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Future Lipidol. Author manuscript; available in PMC 2014 February 19.

Published in final edited form as:
Future Lipidol. 2008 August 1; 3(4): 453–467. doi:10.2217/17460875.3.4.453.

Roles of Eicosanoids in Prostate Cancer

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Summary

Eicosanoids, the metabolites of arachidonic acid, have diverse functions in the regulation of cancer including prostate cancer. This review will provide an overview of the roles of eicosanoids and endocannabinoids and their potential as therapeutic targets for prostate cancer treatment.

Keywords

Arachidonic acid; cyclooxygenase; cytochrome P450; eicosanoids; endocannabinoids; lipoxygenase; prostate cancer

Prostate cancer is among the most diagnosed malignancies and contributes to cancer-related mortality rate in men. The vast majority of morbidity and mortality results from spread of the tumor beyond the prostate gland and/or tumor becoming hormone refractory. The process of metastasis is a complex multistage process consisting of a series of sequential, interrelated steps that include growth, vascularization, adhesion, extravasation, and invasion. The discovery of new molecular targets to inhibit cell proliferation, growth, and invasion/migration is among the most important endeavors in prostate cancer therapy.

High fat diets, particularly ω-6 polyunsaturated fatty acids, are associated with prostate cancer development and progression [1, 2] and prostate cancer cell growth [3, 4]. On the other hand, diets rich in ω-3 fatty acids are associated with the lower incidents of the disease in some studies [1, 5], whereas other reports indicated no evidence of a significant reduced risk of prostate cancer [6] or even increased risk [7]. These opposing roles of fatty acids are consistent with the fact that diet is an important factor in the coincidence of prostate cancer. The high ratio of ω-3/ω-6 fatty acids in the diet has been suggested to prevent prostate cancer [8]. Although in one study showed that plant-based foods and fish diets do not reduce the prostate specific antigen (PSA) levels in prostate cancer patients, they significantly increase the PSA doubling times [9].

Arachidonic acid (AA, 20:4 ω-6) is one of the major polyunsaturated ω-6 fatty acids. AA is metabolized by three groups of oxygenases namely cyclooxygenases (COX), lipoxygenases (LOX) and cytochrome P450s (CYP) to a number of biologically active eicosanoids (Figure 1). This review will focus on the role of these AA metabolites in prostate cancer. Eicosanoids have diverse roles in the regulation of cellular functions and they have been extensively studied as important lipid mediators in cardiovascular systems. However, their roles in cancer, particularly prostate cancer are much less investigated.

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I. Cyclooxygenase (COX) Pathways

There are two well-characterized COX isoenzymes, COX-1 and COX-2. A splice variant of COX-1 which retains intron one and a frameshift mutation has been named COX-3, COX-1b, or COX-1 variant (COX-1v) [10]. COX-1 is constitutively expressed in most cells while COX-2 is an inducible enzyme. The COX pathway is the most studied in prostate cancer. COX-2 is overexpressed in prostate cancer tissues [11–19]. The immunohistochemistry staining of COX-2 increases with prostate tumor grade [20], suggesting that COX-2 has a role in prostate cancer development and progression [21]. Contrarily, several studies did not find a consistent and significant difference in COX-2 expression in normal and prostate cancer tissues [22–24], but the overexpression of COX-2 correlated with the chronic inflammatory lesions [19, 23]. A similar controversy exists concerning the expression of COX-2 in human prostate cancer cells compared with normal epithelial cells. Some studies demonstrated the high COX-2 expression in prostate cancer cells while others reported the low or absent COX-2 expression [21, 24–28]. Similarly, the effects of nonselective COX inhibitors such as nonsteroidal anti-inflammatory drugs (NSAIDs) and specific COX-2 inhibitors on prostate cancer cell proliferation and invasion are complex and not uniform, and their association with reduced risk of prostate cancer is not conclusive [28–44].

Within the cyclooxygenase active site, COX inserts molecular oxygen at C11 and C15 to form prostaglandin G_2 (PGG_2); then, its peroxidase active site reduces PGG_2 to PGH_2 [45]. Subsequently, specific synthases or isomerases convert PGH_2 to various prostaglandins (PGs) and thromboxanes (TXs) (Figure 2). Common COX metabolites of AA are PGI_2, PGD_2, PGE_2, $PGF_{2\alpha}$, PGJ_2, and TxA_2. PGI_2 and TxA_2 are unstable and are rapidly converted to the stable 6-keto-$PGF_{1\alpha}$ and TxB_2, respectively.

I.1 Prostaglandins and prostate cancer

The plasma PGI_2 concentrations (detected as 6-keto-$PGF_{1\alpha}$) in normal men are similar to patients with benign prostatic hypertrophy (BPH) but the levels rise with advancing disease and varied with the degree of tumor differentiation [46]. Interestingly, PGI_2 and its stable analogs inhibit metastasis of prostate cancer [47–49]. The role of endogenous PGI_2 in prostate cancer is still unclear and has not been studied in recent years.

