WOMEN IN CANCER THEMATIC REVIEW

Ovarian cancer–peritoneal cell interactions promote extracellular matrix processing

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Abstract

Ovarian cancer has a distinct tendency for metastasising via shedding of cancerous cells into the peritoneal cavity and implanting onto the peritoneum that lines the pelvic organs. Once ovarian cancer cells adhere to the peritoneal cells, they migrate through the peritoneal layer and invade the local organs. Alterations in the extracellular environment are critical for tumour initiation, progression and intra-peritoneal dissemination. To increase our understanding of the molecular mechanisms involved in ovarian cancer metastasis and to identify novel therapeutic targets, we recently studied the interaction of ovarian cancer and peritoneal cells using a proteomic approach. We identified several extracellular matrix (ECM) proteins including, fibronectin, TGFBI, periostin, annexin A2 and PAI-1 that were processed as a result of the ovarian cancer–peritoneal cell interaction. This review focuses on the functional role of these proteins in ovarian cancer metastasis. Our findings together with published literature support the notion that ECM processing via the plasminogen–plasmin pathway promotes the colonisation and attachment of ovarian cancer cells to the peritoneum and actively contributes to the early steps of ovarian cancer metastasis.

Key Words
- ovarian cancer
- extracellular matrix
- plasmin
- annexin A2
- tumour microenvironment

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Introduction

Ovarian cancer is the most lethal gynaecological cancer and the sixth most common cause of cancer-related death among Western women (Torre *et al.* 2015). Although ovarian cancers represent 30% of cancers of the female genital tract, they are responsible for half of the deaths (Torre *et al.* 2015). The disproportionately high mortality rate is attributed to the late presentation of the disease. Despite advances in surgery and chemotherapies, no substantial improvement in ovarian cancer survival has been observed over the last two decades (Coleman *et al.* 2013). A greater understanding of the mechanisms involved in the metastasis of ovarian cancer will aid in the discovery of novel molecular diagnostic or prognostic markers and the identification of novel therapeutic targets.

Ovarian cancer peritoneal microenvironment

Ovarian cancer research over the last 30 years has focused predominantly on the cancer cells themselves

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and until more recently has largely ignored the tumour microenvironment. The tumour microenvironment composed of blood vessels, leukocytes, stem cells, fibroblasts and the extracellular matrix (ECM) is increasingly implicated as a key controlling factor in tumour progression. This is particularly the case for the growth and progression of solid tumours such as ovarian cancer. The primary microenvironment for ovarian cancer cells at the metastatic site is the peritoneum, a single layer of mesothelial cells covering the abdominal cavity and its organs (Fig. 1A). Implantation and invasion occurs within a tumour–host interface where cancer and peritoneal cells exchange proteins and peptides, which modify the local ECM and promote metastasis (Gardner *et al.* 1995, Strobel & Cannistra 1999, Freedman *et al.* 2004, Ricciardelli & Rodgers 2006, Said *et al.* 2007, Heyman *et al.* 2008, Kenny *et al.* 2008). Several ECM molecules have recently been identified to regulate the adhesion and invasion of ovarian cancer cells to peritoneal cells; however, an understanding of the cellular and molecular mechanisms involved are only just beginning to emerge (Gardner *et al.* 1996, Freedman *et al.* 2004, Heyman *et al.* 2008, Kenny *et al.* 2008). A greater understanding of these processes would potentially lead to the discovery of novel molecular targets to block this critical step of ovarian cancer metastasis. To identify potential novel therapeutic targets for advanced ovarian cancer, our group has recently explored the ovarian cancer–peritoneal cell interaction, using an *in vitro* co-culture system (Ween *et al.* 2011, Lokman *et al.* 2013). When peritoneal mesothelial cells (LP-9) and ovarian cancer cells (OVCAR-5) were grown in direct contact co-culture, we observed the formation of cellular aggregates or spheroids after 48–96 h of culture (see asterisks, Fig. 1B). There was also clear differences in the protein profiles of the conditioned media (CM) or secretome collected from ovarian cancer cells (OVCAR-5, SKOV-3) and the peritoneal cells cultured alone compared with direct co-culture whereby cells can physically interact with each other (Fig. 1C). OVCAR-5 has characteristics of high-grade serous carcinoma (Anglesio *et al.* 2013, Mitra *et al.* 2015), and SKOV-3 cells are atypical non-serous carcinoma cells with mesenchymal characteristics (Anglesio *et al.* 2013, Tan *et al.* 2013). Further studies are required to confirm whether the co-culture findings are generalisable to other ovarian cancer subtypes.

Table 1 summarises all the proteins that were identified to be differentially expressed in the co-culture secretome (OVCAR-5 and LP-9 cells) by both 1D and 2D electrophoresis through both direct co-culture and indirect co-culture where cells cannot physically interact

