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Eicosanoids and cancer

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Abstract

Eicosanoids, including prostaglandins and leukotrienes, are biologically active lipids that have been implicated in various pathological processes, such as inflammation and cancer. This Review highlights our understanding of the intricate roles of eicosanoids in epithelial-derived tumours and their microenvironment. The knowledge of how these lipids orchestrate the complex interactions between transformed epithelial cells and the surrounding stromal cells is crucial for understanding tumour evolution, progression and metastasis. Understanding the molecular mechanisms underlying the role of prostaglandins and other eicosanoids in cancer progression will help to develop more effective cancer chemopreventive and/or therapeutic agents.

A large body of evidence indicates that genetic mutations, epigenetic changes, chronic inflammation, diet and lifestyle are risk factors for cancer[1-3]. Epidemiological and animal studies provide evidence that a high-fat diet can be associated with an increased risk for cancer, in particular colorectal, breast, pancreatic and prostate cancer[3]. Arachidonic acid is one major ingredient of animal fats and the biologically active lipids derived from this substrate have crucial roles in chronic inflammation and cancer. The metabolism of arachidonic acid by cyclooxygenase (COX), lipoxygenase (LOX) and P450 epoxygenase pathways generates eicosanoids, including prostanoids, leukotrienes, hydroxyeicosatetraenoic acids (HETEs), epoxyeicosatrienoic acids (EETs) and hydroperoxyeicosatetraenoic acids (HPETEs) (FIG. 1). Epidemiological, clinical and animal studies provide evidence that activation of COX and LOX pathways during chronic inflammation and carcinogenesis results in aberrant metabolism of arachidonic acid, which may be one mechanism for the contribution of dietary fats to carcinogenesis.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to have beneficial effects on reducing the risk of developing some solid tumours, including the four most prevalent

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Competing interests statement
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DATABASES
Entrez Gene: http://www.ncbi.nlm.nih.gov/genePtges
National Cancer Institute Drug Dictionary: http://www.cancer.gov/drugdictionary/celecoxib
UniProtKB: http://www.uniprot.org
5-LOX | 12-LOX | 15-LOX-1 | 15-LOX-2 | BLT1 | BLT2 | CCR7 | COX1 | COX2 | CysLT1 | CysLT2 | DP | EGFR | EP1 | EP2 | EP3 | EP4 | FLAP | FP | GPR44 | IP | PPARδ | PPARγ | PTGDS | TP

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cancers worldwide: breast, colon, lung and prostate cancer[4]. NSAIDs exert some of their anti-inflammatory and anti-tumour effects by reducing prostanoid production through the inhibition of COX enzyme activity. In addition, emerging evidence suggests that LOX pathways are also involved in carcinogenesis. In general, 5-LOX (also known as ALOX5) and 12-LOX (also known as ALOX12) have potential procarcinogenic roles, whereas 15-LOX-2 (also known as ALOX15B) is thought to have an anti-carcinogenic effect, and the role of 15-LOX-1 (also known as ALOX15) remains controversial[5]. As 5-LOX has been shown to have a major role in carcinogenesis, understanding the contribution of each COX-derived prostanoid and 5-LOX-derived leukotriene in the pathogenesis of cancer could enable identification of new and safer therapeutic and chemopreventive agents with reasonable benefit and fewer side effects.

In this Review, we focus on recent insights into the roles of prostanoids and leukotrienes in several epithelial-derived malignancies, from their involvement in governing tumour epithelial cell proliferation, survival, and migration and invasion to their involvement in adapting the tumour microenvironment by influencing angiogenesis, inflammation and immunosuppression.

Prostanoid and leukotriene biosynthesis

The importance of the prostanoid and leukotriene biosynthetic pathway in carcinogenesis and chronic inflammation is supported by population studies, clinical trials and animal experiments. COX enzymes (correctly referred to as prostaglandin G/H synthases) exist in two isoforms: COX1 (also known as PTGS1) and COX2 (also known as PTGS2). *COX2* is an immediate-early response gene that is normally absent from most cells but is highly induced at sites of inflammation and during tumour progression[6]. Our laboratory was the first to report that COX2 expression is upregulated in colorectal cancer[7]. Multiple follow-up studies have revealed that COX2 levels are increased in other premalignant and malignant solid tumours, including those of the stomach, oesophagus, liver, pancreas, head and neck, lung, breast, prostate and bladder, and increased COX2 expression is associated with decreased survival among these cancer patients[8]. By contrast, COX1 was thought to be a housekeeping enzyme responsible for maintaining basal prostanoid levels that are important for tissue homeostasis. However, upregulation of COX1 expression has been observed in ovarian cancer[9]. Although most attention has been focused on the cyclooxygenase pathway, a few reports have indicated that 5-LOX is generally absent in normal epithelia but is induced by pro-inflammatory stimuli and is often constitutively expressed in various epithelial cancers including those of the colon, oesophagus, lung, prostate and breast[5]. As other LOX isoforms are not involved in leukotriene synthesis, the relevance of their expression and function is not included in this Review.

At a glance

- The altered metabolism of arachidonic acid by cyclooxygenase (COX) and lipoxygenase (LOX) is a common feature of several epithelial-derived malignancies and has been shown to have crucial roles in cancer progression.
- The production of arachidonic acid-derived prostanoids and leukotrienes occurs in single cells or takes place in a complex manner in which these biologically active lipids, specifically leukotrienes, are generated by transcellular biosynthesis through the cooperation of multiple different types of cells in the tumour and inflamed tissues.
- Pro-inflammatory prostaglandins and leukotrienes promote tumour growth by regulating tumour epithelial cells themselves and orchestrating the complex interactions between transformed epithelial cells and surrounding stromal cells to

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establish the tumour microenvironment that facilitates tumour-associated angiogenesis and evades attack by the immune system.

- Prostaglandins and leukotrienes can modulate tumour epithelial cell proliferation, apoptosis, and migration and invasion through multiple signalling pathways in both an autocrine and paracrine fashion.
- Prostaglandins and leukotrienes are central molecules in the regulation of stem cell homeostasis.
- Pro-inflammatory prostaglandins and leukotrienes are key mediators in the crosstalk between tumour epithelial cells and their surrounding stromal cells in establishing a tumour microenvironment with chronic inflammation and immunosuppression.
- Although non-steroidal anti-inflammatory drugs (NSAIDs), which target COX enzymes, are still among the most promising chemopreventive agents for cancer, cardiovascular and gastrointestinal side effects have dampened enthusiasm for their use as chemopreventive agents. Understanding the roles of prostaglandins and leukotrienes in epithelial-derived tumours and their microenvironment may help to develop cancer biomarkers and chemopreventive and/or therapeutic agents with a greater benefit and fewer side effects than NSAIDs.

Prostanoid biosynthesis

Cyclooxygenase enzymes catalyse the conversion of arachidonic acid to prostanoids, including prostaglandins and thromboxane A_2 (TXA_2) (FIG. 1). The prostaglandins exert their biological effects in an autocrine or paracrine manner by binding to their cognate cell surface receptors, which belong to the G protein-coupled receptor (GPCR) family. These receptors are designated DP (also known as PTGDR) and GPR44 for prostaglandin D_2 (PGD_2); EP1, EP2, EP3 and EP4 (also known as PTGER1, PTGER2, PTGER2 and PTGER4, respectively) for PGE_2; FP (also known as PTGFR) for $PGF_{2\alpha}$; IP (also known as PTGIR) for PGI_2; and TP (also known as TBXA2R) for TXA_2. In some cases, however, certain prostaglandins and their metabolites bind nuclear receptors such as peroxisome proliferator-activated receptors (PPARs). For example, PGI_2 can transactivate PPARδ, and a PGD_2 dehydration product, 15-deoxy-Δ12,14-PGJ_2 (15dPGJ_2), is a natural ligand for PPARγ. PGE_2 can also indirectly activate PPARδ in certain contexts[10]. The specific action of the different prostaglandins in a particular type of tissue predominantly depends on the cell type-specific expression of their cognate receptors as well as prostaglandin production. In addition to their synthesis, the steady-state extracellular levels of prostaglandins also depend on a carrier-mediated transport process, as well as inactivation in the cytoplasm. These processes are regulated by prostaglandin transporter (PGT; an influx transporter), multidrug resistance-associated protein 4 (MRP4; an efflux transporter) and hydroxyprostaglandin dehydrogenase 15-(NAD) (HPGD; also known 15-PGDH). For example, PGE_2 and $PGF_{2\alpha}$ are rapidly metabolized *in vivo* by 15-PGDH to a stable 13,14-dihydro-15-keto-PGE_2 (PGEM) and 13,14-dihydro-15-keto-$PGF_{2\alpha}$, respectively. Other prostaglandins are mainly metabolized in a non-enzymatic manner[11].