PGE_2 is the most characterized in prostate cancer. Since early 1980's, the effects of PGE_2 in prostate cancer has been recognized [50]. In BPH and prostate cancer tissues, PGE_2 is the only major PG that is produced in significant amounts by the prostate and its levels are higher in prostate cancer tissues [51]. PGE_2 stimulates growth of prostate cancer cells including PC-3 and LNCaP cells [52, 53]. Interestingly, in PC-3 ML cells, exogenously added PGE_2 increases hypoxia inducible factor-1alpha (HIF-1α) protein and induces nuclear localization of HIF-1α [54], which in turn induces transcription of many genes associated with cell growth. Conversely, selective COX-2 inhibitors such as meloxicam and NS-398 decrease HIF-1α levels and nuclear translocation. This pathway is supported by the positive feedback mechanism that PGE_2 upregulates the expression of COX-2 mRNA, its own synthesizing enzyme [52, 53]. These results suggest a cycle of stimulation of COX-2 and PGE_2 that promotes prostate cancer progression. PGE_2 stimulates growth and invasion of prostate cancer cells through multiple signaling pathways. For examples, PGE_2 activates protein kinase A (PKA) pathway to induce the expression of c-fos mRNA and growth in PC-3 cells [55]. PGE_2 increases the secretion of vascular endothelial growth factor (VEGF) and cyclic adenosine monophosphate (cAMP) in PC-3 cells but less in DU-145 and LNCaP cells [56]. PGE_2 activates the interleukin-6 signaling pathway to promote prostatic intraepithelial neoplasia cell growth, providing evidence that overexpression of COX-2 and PGE_2 mediate prostate cancer development and progression through the IL-6 signaling

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pathway [57]. NS-398, a specific COX-2 inhibitor, inhibits invasion of PC-3 and DU-145 cells by reducing the matrix metalloproteinases (proMMP-2, MMP-9 and proMMP-9) [58]. In this case, PGE_2 alone does not increase cell invasion of PC-3 and DU-145 cells but reverses the NS-398-reduced cell invasion [58]. In a later study, PGE_2 does not stimulate invasion of low invasive PC-3 cells but induces invasion of high invasive PC-3 cells [59]. These results suggest that the endogenous PGE_2 may be necessary for rendering cell invasion; however, cells may require a high level of exogenous PGE_2 or cooperation with other factors to induce cell invasion [59].

PGD_2 is transformed to 15-deoxy-$\Delta^{12,14}$-PGD_2 (15-d-PGD_2) and 15-deoxy-$\Delta^{12,14}$-PGJ_2 (15-d-PGJ_2) in some cells. PGD_2 produced by normal prostate stromal cells suppresses the growth of prostate cancer PC-3, DU-145, and LNCaP cells [60]. PGD_2 and its metabolites inhibit prostate cancer cell growth by the activation of peroxisome proliferator-activated receptor γ (PPARγ) in the order of 15-d-PGJ_2 > 15-d-PGD_2 > PGD_2 [60]. 15-d-PGJ_2 is an effective ligand for PPARγ and it induces apoptosis and nonapoptotic cell death in prostate cancer cells dependent and independent of PPARγ activation [61–66]. Interestingly, 15-d-PGJ_2 increases the expression of PPARγ and VEGF in PC-3 cells [67]. However, in a later study, 15-d-PGJ_2 did not increase the expression of PPARγ but blocked the serum-induced COX-2 expression in PC-3 cells [65]. Exogenous PGD_2 is an antiinvasive factor and inhibits invasion of PC-3 cells in a concentration-dependent manner [59]. The importance of endogenous PGD_2 is not clear.

I.2 Thromboxane and prostate cancer

Only few studies addressed the association of thromboxane and prostate cancer. For example, UK 38485, a thromboxane synthase (TxS) inhibitor reduced the pulmonary metastasis in prostate cancer bearing rats [47] and oestrogen therapy reduced the urinary concentrations of 2,3-dinor TxB_2 and increased the ratio of PGI_2 to TxB_2 in prostate cancer patients [68]. The expression of TxS and TxA_2 receptor (TP) are elevated in less differentiated or advanced tumor tissues [69, 70], suggesting the roles of TxS, TP and TxA_2 in prostate tumorigenesis. Differential expression of TxS was observed in different types of human prostate cancer cells with high expression in PC-3, PC-3M, and ML-2 cells and low expression in normal prostate epithelial, DU-145 and LNCaP cells [69]. TxS and TxA_2 may regulate prostate cancer progression through the activation of cell motility as the inhibition of TxS reduces motility of PC-3 cells while overexpression of TxS increases motility of DU-145 cells [69]. In PC-3 cells, TxA_2 activates extracellular signal-regulated kinases (ERKs), transactivates EGF receptor (EGFR), and stimulates the release of MMPs [71]. These signaling pathways are important in the regulation of cell proliferation and invasion.

I.3 Prostanoid receptors and prostate cancer

Prostanoid receptors are G-protein coupled receptors that are activated by prostanoids. Each prostanoid can activate its own receptor namely DP, EP, FP, IP and TP for PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and TxA_2, respectively. There are only one type of FP and IP receptors but two subtypes for DP (DP_1 and DP_2) and TP (TP_α and TP_β) receptors and four subtypes for EP (EP_1, EP_2, EP_3, and EP_4) receptors [72]. Among these receptors, EP and TP receptors have been characterized in prostate cancer. The immunostaining of EP_1 receptor is higher in cancer cells of prostate tissues than in nontumor containing glands and correlated with Gleason scores [73]. EP_2 and EP_4 are higher in cancer tissues than nontumor glands but neither receptor correlate with the pathologic features. These findings suggest that EP receptors, particularly EP_1 receptor, may have an important role in prostate cancer progression. Interestingly, EP_2 and EP_4 receptors but not EP_1 and EP_3 receptors, are present in prostate cancer cell lines [55, 56]. Thus, the cell lines do not express the same EP receptor subtypes as prostate tumors. The activation of EP_2, and possibly EP_4, receptor in PC-3 cells

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by PGE_2 activates PKA pathway to increase cell growth but are less effective in DU-145 and LNCaP cells [55, 56]. Calcitriol (1,25-dihydroxyvitamin D_3) inhibits prostate cancer cell growth and differentiation by down regulating the expression of COX-2 and EP_2 and FP receptors [74–80]. These studies further indicate that COX-2 and prostanoid receptors have important role in prostate cancer.