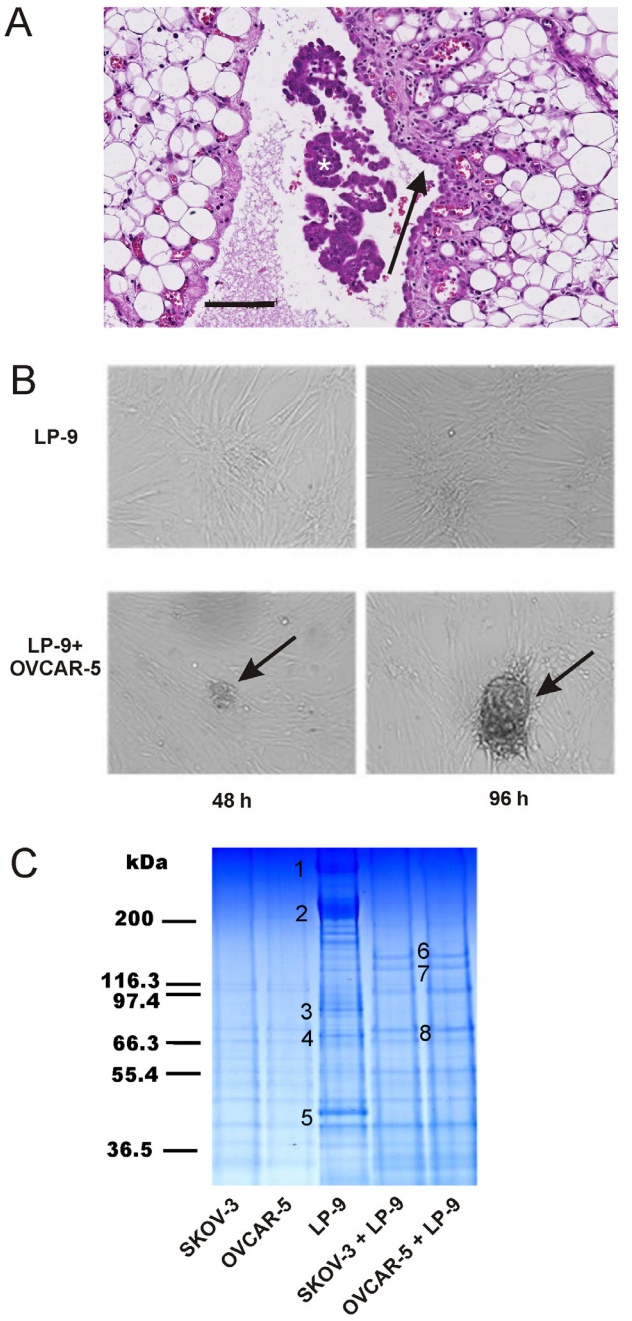

Figure 1
(A) H&E section of a serous ovarian carcinoma implant in the omentum. Black arrow indicates the layer of mesothelial cells. White asterisk indicates the metastatic ovarian cancer cells. (B) Direct co-culture of mesothelial peritoneal cells (LP-9) with OVCAR-5 cells induces cell aggregation (black arrow) most evident after 96 h. (C) A monolayer of LP-9 cells was exposed to a suspension of OVCAR-5 or SKOV-3 cells for 48 h to mimic the *in vivo* situation of ovarian cancer metastasis and the CM collected, precipitated in acetone, and run on an SDS gel and stained with Coomassie blue. Selected bands present in either the single cell culture or the co-culture only were excisioned and analysed by mass spectrometry (Maldi TOF/TOF). Band 1 = fibronectin, Band 2 = fibronectin, Band 3 = periostin, Band 4 = TGFBI, Band 5 = PAI-1, Band 6 = CK-1, Band 7 = fibronectin, Band 8 = fibronectin.

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Table 1 Summary of proteins identified in the secretome by direct and indirect peritoneal (LP-9)–ovarian cancer (OVCAR-5) cell co-culture.

Protein	Direct co-culture	Indirect co-culture	Full length expressed by peritoneal cells	Full-length size (kDa)	Fragments identified (kDa)	Potential therapies
Annexin A2	**Cleaved**	**Cleaved**	**Yes**	**39**	**34**	**Neutralising annexin A2 Ab annexin A2 siRNA, all-trans retinoic acid (ATRA) and plasmin inhibitors (Olwill *et al.* 2005, Liu *et al.* 2011, McCormack 2012, Lokman *et al.* 2013)**
Annexin A6	Cleaved	Cleaved	Yes	76	34	NA
Fibronectin	**Cleaved**	**ND**	**Yes**	**266**	**120, 70**	**Blocking FN1 Ab (Kaspar *et al.* 2006) and integrin antagonists (Desgrosellier & Cheresh 2010)**
Transforming growth beta induced protein (TGFBI)	**Cleaved**	**Cleaved**	**Yes**	**75**	**65, 60**	**Neutralising TGFBI Ab, TGFBI siRNA blocking peptide, TGFBI peptide, fastatin and integrin antagonists (Nam *et al.* 2005, Desgrosellier & Cheresh 2010, Ween *et al.* 2010)**
Keratin-1	Cleaved	Cleaved	ND	66	55, 50, 48, 44, 40, 34, 33, 28, 20	NA
Keratin 5	ND	Cleaved	ND	62	48	NA
Keratin 6C	ND	Cleaved	ND	60	48	NA
Keratin 9	Cleaved	Cleaved	ND	62	50, 48, 34	NA
Keratin 10	Cleaved	Cleaved	ND	60	55, 50, 44, 36, 34	NA
Keratin 14	ND	Cleaved	ND	52	48	NA
Keratin 16	ND	Cleaved	ND	52	48	NA
Elongation factor 2 (EEF-2)	ND	Cleaved	ND	96	34	NA
Periostin	**Full-length lost**	**Unknown**	**Yes**	**94**	**NA**	**Blocking Ab and periostin siRNA (Zhu *et al.* 2011)**
Plasminogen activator inhibitor-1 (PAI-1)	**Cleaved**	**Cleaved**	**Yes**	**45**	**44**	**Small molecule inhibitor TM5275 (Mashiko *et al.* 2015)**
Transketolase (TKT)	Cleaved	Cleaved	Yes	69	43	TKT siRNA and thiamine analogue oxythiamine (Ricciardelli *et al.* 2015)

Ab, antibody; NA, not assessed; ND, not determined. Highlighted proteins are focused in this review.

but share the same culture media. This review will focus on ECM proteins that were processed by the ovarian cancer–peritoneal cell interaction including fibronectin, transforming growth factor-beta-induced protein (TGFBI), periostin, annexin A2 and plasminogen activator inhibitor (PAI-1) and their functional role in ovarian cancer metastasis.