Leukotriene biosynthesis

The 5-LOX enzyme interacts with a 5-LOX-activating protein (FLAP) and converts arachidonic acid to the unstable leukotriene A_4 (LTA_4) through an HPETE. FLAP enhances the activity of 5-LOX by binding to arachidonic acid and presenting it to 5-LOX. LTA_4 is subsequently converted to 5-HETE, or hydrolysed into biologically active LTB_4 by LTA_4 hydrolase, or to the cysteinyl leukotriene (CysLT), LTC_4, by LTC_4 synthase. LTC_4 is then

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converted to another CysLT, LTD_4, which is sequentially metabolized to LTE_4 (FIG. 1). LTB_4 and LTD_4 are the most potent leukotrienes. They exert their biological effects through the activation of GPCRs. LTB_4 can bind to two receptors, BLT1 (also known as LTB4R) with high affinity and BLT2 (also known as LTB4R2) with low affinity; CysLTs bind to at least two distinct receptors, CysLT1 (also known as CYSLTR1) and CysLT2 (also known as CYSLTR2). Like LTB_4 receptors, CysLT1 has a high affinity for CysLTs — which is higher for LTD_4 than LTC_4 — whereas CysLT2 has a lower overall affinity for CysLTs that is equal for LTD_4 and LTC_4. BLT1 and CysLT1 are exclusively expressed in leukocytes, whereas BLT2 and CysLT2 are expressed in a wide variety of cells.

Transcellular biosynthesis

Eicosanoid biosynthesis can occur in a single cell that contains the complete complement of enzymes, but the production of eicosanoids in a tissue, in particular in tumour tissues and sites of inflammation, takes place in a more complex manner in which some of these biologically active lipids, specifically leukotrienes, are generated by transcellular biosynthesis through the cooperation of multiple different cell types.

The leukotrienes are primarily produced by stimulated leukocytes that express the enzymes required for their synthesis. Epithelial and endothelial cells can also generate LTB_4, LTC_4 and LTD_4 at inflammatory sites through transcellular metabolism by which epithelial or endothelial cells use LTA_4 that is released from immune cells, in particular neutrophils, as epithelial and endothelial cells express LTA_4 hydrolase[12]. However, leukocytes can also use arachidonic acid that is secreted from epithelial cells as a substrate to generate leukotrienes. Transcellular leukotriene biosynthesis has been observed during inflammation *in vivo*[13]. Therefore, the transcellular biosynthesis between epithelial or endothelial and immune cells can generate the overproduction of leukotrienes, which in turn further amplifies the inflammatory response. Additional research is needed to determine the extent of transcellular biosynthesis in the tumour microenvironment. To date, there is no published evidence demonstrating transcellular biosynthesis of prostaglandins between immune and epithelial cells, although this is reported to occur between platelets and endothelial cells[12].

Eicosanoids in cancer

Prostanoids and cancer

Among prostanoids, proinflammatory PGE_2 has a predominant role in promoting tumour growth. PGE_2 is the most abundant prostaglandin that is found in various human malignancies, including colon, lung, breast, and head and neck cancer, and is often associated with a poor prognosis[14-17]. By contrast, 15-PGDH is highly expressed in normal tissues but is ubiquitously lacking in human colon, gastric, lung and breast cancer[18-21]. Lack of 15-PGDH expression in these tumours results in increased endogenous PGE_2 levels. Multiple lines of evidence from mouse models of colorectal cancer (CRC) demonstrate that COX2-derived PGE_2 promotes tumour growth. PGE_2 treatment blocks NSAID-induced regression of small intestinal adenomas in $Apc^{Min/+}$ mice[22] and increased endogenous PGE_2 levels through the loss of 15-PGDH inhibit the anti-tumour effects of celecoxib in the azoxymethane (AOM) mouse model[23]. Direct evidence that PGE_2 promotes tumour growth comes from recent studies showing that PGE_2 treatment dramatically increased both small and large intestinal adenoma burden in $Apc^{Min/+}$ mice and significantly enhanced AOM-induced colon tumour incidence and multiplicity[10,24]. Furthermore, increased endogenous PGE_2 through the genetic deletion of *15-Pgdh* promotes colon tumour growth in $Apc^{Min/+}$ and AOM mouse models[25]. By contrast, inhibition of endogenous PGE_2 through the genetic deletion of prostaglandin E synthase (*Ptges*) suppresses intestinal tumorigenesis in $Apc^{Min/+}$ and AOM models[26]. The central role of PGE_2 in colorectal tumorigenesis has been further confirmed by evaluating mice with a

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homozygous deletion of individual PGE_2 receptors[27-29]. Limited information is available regarding the role of PGE_2 signalling in animal models of other cancers. Increased PGE_2 levels through the overexpression of COX2 and PTGES cause gastric tumorigenesis in *Wnt1*-transgenic mice driven by the keratin 19 (*Krt19*) promoter[30]. Deletion of the EP2 receptor inhibits murine lung tumorigenesis that is induced by a chemical carcinogen[31] and significantly suppresses COX2-induced mammary hyperplasia in mice[32]. Similarly, an EP1 antagonist inhibits chemically induced breast cancer development in rats[33]. Collectively, these studies demonstrate that PGE_2 plays an important part in cancer progression.

The role of PGD_2 in carcinogenesis remains ambiguous. Disruption or overexpression of PGD_2 synthase (PTGDS) in $Apc^{Min/+}$ mice accelerates or reduces intestinal tumour growth[34], suggesting that PGD_2 has anti-tumour effects. However, the evidence that genetic disruption of its receptor (*DP*) has no effect on colon tumour formation in the AOM mouse model does not support the hypothesis that PGD_2 has anti-tumour effects[28]. One possible explanation for the differences in phenotype caused by PTGDS compared with DP in mouse models is that the PGD_2-derived product $15dPGJ_2$ inhibits tumour growth by binding to PPARγ. It is well established that the activation of PPARγ inhibits tumour growth through anti-proliferative, pro-apoptotic, pro-differentiation and anti-angiogenic effects in cell lines and animal models[35]. Alternatively, overexpression of PTGDS might shift the conversion of PGH_2 away from PGE_2, which in turn would suppress tumour growth. Further investigation is required to assess the role of PGD_2 and its receptors in cancer progression.

Little information regarding the role of other prostaglandins in animal models of cancer is available; however, disruption of FP, IP or TBXA2R receptors does not affect colon tumour formation in the AOM mouse model[28], suggesting that these receptors are not involved in CRC progression. The question is now whether these receptors modulate tumour growth in other models of CRC or in other types of cancer. A role for $PGF_{2\alpha}$ in tumorigenesis has been suggested as it can enhance carcinogen-induced transformation of fibroblasts *in vitro* through the induction of COX2 (REF. [36]). Activation of PPARδ accelerates intestinal tumour growth in $Apc^{Min/+}$ mice[37], supporting the idea that PGI_2 might promote colon tumour progression through this receptor. Further work is required to explore the role of PGI_2 in colon carcinogenesis and other cancers.

Leukotrienes and cancer

Compared with prostaglandins, much less is known about the pro-inflammatory leukotrienes in cancer. However, emerging data suggest that leukotrienes can have an important role in carcinogenesis.

LTB_4 levels are increased in human colon and prostate cancer[38,39], and the expression of LTB_4 receptors is increased in human pancreatic cancer[40]. LTB_4 expression is also increased in HRAS-v12-transformed cells and the receptor BLT2 is required for Ras-induced transformation *in vivo*[41]. Furthermore, inhibition of LTB_4 synthesis by treatment with an LTA_4 hydrolase inhibitor, bestatin, reduced the burden of oesophageal adenocarcinoma in a rat model[42].

The CysLT1 receptor is highly expressed in human colon and prostate cancers and negatively correlates with patient survival[43,44]. Increased CysLT1 expression in CRC correlates with the ability of LTD_4 to induce proliferation and inhibit apoptosis. By contrast, reduced expression of the CysLT2 receptor is associated with a poor prognosis in patients with CRC, and CysLT2 signalling is involved in inducing apoptosis and terminal differentiation[45]. However, comparatively little is known about the effects of CysLT2 on signalling and biological function.