Activation of TP by thrombin-induced TxA_2 release or U46619 enhances cell invasion of PC-3 and DU-145 cells by the activation of the small GTPase RhoA [81]. This observation was further confirmed by a recent study that RhoA is activated by TP activation leading to an increase of cell motility and cytoskeleton reorganization of prostate cancer cells [82]. These studies suggest that the function of TxA_2 in prostate cancer progression is mainly through the regulation of RhoA-mediated cell motility.

II. Lipoxygenase (LOX) Pathways

Lipoxygenases (LOX) are a family of non-heme containing oxygenases that insert molecular oxygen into polyunsaturated fatty acids such as AA at specific double bond positions. There are four LOXs, namely 5-LOX, 8-LOX, 12-LOX, and 15-LOX that metabolize AA to corresponding hydroperoxides (HPETEs). The HPETEs are reduced to their corresponding hydroxyeicosatetraenoic acids (HETEs) (Figure 3). Recent studies have demonstrated that LOXs are diversified enzymes in different species or organs including platelet 12-LOX, leukocyte 12-LOX, epidermal 12-LOX, 12(R)-LOX, 15-LOX-1, and 15-LOX-2. In recent years, LOXs have gained more attention as regulators of cancer and strong evidence indicates that 5-LOX, platelet 12-LOX and 15-LOX-1 are tumorigenic while 8-LOX and 15-LOX-2 are potentially anti-tumoricgenic.

II.1 5-LOX and prostate cancer

In 5-LOX pathway, 5-LOX metabolizes AA to 5-HPETE and then to 5(S)-HETE. 5-HPETE is also converted to the unstable epoxide leukotriene A_4 (LTA_4), which is further hydrolyzed to LTB_4, and other leukotriene metabolites. LTA_4 is also metabolized to cysteinyl leukotrienes (Cys-LTs) such as LTC_4, LTD_4, and LTE_4, and these Cys-LTs can be further metabolized to numerous leukotriene derivatives [83].

5-LOX protein is slightly detected in benign prostatic hyperplasia (BPH) and normal prostate tissues but it is markedly increased in prostatic intraepithelial neoplasia (PIN) and prostate cancer tissues [84]. 5-LOX is also present in human prostate cancer cell lines and 5-LOX inhibitors effectively inhibit cell growth through the induction of apoptosis [84–87]. Specific 5-LOX inhibitors, AA861 and 5-lipoxygenase activating protein (FLAP) inhibitor, MK886, strongly inhibit the AA-stimulated growth of PC-3 and LNCaP cells [88, 89]. Conversely, exogenously added 5-HETE enhances cell growth similar to AA. 5-HETE also reverses the inhibitory effect of MK886, suggesting that the AA-induced prostate cancer cell growth is from the 5-LOX metabolism of AA to 5-HETE. The activation of apoptosis by MK886 is from its inhibition of 5-HETE production, stimulation of the mitochondrial permeability, externalization of phosphatidylserine, and degradation of DNA [89]. In PC-3 cells, 5-HETE activates extracellular signal-regulated kinases and Akt, and these responses are blocked by pertussis toxin, suggesting that 5-HETE stimulates cell growth by a receptor-dependent mechanism [90].

5-HETE can undergo dehydrogenated to 5-oxoeicosatetraenoic acid (5-ox-ETE). 5-oxo-ETE and its precursor, 5-HETE, reverse the selenium-induced apoptosis in human prostate cancer cells [91]. A G-protein coupled receptor for 5-oxo-ETE with less affinity for 5-HETE has been recently identified [92–94]. This 5-oxo-ETE receptor is expressed in PC-3 cells in higher amounts than in LNCaP cells [95]. Inhibiting expression of 5-oxo-ETE receptor by

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siRNA significantly reduces cell viability of PC-3 cells, suggesting that 5-oxo-ETE and its receptor have a critical role in prostate cancer cell survival [95].

Among the Cys-LTs, LTD_4 is the most potent agonist for cysteinyl LT receptor type 1 (CysLT1R) and type 2 (CysLT2R) [96]. LTD_4 activates different intracellular signaling pathways through these receptors to promote cell growth and survival. Interestingly, CysLT1R is present in prostate tissues and prostate cancer cells [97]. Low expression of CysLT1R is detected in BPH and normal prostate tissues but highly expressed in PIN and prostate cancer tissues with a correlation with grades of tumor. Furthermore, CysLT1R antagonist induces early apoptosis in prostate cancer cells, indicating its antiproliferative potential in prostate cancer [97].

II.2 12-LOX and prostate cancer

Platelet-type (P-), leukocyte-type (L-) and epidermal-type (E-) 12-LOX metabolize AA to 12(S)-HETE [98, 99]. 12(R)-LOX has been cloned from human keratinocytes [100], and produces 12(R)-HETE from AA. P-12-LOX mRNA levels are elevated in prostate cancer cells and in about 40% prostate cancer tissues compared to the matching normal prostate tissues from the same patients [101, 102], suggesting that it may be a diagnostic marker for prostate cancer advancement. 12-LOX protein is slightly detected in BPH and normal prostate tissues but it is markedly increased in PIN and prostate cancer tissues [84]. P-12-LOX may regulate prostate cancer development and progression by promoting angiogenesis [103–108], and it increases the metastatic potential of prostate cancer cells [109, 110]. On the other hand, L-12-LOX is expressed in human cancer tissues and cells [111] including PC-3 cells [112]; however, its role in prostate cancer is not clear.