Role of fibronectin in ovarian cancer

Fibronectin (encoded by the gene *FN1*) is a 440 kDa, 2390 amino acid long prototypic ECM comprising three different homologous repeating units or modules arranged into protease-resistant domains, which are separated by protease susceptible regions (Romberger 1997). Although fibronectin has many biological activities, its role in cancer is well documented: promotion of cell adhesion and migration, key steps in the metastatic process (Nagai *et al*. 1991, Kenny *et al*. 2008). Fibronectin cell-adhesive sites have been identified in protease-resistant fragments of 110–120, 75 and 37 kDa, which are derived from the internal section of the protein (Ruoslahti *et al*. 1981, Hayashi & Yamada 1983, Zardi *et al*. 1985, Nagai *et al*. 1991). The cell-adhesive activity attributed to these cleaved fragments is mediated via an Arg-Gly-Asp (RGD) motif that serves as a ligand recognition site for several integrins (Pierschbacher & Ruoslahti 1984, Yamada & Kennedy 1984).

High fibronectin levels have been observed in the ovarian tumour stroma surrounding the tumour nests and in ascites fluid from ovarian cancer patients (Wilhelm *et al*. 1988, Demeter *et al*. 2005). Increased fibronectin expression correlated significantly with high tumour stage and reduced overall ovarian cancer survival (Franke *et al*. 2003, Demeter *et al*. 2005). A more recent study has shown increased fibronectin levels in the tumour stroma of omental metastases compared with those in the omentum of patients with benign disease (Kenny *et al*. 2014). A pro-tumourigenic role for fibronectin was confirmed by the reduction in invasion and metastasis of SKOV3ip1 ovarian cancer cells in fibronectin knockout mice (Kenny *et al*. 2014). Using the recently described CSIOVDB, a microarray gene expression database of epithelial ovarian cancer (Tan *et al*. 2015), we confirmed that *FN1* expression was significantly increased in tumour stroma and peritoneal tumours compared with that in primary ovarian tumours. *FN1* was higher in serous ovarian cancers than that in other subtypes and elevated in stage II-IV compared with stage I tumours. *FN1* was also increased in grade 2 and grade 3 tumours compared with that in grade 1 tumours and elevated in tumours resistant to 1st-line chemotherapy compared with sensitive tumours. Furthermore, *FN1* was significantly correlated with an epithelial mesenchymal transition (EMT) score ($\rho = 0.37$, $P = 1.19 \times 10^{-115}$), and *FN1* levels higher than the median were significantly associated with both reduced overall survival (OS) ($P < 0.0001$) and reduced disease-free survival (DFS) ($P < 0.0001$). Multivariate analysis showed that *FN1* expression was an independent predictor of DFS. The highest *FN1* expression was observed in the mesenchymal (MES) subtype that is most metastatic and has the poorest prognosis. In the MES subtype, increased *FN1* expression was associated with both reduced OS ($P = 0.0137$) and DFS ($P = 0.0222$).

In our ovarian cancer peritoneal co-culture study, we detected increased levels of fibronectin fragments (120 and 70 kDa, bands 7 and 8, Fig. 1C) and decreased full-length FN (bands 1 and 2, Fig. 1C). Full-length FN was very abundant in the LP-9 secretome but not detected in SKOV-3 or OVCAR-5 CM (Fig. 1C). The fibronectin fragments (120 and 70 kDa) are similar to those observed using a 3D culture model of peritoneal and ovarian cancer cells and omental metastases (Kenny *et al*. 2008, 2014). Kenny *et al*. showed that fibronectin cleavage could be mediated by MMP-2 and ovarian cancer cells (SKOV3ip1 and Hey A8) preferentially bound to the fibronectin fragments via $\alpha_5\beta_1$ integrin (Kenny *et al*. 2008). However, other proteases including MMP-3 (Wilhelm *et al*. 1993), MMP-19 (Stracke *et al*. 2000), MT1-MMP (Ohuchi *et al*. 1997) and MMP-7 (Quantin *et al*. 1989) can also cleave fibronectin, as well as kallikrein-7 which is upregulated in ovarian cancer cells (Dong *et al*. 2010). Plasmin can also cleave fibronectin to similar-sized fragments as those observed in our study (Quigley *et al*. 1987, Wachtfogel *et al*. 1988, Horowitz *et al*. 2008). As we have shown that plasmin levels are increased during ovarian cancer co-culture with LP-9 cells (Ween *et al*. 2011), fibronectin cleavage observed in the peritoneal ovarian cancer cell co-culture is likely to be mediated by plasmin which in turn can also activate MMPs including MMP-2. Together these findings suggest that fibronectin processing by proteases including plasmin and MMPs increases ovarian cancer cell adhesion to the mesothelial cells via integrin receptors. The confirmed critical involvement of fibronectin in adhesion and ovarian cancer metastasis strongly justifies the development of therapeutic strategies to inhibit fibronectin production and/or processing.

A humanised fibronectin antibody, L19, targeting the ED8 region of fibronectin has been used for cancer imaging in rodents and humans and has successfully inhibited

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tumour growth in orthotopic rodent models when fused with various cytokines and chemokines including IL2, IL12, TNFα and INF-γ (reviewed in Kaspar *et al*. 2006). Both L19-IL2 (Darleukin) and L19-TNF (Fibromun) have shown promising results in phase I clinical trials in patients with advanced cancer and are currently being evaluated in further phase I/II trials (Danielli *et al*. 2015).