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Mechanisms of eicosanoids in carcinogenesis

To understand the mechanism(s) underlying the effects of prostaglandins and leukotrienes on cancer progression, researchers have been investigating precisely how these lipids affect cancer biology. As mentioned earlier, pro-inflammatory eicosanoids are abundantly produced by various types of cancer cells and their surrounding cells. These biologically active lipids can modulate tumour progression through several mechanisms, such as by directly activating their receptors on tumour epithelial cells to regulate cell proliferation, apoptosis, migration and invasion; directly inducing epithelial cells to secrete growth factors, pro-inflammatory mediators and angiogenic factors that switch a normal microenvironment to one that supports tumour growth and spread; and directly binding receptors on stromal cells to promote a tumour-supportive microenvironment by inducing angiogenesis and evading attack by the immune system (FIG. 2).

The role of prostaglandins and leukotrienes in tumour epithelial cells

Prostaglandins and leukotrienes can modulate tumour cell proliferation, differentiation and apoptosis through multiple signalling pathways in both an autocrine and paracrine fashion (FIG. 3; TABLE 1). PGE_2 induces proliferation by activating at least two signalling pathways: Ras–Erk and glycogen synthase kinase-3β (GSK3β)–β-catenin in colon and lung cancer cells[46-48]. In breast cancer, PGE_2 can upregulate aromatase production in stromal fat cells and concomitantly oestrogen production, which stimulates tumour cell proliferation[49]. In addition, PGE_2 promotes colon tumour cell survival by activating a PI3K–Akt–PPARδ cascade in $Apc^{Min/+}$ mice[10]. PGE_2 upregulation of BCL-2, an anti-apoptotic protein, and induction of nuclear factor-κB (NF-κB) transcriptional activity might also be involved in PGE_2-induced inhibition of apoptosis[50,51]. Similarly, $PGF_{2\alpha}$ induces cell proliferation through an FP–Erk–fibroblast growth factor 2 (FGF2)–FGF receptor 1 (FGFR1)–Erk cascade in endometrial tumour cell lines[52]. By contrast, PGD_2 secreted by stromal cells inhibits prostate tumour cell growth *in vitro* through a PPARγ-dependent mechanism[53].

Knock down of LTA_4 hydrolase inhibits anchorage-independent growth of HCT-116 colon cancer cells, suggesting that leukotrienes are involved in cell growth regulation[54]. Indeed, LTA_4 hydrolase-derived LTB_4 stimulates cell proliferation and promotes cell survival through a BLT1-Erk pathway in colon tumour cell lines[55], and induces cell proliferation through both Mek–Erk and PI3K–Akt pathways in human pancreatic cancer cell lines[56]. Activation of the LTD_4–CysLT1 axis promotes cell proliferation and survival through multiple parallel pathways such as GSK3β–β-catenin, protein kinase C (PKC)–Raf–ERK1 and ERK2, BCL-2 and COX2 in non-transformed human intestinal epithelial cell lines[57-59] and induces cell proliferation but not survival in CRC cell lines[60]. By contrast, inhibition of LTD_4 signalling by a CysLT1 antagonist can induce apoptosis in prostate cancer cell lines[44]. The LTD_4 induction of COX2, as well as PGE_2 production, implies that crosstalk exists between the 5-LOX and COX2 pathways. Consistent with the negative correlation of $CysLT_2$ expression with a poor prognosis in patients with CRC, $CysLT_2$ signalling leads to terminal differentiation and growth inhibition in colon carcinoma cell lines[45].

In addition, prostaglandins and leukotrienes also affect the migration and invasion of carcinoma cells. Our group has demonstrated that PGE_2 induces CRC cell migration and invasion through epidermal growth factor receptor (EGFR)–PI3K–Akt signalling *in vitro*[61]. Subsequently, we found that PGE_2 induction of an EP4–β-arrestin 1–SRC complex was crucial in transactivating EGFR to induce downstream Akt signalling and stimulate CRC cell migration *in vitro*, as well as the metastatic spread of disease to the liver *in vivo*[62]. The SRC–EGFR pathway also mediates PGE_2-induced human hepatocellular carcinoma cell invasion *in vitro*[63]. These studies revealed that activation of PGE_2 receptors transactivates EGFR through an intracellular mechanism. It

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has been reported that PGE_2 transactivation of EGFR depends on the extracellular release of an EGF-like ligand *in vitro*[64]. PGE_2 can also induce cell migration and invasion through other signalling pathways, including the induction of matrix metalloproteinase 2 (MMP2) through an Erk–ETS1 cascade in pancreatic cancer cell lines[65] and the upregulation of C-C chemokine receptor 7 (CCR7) through EP2 and EP4 in breast cancer cell lines[66]. In addition, treatment with an EP4 antagonist inhibits lung carcinoma cell migration and invasion *in vitro* and *in vivo*[67]. Similar to PGE_2, $PGF_{2\alpha}$ also stimulates motility and invasion of colon[68] and endometrial[69] carcinoma cell lines and TXA_2 of prostate carcinoma cell lines[70]. Relatively little is known about the ability of leukotrienes to regulate tumour cell migration and invasion. In an *in vivo* study, an LTB_4 antagonist was shown to inhibit the metastatic spread of pancreatic cancer cells to the liver and other organs[71]. In an *in vitro* study, LTD_4 induced non-transformed intestinal cell migration through the activation of a PI3K–Rac cascade[72].

Solid tumours are thought to originate from a single replication-competent cell (stem cell or proliferative progenitor cell)[1]. Recent studies have established that both prostaglandins and leukotrienes are central molecules in the regulation of stem cell homeostasis. PGE_2 protects mouse embryonic stem cells from undergoing apoptosis through an EP2–PI3K–Akt cascade[73] and regulates growth and development of both embryonic haematopoietic stem cells and adult stem cells in several different organisms[74,75]. Similarly, LTB_4 and LTD_4 stimulate the proliferation of several types of stem and progenitor cells[76-79]. Collectively, the novel functions of these biologically active lipids on stem cell growth and maturation might suggest their ability to regulate cancer stem cell growth. This deserves considerable attention, and future research must be directed towards obtaining a better understanding of the role of prostaglandins and leukotrienes in regulating progenitor cells in solid tumours.

The role of eicosanoids in the inflammatory microenvironment

Chronic inflammation causes stromal cells to produce pro-inflammatory mediators, including eicosanoids, cytokines and chemokines, that shift the tissue microenvironment from normal to aberrant. In general, the inflammatory microenvironment, which is associated with changes in leukocyte profiles as well as their functionality, can initiate epithelial cell transformation and promote tumour growth, angiogenesis and metastasis[80]. A growing body of evidence demonstrates that prostaglandins and leukotrienes are key immunomodulators mediating the crosstalk between epithelial cells and their surrounding stromal cells in the tumour microenvironment (FIG. 4).

The normal presence and trafficking of immune cells into the mucosal compartment has been termed physiological inflammation. In response to tumour-associated or chronic inflammation, transformed or normal epithelial cells and tissue-resident immune cells locally secrete cytokines, chemokines and pro-inflammatory eicosanoids that recruit additional leukocytes from the circulation into the tissue. The common pathological changes associated with chronic inflammation include increased infiltration of dysregulated immune cells, production of pro-inflammatory mediators, diminished epithelial integrity and deficient feedback systems that normally downregulate the mucosal response to antigens. Furthermore, the immune cells recruited to the tumour microenvironment are phenotypically different from the normal immune cells and can maintain inflammation and induce angiogenesis[80]. For example, the massively recruited macrophages in the mucosa of active inflammatory bowel disease (IBD) are phenotypically different from normal macrophages and have a major role in chronic mucosal inflammation by secreting many pro-inflammatory cytokines[81].