The role of 12(S)-HETE in promoting prostate cancer growth and metastasis is well-established [106, 107] while the role of 12(R)-HETE in prostate cancer is not known. Urinary levels of 12(S)-HETE are elevated in prostate cancer and BPH patients but decreased to the levels in normal men following radical prostatectomy. These findings suggest that 12(S)-HETE may have a potential role as a marker in prostatic diseases [113]. 12-LOX inhibitors, baicalein and *N*-benzyl-*N*-hydroxy-5-phenylpentamide (BHPP) decrease proliferation of PC-3 and DU-145 cells, suppress cyclin D_1 and D_3, and arrest cell cycle at G_0/G_1 phase and exogenous 12(S)-HETE blocks the baicalein-induced apoptosis in DU-145 cells [105]. The activity of 12(S)-HETE in proliferation, motility and angiogenesis in PC-3 cells is mediated by the activation of nuclear factor-kappa B (NF-κB) via the degradation of IkappaB and NF-κB translocation to the nucleus initiating NF-κB-induced transcription [106]. Overexpression of 12-LOX in PC-3 cells or treatment of cells with 12(S)-HETE also increases expression of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins [107], increases the PI-3K activity and VEGF expression. These effects of 12-LOX are blocked by either baicalein or LY294002, a PI-3K inhibitor [114]. These treatments lead to prolonged cell survival of prostate cancer cells. Role of other 12-LOX metabolites of AA such as hepoxilins in prostate cancer is not known.

II.3 15-LOX and prostate cancer

There are two isoforms of 15-LOX, 15-LOX-1 and 15-LOX-2 [115, 116]. Both isoforms metabolize AA to 15(S)-HETE, although AA is the preferred substrate for 15-LOX-2 and linoleic acid (LA) is the preferred substrate for 15-LOX-1. 15-LOX-1 is present in PC-3 cells and human normal prostate tissues and its expression is significantly higher in prostate cancer tissues [117]. 15-LOX-1 is localized in secretory cells of peripheral zone of glands, prostatic ducts and seminal vessels, but not in the basal layer or stroma. These findings suggest that 15-LOX-1 is tumorigenic. Overexpression of 15-LOX-1 increases cell proliferation in PC-3 cells which is reversed by the specific 15-LOX-1 inhibitor, PD146176

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[118]. In 15-LOX-1 transfected PC-3 cells, insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-1 receptor (IGF-1R) are increased [119]. IGF-1R in normal and prostate cancer tissues is correlated well with expression of 15-LOX-1, suggesting that 15-LOX-1 promotes prostate tumorigenesis by mediating IGF-1R expression and activation. A recent study identified methylation of a CpG island in 15-LOX-1 promoter in prostate cancer cells and prostate cancer tissues but much less methylation in normal tissues [120], suggesting the requirement for promoter methylation for 15-LOX-1 expression in prostate cancer.

In benign prostate tissues, 15-LOX-2 protein is located mainly in secretory cells of peripheral zone glands and large prostatic ducts, and is not detected in the basal cell layer, stroma, ejaculatory ducts, seminal vesicles, or transitional epithelium [121]. Thus, its distribution differs from 15-LOX-1. Interestingly, 15-LOX-2 is absent in the majority of prostate cancer tissues, and the reduction of staining is greater in higher Gleason scores [122]. This leads to the implication that 15-LOX-2 may function as a prostate cancer suppressor [123]. The expression of 15-LOX-2 correlates well with the concentration of 15-HETE, which is high in normal tissues and markedly reduced or undetectable in prostate cancer tissues [121]. In PC-3 cells, exogenous 15-HETE inhibits cell proliferation and reduces PPARγ expression but upregulates the PPAR response element [124]. These findings indicate that 15(S)-HETE is a ligand for PPARγ and the loss of 15-LOX-2 may contribute to an increase of cell proliferation and a decrease of differentiation in prostate cancer. The cross talk between 15-LOX-2 gene and PPARγ has been identified, which is mediated by 15(S)-HETE and it may contribute to the diverse effects in normal and prostate cancer cells [125, 126].

Factors that contribute to the opposing effects of 15-LOX-1 and 15-LOX-2 are not well understood. One possibility is that 15-LOX-1 metabolizes the preferred substrate, LA, to 13(S)-hydroxyoctadecadienoic acid (13(S)-HODE). 13-HODE has been shown at higher amounts in prostate cancer tissues than adjacent normal tissues [117, 127]. More compelling evidence is from the study that demonstrated exogenous 13(S)-HODE increases the PPARγ phosphorylation while 15(S)-HETE decreases the PPARγ phosphorylation in PC-3 cells [115].

Whether other 15-LOX metabolites of AA such as lipoxins have role in prostate cancer is not known.

III. Cytochrome P450 Pathways

Cytochrome P450s (CYPs) are a large class of heme-containing enzymes that metabolize a variety of endogenous and exogenous substrates. CYP hydroxylases and CYP epoxygenases metabolize free AA to biologically active eicosanoids (Figure 4). CYP hydroxylases including CYP2E, 3A, 4A, and 4F convert AA to 20-, 19-, 18-, 17-, or 16-HETE [128–130]. Among these HETEs, 20-HETE (the metabolite of CYP ω-hydroxylases) has been intensely studied and it activates many signaling pathways to regulate vascular functions. CYP epoxygenases including CYP1A, 1B, 2C, 2D, and 2J convert AA to 14,15-, 11,12-, 8,9-, and 5,6-epoxyeicosatrienoic acids (EETs) [131–134]. EETs can be further metabolized by soluble epoxide hydrolase to their corresponding regioisomeric dihydroxyeicosatrienoic acids (DHETs). In human, CYP2C8, 2C9 and 2J2 have prominent roles in AA metabolism [135]. Only recently roles of these HETEs and EETs in cancer received attention.