Integrin antagonists have also been used to target fibronectin interactions. These include monoclonal antibodies that target αvβ3 (Vitaxin) and α5β1 (Volociximab) integrins as well as cyclic peptides to the RGD sequence (e.g., Cilengitide). Phase I and II trials with Vitaxin showed some efficacy in solid cancers and metastatic melanoma (reviewed in Desgrosellier & Cheresh 2010). Volociximab was well tolerated and showed promising results in phase I trials with various solid tumours (Ricart *et al*. 2008); however, it has shown insufficient clinical activity in ovarian cancer patients with platinum resistant disease (Bell-McGuinn *et al*. 2011). Although promising in phase I trials, Cilengitide, an inhibitor of both αvβ3 and αvβ5 integrins, has shown limited clinical efficacy in phase II/III trials in patients with glioblastoma (Eisele *et al*. 2014, Stupp *et al*. 2014) and metastatic castrate-resistant prostate cancer (Bradley *et al*. 2011). Targeting either fibronectin or integrin interactions remain promising treatment options for many cancers including ovarian cancer and need further evaluation.

Role of TGFBI in ovarian cancer

TGFBI (also known as βigH3) is a transforming growth factor beta (TGFβ) inducible-secreted ECM protein. Two isoforms of TGFBI with molecular weights 78 and 68 kDa have been reported to date (Gibson *et al*. 1989), which are encoded by a single gene, *TGFBI* (Schorderet *et al*. 2000). TGFBI protein contains a signal peptide in the first 24 amino acid residues at the N-terminus, a cysteine-rich EMI domain, four highly conserved fasciclin (FAS) domains and several integrin-binding motifs including the RGD motif in the C–terminus, which serves as a ligand-recognition site for several integrins (LeBaron *et al*. 1995, Ohno *et al*. 1999, Bae *et al*. 2002, Jeong & Kim 2004, Kim & Kim 2008). Other integrin-binding motifs include the NKDIL motif (amino acids 354–358) (Kim *et al*. 2000), the EPDIM motif (amino acids 617–621) (Kim *et al*. 2000) in the second and fourth FAS-1 domains, respectively, and the YH18 motif (amino acids 563–580) in the fourth FAS-1 domain, which can support αvβ5 integrin-mediated adhesion of lung fibroblast MRC-5 cells (Kim *et al*. 2002), vascular smooth muscle cells (Lee *et al*. 2006) and endothelial cells (Nam *et al*. 2003).

TGFBI plays a major role in the adhesion and migration of a wide range of cells including keratinocytes, fibroblasts, chondrocytes, osteoblasts, endothelial cells and cancer cells (reviewed by Thapa *et al*. 2005). Effects of TGFBI on adhesion are mediated through interactions with various integrins including α1β1, α3β1, αvβ3 and αvβ5 (LeBaron *et al*. 1995, Ohno *et al*. 1999, Bae *et al*. 2002, Jeong & Kim 2004, Kim & Kim 2008) via the different integrin-binding motifs. TGFBI also functions as a linker protein and connects many matrix proteins including collagens (type I, II and IV), fibronectin (Billings *et al*. 2002) and proteoglycans (biglycan and decorin) with each other (Gibson *et al*. 1997, Billings *et al*. 2002, Hanssen *et al*. 2003, Reinboth *et al*. 2006).

There are conflicting data in the literature reporting that TGFBI may have a tumour suppressive as well as a tumour-promoting role in different types of cancer cells (reviewed in Ween *et al*. 2012). Loss of *TGFBI* expression has been described in several cancers including ovarian cancer, and promoter hypermethylation has been identified as an important mechanism for the silencing of the *TGFBI* gene (Kang *et al*. 2010, Wang *et al*. 2012). There are only a few studies that have investigated the effects of TGFBI on tumour cell function, and the knowledge about the role of TGFBI in ovarian cancer is still limited. Studies have shown that the level of *TGFBI* in ovarian cancer tissues is predictive of the disease response to the treatment with the aromatase inhibitor letrozole (Walker *et al*. 2007) or the chemotherapeutic drug paclitaxel (Ahmed *et al*. 2007). Our previous findings suggest that TGFBI is downregulated in ovarian cancer and that high concentration of TGFBI induced ovarian cancer cell death, which supports a tumour suppressor role (Ween *et al*. 2010).

However, there are also convincing data reporting a tumour-promoting role for TGFBI. Using CSIOVDB (Tan *et al*. 2015), *TGFBI* expression was significantly increased in tumour stroma and peritoneal tumours compared with that in primary ovarian tumours. *TGFB1* expression was the highest in serous and endometrioid ovarian cancers compared with other subtypes and elevated in stage III and stage IV compared with stage I tumours. *TGFB1* expression was also increased in grade 3 compared with that in all other grades and elevated in tumours resistant or refractory to 1st-line chemotherapy compared with sensitive tumours. Furthermore, *TGFB1* was significantly correlated with an EMT score ($\rho=0.178$, $P=6.21\times10^{-26}$) and levels higher than fourth quartile (Q4) were

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significantly associated with both reduced OS (P=0.0007) and DFS (P=0.0016). The highest *TGFB1* expression was observed in the MES subtype, and increased *TGFBI* expression in this subtype was associated with both reduced OS (P=0.0038, HR=1.40, 95% CI: 1.11–1.75) and DFS (P=0.0003, HR=1.50, 95% CI: 1.21–1.87). We have shown TGFBI to be abundantly expressed by peritoneal cells, and recombinant TGFBI increased the metastatic potential of ovarian cancer cells by promoting cell motility, invasion and adhesion to peritoneal cells (Ween *et al*. 2010). Together these findings support the tumour-promoting role of TGFBI.