Although epidemiological and experimental evidence strongly implicates chronic inflammation as a risk factor for cancer, the mechanisms by which inflammation and inflammatory mediators result in neoplastic transformation and progression have not been

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completely resolved. A strong association between chronic inflammation and malignant diseases occurs in CRC that arises in patients with IBD. The role of PGE_2 in IBD is the best characterized example of the role of prostaglandins in chronic inflammation. PGE_2 exacerbates inflammation and disease severity through increasing the infiltration of neutrophils and T helper 17 (T_H17) cells to the colonic tissue in a murine model of IBD[82]. Several lines of evidence further suggest that PGE_2-induced expansion of inflammatory T_H17 cells depends on the involvement of T cells and dendritic cells. PGE_2 shifts the interleukin-12 (IL-12)/IL-23 balance in dendritic cells through EP2 and EP4 receptors in favour of IL-23, which in turn increases the number of T_H17 cells *in vitro*[82]. IL-12 promotes T helper 1 (T_H1) responses and suppresses T_H17 development and function, whereas IL-23 is essential for T_H17 expansion and survival. PGE_2 also facilitates IL-23-induced T_H17 expansion from peripheral blood mononuclear cells and naive T cells *in vitro*[83,84], induces T_H1 cell differentiation *in vitro* and promotes inflammation through T_H1 and T_H17 cells in an animal model of chronic inflammation through the EP4 receptor[85]. In addition, PGE_2 induces dendritic cell migration *in vitro* by upregulation of CCR7 (REF. [86]). By contrast, PGD_2 inhibits the migration of dendritic cells to the lymph nodes *in vivo*[87]. During chronic inflammation, dendritic cells secrete large amounts of inflammatory cytokines that further recruit monocytes and immature dendritic cells into inflamed tissues.

Leukotrienes are powerful lipid mediators of inflammation in various acute and chronic inflammatory and allergic diseases, including IBD[88]. In fact, urinary LTE_4 can serve as a biomarker for IBD[89]. Similar to chemokines, LTB_4 is another potent chemoattractant and activator of neutrophils, eosinophils, basophils, T cells, dendritic cells and macrophages in inflammatory sites[90-93]; a Rac–Erk signalling cascade might also be responsible for LTB_4-induced chemotaxis[94]. Similar to PGE_2, LTB_4 promotes the migration of dendritic cells though the upregulation of CCR7 *in vitro* and *in vivo*[95]. However, it is not clear whether Rac–Erk signalling mediates LTB_4-induced CCR7 expression. Collectively, these studies show that pro-inflammatory prostaglandins and leukotrienes could stimulate tumour growth through establishing an inflammatory microenvironment.

The role of eicosanoids in tumour immunosuppression

It is well accepted that cooperative interactions between carcinoma cells and other cells in the tumour microenvironment contribute to cancer progression. Tumour epithelial cells secrete cytokines, chemokines and pro-inflammatory eicosanoids that recruit and reprogramme various pro-inflammatory leukocytes to establish an immunosuppressive tumour microenvironment. Of prostaglandins and leukotrienes, only PGE_2 has been shown to have a clear role in the regulation of tumour immunosuppression through T cells, $CD8^+$ cytotoxic T cells, regulatory T cells, dendritic cells and myeloid-derived suppressor cells (MDSCs) (FIG. 5). PGE_2 helps to shift the tumour microenvironment from anti-tumour T_H1 responses to immunosuppressive T helper 2 (T_H2) responses by downregulation of T_H1 cytokines (tumour necrosis factor-α (TNFα), interferon-γ (IFNγ) and IL-2) and upregulation of T_H2 cytokines (IL-4, IL-10 and IL-6) in immune cells[96-98]. Moreover, PGE_2 directly inhibits the activity of cytotoxic T cells through the upregulation of a CD94 and NKG2A complex and induces regulatory T cell function *in vitro*[99,100]. PGE_2 produced by tumour cells can also indirectly abolish the antitumour effects of cytotoxic T cells *in vivo* and *in vitro* through the downregulation of both direct antigen presentation by tumour cells and cross-presentation by dendritic cells[101]. For example, an *in vitro* study showed that PGE_2 switches the function of dendritic cells from induction of immunity to T cell tolerance through the upregulation of CD25 and indoleamine 2,3-dioxygenase[102]. In addition to modulating T cell and dendritic cell function, PGE_2 modulates cancer-associated immunosuppression through the inhibition of dendritic cell differentiation and T cell proliferation *in vivo*[103,104]. Furthermore, PGE_2 promoted mammary tumour progression through the induction of MDSCs *in vivo*[105].

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Collectively, the effects of PGE_2 on the immune system may allow neoplastic cells to evade attack. To our knowledge, there is nothing further reported in the literature indicating the participation of other prostaglandins and leukotrienes in cancer-associated immunosuppression.

Angiogenesis—It is widely recognized that angiogenesis is required for tumours to grow beyond a certain size and to metastasize. To develop a stable blood supply for tumour growth, many cells in the tumour microenvironment, including tumour epithelial cells, stromal cells and immune cells, secrete various proangiogenic factors that stimulate endothelial cell recruitment, proliferation, migration and tubule formation. Numerous *in vitro* and *in vivo* studies indicate that prostaglandins and leukotrienes modulate angiogenesis at different levels (FIG. 6).

Homozygous deletion of *Ep2* completely abrogates the induction of vascular endothelial growth factor (VEGF) in the intestinal polyp stroma of $Apc^{\Delta 716}$ mice and inhibits intestinal polyp growth, demonstrating that PGE_2 induction of VEGF is important for tumour growth in this mouse model[29]. Moreover, PGE_2 induced expression of CXCL1, a pro-angiogenic chemokine, in human CRC cells, and the release of CXCL1 from tumour epithelial cells in turn stimulated microvascular endothelial cell migration and tube formation *in vitro* and *in vivo*[106]. Activation of EP2 receptors by PGE_2 induces FGF2 expression through potential multiple protein kinase A (PKA), SRC, EGFR, and ERK1 and ERK2 signalling pathways in an endometrial adenocarcinoma cell line and in endometrial adenocarcinoma tissue explants[107]. PGE_2 released from mammary tumour epithelial cells induces angiogenesis through the induction of pro-angiogenic factors through a cyclic AMP-dependent PKA pathway *in vivo* and *in vitro*[108]. PGE_2 can also induce VEGF secretion in ovarian, prostate and gastric cancer cell lines through the activation of EGFR downstream of EP2 and EP4 (REFS [109-111]). Similar to PGE_2, $PGF_{2\alpha}$ induces VEGF expression through an FP–EGFR–Ras–Erk pathway in an endometrial adenocarcinoma cell line[112]. Moreover, $PGF_{2\alpha}$-FP signalling can stimulate the secretion of CXCL1 in endometrial tumour cells to promote neutrophil infiltration in mouse xenograft tumours[113]; neutrophil infiltration has also been shown to be essential for angiogenesis in other tumour models[114]. In tumour implantation models, increased TXA_2 levels as a result of overexpression of TXA_2 synthase in colon-26 adenocarcinoma cells accelerated tumour growth and tumour-associated angiogenesis in syngeneic BALB/c mice[115].

In addition to inducing the production of angiogenic factors in epithelial cells, prostaglandin signalling in stromal cells also contributes to angiogenesis. A host PGE_2–EP2 signal is required for tumour angio genesis by enhancing endothelial cell motility and vascular hyperpermeability in a mouse model of breast cancer[116]. Similarly, the host PGE_2–EP3 signal is a prerequisite for vEGF expression in the stroma and tumour angiogenesis in a mouse model of lung carcinoma[117]. In endothelial cells, PGE_2 not only upregulates VEGF and FGF2 expression through the stimulation of an ERK2-JUN N-terminal kinase 1 (JNK1) signalling pathway, which is important for inducing cell growth and survival[118], but also promotes αVβ3 integrin-dependent migration and spreading of endothelial cells[119] and mediates VEGFand FGF2-induced CXCR4-dependent neovessel assembly *in vivo*[120]. In addition, TXA_2 mediates the effects of COX2 on endothelial cell migration and angiogenesis *in vitro* and *in vivo*[121]. Intriguingly, VEGF and FGF2 induce COX2, and subsequently PGE_2 and PGI_2, in endothelial cells, suggesting that the effects of PGE_2 on regulation of VEGF and FGF2 are probably amplified through a positive feedback loop[120]. In contrast to PGE_2 signalling, deficiency of the DP receptor in the host accelerates tumour growth of implanted lung carcinomas by stimulating angiogenesis[122], suggesting that the host PGD_2–DP signal inhibits tumour growth by inhibiting angiogenesis.