Recent studies have demonstrated that CYPs and particularly the EETs have roles in many types of cancer. CYP2C and 3A are variably expressed in normal and neoplastic tissues of different human organs [136]. CYP2C9 has been associated with an increased risk of colorectal cancer [137] and lung cancer [138, 139]. CYP2J2 expression is detected in many types of human cancer tissues and cancer cell lines while it is not detected in adjacent

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normal tissues and normal cells [140]. Overexpression of CYP2J2 or addition of exogenous EETs in cancer cells increases cell proliferation and inhibits apoptosis by the activation of MAPK and PI-3 kinase-Akt signaling pathways and the EGFR phosphorylation [140]. CYP2J2 and EETs also promotes cancer cell migration and invasion through the upregulation of MMPs and CD44 and down regulation of the antimetastatic genes *CD82* and *nm-23* [141]. A comprehensive analysis of CYP2C8, 2C9, and 2J2 in human cancer tissues and their surrounding normal tissues using tissue microarrays has been reported [142]. Interestingly, these enzymes exhibit diverse expression patterns in different organ tissues.

Numerous studies have demonstrated the roles of CYPs in prostate cancer but not in the association with the synthesis of eicosanoids. CYP1A, 2C, and 3A are present in 63, 25, and 61% of human prostate cancer tissues, respectively [143]. A genetic polymorphism of CYP1A1 has been proposed to associate with prostate cancer susceptibility [144]. Interestingly, CYP2C8 and 2C9 are detected in prostate cancer tissues but CYP2J2 is not detected in those tissues [142]. In prostate cancer cells, PC-3, DU-145, and LNCaP cells express CYP1A1 and 1A2 while normal prostate cells do not express CYP1A1 [145]. Although roles of these CYPs in prostate cancer are not currently understood, their presence in prostate cancer cells and tissues suggest that they may play roles in AA metabolism and regulation of prostate cancer. A clinical implication of CYP eicosanoids in prostate cancer has been demonstrated by higher urinary levels of 20-HETE in BPH and prostate cancer patients than normal men [113]. Radical prostatectomy reduces the urinary levels of 20-HETE to the values in normal men, suggesting that 20-HETE may be involved in prostatic diseases. The CYP pathway may prove to be important in prostate cancer progression and deserves further investigation.

IV. Endocannabinoids and Prostate Cancer

Endocannabinoids (eCBs) are endogenously produced lipids and bind to cannabinoid (CB) receptors to initiate signaling pathways. These lipid mediators are derivatives of fatty acids. Two well characterized AA-containing eCBs are arachidonylethanolamide (anandamide, AEA) [146] and 2-arachidonoylglycerol (2-AG) [147, 148] (Figure 5). A putative endocannabinoid, 2-arachidonylglyceryl ether (noladin ether, NE) is more enzymatically stable [149–151] and it has been used for investigating pharmacological functions of eCBs. Although NE was first identified in porcine brain [152] and rat brain regions [153], it was not detected in the brains of various mammalian species [154, 155].

Endocannabinoids function through the activation of CB receptors. However, several biological effects of eCBs occur through non-CB receptor mechanisms [156, 157]. In either case, the balance between synthesis and metabolism of eCB is critical to maintaining the endogenous concentrations of eCBs. Hydrolysis of eCBs is an important regulatory step that limits the actions of eCBs in many physiological and pathological processes. AEA is hydrolyzed by fatty acid amide hydrolase (FAAH) [158–160] and 2-AG is hydrolyzed by FAAH and monoacylglycerol lipase (MGL) [161–163] to free AA. Hydrolysis of AEA and 2-AG will decrease the activity of eCBs and will liberate free AA as the substrate for the enzymes in the AA cascade discussed above. It is now recognized that the inhibition of hydrolysis is a potential therapeutic target for cancer treatment [160, 164, 165].

Endocannabinoids regulate growth and migration of a variety of cancer cells and have therapeutic potential in cancer treatment [160, 164–177]. In prostate cancer, AEA, acting through the CB1 receptor, inhibits the EGF-induced proliferation of prostate carcinoma cells [178] by decreasing EGFR expression and increasing ceramide production. LNCaP cells are the least sensitive to AEA and PC-3 cells are the most sensitive to AEA in the inhibition of proliferation. These observations correlated well with the high expression of FAAH

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(enzyme hydrolyzing AEA) in LNCaP cells and extremely low expression of FAAH in PC-3 cells [179]. AEA, 2-AG and HU-210 (a synthetic CB receptor agonist) inhibit prolactin-induced proliferation of DU-145 cells through the activation of CB1 receptors [180]. However, (R)-methanandamide (a synthetic AEA analog) increases proliferation of androgen-dependent LNCaP cells through CB1 and CB2 receptors and the PI3K pathway to increase androgen receptor expression [181]. NE and CB1 receptor agonists inhibit invasion of PC-3 and DU-145 cells [182] and AEA inhibits invasion of PC-3 cells [179]. Inhibition of eCB hydrolysis by either pharmacological inhibitors or siRNA knockdown of the FAAH inhibits invasion of these cells [179, 183]. The combination of eCB hydrolysis inhibition and treatment with exogenous eCBs further inhibit cell invasion [179]. LNCaP cells, with high eCB hydrolytic activity, are not sensitive to treatments with eCBs or CB1 receptor agonists unless the eCB hydrolysis is blocked [179]. Furthermore, 2-AG can increase cell invasion due to its hydrolysis to AA and subsequent metabolism to 12-HETE [112], but it will inhibit invasion in the presence of the hydrolysis inhibitors [179]. These studies demonstrated that eCBs regulate prostate cancer proliferation and invasion, and their hydrolysis can dictate the differential effects of eCBs and responses.