Full-length TGFBI was abundant in the LP-9 secretome (band 4, Fig. 1C) and processed to smaller isoforms when co-cultured directly with OVCAR-5 and SKOV-3 cells (Ween *et al*. 2010). TGFBI processing was observed when ovarian cancer cells and peritoneal cells were in direct physical contact in culture or when the cells shared the same growth media in the indirect co-culture system (Ween *et al*. 2011). TGFBI processing did not occur when conditioned media from peritoneal cells was added to cultured ovarian cancer cell lines or when conditioned media from ovarian cancer cells was added to the cultured peritoneal cells. These findings suggest that TGFBI processing is regulated by a cross-talk mechanism between both ovarian cancer and peritoneal cells and is not mediated just by proteases expressed by ovarian cancer cells. We also showed that TGFBI cleavage in the ovarian cancer and peritoneal cell co-culture was mediated by plasmin (Ween *et al*. 2011). Plasmin activity was increased in the conditioned medium of co-cultured OVCAR-5 and LP-9 cells, whereas no plasmin activity could be detected in the conditioned medium collected from those cells cultured alone (Ween *et al*. 2011). Furthermore, plasmin cleaved TGFBI in the same region as observed in the ovarian cancer–peritoneal cell co-culture, and this could be inhibited by a cocktail of protease inhibitors, including serine protease inhibitors. It is likely that TGFBI expression and function in cancer cells appear to be cell type specific and are affected not only by TGFBI concentration but also by processing events by protease enzymes, which can liberate integrin-binding sites. As truncated forms of TGFBI have been well documented to have differing functions (Zamilpa *et al*. 2009, Irigoyen *et al*. 2010), it is likely that alterations in TGFBI processing in different cell types is an important factor contributing to the disparate findings in literature. Whether TGFBI functions as a tumour suppressor or tumour promoter may also be dependent on interactions between other ECM proteins and specific integrin receptors present in the tumour microenvironment. Our findings suggest that increased plasmin production and TGFBI cleavage are early events in the process of ovarian cancer metastasis. Further studies are required to investigate the role of cleaved TGFBI in ovarian cancer metastasis and develop therapeutic strategies to target TGFBI. Like fibronectin, TGFBI may also be targeted by integrin antagonists (Desgrosellier & Cheresh 2010). Other potential therapies to target TGFBI include TGFBI-blocking peptides (Nam *et al*. 2005), TGFBI siRNA as well as TGFBI-blocking antibodies (Ween *et al*. 2010, 2012). These strategies have not yet been tested in 3D or *in vivo* ovarian cancer models.

Role of periostin in ovarian cancer

Periostin (encoded by gene *POSTN*) is also a member of the FAS family and upregulated by TGFβ-like TGFBI (Horiuchi *et al*. 1999). Periostin is a unique ECM protein in collagen-rich connective tissues, such as periodontal ligament, periosteum, fascia of skeletal muscles and cardiac valve (Takeshita *et al*. 1993, Horiuchi *et al*. 1999, Kruzynska-Frejtag *et al*. 2001, 2004, Norris *et al*. 2007), and upregulated in a wide range of tumours including ovarian cancer (Gillan *et al*. 2002, Kudo *et al*. 2007, Morra & Moch 2011, Hong *et al*. 2013). Periostin is detected in the ascites of ovarian cancer patients (Gillan *et al*. 2002) and associated with late-stage disease and ovarian cancer relapse (Zhu *et al*. 2010). Periostin can increase the motility of the ovarian cancer cells and their adhesion to the peritoneum via integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ (Gillan *et al*. 2002). Recombinant periostin increased the adhesion and invasion of SK-OV-3 ovarian cancer and expression of MMP-2 (Choi *et al*. 2011). *TGFBI/POSTN* correlated genes could identify a subgroup of high-grade serous ovarian cancer patients with reduced OS (Karlan *et al*. 2014). *POSTN* was identified as a gene in the 'reactive stroma' gene signature that is associated with primary chemotherapy resistance and predicted shorter DFS after 1st-line chemotherapy (Ryner *et al*. 2015). Treatment with recombinant periostin promoted ES-2 cell resistance to both carboplatin and paclitaxel *in vitro* (Ryner *et al*. 2015). A recent study has shown stromal periostin and not tumour periostin is an independent predictor of OS and DFS in epithelial ovarian cancer (Sung *et al*. 2016). Using the CSIOVDB (Tan *et al*. 2015), *POSTN* expression was significantly increased in tumour stroma and peritoneal tumours compared with that in primary ovarian tumours. *POSTN* was highest in serous ovarian tumours compared with that in other subtypes and elevated in stage II-IV compared with stage I tumours. *POSTN* was also increased

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in grade 2 and grade 3 compared with grade 1 tumours and elevated in tumours resistant or refractory to 1st-line chemotherapy compared with sensitive tumours. Furthermore, *POSTN* was significantly correlated with an EMT score ($\rho = 0.32$, $P = 3.62 \times 10^{-84}$), and levels higher than the median were significantly associated with both OS ($P < 0.0001$) and DFS ($P < 0.0001$). Multivariate analysis showed that *POSTN* expression was an independent predictor of PFS and the highest *POSTN* expression was observed in the MES subtype.

Abundant periostin was produced by LP-9 mesothelial cells and no matching band appeared in the OVCAR-5 or SKOV-3 ovarian cancer CM (band 3, Fig. 1C). These findings suggest that periostin is also cleaved like TGFBI in co-cultured ovarian cancer–LP-9 cells. Unlike fibronectin and TGFBI, periostin cleavage has not been described previously. The function of cleaved periostin is not known, and further studies are required to investigate its role in ovarian cancer metastasis. Potential therapies to target periostin include periostin siRNA and a periostin blocking antibody (MZ-1) which inhibited intra-peritoneal metastasis of A2780 tumour cells (Zhu *et al.* 2011). Further studies are required to investigate the ability of periostin-blocking antibodies to inhibit the growth and invasion in additional *in vivo* ovarian cancer models.

