REVIEW

Inflammatory events in endometrial adenocarcinoma

Alison E Wallace, Douglas A Gibson, Philippa T K Saunders and **Henry N Jabbour**

MRC Human Reproductive Sciences Unit, The Queen's Medical Research Institute, Centre for Reproductive Biology, 47 Little France Crescent, Edinburgh EH16 4TJ, UK

(Correspondence should be addressed to H N Jabbour; Email: h.jabbour@hrsu.mrc.ac.uk)

Abstract

Endometrial adenocarcinoma is the most common gynaecological malignancy in western countries. Many of the established risk factors for developing endometrial cancer are associated with excess exposure to oestrogen unopposed by progesterone. These include nulliparity, late onset of the menopause, post-menopausal hormone replacement therapy and obesity. However, a number of risk factors also promote inflammation, another feature proposed to influence cancer development. The human cycling endometrium undergoes regular and cyclical episodes of inflammation. Moreover, hormonal and genetic changes that occur early in the development of endometrial adenocarcinoma can exacerbate the local inflammatory environment. Via alterations in the expression of local mediators and immune cell function, these may contribute to the development of endometrial cancer. This review discusses the contribution of inflammation to the initiation and progression of endometrial adenocarcinoma. Manipulation of inflammatory pathways may therefore represent a therapeutic target in endometrial adenocarcinoma.
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Introduction

Endometrial adenocarcinoma, the neoplastic growth of endometrial epithelial cells, is the most common gynaecological malignancy in western, developed, countries (Doll *et al.* 2008). Post-menopausal women are mainly affected, with ~86% of patients being over 50 years of age (Akhmedkhanov *et al.* 2001). The risk factors associated with endometrial adenocarcinoma include nulliparity (Albrektsen *et al.* 1995), late menopause onset (Kalandidi *et al.* 1996) and use of oestrogen-only hormone replacement therapy (HRT) (Grady *et al.* 1995, Beral *et al.* 2005, Karageorgi *et al.* 2010). Notably, a high body mass index increases the risk of developing endometrial cancer, and these patients have a poorer prognosis (Bergstrom *et al.* 2001, Gates *et al.* 2006, Rieck & Fiander 2006, Reeves *et al.* 2007). A shared feature of these risk factors is an increased or prolonged exposure to oestrogens. This has led to the 'unopposed oestrogen hypothesis' to explain the development of endometrial adenocarcinoma. This proposes that an exposure to high oestrogen and low progesterone levels increases proliferation of endometrial cells, and therefore the risk of cancer development (Akhmedkhanov *et al.* 2001). However, a number of risk factors associated with the development of endometrial adenocarcinoma also promote another process implicated in the development of cancers – namely inflammation.

The concept that cancer and inflammation are linked was suggested as far back as the 19th century by Virchow. After observing leukocyte influxes in cancers of tissues that had experienced chronic inflammatory conditions, he suggested that the leukocytes may be the cause of tumour growth (reviewed in Balkwill & Mantovani (2001)). Inflammatory pathways have now been proposed to influence cancer development by two mechanisms, termed the intrinsic and extrinsic pathways (Colotta *et al.* 2009, Mantovani *et al.* 2009). In the former, after the initiation of cancer by genetic mutations, the expression of inflammatory agents is increased, leading to the promotion of tumour growth. In the extrinsic pathway, current inflammatory conditions lead to the initiation of cancer.

Epidemiological data have strengthened the extrinsic inflammatory hypothesis of cancer initiation, as inflammatory diseases have been shown to predispose sufferers to certain types of cancer. For example, inflammatory bowel disease is associated with an increased risk of colon cancer (Flossmann & Rothwell 2007), prostatitis is associated with an increased risk of prostate cancer (Sandhu 2008) and infection with certain microbes can lead to increased risk of gastric cancer (Suzuki *et al.* 2009). Additionally, long-term intake of non-steroidal anti-inflammatory drugs (NSAIDs) in 'at risk' patients significantly reduces cancer incidence (Dannenberg & Subbaramaiah 2003, Flossmann & Rothwell 2007). The alternative intrinsic pathway hypothesis states that after cancer development, production of inflammatory mediators by cells is an ensuing feature that promotes tumour progression. The resulting inflammatory milieu comprises

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inflammatory mediators such as cytokines and prostaglandins, leukocytes, and extensive tissue remodelling including angiogenesis. This hypothesis is strengthened by studies inhibiting inflammatory conditions in tumours. In numerous *in vivo* models of cancer, prevention of cytokine signalling leads to a decrease in tumour growth or even tumour regression (Sparmann & Bar-Sagi 2004, Loberg *et al.* 2007, Singh *et al.* 2009*b*). Furthermore, trials of antagonists of the pro-inflammatory cytokine tumour necrosis factor (TNF) in renal cancer patients have produced promising prognostic results at 12 months (Harrison *et al.* 2007). These studies support the hypothesis that inflammatory pathways occurring in tumours can promote cancer growth.

In this review, the contribution of inflammation to the initiation and progression of endometrial adenocarcinoma will be discussed. The concept that the normal cycling endometrium can be considered as a site of regular, repeated, inflammation will be considered, as will aspects of this process that may contribute to cancer development. Additionally, hormonal and genetic changes which occur early in the development of endometrial adenocarcinoma and lead to an upregulation of inflammatory mediators will be outlined.

Clinical characteristics of endometrial adenocarcinoma

Endometrial tumours are histologically classified into well-, moderately or poorly differentiated cancers, based on tissue architecture and the amount of solid tumour present (Ellenson & Wu 2004). In 1983, it was proposed that endometrial adenocarcinoma can be broadly divided into two types (Bokhman 1983). Type I endometrial adenocarcinoma is associated with patients displaying increased oestrogen levels and hyperlipidaemia, and is often related to obesity. These tumours are the most common, occurring in ~85% of patients, and they generally display low invasion with a good prognosis. These are usually classified as well- or moderately differentiated tumours; however, they can progress to become invasive and poorly differentiated. Type II endometrial adenocarcinoma is independent of oestrogen stimulation, and these are more aggressive, poorly differentiated tumours with a morphology consisting of cells growing in papillary patterns (Hendrickson *et al.* 1982). This dualistic model has been strengthened by more recent studies demonstrating that the two types of endometrial adenocarcinoma can be divided not only by morphology but also by genetic mutations (Tashiro *et al.* 1997, Lax *et al.* 2000, Catasus *et al.* 2009). There are overlapping features between the two types; however, due to its prevalence, most data discussed herein focus on type 1 endometrial adenocarcinoma.

