor prognosis and decreased survival. However, as the present review highlights, the expression pattern of each individual MMP varies depending on the type of tumor, tumor stage, patient diagnosis, means of MMP identification (such as PCR), enzyme activity or immunohistochemistry, and even potentially the patient population. This variability is highlighted by studies that have examined the overexpression of MMPs related to polymorphisms in the respective MMP promoter or the differences in MMP expression in different cancer cell lines. Variability in the ability to detect MMP expression and activity may obfuscate any conclusions regarding any one MMP in the initiation, progression, metastasis, and invasion of a specific tumor.

Additionally, emerging evidence suggests that MMPs may have non-proteolytic actions working through the hemopexin domain (Correia *et al.* 2013). With sensitive advances in technology, such as RNAseq, proteomics, and 3D modeling, a more concise picture of the involvement of the MMP family in the development and progression of ovarian cancer should emerge. This will allow for the development of small-molecule MMP inhibitors that block both the proteolytic and non-proteolytic actions of the MMPs that could be used as an adjuvant therapy in conjunction with existing therapies to combat ovarian cancer.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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