Role of annexin A2 in ovarian cancer

Annexin A2 (encoded by gene *ANXA2*) is a phospholipid and calcium-binding protein, which is involved in actin and cytoskeleton regulation (Hayes *et al.* 2006) and serves as a receptor for ECM proteins such as collagen I, cathepsin B, tissue plasminogen activator (t-PA) and plasminogen (Mai *et al.* 2000). It is found in a range of cells such as endothelial cells, epithelial cells and tumour cells (Mai *et al.* 2000) and exists as a 36 kDa monomer in the cytoplasm or a 94 kDa protein in cell membrane, which contains two annexin A2 monomers and two 11 kDa molecules known as p11 or s100A10 (Gerke & Moss 2002).

Annexin A2 hetero-tetramer plays an important role in the plasminogen–plasmin pathway and annexin A2 acts as a t-PA receptor on the surface of endothelial and cancer cells, which activates the conversion of plasminogen into plasmin (Cesarman *et al.* 1994, Kassam *et al.* 1998*a*) and facilitates ECM degradation leading to enhanced cell migration (Balch & Dedman 1997), invasion (Diaz *et al.* 2004), angiogenesis (Ling *et al.* 2004) and metastasis (Mai *et al.* 2000) (Fig. 2). Plasminogen serves as a binding site for annexin A2 at lysine 307 in endothelial cells (Cesarman *et al.* 1994) and S100A10 protein at lysine residues at the carboxyl terminal in epithelial cells (Kassam *et al.* 1998*b*), which results in plasmin production. Annexin A2-dependent plasmin generation has been demonstrated to be essential for the invasion and migration of invasive breast cancer cells (Sharma *et al.* 2006). Annexin A2 increases cancer cell proliferation and cell survival via the ERK1/2 and MAPK pathway (Shiozawa *et al.* 2008) and is a substrate for src kinase and regulates tyrosine 23 phosphorylation of annexin A2 to enhance cancer cell invasion (Zheng *et al.* 2011). Annexin A2 also plays a role in actin cytoskeletal rearrangement and regulates cancer cell migration (Zhao *et al.* 2010).

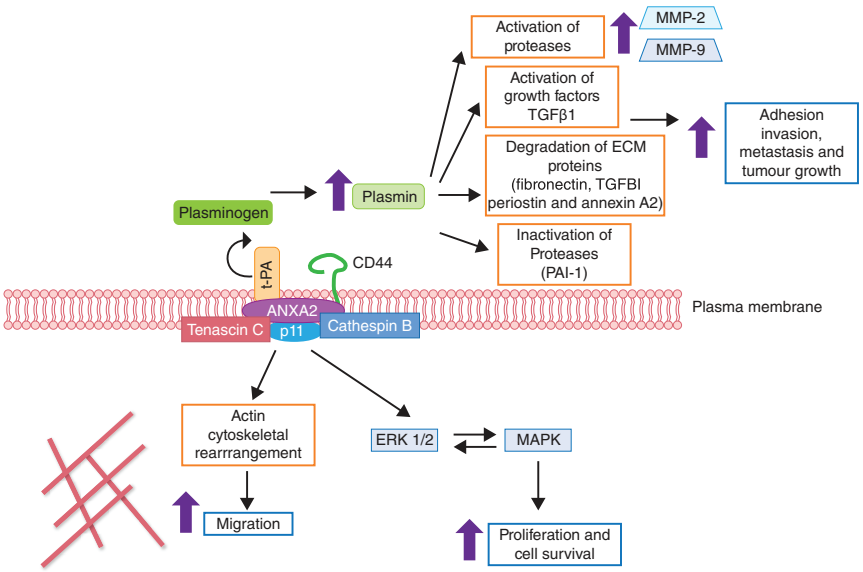

Figure 2
Role of annexin A2 in the activation of the plasminogen–plasmin system. Annexin A2 with p11 protein (S100A10) forms an annexin A2 heterotetramer complex on the plasma membrane which co-localise with CD44, tenascin-C, cathepsin B and tissue plasminogen activator (t-PA). Annexin A2-mediated t-PA-dependent plasmin generation leads to the activation of growth factors, activation of proteases including MMPs, inactivation of proteases (PAI-1), degradation of extracellular matrix (ECM) proteins including fibronectin, TGFBI, periostin and annexin A2, which all act to increase cancer cell adhesion invasion, metastasis and tumour growth. Annexin A2 also increases cancer cell proliferation and cell survival via the ERK1/2 and MAPK pathway and plays a role in actin cytoskeletal rearrangement and regulates cancer cell migration.

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Overexpression of annexin A2 has been demonstrated in several cancer types such as breast, pancreas, colorectal and prostate cancer (reviewed in Lokman *et al*. 2011). Annexin A2 mRNA is upregulated 3-fold in metastatic ovarian cancer tissues compared with that in normal ovarian tissue (Tchagang *et al*. 2008). A proteomic study reported that annexin A2 was upregulated in ovarian cancer cell lines with high invasive capacity compared with those with low invasive capacity (Sodek *et al*. 2008), and annexin A2 expression is increased in ovarian cancer tissues compared with that in the normal tissues (Tchagang *et al*. 2008, Zhuang *et al*. 2015). We have recently shown that annexin A2 is highly expressed in 90% of serous ovarian cancers and actively involved in the process of ovarian cancer metastasis (Lokman *et al*. 2013). Furthermore, stromal annexin A2 but not tumour annexin A2 was found to be an independent predictor of OS in serous ovarian cancer patients (Lokman *et al*. 2016). Examining *ANXA2* expression using Kaplan–Meier plotter (Gyorffy *et al*. 2012), we found that high *ANXA2* mRNA levels in stage III serous ovarian cancers were associated with the MES subtype, reduced PFS ($P=0.023$) and OS ($P=0.038$) (Lokman *et al*. 2016). Using the recently described CSIOVDB that does not distinguish ovarian cancer histological subtypes (Tan *et al*. 2015), we confirmed that *ANXA2* expression was significantly increased in tumour stroma and peritoneal tumours compared with that in primary ovarian tumours. However, *ANXA2* expression was not associated with OS or DFS using median or 4th quartile as cut points in this database. These findings highlight the importance of looking at both protein and mRNA levels as well as ovarian cancer subtype and cellular localisation to assess the relationship of potential prognostic markers with patient outcome.