Inflammation in the normal menstrual cycle

The uterus is a uniquely dynamic organ, and the endometrial lining is a highly specialised tissue consisting of a 'functional' layer closest to the uterine lumen supported by a basal layer adjacent to the myometrium. In pre-menopausal women, the endometrium undergoes regular cycles of proliferation, angiogenesis and differentiation in response to cyclical changes in sex steroid hormones (oestrogen and progesterone) secreted by the ovary. If implantation of an embryo does not occur during the progesterone-dominated secretory phase, the functional layer is shed as a consequence of the demise of the corpus luteum. This results in a decline in progesterone and menses occur (Jabbour *et al.* 2006). The human menstrual cycle was first explicitly likened to an inflammatory wound healing process in 1986 by Finn, who described the similarities of the two processes. These include increased blood flow and vessel permeability, the differentiation (decidualisation) of stromal tissue, which resembles the granulation tissue of wound healing, and the infiltration of immune cells (Finn 1986). Subsequent evidence has strengthened this analogy by examining in more detail the tissue remodelling, cytokine expression and leukocyte influxes that occur in the human endometrium (Salamonsen 2003, Jabbour *et al.* 2006). In the process of wound healing, an infiltration of leukocytes in response to cytokine production occurs before the re-growth of tissue mediated by growth factors such as epidermal growth factor (EGF) and platelet-derived growth factor. Angiogenesis is mediated by local mediators including vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF; Barrientos *et al.* 2008). In the normal menstrual cycle, these events are mirrored by the influx of leukocytes at the time of tissue breakdown at menstruation, and the re-growth of the endometrium during the proliferative phase under the control of the same growth factors and angiogenic mediators (Critchley *et al.* 2001*a*).

At menstruation, degradation of the extracellular matrix occurs, and the upper layer of the endometrium is shed, drawing comparisons to tissue injury. The most notable inflammatory aspect of menstruation is the large influx of immune cells that comprise uterine natural killer (NK) cells, macrophages, neutrophils and eosinophils (Critchley *et al.* 1999). Immune cells are crucial in the process of menstruation, as demonstrated by the irregular endometrial breakdown and repair in a mouse model deficient in neutrophils (Kaitu'u-Lino *et al.* 2007). Inflammatory chemokines such as macrophage inflammatory protein-1α are released from the denuded epithelium during menstruation, and this may promote infiltration of macrophages, which then contribute to the tissue destruction and promotion of apoptosis seen at menstruation (Akiyama *et al.* 1999). In wound healing or inflammatory situations, the similar infiltration of leukocytes such as macrophages and neutrophils acts to breakdown the extracellular matrix by phagocytosis of cell and matrix material (Uutela *et al.* 2004).

The endometrium then enters the proliferative phase of the menstrual cycle, which starts on days 2–3 of the menstrual cycle, and is a period of tissue remodelling. This phase entails the growth of the endometrium in response to rising

concentrations of oestrogen and a number of locally produced angiogenic and growth factors. These include chemokines such as interleukin 8 (IL8), which is expressed in the epithelial cells (Arici *et al.* 1998) and perivascular cells (Critchley *et al.* 1994). Macrophage chemoattractant protein-1 is also produced in the stroma and perivascular cells (Jones *et al.* 1997). CCL5 (also known as RANTES) is chemotactic for monocytes and activated T cells, and is expressed in the proliferative endometrial stroma (Hornung *et al.* 1997). The upregulation of these cytokines causes the infiltration of macrophages and neutrophils seen at this stage of the cycle (Kelly *et al.* 1994). Macrophages are able to secrete growth factors such as EGF (Schultz *et al.* 1991) and heparin-binding EGF (Edwards *et al.* 2009) and so may contribute to endometrial re-growth by this mechanism. Macrophages also produce a range of angiogenic factors (Lin *et al.* 2006) including VEGF in the endometrium (Gargett *et al.* 2001). Neutrophils at this stage of the cycle are observed adjacent to the vasculature, and produce VEGF, and therefore may be involved in vascular remodelling (Gargett *et al.* 2001). These factors are also all produced to orchestrate wound healing in inflammatory situations (Barrientos *et al.* 2008).

The secretory phase of the menstrual cycle follows the proliferative phase, and in the mid-secretory phase, the endometrium is receptive to embryo implantation. A number of cytokines are up-regulated during this phase, including IL11 (Dimitriadis *et al.* 2000), leukemia inhibitory factor (Cullinan *et al.* 1996) and IL6 (Tabibzadeh *et al.* 1995). These factors are thought to aid adhesion and invasion of the blastocyst into the endometrium (Marwood *et al.* 2009). Increased permeability of the endometrial vasculature is reported in many animal species to facilitate implantation (Rowe *et al.* 2003, Pakrasi & Tiwari 2007).

The inflammatory nature of the normal menstrual cycle is therefore reflected by chemokine expression by endometrial cells and leukocyte infiltration into the endometrium. As described, chronic inflammatory conditions in tissues have been demonstrated to predispose to cancer (Flossmann & Rothwell 2007, Sandhu 2008, Suzuki *et al.* 2009). The local regulation of the molecular pathways that contribute to exacerbated angiogenesis and immune cell function in endometrial cancer remains largely unidentified. Understanding how inflammation and its resolution are tightly controlled in normal endometrial events such as menstruation may help shed some insight about the molecular events that lead to their exacerbated activities in cancer.

Hormones and inflammation in endometrial adenocarcinoma

Oestrogen and progesterone signalling

In addition to circulating steroid hormones, evidence for local biosynthesis of oestrogens associated with the expression of enzymes such as CYP19A1 (aromatase) has been documented in endometrial carcinomas (Bulun *et al.* 1994). Oestradiol (OE_2) has been measured in tumour tissues and correlated with the rate of tumour invasion in both pre- and post-menopausal women (Berstein *et al.* 2003). Steroid hormone action is classically mediated by receptors that act as ligand-activated transcription factors. Oestrogen and progesterone can each bind two main receptor isoforms oestrogen receptor (ESR1) and ESR2, and progesterone receptor A (PGRA) and PGRB, respectively. Expression of ESRs in normal pre-menopausal endometrium has been well documented with the expression of ESR1 being intense in both glands and stroma during the proliferative, oestrogen-dominant phase but reduced in the secretory phase following the post-ovulatory rise in progesterone (Critchley *et al.* 2001*b*). Oestrogen promotes endometrial proliferation (Ferenczy *et al.* 1979) and vascularisation (Hastings *et al.* 2003). Studies using mice with targeted deletion of the ESR1 gene have reported that this subtype plays an essential role in uterine cell proliferation and expression of the progesterone receptor gene (reviewed in Couse & Korach (1999)). Additionally, studies in cell lines have suggested that ESR2 acts as an inhibitory modulator of ESR1-stimulated gene transcription (Hall & McDonnell 1999), and differential activation of reporter genes by ESR1 and ESR2 in response to selective ESR modulators (SERMs) has been described (Paech *et al.* 1997). The net action of oestrogen or SERMs on endometrial gene expression and cell proliferation will therefore be influenced both by the pattern of expression of ESR subtypes and the relative levels of expression of ESR1 and ESR2 in cells where they are co-expressed. Notably gene array analysis has identified specific differences in the response of primary endometrial cells to OE_2 and tamoxifen (a SERM frequently used in the treatment of breast cancer) with the latter most closely resembling gene expression patterns in malignant endometrium (Pole *et al.* 2005). It has been reported that total concentrations of ESR2 mRNAs decrease in the post-menopausal endometrium (Jazaeri *et al.* 2001) which might make post-menopausal endometrium more sensitive to oestrogens through unopposed ESR1 action. An imbalance in ESR isoform expression could therefore have a significant effect in oestrogen-driven hyperplasia and tumourigenesis especially if this occurred in parallel with anovulatory cycles such as during the menopausal transition (Hale *et al.* 2002).