Conclusions

The ω-6 polyunsaturated fatty acid, AA, plays various important roles in prostate cancer. AA can be metabolized to numerous metabolites and act as endogenous lipid signaling molecules that may have diverse effects on prostate cancer cells. The balance and/or specific pathways of synthesis, degradation, and signal transduction activation will dictate prostate cancer cell fate and cancer development and progression.

Future perspective

The AA metabolism is complex and consists of multiple pathways to produce numerous eicosanoids by specific oxygenases. In prostate cancer, some of these enzymes and eicosanoids are tumorigenic and some are antitumorigenic. Several of them are potential targets in clinical applications. Although the AA pathways have been demonstrated as regulators in prostate cancer for several decades, their functions are not fully understood and merit further study. In particular, a better understanding of signaling pathways by these lipid mediators is needed to advance the field for cancer prevention and treatment. A new pathway of AA metabolism by CYP in cancer may be important in prostate cancer. Lastly, endocannabinoids, endogenous AA-containing signaling molecules have significant roles in proliferation and migration/invasion of prostate cancer cells. Thus, further studies will elucidate their function as therapeutic targets for prostate cancer.

Acknowledgments

This work was supported by the grants from the Breast Cancer Showhouse, Medical College of Wisconsin Cancer Center, and the National Institute of Health, HL-51055, HL-37981, and DA-09155.

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Executive summary

Introduction

- Prostate cancer cell growth and invasion/migration leads to significant morbidity and mortality.
- Arachidonic acid (AA) has been recognized as protumorigenic.
- AA is metabolized by COX, LOX, and CYP to biologically active eicosanoids. These enzymes and eicosanoids have diverse cellular functions.

Cyclooxygenase pathway

- COX-2 is a prostate cancer promoter and it is expressed in prostate cancer tissues and cells. PGE_2 is the major COX metabolite of AA in prostate cancer cells and tissues.
- PGI_2 and PGD_2 are antitumorigenic while PGE_2 and TxA_2 are tumorigenic by acting through their prostanoid receptors.

Lipoxygenase pathway

- 5-LOX and its metabolites such as 5-HETE, 5-oxo-ETE and Cys-LTs are tumorigenic. 5-HETE and 5-oxo-ETE activate 5-oxo-ETE receptor and Cys-LTs are ligands for Cys-LT1R and Cys-LT2R.
- 12-LOX is highly expressed in prostate cancer tissues and cells. 12-LOX and it metabolite, 12-HETE are tumorigenic.
- 15-LOX-1 is highly expressed in prostate cancer tissues but 15-LOX-2 is not detected in prostate cancer tissues. 15-LOX-1 is tumorigenic while 15-LOX-2 is antitumorigenic. The major 15-LOX-1 metabolite from LA is 13(S)-HODE and the major 15-LOX-2 metabolite form AA is 15(S)-HETE. 15(S)-HETE is a ligand for PPARγ.

Cytochrome P450 pathway

- AA is metabolized by CYP hydroxylases to HETEs and by CYP epoxygenases to EETs.
- Some isoforms of CYP epoxygenases and EETs have been shown to stimulate cancer progression. Their roles in prostate cancer are not known.

Endocannabinoids

- Endocannabinoids, acting through CB1 receptor inhibit proliferation and invasion of prostate cancer cells.
- Hydrolysis of endocannabinoids affects the activity of endocannabinoids in the regulation of prostate cancer cells because it reduces the ligand concentrations and liberates the free AA.
- Endocannabinoids may regulate prostate cancer cells by non-receptor-mediated mechanisms.