Peptide analysis of the annexin A2 protein spots identified in the co-culture CM samples failed to identify any annexin A2 peptides in the N-terminal domain (amino acid 1-35) (Ween *et al*. 2010). These findings suggest that there is cleavage of annexin A2 in the N-terminal domain as a result of the co-culture interactions. The N-terminal domain of annexin A2 consists of multiple phosphorylation sites including a tyrosine at position 23 (Bellagamba *et al*. 1997) and Ser^{25} (Gould *et al*. 1986). Cleavage of annexin A2 at the N-terminal domain by plasmin has been reported in monocytes (Laumonnier *et al*. 2006) and endothelial cells (Kassam *et al*. 1998*b*) resulting in loss of the first 27 amino acid residues and a band at approximately 33–34 kDa similar to that seen in our co-culture study (Ween *et al*. 2010). Matrilysin (MMP-7) cleaves annexin A2 at Lys^{10} in the N-terminal, which results in a truncated 35 kDa form of annexin A2 (Tsunezumi *et al*. 2008). Tsunezumi and coworkers reported that the first 9 amino acids of annexin A2 bound to the t-PA molecule more efficiently than intact annexin A2 and could assist in tumour invasion and metastasis of colorectal and breast cancer cell lines (Tsunezumi *et al*. 2008). Binding sites of the S100A10 proteins and t-PA have been identified in the N-terminal domain of annexin A2 at the amino acids residues 1–14 and 8–13, respectively (Kube *et al*. 1992, Cesarman *et al*. 1994). Recent data suggest that annexin A2 does not bind plasminogen directly but rather acts to transport S100A10 to the cell surface (Madureira *et al*. 2011, Bydoun & Waisman 2014). Our findings suggest that the extracellular form of annexin A2 found in the cancer-associated stroma in the ovarian cancer tissues may represent a cleaved and secreted form of annexin A2, which may assist in ovarian cancer progression and metastasis. As annexin A2 lacks a signal peptide and is not secreted via the endoplasmic reticulum pathway, the mechanism that regulates annexin A2 secretion remains unknown. Further studies are required to investigate the functional role of cleaved annexin A2 in ovarian cancer. Targeting the annexin A2 signalling pathway with annexin A2 neutralising antibodies is a promising strategy to inhibit ovarian cancer invasion and metastasis (Lokman *et al*. 2013).

Alternative strategies to target annexin A2 signalling are treatment with all-trans retinoic acid (ATRA) or plasmin inhibitors such as tranexamic acid. ATRA, an active metabolite of vitamin A, is currently used clinically for acute promyelocytic leukaemia (APL) to improve bleeding symptoms caused by excessive plasmin production seen in this condition (Olwill *et al*. 2005). ATRA has been shown to inhibit annexin A2 and S100A10 expression in leukaemic cells (Olwill *et al*. 2005) and is a promising compound for the treatment of a variety of cancers because of its low toxicity.

Tranexamic acid, a synthetic derivative of the amino acid lysine, is an anti-fibrinolytic agent that blocks plasmin production and prevents the dissolution of fibrin clots (Mezzano *et al*. 1999). It is used clinically to reduce bleeding during surgery and is also an established treatment for gynaecological bleeding disorders such as heavy menstrual bleeding and postpartum haemorrhage (McCormack 2012). Tranexamic acid is generally well tolerated and has a favourable safety profile. Further studies are required to test the ability of annexin A2-blocking antibodies, ATRA and plasmin inhibitors including tranexamic acid to inhibit ovarian cancer

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growth and invasion in both 3D and *in vivo* models of ovarian cancer.

Role of PAI-1 in ovarian cancer

PAI-1 (encoded by gene *SERPINE1*) belongs to the superfamily of the serine protease inhibitors (serpins) and functions as an inhibitor of both t-PA and urokinase plasminogen activator (u-PA), which converts plasminogen to its active form plasmin (van Mourik *et al*. 1984, Adams *et al*. 1991, Kwaan & McMahon 2009). Plasmin primarily functions to degrade not only fibrin clots but also ECM molecules either directly or indirectly by activating MMPs (Didiasova *et al*. 2014). Plasmin proteolysis contributes to both physiological processes such as tissue remodelling and pathological processes including cancer invasion and metastasis (Castellino & Ploplis 2005).

As PAI-1 inhibits plasmin generation, it would be expected to be reduced in cancers; however surprisingly, PAI-1 is increased in most cancers including ovarian cancer and increased levels of both PAI-1 and u-PA are associated with reduced ovarian cancer survival (Kuhn *et al*. 1994, Konecny *et al*. 2001, Mashiko *et al*. 2015). To date, the molecular mechanism of this paradox has not been explained (Didiasova *et al*. 2014) and may be due the incomplete understanding of the complex plasminogen–plasmin system and its interactions with other factors in tumours (Kwaan *et al*. 2013). There is considerable controversy in the literature with some studies demonstrating PAI-1 is required for tumour growth (McMahon & Kwaan 2015) and tumour adhesion (Palmieri *et al*. 2002), whereas others have found it to inhibit tumour cell binding to the ECM (Czekay *et al*. 2003). The effect of PAI-1 on tumour growth is likely to be dependent on its abundance (McMahon *et al*. 2001), but it appears that PAI-1 also has functions which are independent of the of plasminogen–plasmin system (Czekay & Loskutoff 2009). PAI-1 knockdown resulted in reduced growth and increased apoptosis of ovarian cancer cell lines, and a small molecule inhibitor of PAI-1 (TM5275) blocked the proliferation of ovarian cancer cells with high PAI-1 expression (Mashiko *et al*. 2015).