In premenopausal women, activation of PGR during the secretory phase of the cycle results in reduced endometrial proliferation. If progesterone biosynthesis is inadequate, the endometrium can become hyperplastic, and this increases the risk of developing endometrial adenocarcinoma. Expression of PGR is under the control of both oestrogen and progesterone, which induce PGR synthesis and downregulate PGR expression respectively (Horwitz & McGuire 1978, Alexander *et al.* 1989). The two PGR isoforms have distinct functions. PGRA acts as a transcriptional repressor, and has a major role in the endometrium by inhibiting oestrogen-induced proliferation. PGRB has an

activating role in the endometrium by acting as an endometrial oestrogen agonist (Doll *et al.* 2008).

Expression of ESRs and PGR in endometrial cancer is grade dependent, and decreased expression of ESR1 and PGR in poorly differentiated cancers has been documented, even though the expression of ESR2 is maintained (Hanekamp *et al.* 2003, Collins *et al.* 2009). Notably, expression of PGR is associated with better disease-free survival (Ito *et al.* 2007). Expression of PGR is downregulated in more aggressive tumours, such as malignant mixed Mullerian tumours (5% of all endometrial cancers), that do not respond to endocrine treatment. The ratio of PGR isoform expression is important as alterations may precede changes leading to endometrial carcinoma. For example, an increase in PGRB due to a polymorphism in PGR promoter alters PGR isoform ratio, and is associated with an increased risk of developing endometrial cancer (Doll *et al.* 2008). Loss of PGR expression is associated with late-stage disease that is unresponsive to progesterone treatment. Progesterone has been shown in the PGR-expressing Ishikawa cell line to downregulate genes involved in invasion and metastasis such as *CD44*, and *CSPG/Versican*, which are upregulated in endometrial tumours that lack PGR. Therefore, progesterone exposure and receptor expression can affect tumour cell invasion and metastasis (Hanekamp *et al.* 2003).

Oestrogen, progesterone and inflammation

Homeostasis in reproductive tissues requires integration of the hormonal signals described above and inflammatory signals. Pro-inflammatory signals can switch repressed steroid hormone receptors into transcriptional activators (Brosens *et al.* 2006). Oestrogens can influence inflammatory processes, although their role is recognised as complex and cell context dependent (reviewed in Straub (2007)). For example, oestrogens are associated with decreased severity of inflammatory disease symptoms during pregnancy, but women also show an increased incidence of autoimmune disease, indicating that pro-inflammatory functions of female sex hormones also exist (Nilsson 2007). In the normal endometrium, oestrogen upregulates the expression of a number of inflammatory cytokines including IL6 (Jacobs *et al.* 1992). Production of this cytokine, in both the KLE and RL95 endometrial adenocarcinoma cell lines after oestrogen stimulation, has also been demonstrated (He *et al.* 2009). Other inflammatory mediators upregulated by oestrogen include IL1, TNF-α, and matrix metalloproteinases (MMPs) (Modugno *et al.* 2005, He *et al.* 2009), and IL1B can enhance the actions of oestrogen (King *et al.* 2009). Oestrogen can also activate nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) signalling in endometrial cancer, a key transcription factor regulating the expression of many inflammatory mediators (Seo *et al.* 2004). The potential interactions of oestrogen and inflammatory signals are summarised in Fig. 1.

Progesterone can negatively influence production of a number of inflammatory mediators. A number of *in vitro* studies demonstrate that progesterone can inhibit cytokine release from murine and human uterine cells (Ito *et al.* 1994, Kelly *et al.* 1994, 1997). Many of these cytokines are under the control of NFκB. For example, in the Hec50co poorly differentiated endometrial adenocarcinoma cell line, progesterone inhibits NFκB activation by inducing accessory proteins which form a complex, inhibiting NFκB activity

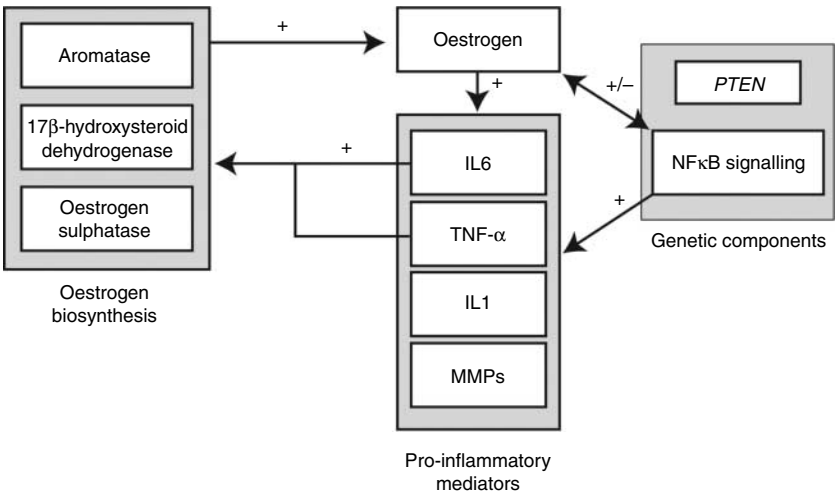

Figure 1 Interactions between oestrogen, inflammatory mediators and genetic aspects of endometrial adenocarcinoma. Oestrogen stimulates the production of pro-inflammatory mediators such as IL6 and TNF-α, which in turn can stimulate oestrogen biosynthesis. Both oestrogen and *PTEN* mutation can also stimulate NFκB activity, further promoting inflammation. Thus, oestrogen-mediated stimulation of pro-inflammatory factors and activation of NFκB signalling can promote a pro-oestrogen, pro-inflammatory state.

(Davies *et al.* 2004). *In vivo* data have demonstrated that mice lacking PGR have increased inflammatory responses in the uterus, with an increased infiltration of leukocytes and extensive tissue remodelling (Lydon *et al.* 1995). Progesterone also stimulates the production of prostaglandin dehydrogenase and inhibits cytokine-induced transcription of cyclooxygenase2 (*COX2*), thereby reducing prostaglandin production and consequent inflammation (Ishihara *et al.* 1995, van der Burg & van der Saag 1996) Therefore, as endometrial adenocarcinoma is characterised by increased oestrogen to progesterone signalling, an increase in inflammatory mediators may occur, thus promoting tumour growth.