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The physiological significance of leukotrienes in angiogenesis is much less well characterized than that of the prostaglandins. LTB_4 induced endothelial cell migration and tube formation *in vitro* and stimulated VEGF-induced angiogenesis through the BLT2 receptor *in vivo*[123]. Similarly, LTC_4 induced endothelial cell proliferation *in vitro*[124] and LTC_4 and LTD_4 promoted angiogenesis in the chick chorioallantoic membrane system[125]. In addition, LTB_4 enhances hypoxia-induced microvascular alterations *in vivo*[126].

In addition to the involvement of PGE_2 and leukotrienes in signalling crosstalk between tumour epithelial and endothelial cells, PGE_2 also stimulates immune cells to produce pro-angiogenic factors. For example, PGE_2 promotes mast cells to release VEGF and the chemokine CCL2 *in vitro*[127,128]. CCL2 can induce tumour-associated angiogenesis[129] by directly recruiting endothelial cells that express its receptor CCR2 *in vitro* and *in vivo*[130], by inducing VEGF release from macrophages through a COX2-PGE_2 pathway *in vitro*[131], and/or by indirectly attracting more tumour-associated monocytes and macrophages, which are phenotypically distinct from normal macrophages in their ability to promote angiogenesis in mice[132]. LTB_4 induces neutrophil-mediated vascular permeability *in vitro* and *in vivo*[133]. Moreover, inhibition of CysLT production by the deletion of LTC_4 synthase reduces vascular permeability in zymosan A-induced, monocyte and macrophage-mediated peritoneal inflammation and in immunoglobulin E-dependent, mast cell-mediated passive cutaneous anaphylaxis[134], suggesting that CysLTs promote inflammation-mediated vascular permeability.

Therapeutic and chemopreventive agents

A retrospective cohort study shows that aspirin, a nonselective NSAID, specifically reduces cancer risk in the subgroup of patients whose colon tumours expressed higher levels of COX2 (REF. [135]). In addition to prevention, regular aspirin use after the diagnosis of CRC at stages I, II and III improves overall survival, especially among individuals whose tumours overexpress COX2 (REF. [136]). However, the prolonged use of non-selective NSAIDs is associated with adverse gastrointestinal side effects. Long-term use of high doses of selective COX2 inhibitors is currently not recommended because of the unacceptable cardiovascular side effects in certain patients, especially those with a history of atherosclerotic heart disease[137]. However, a selective COX2 inhibitor (celecoxib) is still approved by the US Food and Drug Administration for use as an adjuvant treatment in patients at a high risk for developing CRC, such as those with familial adenomatous polyposis. It has been proposed that some of the adverse effects related to NSAID use are associated with a global reduction in prostanoid production[138]. For instance, COX2 deficiency in mice contributes to the pro-atherogenic properties of high-density lipoprotein cholesterol, with increased lipid deposition in the aorta and the dramatic imbalance in circulating prostanoids[139]. One hypothetical method to avoid the cardiovascular side effects of COX2 inhibition would be to target only COX-derived PGE_2 signalling that mediates the tumour-promoting effects of COX2. For example, antagonists of PGE_2 receptors have been developed and show promising effects for preventing and/or inhibiting growth of different types of tumours, including colon, oesophageal, lung and breast in preclinical animal models[27-29,33,67,140].

Inhibition of the 5-LOX pathway may also be useful for cancer therapy. For example, a 5-LOX inhibitor, zileuton, has been shown to prevent lung tumorigenesis in carcinogen-treated mice[141]. A combined treatment regimen using a selective COX2 inhibitor and a 5-LOX inhibitor not only had additive effects on reducing tumour growth in mouse xenograft models of human colon, oesophageal, breast and skin cancer[142-145], but also reduced liver metastases in a hamster model of chemically induced ductal pancreatic adenocarcinoma[146]. Moreover, blockage of leukotriene production by the LTA_4 hydrolase inhibitor bestatin reduced tumour burden in rats, as described above[42]. The LTB_4 receptor antagonist, LY293111, significantly inhibits tumour growth and metastases in a fluorescent orthotopic model of pancreatic

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cancer[71] and a mouse xenograft model of human CRC[147]. Unfortunately, the results from two Phase II trials showed that LY293111 did not improve progressionfree survival in patients with non-small-cell lung or pancreatic cancer[148]. In addition, a CysLT1 receptor antagonist, zafirlukast, reduced tumour burden in a mouse model of carcinogen-induced lung tumours[149]. Although NSAIDs are still among the most promising chemopreventive agents for cancer, cardiovascular and gastrointestinal side effects have dampened enthusiasm for their use as chemopreventive agents. Therefore, it is now crucial to evaluate whether the antagonists of PGE_2 and leukotriene receptors have better specificity for human cancer prevention and treatment.

Summary

Many strategies exist to develop more effective cancer prevention and treatment options. Chemoprevention and targeted therapies are being carefully evaluated on several fronts as effective measures to achieve better cancer control. A big challenge remains to develop chemopreventive agents that are both effective and safe. An entirely new approach, referred to as personalized cancer prevention and treatment, is likely to have an important role in achieving these goals. This idea is supported by the observations that patients whose colon tumours express higher levels of COX2 benefit from regular aspirin use in cancer prevention and risk reduction[135,136], and that patients whose tumours express a mutant form of *KRAS* do not benefit from EGFR-specific therapy with cetuximab or panitumumab[150]. However, this approach relies on a foundation of knowledge derived from the molecular basis of carcinogenesis to the molecular characterization of individual cancers. Understanding the role of eicosanoids in tumorigenesis and profiling these biologically active lipids in each patient are two crucial steps towards this personalized approach as they may be biomarkers for predicting which patients respond to NSAIDs in prevention and/or as intermediate markers for assessing response during treatment.

In addition to biomarkers, certain eicosanoids are also potential drug targets for personalizing cancer prevention and/or treatment. The evidence that proinflammatory eicosanoids such as PGE_2, LTB_4 and LTD_4 promote tumour growth and metastasis, whereas anti-inflammatory PGD_2 suppresses tumour growth will provide a rationale to develop the next generation of personalized cancer preventive agents. Therefore, it is now crucial to evaluate whether these prostaglandin and leukotriene receptor antagonists and agonists, as well as agents that lower cellular levels of pro-inflammatory prostaglandins and leukotrienes, have better efficacy with fewer adverse effects than NSAIDs. For example, the activators of 15-PGDH and inhibitors of PGE_2 synthases, LTA_4 hydrolase and LTC_4 synthases may be useful agents for future studies.

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Glossary

Cysteinyl leukotriene (CysLT)	Leukotriene that contains the amino acid cysteine conjugated to the lipid backbone.
$Apc^{Min/+}$ mice	Carry a point mutation in one *Apc* allele and spontaneously develop intestinal adenomas. Used as a model for human familial adenomatous polyposis and for human sporadic colorectal cancer.

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Azoxymethane (AOM) mouse model	One of the chemically induced colorectal cancer models in which mice are exposed to a chemical carcinogen, AOM.
T helper 17 (T_H17) cells	A functional subset of $CD4^+$ T helper cells that secrete particular inflammatory cytokines, including interleukin-17, which mediate pathogenic responses in autoimmune diseases.
Dendritic cells	Bone marrow-derived immune accessory cells that function as antigen-presenting cells for naive T cells and that lead to the initiation of adaptive immune responses to protein antigens.
Cytotoxic T cells	A subgroup of T cells (also known as $CD8^+$ T cells or killer T cells) that are capable of recognizing and inducing the death of infected somatic or tumour cells. $CD8^+$ T cells are recognized as cytotoxic T cells once they become activated.
Regulatory T cells	A T cell subpopulation that suppresses activation of other T cells and maintains immune system homeostasis and peripheral tolerance to self-antigens.
Myeloid-derived suppressor cells (MDSCs)	Immature myeloid cells with potent immunosuppressive functions.
Cross-presentation	A mechanism by which a professional antigen-presenting cell takes up, processes and presents extracellular antigens from a third cell (for example, a virus-infected or tumour cell) with major histocompatibility complex class I molecules to activate a naive $CD8^+$ T cell.
T cell tolerance	Unresponsiveness of the adaptive immune system to antigens, as a result of the inactivation or death of antigen-specific T cells, which is induced by exposure to the antigens.
$Apc^{\Delta 716}$ mice	Generated by inserting neomycin into exon 15 of *Apc*, which results in truncated APC at codon 716. Spontaneously develop intestinal adenomas and are another model for human familial adenomatous polyposis and sporadic colorectal cancer.
Chick chorioallantoic membrane system	A biological assay using the well-vascularized chorioallantoic membrane of the chicken egg to evaluate the biological activity of pro-angiogenic and anti-angiogenic factors.