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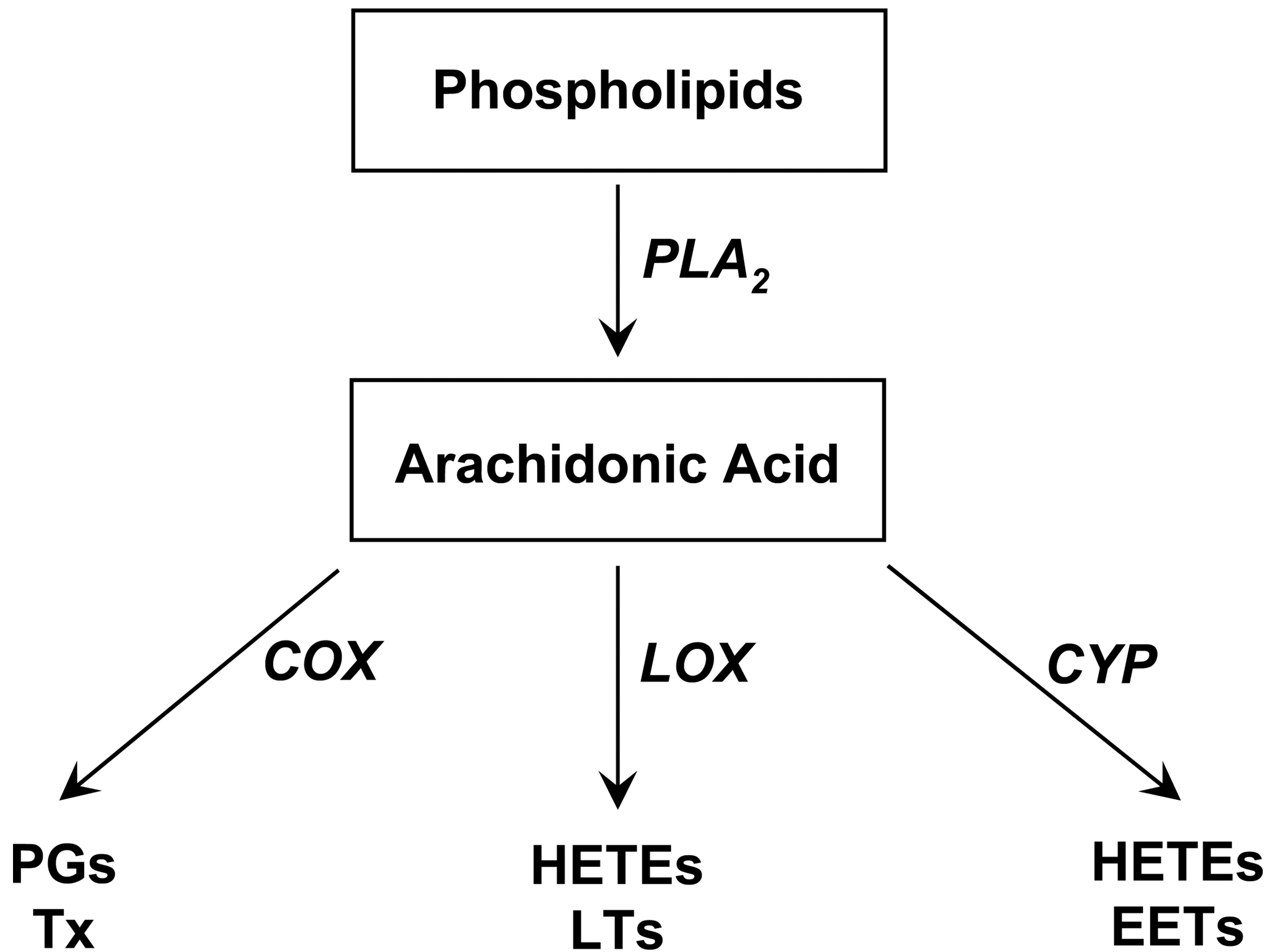

Figure 1.
Arachidonic acid metabolic pathways. Free arachidonic acid (AA) is formed mainly from the metabolism of membrane phospholipids by phospholipase A_2 (PLA_2). Free AA is metabolized by cyclooxygenases (COX) to prostaglandins (PGs) and thromboxane (Tx), by lipoxygenases (LOX) to hydroxyeicosatetraenoic acids (HETEs) and leukotrienes (LTs), and by cytochrome P450s (CYP) to HETEs and epoxyeicosatrienoic acids (EETs).

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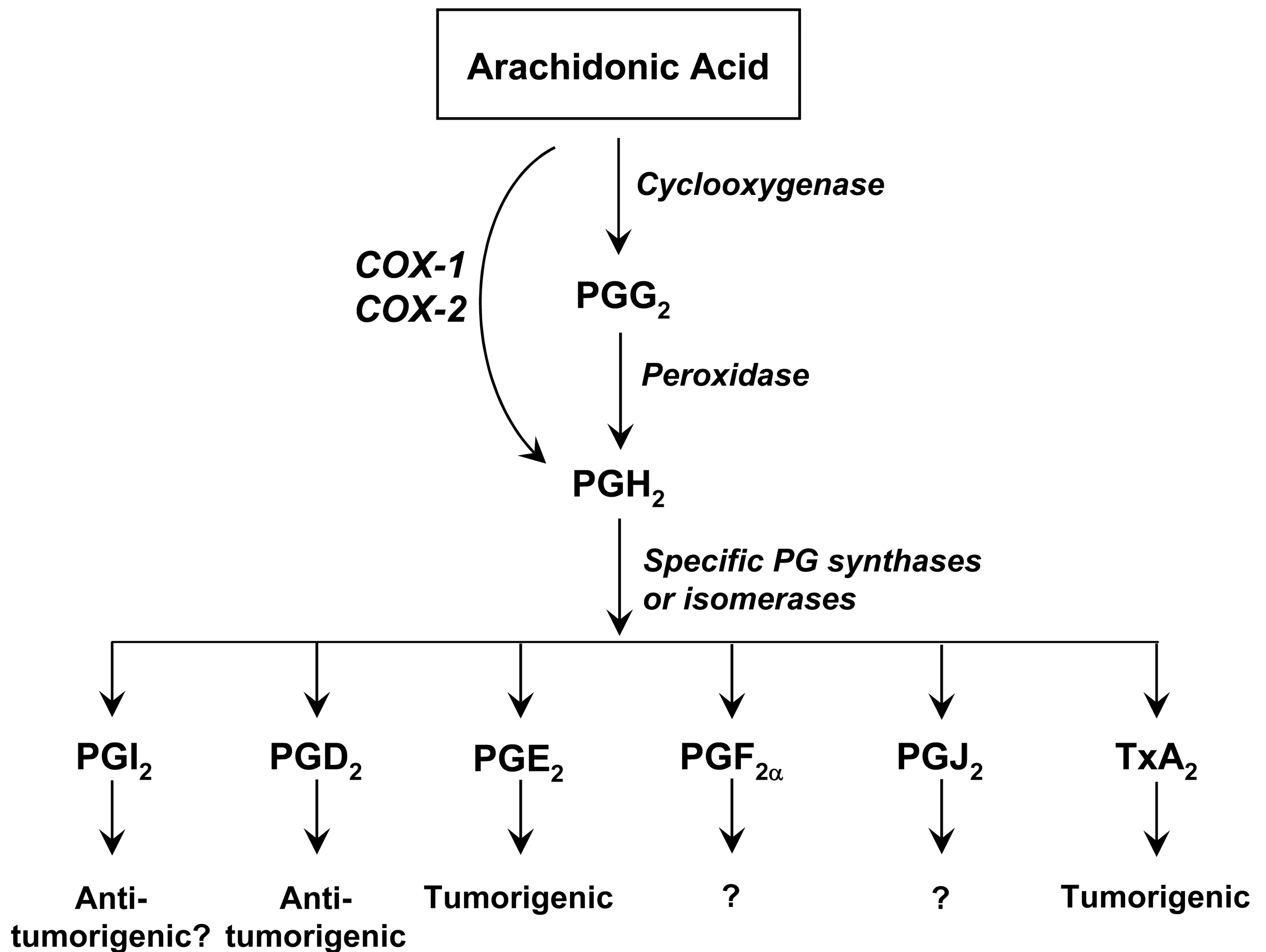