The pro-inflammatory milieu in endometrial cancer can also directly increase oestrogen production (Modugno *et al.* 2005). IL6 can stimulate oestrogen synthesis and can act synergistically with TNF-α to increase aromatase, 17β-hydroxysteroid dehydrogenase and oestrone sulfatase activity, thus increasing local oestrogen biosynthesis (Modugno *et al.* 2005, Salama *et al.* 2009). TNF-α increases local oestrogen biosynthesis in human endometrial glandular epithelial cells and directs oestrogen metabolism to produce more hormonally active and carcinogenic metabolites. Thus, TNF-α can act as a potential auto- and paracrine regulator of endometrial steroidogenesis (Salama *et al.* 2009).

Oestrogen metabolites can influence uterine activity in different ways. 16α-Hydroxylation and 4-hydroxylation metabolites are potent oestrogens in the uterus, whereas 2-hydroxylation products such as 2-hydroxyoestradiol and 2-methoxyoestradiol do not stimulate the uterus (Martucci & Fishman 1977). 2-Methoxyoestradiol may even be protective in the uterus as it seems to inhibit tumour growth, induce apoptosis as well as inhibiting inflammatory cytokines IL6 and TNF-α production (Purohit *et al.* 1999, Purohit & Reed 2002). Oestrogen metabolism could therefore affect endometrial cancer risk depending on which pathways are favoured. Smoking is associated with a shift to 2-hydroxylation pathway (Michnovicz *et al.* 1986) which produces metabolites that do not stimulate uterine growth and may inhibit tumour growth. This may account for some of the protective effect that is associated with smoking and endometrial cancer.

Therefore, endometrial cancer is characterised by alterations in steroid receptor isoform expression leading to an increased ratio of oestrogen to progesterone signalling. This can promote endometrial proliferation and increase inflammatory mediators, leading to the promotion of tumour growth.

Androgens

Polycystic ovarian syndrome is a common condition associated with elevated circulating androgens. A recent systematic review (Chittenden *et al.* 2009) reported that women with PCOS are more likely to develop endometrial and ovarian cancers. Androgen receptors (ARs) are expressed in the endometrium throughout the menstrual cycle, with highest concentrations in stromal fibroblasts during the proliferative phase and upregulation in the expression in epithelial cells coincident with progesterone withdrawal (Critchley & Saunders 2009). Overexpression of AR and steroid co-activators in the endometrium of women with polycystic ovarian syndrome has been described (Giudice 2006). It has been suggested that CAG repeat polymorphisms in the first exon of the AR gene could be associated with increased endometrial cancer risk due to reduced capacity of AR to recruit coregulators and transcriptional components (McGrath *et al.* 2006), although this has been disputed (Ju & Kim 2007, Yang *et al.* 2009). Expression of AR and 5α-reductase type 1 and type 2 enzymes has been detected in 88 and 80% of endometrial adenocarcinomas respectively (Ito *et al.* 2002). As overexpression of aromatase has been reported to occur in 50% of endometrial adenocarcinomas, testosterone may act directly to modulate cell activity but also following conversion to dihydrotestosterone (DHT) or OE_2 (Ito *et al.* 2002). In the Ishikawa endometrial adenocarcinoma cell line, expression of AR was induced by oestrogen or DHT, and down-regulated by the progestin medroxyprogesterone acetate (MPA) or the anti-androgen hydroxyflutamide (Lovely *et al.* 2000, Apparao *et al.* 2002). There is evidence to suggest that the regulation of insulin-like growth factor 1 (IGF1) by androgens may influence endometrial cell proliferation (Sahlin *et al.* 1994, Gori *et al.* 1999). Expression of IGF1 is also up-regulated by oestrogen in Ishikawa cells, and treatment with recombinant IGF1 stimulated cell proliferation in a dose-dependent fashion (Kashima *et al.* 2009). Androgens may therefore have both a direct, AR-mediated impact and an indirect, ESR-mediated impact on endometrial proliferation and inflammation.

Glucocorticoids

Glucocorticoids are well-known anti-inflammatory agents, and have been shown to limit the production of cytokines and prostaglandin synthesis. The glucocorticoid receptor (GR), as well as enzymes capable of biosynthesis of cortisol, is expressed in the human endometrium (Bamberger *et al.* 2001, McDonald *et al.* 2006). Little is known about the role of glucocorticoids in endometrial cancer; however, GR expression has been shown to be altered with HRT (Vani *et al.* 2008), which may suggest that GR expression could be affected by altered steroid signalling in endometrial cancer.

Genetic and cellular changes contributing to inflammation in endometrial adenocarcinoma

A number of genetic mutations are associated with endometrial adenocarcinoma. These often occur in genes encoding proteins which contribute to an inflammatory microenvironment, impacting on cytokine expression, leukocyte infiltration and tissue remodelling.

PTEN

The most common genetic mutation in endometrial adenocarcinoma is in the tumour suppressor gene *PTEN*, leading to its inactivation (Tashiro *et al.* 1997). *PTEN* encodes the phosphatase and tensin homologue protein, which is a lipid phosphatase that downregulates phosphatidylinositol-(3,4,5)-trisphosphate (PIP_3) by converting it into PIP_2. PIP_3 activates AKT signalling; therefore, the common inactivation of *PTEN* found in endometrial adenocarcinoma can upregulate AKT signalling and subsequently impact on the signalling pathways regulated by this protein. These include control of cellular proliferation, adhesion and migration (Maehama & Dixon 1998). The impact of this mutation on endometrial adenocarcinoma development was recently demonstrated by the conditional deletion of *Pten* in the endometrium of a mouse model. This rapidly induced endometrial cancer formation (Daikoku *et al.* 2008). *PTEN* and AKT have also been linked to the control of NFκB. In endometrial adenocarcinoma cell lines containing mutated *PTEN*, increased levels of AKT phosphorylation resulted in the presence of activated NFκB in the nucleus (St-Germain *et al.* 2004).

NFκB

NFκB transcription factors bind to NFκB-binding sites on DNA to initiate the transcription of numerous cytokines and inflammatory mediators. NFκB activation can occur downstream of growth factor receptors and G-protein-coupled receptors after the activation of the phosphatidylinositol 3-kinase and AKT signalling pathway (Ye 2001). This method of activation in cancer is commonly due to the genetic alterations in tumour cells (Courtois & Gilmore 2006). It is also activated by inflammatory cytokines such as IL1, and Toll-like receptor signalling (Pomerantz & Baltimore 2002). The final step in the NFκB signalling pathway occurs when the inhibitory IκB complex is phosphorylated by the IκB kinases (IKKs). The dissociation of IκB from NFκB allows the translocation of NFκB to the nucleus and initiation of gene transcription (Ye 2001). In cancer, NFκB activation by these pathways leads to the development of numerous characteristics of inflammation. The involvement of NFκB in tumour development has been demonstrated in tissues displaying chronic inflammation. For example, a conditional knock-out of IKK, and therefore NFκB signalling, was introduced into a mouse model of gastric cancer which develops from chronic colitis. In these mice, tumour incidence was decreased by 75%, and this was associated with an increase in epithelial cell apoptosis and a decrease in inflammatory cytokine production by leukocytes. This provided a direct proof of the role of inflammation in initiation of this cancer type (Greten *et al.* 2004). Furthermore, NFκB activation contributes to tumour progression in tissues, in which cancer initiation is not linked to chronic inflammation. In ovarian cancer, for example, increased NFκB signalling has been identified which promotes tumour progression through the production of various angiogenic and mitogenic cytokines such as IL8 and CXCL1 (Chen *et al.* 2008).