Using CSIOVDB (Tan *et al*. 2015), *SERPINE1* expression was significantly increased in tumour stroma and peritoneal tumours compared with that in primary ovarian tumours. *SERPINE1* was the highest in mucinous-LMP compared with other subtypes and elevated in stage II-IV compared with stage I tumours. *SERPINE1* was also increased in grade 2 and grade 3 that that in grade 1 tumours. Furthermore, *SERPINE1* was significantly correlated with an EMT score ($\rho=0.317$, $P=6.86\times10^{-81}$), and levels higher than median were significantly associated with both OS ($P=0.001$) and DFS ($P=0.0013$). The highest *SERPINE1* expression was observed in the MES subtype, and in this subtype, increased *SERPINE1* expression was associated with reduced DFS ($P=0.039$).

We found that full-length PAI-1 was present in LP-9 culture (band 5, Fig. 1C), but PAI-1 was cleaved at the Arg^{346}-Met^{347} position in both direct and indirect ovarian cancer–peritoneal cell co-culture (Table 1). Cleavage at this site by the prostatic serine protease human kallikrein 2 has been shown to inactivate PAI-1 and prevent the inactivation of u-PA and t-PA (Mikolajczyk *et al*. 1999). A previous study found that HRA ovarian cancer conditioned media was able to stimulate PAI-1 production but did not affect u-PA levels in mesothelial cells (Hirashima *et al*. 2003). Ovarian cancer cells also produce a range of kallikreins, which are known to stimulate the plasminogen conversion to plasmin (Shih Ie *et al*. 2007). It is possible that a kallikrein produced by ovarian cancer cells may influence ovarian cancer cell–mesothelial cell interactions and the extracellular proteolytic cascade by several mechanisms, which include (1) inhibition of PAI-1 and (2) activation of u-PA, which results in (3) increased plasmin production in the ovarian cancer–peritoneal cell co-culture and leads to (4) ECM processing and enhanced metastasis. Targeting PAI-1 in the peritoneal microenvironment is a promising approach to inhibit ovarian cancer metastasis but needs further evaluation. To date, the small molecule inhibitor of PAI-1 (TM5275) has only been tested on ovarian cancer cells *in vitro* (Mashiko *et al*. 2015).

Summary and Conclusions

Our study of the ovarian cancer peritoneal interaction has highlighted a key link between the annexin A2 signalling pathway and the activation of the plasminogen–plasmin system (Fig. 2). When we co-cultured peritoneal cells with ovarian cancer cells, whether in direct physical contact or indirect co-culture in which both cell types shared the same media, we observed that a proteolytic response was triggered by the interaction between ovarian cancer and peritoneal cells. A number of ECM proteins including fibronectin, TGFBI, periostin, annexin A2 and PAI-1 were processed by the ovarian cancer–peritoneal cell interaction (Fig. 2). Interestingly, mRNA levels of these proteins can predict ovarian cancer outcome and are all elevated in the MES ovarian cancer subtype, the most metastatic and subtype with the poorest prognosis. Furthermore, these proteins can all be cleaved either directly by plasmin or

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indirectly via MMP activation. We have confirmed that TGFBI and annexin A2 can be processed by plasmin, which is also increased by the ovarian cancer–peritoneal cell interaction (Ween *et al*. 2010, Lokman *et al*. 2013). Although the function of processed forms of periostin and annexin A2 is not known, truncated forms of fibronectin, TGFBI and PAI-1 have been documented to have differing functions (Mikolajczyk *et al*. 1999, Kenny *et al*. 2008, Zamilpa *et al*. 2009, Irigoyen *et al*. 2010).

Emerging evidence indicate that annexin A2 and S100A10 play a significant role in the plasminogen–plasmin system and the interaction among annexin A2, S100A10 and t-PA mediates the conversion of plasminogen to plasmin, which facilitates MMP activation, growth factor activation and ECM degradation all leading to enhanced cancer cell migration and invasion (Fig. 2). Together with published literature our recent findings add to our understanding of the interaction between ovarian cancer and peritoneal cells and suggest that increased plasmin production and ECM cleavage are early events in the process of ovarian cancer metastasis. It has been well recognised that proteolysis of ECM proteins can release ECM fragments called matrikines, which exert differing biological activities than native proteins (Ricard-Blum & Salza 2014). Matrikines have been shown to trigger pro-tumourigenic activity as well as anti-tumourigenic and anti-angiogenic effects and thus have been investigated as novel biomarkers and anti-cancer agents (Ricard-Blum & Salza 2014). A greater understanding of the interactions between ECM fragments and other interacting proteins in the plasminogen–plasmin system will help decipher the molecular mechanisms regulating peritoneal metastasis. Potential therapies to target the ECM molecules in this review are highlighted in Table 1. Targeting the annexin A2 signalling pathway with annexin A2-neutralising antibodies (Lokman *et al*. 2013) or the plasminogen–plasmin system with plasmin inhibitors to inhibit proteolytic responses triggered by the peritoneal–ovarian cancer cell interaction is a promising strategy to inhibit ovarian cancer metastasis.

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

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