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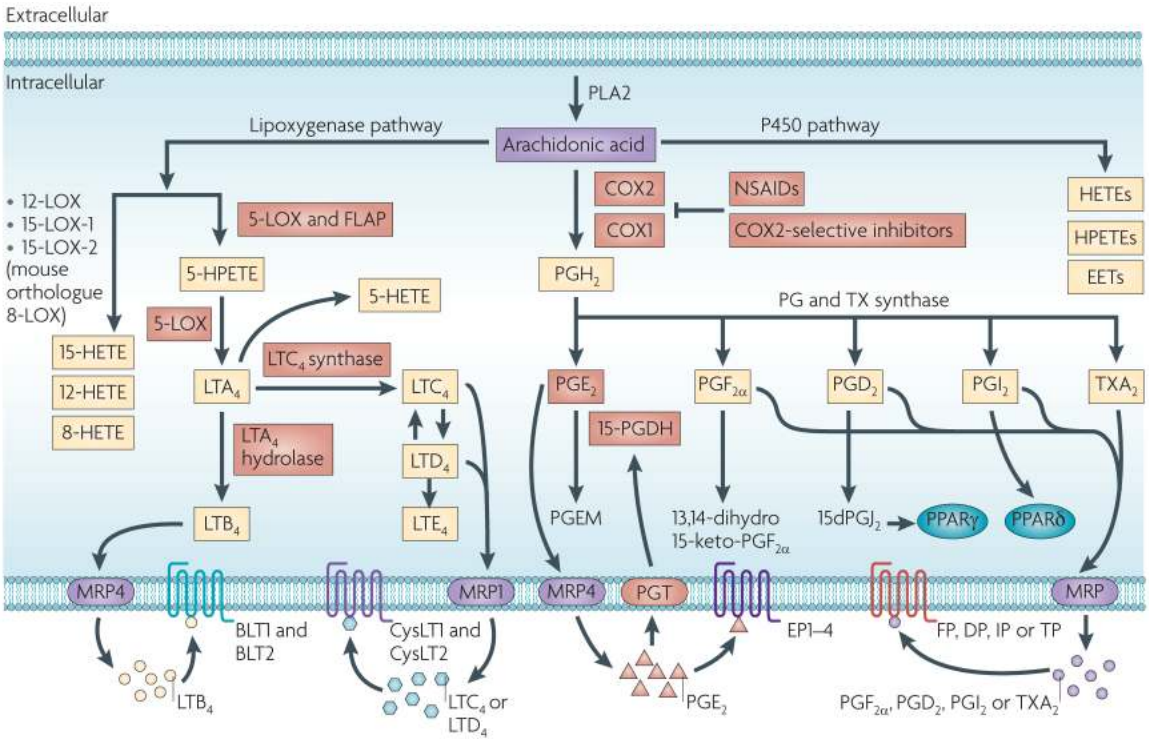

Figure 1. An overview of eicosanoid synthesis pathways

Arachidonic acid is a polyunsaturated fatty acid that constitutes the phospholipid domain of most cell membranes and is liberated from the cellular membranes by cytoplasmic phospholipase A2 (PLA2). Free arachidonic acid can be metabolized to eicosanoids through three major pathways: the cyclooxygenase (COX), the lipoxygenase (LOX) and the cytochrome P450 monooxygenase pathways. In the COX pathway, the key step is the enzymatic conversion of arachidonic acid to the intermediate prostaglandin G_2 (PGG_2), which is then reduced to an intermediate PGH_2 by the peroxidase activity of COX. PGH_2 is sequentially metabolized to prostanoids, including prostaglandins (PGs) and thromboxanes (TXs) by specific prostaglandin and thromboxane synthases. LOXs convert arachidonic acid into biologically active metabolites such as leukotrienes and hydroxyeicosatetraenoic acids (HETEs); P450 metabolizes arachidonic acid into epoxyeicosatrienoic acids (EETs), HETEs and hydroperoxyeicosatetraenoic acids (HPETEs). In the 5-LOX pathway, arachidonic acid is converted to an intermediary 5-HPETE, which is further metabolized to form the unstable leukotriene A_4 (LTA_4). LTA_4 is subsequently converted to 5-HETE, LTB_4, LTC_4, LTD_4 and LTE_4. Each of the prostaglandins and leukotrienes exerts its biological effects by binding to its cognate G protein-coupled receptor. PGI_2 can transactivate the nuclear peroxisome proliferator-activated receptor-δ (PPARδ), and a PGD_2 dehydration product, $15dPGJ_2$, is a natural ligand for PPARγ. The multidrug resistance-associated protein (MRP) gene family is comprised of efflux transporters for both prostaglandins and leukotrienes, and PGT is an influx transporter for prostaglandins. Hydroxyprostaglandin dehydrogenase 15-(NAD) (15-PGDH) mainly metabolizes intracellular PGE_2 and $PGF_{2\alpha}$ to a stable 13,14-dihydro-15-keto-PGE_2 and 13,14-dihydro-15-keto-$PGF_{2\alpha}$. The red boxes indicate the signalling pathways that are discussed in this Review. CysLT, cysteinyl leukotriene; NSAID, non-steroidal anti-inflammatory drug.

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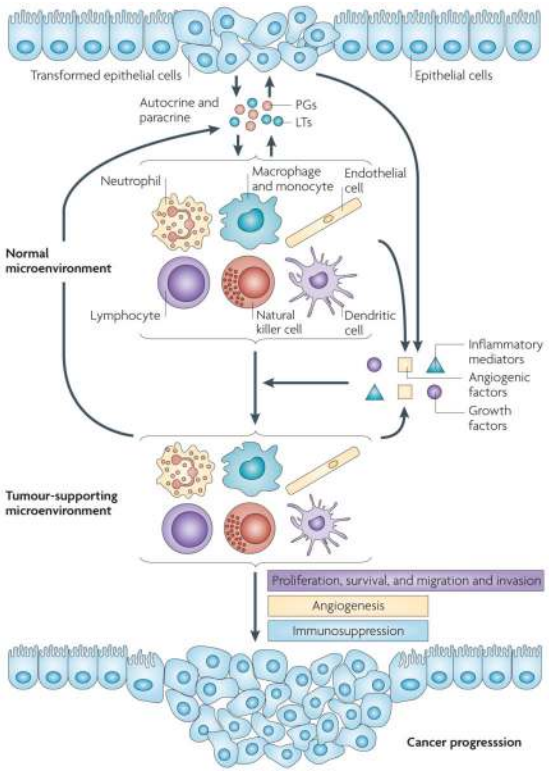

Figure 2. Models of pro-inflammatory prostaglandins and leukotrienes in promoting cancer progression

Following the initiation of epithelial tumours, the reciprocal interactions between transformed epithelial and stromal cells have a key role in facilitating cancer progression. Pro-inflammatory prostaglandins and leukotrienes produced by tumour epithelial cells and their surrounding stromal cells are key mediators in this crosstalk and can accelerate tumour growth and metastasis through several methods. First, the pro-inflammatory prostaglandins (PGs) and leukotrienes (LTs) can directly induce epithelial tumour cell proliferation, survival, and migration and invasion in autocrine and paracrine manners. These pro-inflammatory lipids also stimulate epithelial cells and their surrounding stromal cells to produce growth factors, pro-inflammatory mediators and angiogenic factors, which switch the microenvironment from normal to tumour supporting. The tumour microenvironment, in turn, recruits immune cells and endothelial cells (tumour-infiltrating cells), which produce more pro-inflammatory mediators including eicosanoids, growth factors and angiogenic factors. These factors accelerate tumour growth and stimulate metastatsis through an autocrine loop by inducing angiogenesis and evading attack by the immune system.