In endometrial adenocarcinoma, increased localisation of NFκB to the nucleus has been detected, therefore implying an upregulation of NFκB signalling and hence inflammation (Pallares *et al.* 2004). In addition to the connection to *PTEN* inactivation already described, NFκB is influenced by the hormonal environment in endometrial adenocarcinoma. This further links the unopposed oestrogen hypothesis and inflammation. For example, NFκB can be activated by oestrogen in HEC-1A endometrial adenocarcinoma cells to increase the expression of angiogenic factors including VEGF and FGF, and the cytokines IL1, IL8 and TNF-α (Seo *et al.* 2004). The protease MMP9 is also released by three endometrial adenocarcinoma cell lines, HEC-1A, KLE and AN3CA, following oestrogen-induced NFκB signalling (Oh *et al.* 2009). Increased MMP production is a feature of many tumours leading to increased cancer cell invasion and metastasis. Additionally, in a poorly differentiated endometrial adenocarcinoma cell line, progesterone inhibits NFκB activation by inducing accessory proteins which form a complex inhibiting NFκB activity (Davies *et al.* 2004). This further indicates that the increased oestrogen environment in endometrial adenocarcinoma favours inflammation via the transcription factor NFκB.

Kras

Additional genetic mutations found in endometrial adenocarcinoma are capable of promoting an inflammatory environment. A mutation in the oncogene *Kras* is detected in 9–33% of endometrial adenocarcinomas (Enomoto *et al.* 1990, Lax *et al.* 2000). *Kras* mutations can cause constitutive activation of the extracellular signal-regulated kinase 1/2 (ERK1/2) signalling pathway in the absence of stimuli. This is a mitogen-activated protein kinase pathway, and therefore leads to transcription of numerous genes promoting tumour progression (Mizumoto *et al.* 2007). This mutation is also more commonly found in poorly differentiated cancers (Kohler *et al.* 1992), indicating that it may be associated with a poor prognosis. The phenotypic effects of *Kras* mutations in endometrial adenocarcinoma are yet to be determined, but are likely to involve the activation of multiple pathways regulated by ERK signalling which can promote growth, migration and angiogenesis (Lax *et al.* 2000). In other cancer types, mutations in *Ras* have been linked to inflammatory conditions. For example, constitutive Ras signalling in breast, lung and cervical cancer cell lines promotes the production of inflammatory chemokines including IL8 (Sparmann & Bar-Sagi 2004).

Thus, genetic mutations identified in endometrial adenocarcinoma can contribute to an inflammatory microenvironment, and in some cases tumour initiation.

Local mediators of inflammation in endometrial adenocarcinoma

The hallmarks of an inflammatory environment include local secretion of cytokines and other inflammatory mediators, and the presence of leukocytes. This review has thus far discussed how these features are promoted in endometrial adenocarcinoma by hormonal and genetic alterations to signalling. The contribution of local mediators and leukocytes to the inflammatory environment in endometrial adenocarcinoma will now be considered (summarised in Table 1).

Cytokines and chemokines

Cytokines are small peptides released by cells which can act as growth signals and chemotactic agents. In endometrial adenocarcinoma, cytokines can promote tumour growth by mediating cell invasion and angiogenesis. For example, the pro-inflammatory cytokine TNF-α activates signalling pathways, which are crucial for endometrial adenocarcinoma cell invasion (Choi *et al.* 2009). TNF-α also promoted angiogenesis in a mouse model by the activation of NFκB (Seo *et al.* 2004). IL6 is a further pro-inflammatory cytokine up-regulated in endometrial adenocarcinoma (Slater *et al.* 2006), which is associated with a poor prognosis (Bellone *et al.* 2005).

Chemokines are a subfamily of cytokines, so named for their chemoattractant properties. The chemokine family is divided into four groups based on the position of two cysteine molecules (C) and any other amino acid (X) in the amino terminal of the protein. The groups are known as C, C-C, C-X-C and C-X3-C (Murphy *et al.* 2000). A number of C-X-C chemokines are angiogenic (Strieter *et al.* 1995) and mitogenic (Wang *et al.* 2006*a*, Singh *et al.* 2009*a*). Their tumour-promoting properties have been demonstrated in mouse models of other cancer types such as melanoma, lung

Table 1 The expression of inflammatory mediators in endometrial adenocarcinoma

	Expression in endometrial adenocarcinoma	Phenotypic effect	References
Inflammatory mediator			
Cytokines			
CCL2	Increased	Unknown	Wang *et al.* (2006*a*,*b*)
CXCL1	Increased	Unknown	Wallace *et al.* (2009)
CXCL5	Increased	Unknown	Wong *et al.* (2007)
CXCL12	Unknown	Increased cell proliferation	Zhao *et al.* (2006)
	Unknown	Increased cell migration	Tsukamoto *et al.* 2007
IL1	Increased	Increased angiogenesis	Seo *et al.* (2004)
IL6	Increased	Unknown	Slater *et al.* (2006)
	Increased	Unknown	He *et al.* (2009)
IL8	Increased	Increased angiogenesis	Fujimoto *et al.* (2002)
		Increased metastasis	Berry *et al.* (2001)
IL11	Increased	Unknown	Sales *et al.* (2010)
TNF-α	Increased	Increased angiogenesis	Seo *et al.* (2004)
	Increased	Increased cell invasion	Choi *et al.* (2009)
Leukocytes			
Macrophages	Increased	Unknown	Salvesen & Akslen (1999)
	Increased	Promotion of angiogenesis	Tanaka *et al.* (2002)
	Increased	Unknown	Ohno *et al.* (2004)
	Increased	Promotion of angiogenesis	Soeda *et al.* (2008)
Neutrophils	Increased	Unknown	Wallace *et al.* (2009)
B cells	Increased	Unknown	Hachisuga *et al.* (1997)
T cells	Increased	Unknown	Hachisuga *et al.* (1997)
	Increased (CD8)	Unknown	Kondratiev *et al.* (2004)
	Increased (CD8)	Unknown	Ohno *et al.* (2005)
	Increased (CD4)	Promotion of angiogenesis	Giatromanolaki *et al.* (2008)
NK cells	Decreased (grades 1 and 2 EC)	Unknown	Hachisuga *et al.* (1997)
	Increased (grade 3 EC)		
Prostaglandins			
PGE_2	Increased EP	Increased cAMP expression	Jabbour *et al.* (2001)
	Increased EP	Increased COX2 expression	Tamura *et al.* (2002)
	Increased EP	Increased cell proliferation	Jabbour & Boddy (2003)
	Increased EP	Increased VEGF expression	Sales *et al.* (2004*a*,*b*)
	Increased EP	Increased FGF expression	Battersby *et al.* (2006)
$PGF_{2\alpha}$	Increased FP	Increased cell proliferation	Sales *et al.* (2004*b*)
	Increased FP	Increased VEGF expression	Sales *et al.* (2005)
	Increased FP	Increased FGF expression	Sales *et al.* (2007)
	Increased FP	Increased cell migration	Sales *et al.* (2008*a*,*b*)

