Inflammatory events in endometrial adenocarcinoma

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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.


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...
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. 2009b). 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 I 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. 2001a).

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 chemotactic 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 (Dimittiadis 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 (OE2) 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 stage following the post-ovulatory rise in progesterone (Critchley et al. 2001b). Oestrogen promotes endometrial proliferation (Ferencyz 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 (Ferencyz 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 (Ferencyz 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 (Ferencyz et al. 1979) and vascularisation (Hastings et al. 2003).
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 oestrone 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 oestrone production (Modugno et al. 2005). IL6 can stimulate oestrogen synthesis and can act synergistically with TNF-α to increase aromatase, 17β-hydroxysteroid dehydrogenase and oestrene 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-hydroxyestradiol and 2-methoxyestradiol do not stimulate the uterus (Martucci & Fishman 1977). 2-Methoxyestradiol 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 (Crichtley & 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 OE₂ (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 (PIP3) by converting it into PIP2. PIP3 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. 2006a, Singh et al. 2009a). 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

<table>
<thead>
<tr>
<th>Inflammatory mediator</th>
<th>Expression in endometrial adenocarcinoma</th>
<th>Phenotypic effect</th>
<th>References</th>
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<td>Increased EP</td>
<td>Increased FGF expression</td>
<td>Battersby et al. (2006)</td>
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and prostate cancer (Haghnegahdar et al. 2000, Keane et al. 2004, Singh et al. 2009b). 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, are implicated in the progression of endometrial adenocarcinoma (Berry et al. 2001b, 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. 2006b). 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
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 (Giattromanolaki 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 (Badoial 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 (Schutts 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 (Bonnnette 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 (Fammaru 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 PGE2 and PGF2α 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. 2004a, 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. PGF2α–FP receptor signals via Rho and Rac to increase cell migration (Sales et al. 2008a), and both PGF2α and PGE2 promote Ishikawa endometrial adenocarcinoma cell proliferation (Jabbour & Boddy 2003, Sales et al. 2004b). A further link of PGF2α 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 signalings is an increase in COX2 expression (Fujino & Regan 2003, Sales et al. 2008b); 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, PGE2 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 PGF2α causes a downregulation of ESR1, indicating a possible feedback mechanism. Presence of PGF2α also prevented the oestrogen-mediated upregulation of PGR in Ishikawa endometrial adenocarcinoma cells (Collins et al. 2009). Together, these data promote 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. PGF2α–FP receptor signals via Rho and Rac to increase cell migration (Sales et al. 2008a), and both PGF2α and PGE2 promote Ishikawa endometrial adenocarcinoma cell proliferation (Jabbour & Boddy 2003, Sales et al. 2004b). A further link of PGF2α 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 signalings is an increase in COX2 expression (Fujino & Regan 2003, Sales et al. 2008b); therefore, this positive feedback loop may further amplify prostaglandin signalling in endometrial adenocarcinoma (Jabbour et al. 2005).

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**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 PGE₂, 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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