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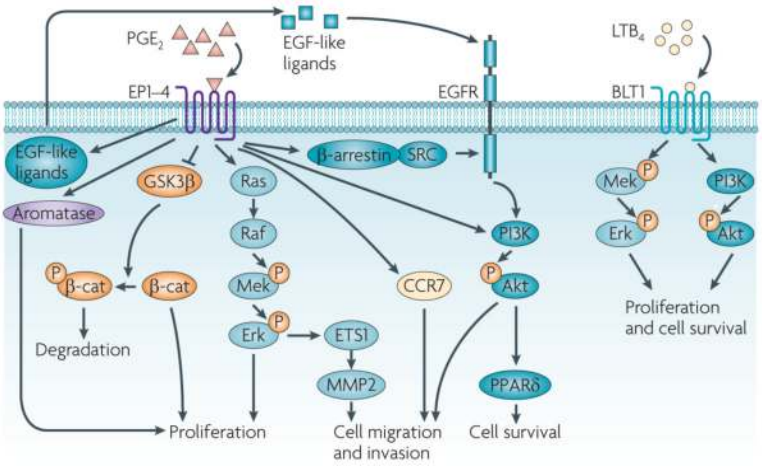

Figure 3. PGE_2 and LTB_4 promote cancer progression through the induction of tumour epithelial cell proliferation, survival, and migration and invasion

Multiple cellular signalling pathways mediate the effects of prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB_4) on the regulation of epithelial tumour cell proliferation, survival, and migration and invasion. PGE_2 stimulates cell proliferation through multiple cascades in both colorectal cancer (CRC) and non-small-cell lung cancer cells. PGE_2 also induces cell proliferation through a glycogen synthase kinase-3β (GSK3β)–β-catenin (β-cat) pathway in CRC cells or by the upregulation of aromatase in breast cancer cells. PGE_2 inhibition of GSK3β reduces β-catenin phosphorylation and thereby prevents its degradation, leading to accumulation, nuclear translocation and functional activity of β-catenin. PGE_2 promotes CRC cell survival by activating a PI3K–Akt– peroxisome proliferator-activated receptor-δ (PPARδ) cascade *in vitro* and *in vivo*. In addition, PGE_2 induces CRC cell migration and invasion through β-arrestin-1–SRC–epidermal growth factor receptor (EGFR)–PI3K–Akt signalling *in vitro* and *in vivo*. PGE_2 transactivation of EGFR also depends on the extracellular release of an EGF-like ligand in CRC cell lines and a normal gastric epithelial cell line. PGE_2 also induces cell migration and invasion through an Erk–ETS1–matrix metalloproteinase 2 (MMP2) cascade in pancreatic cancer cell lines or through the upregulation of C-C chemokine receptor 7 (CCR7) in breast cancer cell lines. LTB_4 stimulates cell proliferation and promotes cell survival through a BLT1–Erk pathway in CRC cell lines or through both Mek–Erk and PI3K–Akt pathways in human pancreatic cancer cell lines. P, phosphorylation.

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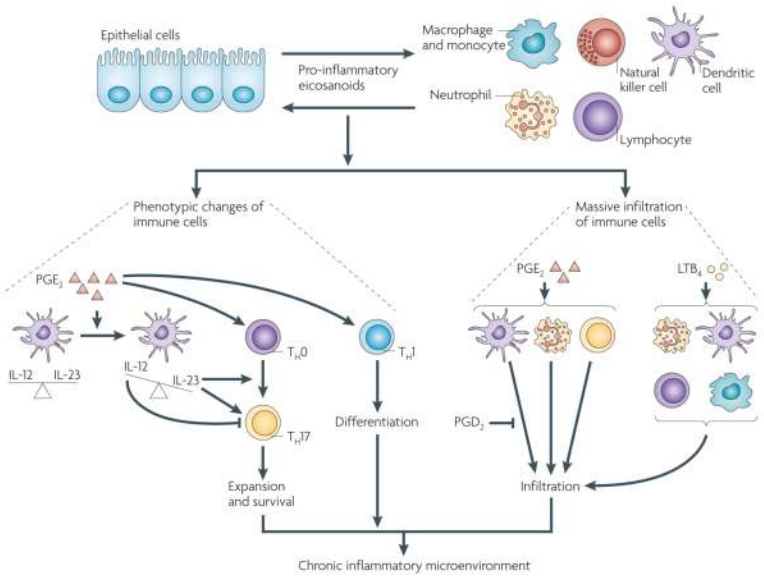

Figure 4. Prostaglandins and leukotrienes are key pro-inflammatory mediators in orchestrating crosstalk between tumour epithelial cells and immune cells

During the initiation of epithelial tumours or chronic inflammation, transformed or normal epithelial cells and tissue-resident immune cells locally secrete pro-inflammatory prostaglandins and leukotrienes such as prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB_4), which recruit large numbers of immune cells from the circulation into the mucosa and reprogramme the immune cells into pro-inflammatory leukocytes. For example, PGE_2 induces expansion of inflammatory T helper 17 (T_H17) cells by regulating interactions between T cells and dendritic cells and facilitates T_H1 differentiation. PGE_2 shifts the interleukin-12 (IL-12)/IL-23 balance in favour of IL-23 through the induction of IL-23 and inhibition of IL-12 expression in dendritic cells. IL-23 is essential for T_H17 expansion and survival, whereas IL-12 suppresses T_H17 development and function. In recruitment of immune cells, PGE_2 induces infiltration of neutrophils and T_H17 cells and enhances dendritic cell migration whereas PGD_2 inhibits dendritic cell migration. LTB_4 has a major role in attracting neutrophils, T cells, dendritic cells and macrophages from the circulation into inflammatory sites. Collectively, PGE_2 and LTB_4 induce the massive infiltration of immune cells and change their functionality, which in turn results in the establishment of a chronic inflammatory microenvironment.

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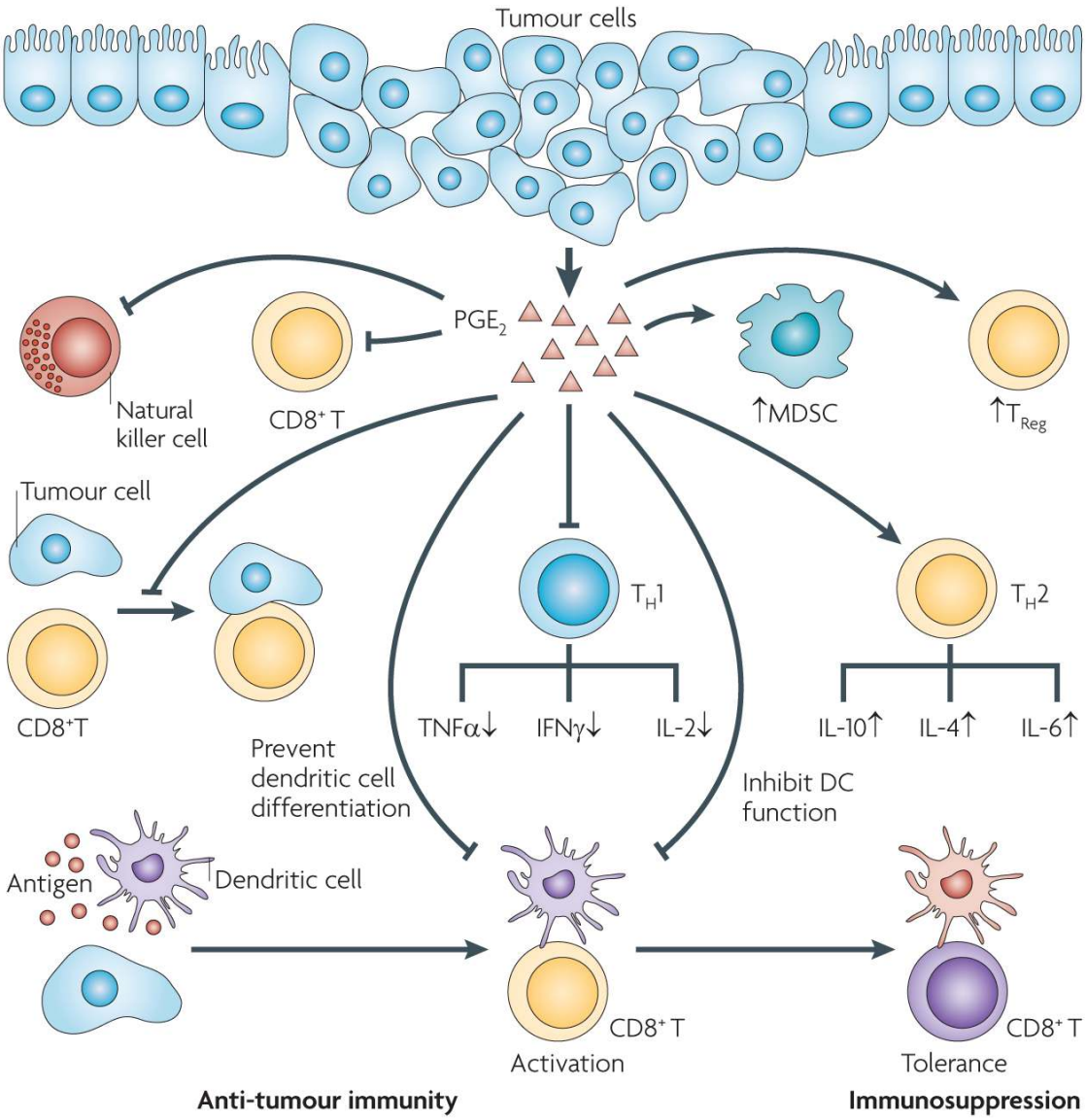