and prostate cancer (Haghnegahdar *et al.* 2000, Keane *et al.* 2004, Singh *et al.* 2009*b*). In endometrial adenocarcinoma, expression of the CXCR4 receptor is elevated. This receptor is activated by the chemokine CXCL12 (also known as stromal cell-derived factor-1; Gelmini *et al.* 2009). *In vitro* studies have demonstrated that signalling of CXCL12 through this receptor increases proliferation, migration and invasiveness of various endometrial adenocarcinoma cell lines (Zhao *et al.* 2006, Tsukamoto *et al.* 2007). Elevated expression of CXCR4 in endometrial adenocarcinoma was also examined in a nude mouse xenograft model, and found to lead to a significantly higher incidence of metastases (Gelmini *et al.* 2009). Notably, a recent study provides evidence for an autocrine loop between the CXCR4/SDF1 and ESR1/ESR2 signalling pathways, which alters growth of breast cancer cells (Sauve *et al.* 2009), and it will be interesting to see if the same applies to endometrial cancers. Other members of the CXC chemokine family, CXCL1 and IL8 (also known as CXCL8), are elevated in endometrial adenocarcinoma (Berry *et al.* 2001, Wallace *et al.* 2009). IL8 expression was associated with increased metastatic potential (Berry *et al.* 2001) and increased angiogenesis in endometrial tumours, as measured by microvascular density counts (Fujimoto *et al.* 2002). CXCL5 expression is also elevated in endometrial adenocarcinoma (Wong *et al.* 2007), and may perform similar functions to IL8.

Other chemokines in addition to those of the CXC family are implicated in the progression of endometrial adenocarcinoma. The chemokine CCL2, also known as monocyte chemotactic protein-1, is up-regulated in endometrial adenocarcinoma cells (Wang *et al.* 2006*b*). CCL2 has been proposed to have direct angiogenic effects on microvascular endothelial cells and migratory effects on neoplastic epithelial cells (Conti & Rollins 2004).

Leukocytes

In addition to direct effects on neoplastic endometrial cells and endothelial cells, cytokines may also promote the development of endometrial adenocarcinoma through the chemo-attraction of immune cells. Leukocytes are a hallmark of inflammation, as well as promoters of inflammation and Virchow's original observation that cancer and inflammation may be linked was based on the observation of leukocytes in tumours (Balkwill & Mantovani 2001). The tumour microenvironment is commonly infiltrated by leukocytes of the innate immune system including macrophages, neutrophils, NK cells and dendritic cells. The cells of the adaptive immune system, T and B lymphocytes, are also found in tumours. Innate immune cells are attracted by the pro-inflammatory cytokines secreted by the tumour. After this initial infiltration, activation of antigen-presenting cells such as dendritic cells may result in the recruitment of adaptive immune cells to the tumour. Leukocytes have been shown to play contrasting roles in tumour promotion and destruction (de Visser *et al.* 2006). In endometrial cancer, the infiltration of macrophages (Salvesen & Akslen 1999, Ohno *et al.* 2004), neutrophils (Wallace *et al.* 2009) and B and T lymphocytes (Yamazawa *et al.* 2001, Chang *et al.* 2005, Ohno *et al.* 2005, 2006, Miyatake *et al.* 2007, Giatromanolaki *et al.* 2008) were increased as compared with normal endometrial tissue. Recent data from our laboratory have compared the presence of neutrophils, macrophages, dendritic cells, T cells, B cells and NK cells in well-, moderately and poorly differentiated endometrial adenocarcinoma. The numbers of neutrophils, macrophages and dendritic cells were significantly increased, and NK cells were significantly decreased in endometrial adenocarcinoma compared with normal endometrial tissue (Fig. 2).

Macrophages have been recently identified as a crucial link between chronic inflammation and the development of cancer, with the evidence that the prevention of macrophage infiltration significantly reduced the incidence and severity of inflammation-induced colon cancer (Popivanova *et al.* 2009). Tumour-associated macrophages have primarily been associated with the promotion of angiogenesis, as evidence in other cancer types has shown that they can secrete a range of angiogenic factors including VEGF and angiopoietins (Bingle *et al.* 2006, Venneri *et al.* 2007). Their contribution to cancer was demonstrated in a mouse model of breast cancer lacking macrophage infiltration. In these mice, a greatly decreased tumour progression and metastasis rate were

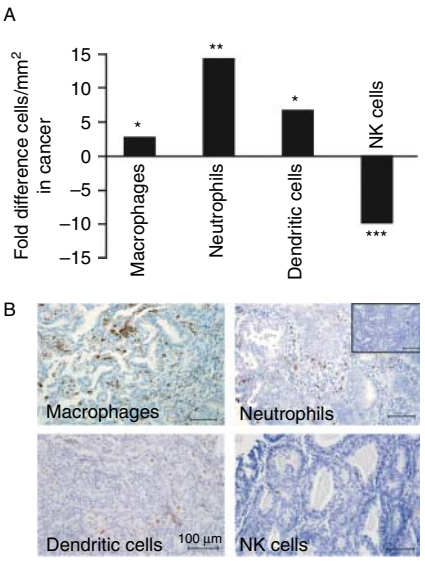

Figure 2 Immune cells in endometrial adenocarcinoma. (A) The number of immune cells/mm^2 in endometrial adenocarcinoma tissue relative to numbers in normal proliferative phase endometrium. The numbers of macrophages, neutrophils and dendritic cells were significantly increased in cancer. The number of NK cells was significantly decreased. Data are displayed as the fold difference between average cell numbers, $*P<0{\cdot}05$, $**P<0{\cdot}01$, $***P<0{\cdot}001$ as compared to normal endometrium. (B) Representative images of neutrophils, macrophages and dendritic cells in endometrial adenocarcinoma. Negative control is inset; scale bars represent 100 µM.

demonstrated, and the re-introduction of macrophages enabled tumour progression to rapidly catch up with control counterparts (Lin *et al.* 2001). Macrophage infiltration has been associated with a poor prognosis in endometrial cancer patients (Salvesen & Akslen 1999, Yang *et al.* 2007). In endometrial adenocarcinoma, the promotion of angiogenesis by macrophages has also been implicated, as macrophages are associated with increased microvascular density (Soeda *et al.* 2008). Furthermore, the promotion of angiogenesis is suggested by a study correlating expression of platelet-derived endothelial cell growth factor (thymidine phosphorylase) by macrophages with increased microvascular density in endometrial adenocarcinoma (Tanaka *et al.* 2002).

Neutrophils are proposed to contribute to tumour progression in a similar mechanism to macrophages, by tissue remodelling through the production of angiogenic factors and proteases. In the normal endometrium, neutrophils are found close to or associated with endothelial microvessels, and express VEGF during or coincident with periods of angiogenesis (Gargett *et al.* 2001). Neutrophils produce angiogenic factors including VEGF and FGF (Gargett *et al.* 2001, Scapini *et al.* 2004, Ai *et al.* 2007), and promote invasion and metastasis through the production of proteases including MMP9 (Ardi *et al.* 2007). In a nude mouse model of breast cancer, an increased infiltration of neutrophils increased invasiveness of the tumour, likely due to protease production (Yao *et al.* 2007). In addition, the depletion of neutrophils in mouse models of fibrosarcoma and colon cancer significantly decreased metastasis in these animals (Tazawa *et al.* 2003, Yamamoto *et al.* 2008). The increase in neutrophil infiltration in endometrial adenocarcinoma induced by elevated chemokine expression has been described (Wallace *et al.* 2009); however, the exact role that they are playing in endometrial adenocarcinoma is as yet unclear.

Most evidence points towards a cytotoxic role for T cells in cancer. Both CD4+ and CD8+ T cells can recognise tumour antigen and eradicate tumours from mouse models through the production of cytokines (Nishimura *et al.* 1999). To support this, a low infiltration of CD8+ T cells into endometrial cancer has previously been associated with a poor prognosis (Kondratiev *et al.* 2004, Ohno *et al.* 2005). However, the plasticity and complexity of immune cell responses to tumours is demonstrated by CD4+ T cells. A subset of these are known as regulatory T cells, as indicated by the specific expression of the cell surface antigen forkhead box p3 (FOXP3) which drives the development of this cell type. These cells have a distinct phenotype which can suppress T cell population expansion and cytotoxicity, and are associated with increased microvascular density and angiogenic factor production including VEGF in endometrial adenocarcinoma (Giatromanolaki *et al.* 2008). Additionally, the production of cytokines by T cells may also recruit other cells of the innate immune system, such as macrophages, and therefore indirectly lead to tumour promotion (Badoual *et al.* 2006).

Dendritic cells are the main antigen-presenting cells of the immune system, which infiltrate tissues as immature cells. Upon the uptake of antigen and in response to inflammatory stimuli, they differentiate into mature dendritic cells capable of activating lymphocytes (Schutyser *et al.* 2003). In cancer, increased numbers of immature dendritic cells in the tumour have been demonstrated to promote immune tolerance to the tumour. Immature dendritic cells taken from the tumour of a mouse model of colon cancer induced lower levels of T cell clonal expansion than mature dendritic cells (Bonnotte *et al.* 2004). It is possible that factors derived by the tumour promote dendritic cell immaturity or inhibit differentiation. For example, VEGF (Gabrilovich *et al.* 1998) and the overexpression of *CCL20* by colon cancer cells have been demonstrated to preferentially recruit immature dendritic cells *in vitro* (Wang *et al.* 2008). Similarly to other leukocytes discussed here, dendritic cells can also produce a host of angiogenic factors, including VEGF (Fainaru *et al.* 2008). However, their role in endometrial adenocarcinoma has not yet been examined.

NK cells are cytotoxic to tumour cells which do not express MHC class I (Zamai *et al.* 2007). Upon recognition, NK cells secrete a variety of lytic factors from specialised granules, able to lyse and promote apoptosis of targeted tumour cells. Therefore, presence of NK cells in a tumour is likely to decrease tumour growth (Zamai *et al.* 2007). In a mouse model of sarcoma, complete depletion of NK cells led to an increased rate of tumour initiation (Smyth *et al.* 2001). Additionally, NK cells can contribute to tumour destruction by the production of anti-angiogenic factors, including interferon-γ (Hayakawa *et al.* 2002). Therefore, the decrease in NK cell infiltration into endometrial adenocarcinoma observed in our laboratory (Fig. 2) indicates a reduction in immune cells with tumour-destructive properties.

Anti-tumourigenic roles of leukocytes

Although much evidence points to a pro-tumourigenic role for inflammation, there is still a controversy surrounding this subject in cancer. This is illustrated well by the actions of chemokines and leukocytes in different cancer types. Increased chemokine expression may drive angiogenesis or cell proliferation, but also an infiltration of immune cells cytotoxic to cancer cells. The cytotoxic nature of lymphocytes has already been discussed, and both neutrophils and macrophages have been shown in mouse models of different cancer types to reduce tumour growth (Lee *et al.* 2000, Lavergne *et al.* 2004). Additionally, the possibility of activating dendritic cells as an anti-tumour therapy is currently being investigated, as some evidence shows that mature dendritic cells can activate cytotoxic lymphocytes (Palucka *et al.* 2010). It may be that the balance of chemokines and leukocytes determines the pro- or anti-tumourigenic outcome. This has been previously suggested regarding macrophage infiltration, where infiltration in very large numbers may lead to tumour destruction (Mantovani *et al.* 2009). In endometrial cancer, no studies as yet show an inhibitory effect of leukocyte

infiltration on tumour growth; however, in some gynaecological cancers, use of immunotherapy to activate the immune system is currently being considered (Kandalaft *et al.* 2010).

Prostaglandins

Prostaglandins are synthesised from arachidonic acid via two isoforms of COX enzymes (termed COX1 and COX2), and much evidence suggests that this signalling pathway contributes to the progression of endometrial adenocarcinoma. High expression of inflammatory COX2 and prostaglandins has been correlated with tumour growth and angiogenesis in several cancer types including prostate, pancreatic and colon cancer (Tsujii *et al.* 1998, Molina *et al.* 1999, Jain *et al.* 2008) and endometrial adenocarcinoma (Tong *et al.* 2000, Jabbour *et al.* 2001). Recently, the importance of COX2 in the early stages of endometrial cancer development was confirmed using a conditional knockout of PTEN in the mouse endometrium (Daikoku *et al.* 2008). The COX2–prostaglandin pathway has also been linked to NFκB, as activation of this upregulates COX2 expression and therefore prostaglandin formation (St-Germain *et al.* 2004).

The prostaglandins PGE_2 and $PGF_{2\alpha}$ signal through G-protein-coupled receptors named E-prostanoid (EP) and F-prostanoid (FP) receptors respectively. EP receptors exist in four isoforms termed EP1–EP4, and EP2, EP4 and FP receptors have been shown to be elevated in endometrial adenocarcinoma (Jabbour *et al.* 2001, Sales *et al.* 2004*a*,*b*). Increased prostaglandin signalling through these receptors promotes a number of features associated with the progression of endometrial adenocarcinoma. For example, EP2 and FP receptor activation leads to an increase in the expression of angiogenic genes, including VEGF and FGF (Battersby *et al.* 2006, Sales *et al.* 2007). Prostaglandin signalling also promotes cellular changes contributing to cancer progression. $PGF_{2\alpha}$–FP receptor signals via Rho and Rac to increase cell migration (Sales *et al.* 2008*a*), and both $PGF_{2\alpha}$ and PGE_2 promote Ishikawa endometrial adenocarcinoma cell proliferation (Jabbour & Boddy 2003, Sales *et al.* 2004*b*). A further link of $PGF_{2\alpha}$ to other features of inflammation has recently been demonstrated, as activation of the FP receptor in endometrial adenocarcinoma led to increased chemokine production and thus increased neutrophil infiltration (Wallace *et al.* 2009). Furthermore, one of the downstream effects of both FP and EP signallings is an increase in COX2 expression (Fujino & Regan 2003, Sales *et al.* 2008*b*); therefore, this positive feedback loop may further amplify prostaglandin signalling in endometrial adenocarcinoma (Jabbour *et al.* 2005).