Figure 5. PGE_2 provides coordinated regulation of tumour immunosuppression

Pro-inflammatory prostaglandin E^2 (PGE_2) produced by tumour epithelial cells and/or their surrounding stromal cells induces immunosuppression through several ways, including: downregulating anti-tumour T helper 1 (T_H1) cytokines and upregulating immunosuppressive T_H2 cytokines; inhibiting $CD8^+$ T cell proliferation and activity, suppressing the anti-tumour activity of natural killer cells and stimulating the expansion of regulatory T cells (T_{Reg} cells) and myeloid-derived suppressor cells (MDSCs); and inhibiting $CD8^+$ T cell anti-tumour functions by impairing the ability of tumour cells to directly present tumour antigen, inhibiting dendritic cell differentiation and switching the function of dendritic cells from induction of immunity to T cell tolerance. The yellow $CD8^+$ T cells have anti-tumour activity and the purple $CD8^+$ T cell does not have anti-tumour activity. The purple dendritic cells have the ability to present tumour antigens from tumour cells with major histocompatibility complex (MHC) class I molecules to activate naive $CD8^+$ T cells. The orange dendritic cell does not have the ability to activate $CD8^+$ T cells (T cell tolerance). IFNγ, interferon-γ; IL, interleukin; TNFα, tumour necrosis factor-α.

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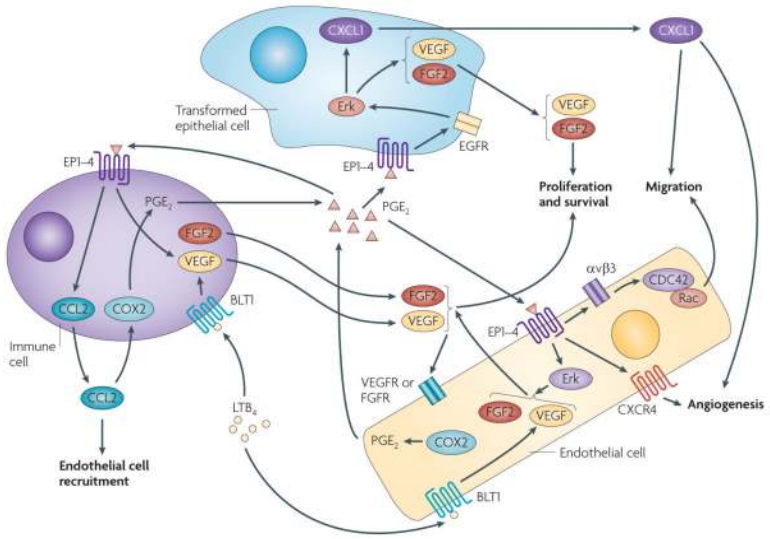

Figure 6. A model of PGE_2 and LTB^4 coordinately regulating angiogenesis in the tumour microenvironment

Pro-inflammatory prostaglandin E_2 (PGE_2) and/or B_4 LTB_4 promote angiogenesis on at least two levels. First, PGE_2 and/or LTB_4 can directly act on epithelial, endothelial and/or immune cells to induce angiogenic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2) and the chemokines CXCL1 and CCL2. In transformed epithelial cells, PGE_2 induces VEGF and CXCL1 secretion through an EP2 or EP4–epidermal growth factor (EGFR)–Erk cascade. In endothelial cells, PGE_2 induces VEGF and FGF2 secretion through a MAPK pathway and LTB_4 also stimulates VEGF expression. Moreover, PGE_2 not only binds to endothelial cells to stimulate cell migration through an αVβ3 integrin–CDC42 and Rac pathway, but also mediates VEGF-and FGF2-induced CXCR4-dependent neovessel assembly *in vivo*. In immune cells, PGE_2 promotes mast cells to release VEGF and CCL2, and LTB_4 stimulates VEGF expression. Secretion of VEGF and FGF2 from tumour epithelial, endothelial and immune cells promotes endothelial cell proliferation and survival, and the chemokine CXCL1 released from tumour epithelial cells stimulates endothelial cell migration and tube formation *in vitro* and angiogenesis *in vivo*. CCL2 can attract endothelial cells to the tumour microenvironment. Interestingly, VEGF and FGF2 induce COX2 and subsequently PGE_2 in endothelial cells, and CCL2 also induces COX2 and PGE_2 in macrophages. Therefore, the effects of PGE_2 on the regulation of VEGF, FGF2 and CCL2 are probably amplified through this positive feedback loop.

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Table 1

Signals that mediate the effects of eicosanoids on carcinoma cell proliferation, survival, and migration and invasion

Lipids	Receptors	Pathways	Functions	Tumour type	In vitro	*In vivo**	refs
PGE_2	EP1–4‡	Ras–Erk	Proliferation	Colorectal	+	+	46
	EP1–4‡	Ras–Erk	Proliferation	Non-small-cell lung	+		48
	EP2	GSK3β–β-catenin	Proliferation	Colorectal	+		47
	EP1–4‡	PI3K–Akt–PPARδ	Survival	Colorectal	+	+	10
	EP1–4‡	BCL-2	Survival	Colorectal	+		50
	EP1–4‡	NF-κB	Survival	Colorectal	+		51
	EP4	SRC–EGFR–PI3K–Akt	Migration and invasion	Colorectal	+	+	61,62
	EP1	SRC–EGFR	Migration and invasion	Hepatocellular	+		63
	EP1–4‡	Erk–ETS1	Migration and invasion	Pancreatic	+		65
	EP2 and EP4	CCR7	Migration and invasion	Breast	+		66
	EP4	PI3K–Akt	Migration and invasion	Lung and colorectal	+	+	67
$PGF_{2\alpha}$	FP	Erk–FGF2–FGFR1–Erk	Proliferation	Endometrial	+		52
	FP	?	Migration and invasion	Colorectal and endometrial	+		68, 69
PGD_2	PPARδ	?	Proliferation inhibition	Prostate	+		53
TXA_2	TP	RHOA	Migration	Prostate	+		70
LTB_4	BLT1	Mek–Erk and PI3K–Akt	Proliferation	Pancreatic	+		56
	BLT1	Erk	Survival	Colorectal	+		55
	?	?	Migration and invasion	Pancreatic		+	71
LTD_4	CysLT1–2‡	GSK3β–β-catenin	Survival	Intestinal	+		57
	CysLT1	PKC–Raf–Erk	Proliferation and survival	Intestinal	+		58
	CysLT1–2‡	COX2 and BCL-2	Survival	Intestinal	+		59
	CysLT1	?	Proliferation	Colorectal	+		60

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Lipids	Receptors	Pathways	Functions	Tumour type	In vitro	*In vivo*[*]	refs
	CysLT1	?	Survival	Prostate	+		44
	CysLT1–2[‡]	PI3K–Akt–Rac	Migration	Intestinal	+		72

BLT1, leukotriene B4 receptor (also known as LTB4R); CCR7, C-C chemokine receptor 7; COX2, cyclooxygenase 2; CysLT1, cysteinyl leukotriene receptor 1; EGFR, epidermal growth factor receptor; EP1, prostaglandin E receptor 1; FGF2, fibroblast growth factor 2; FGFR1, FGF receptor 1; FP, prostaglandin F receptor; GSK3β, glycogen synthase kinase 3β; LTB_4, leukotriene B_4; NF-κB, nuclear factor-κB; PGE_2, prostaglandin E_2; PKC, protein kinase C; PPARδ, peroxisome proliferator-activated receptor-δ; TXA_2, thromboxane A_2; TP, TXA_2 receptor.

[*] *In vivo* indicates animal studies.

[‡] No data available on which receptor mediates the effects of the lipid.