Finally, prostaglandins have also been linked to oestrogen signalling. In other pathologies of the endometrium, PGE_2 has been shown to increase aromatase expression and therefore oestrogen production. Oestrogen can then upregulate COX2 expression and drive prostaglandin synthesis (Tamura *et al.* 2002). However, the COX2 product $PGF_{2\alpha}$ causes a downregulation of ESR1, indicating a possible feedback mechanism. Presence of $PGF_{2\alpha}$ also prevented the oestrogen-mediated upregulation of PGR in Ishikawa endometrial adenocarcinoma cells (Collins *et al.* 2009). Together, these data

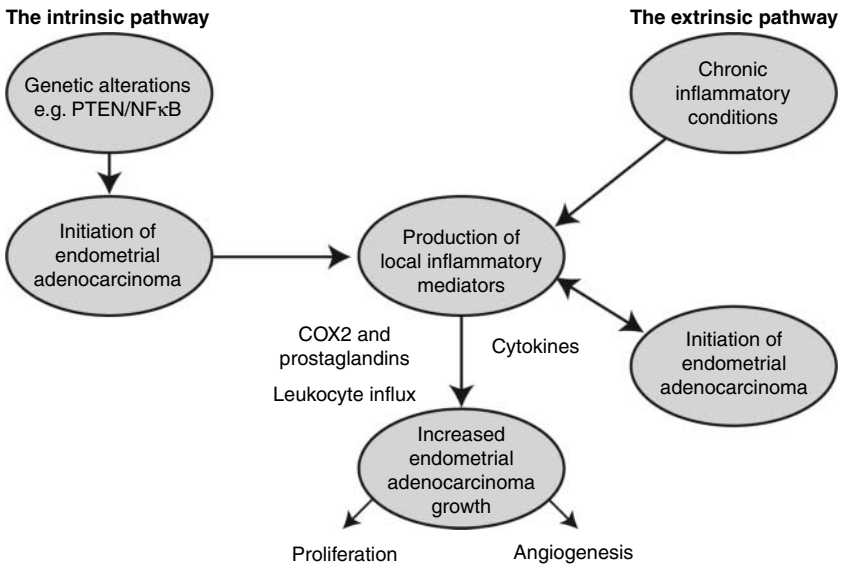

Figure 3 Inflammatory aspects of endometrial adenocarcinoma. Inflammation may contribute to cancer development in different ways. In the intrinsic pathway, after the initiation of cancer by genetic mutations, the expression of inflammatory agents is increased, leading to the promotion of tumour growth. In the extrinsic pathway, current inflammatory conditions lead to the initiation of cancer. In both pathways, further production of inflammatory mediators increases endometrial cancer growth.

suggest a complex interaction between steroid hormone responsiveness and prostaglandin action in endometrial adenocarcinoma.

Conclusions: endometrial adenocarcinoma and inflammation

As described earlier, inflammation in cancer is proposed to function by two pathways (Colotta *et al.* 2009). In the extrinsic pathway, local inflammation promotes malignant transformation of the tissue (Flossmann & Rothwell 2007, Sandhu 2008). In the intrinsic pathway, genetic changes give rise to cancerous cells, which lead to the upregulation of inflammatory pathways promoting tumour progression and growth. To determine the importance of these hypotheses in endometrial adenocarcinoma, epidemiological evidence can be examined. Endometrial adenocarcinoma displays a number of features of inflammation, such as cytokine expression, leukocyte infiltration and tissue remodelling. In the normal endometrium, the insertion of contraceptive intra-uterine devices promotes a local environment of inflammation, with an infiltration of leukocytes and increase in prostaglandin expression (Srivastava *et al.* 1989). However, users of this contraceptive method do not display a higher incidence of endometrial adenocarcinoma (Beining *et al.* 2008). Epidemiological studies have also now been carried out to examine the effects of NSAID use in the development of endometrial adenocarcinoma. In general, these have shown that intake of NSAIDs does not significantly influence the risk of developing endometrial adenocarcinoma (Moysich *et al.* 2005, Viswanathan *et al.* 2008, Danforth *et al.* 2009). This evidence suggests that inflammation in the normal endometrium does not initiate cancer development. However, in subgroups of very obese women, NSAID intake does significantly decrease the risk of endometrial adenocarcinoma development, indicating that the perturbation of inflammatory pathways to the extent found in obesity may contribute to endometrial adenocarcinoma (Viswanathan *et al.* 2008, Fortuny *et al.* 2009).

These epidemiological data suggest that in endometrial cancer, it may generally be the intrinsic pathway which is important in the initiation of tumour development. However, the process is evidently complex, and inflammation may contribute to tumour initiation in certain cases, by working in conjunction with other mechanisms (Fortuny *et al.* 2009). Cancer growth may therefore be initiated by genetic mutations, possibly in endometrial stem cells (Rutella *et al.* 2009), causing uncontrolled proliferation and subsequent cellular changes. These genetic changes may be a result of increased proliferation driven by an increased oestrogen to progesterone ratio in endometrial adenocarcinoma, in agreement with the unopposed oestrogen hypothesis (Jazaeri *et al.* 2001). In further support of the intrinsic pathway, a number of genetic mutations such as those of PTEN and Kras have been associated with the development of endometrial adenocarcinoma in women (Enomoto *et al.* 1990, Tashiro *et al.* 1997). These mutations have also been associated with the upregulation of inflammatory mediators and activation of the inflammatory transcription factor NFκB (St-Germain *et al.* 2004, Daikoku *et al.* 2008). Inflammation further facilitates cancer development and the acquisition of more pro-tumourigenic characteristics by cells (Fig. 3).

Until recently, inflammation was thought to resolve passively, by a gradual diminishment of the mediators involved. Now, the role of active biochemical pathways in the resolution of inflammation is recognised, distinct to anti-inflammatory signalling (reviewed in Serhan *et al.* (2008)). Some of the same lipid mediators which generate inflammatory responses, such as PGE_2, can promote the formation of mediators of inflammation resolution, including the lipoxins and resolvins (Serhan *et al.* 2000). These perform functions such as promoting the clearance of apoptotic leukocytes, and preventing further chemokine expression by these cells (Campbell *et al.* 2007). In endometrial cancer, the role of these resolution mediators is as yet unknown. Endometrial adenocarcinoma at advanced stages has a poor prognosis (Fleming *et al.* 2004). Inhibition of inflammation or manipulation of inflammatory resolution pathways may therefore represent a therapeutic target in endometrial adenocarcinoma.

Declaration of interest

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

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