Figure 2.
Cyclooxygenase pathway of AA. Cyclooxygenase active site of COX converts AA to PPG_2 and peroxidase active site of COX converts PGG_2 to PGH_2. Then, specific prostaglandin synthases or isomerases convert PGH_2 to their corresponding PGI_2, PGD_2, PGE_2, $PGF_{2\alpha}$, PGJ_2, and TxA_2. In prostate cancer, PGI_2 and PGD_2 are antitumorigenic while PGE_2 and TxA_2 are tumorigenic.

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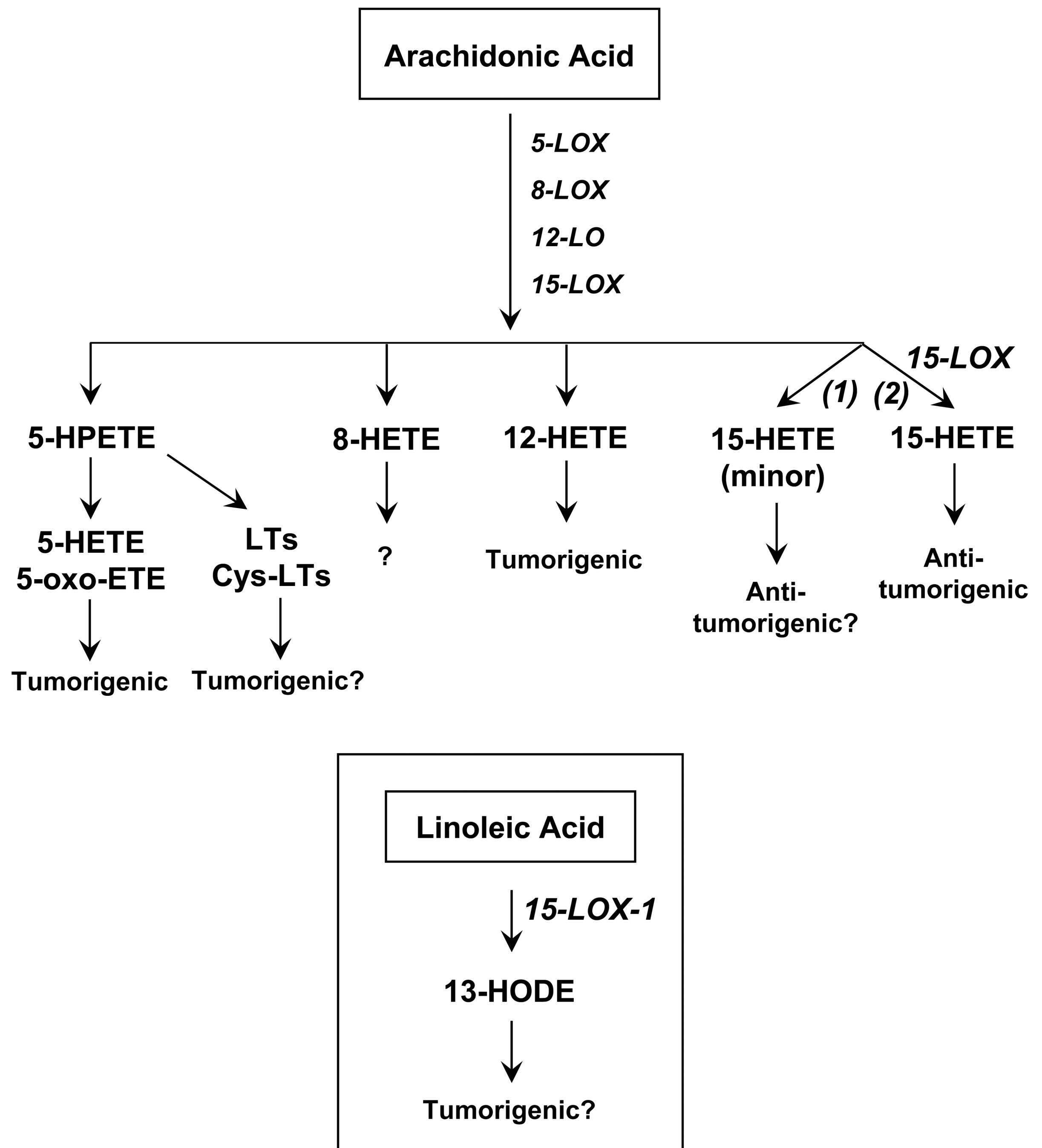

Figure 3.

Lipoxygenase pathway of AA. LOX metabolizes AA to their corresponding isomeric hydroperoxyeicosatetraenoic acids (HPETEs). 5-HPETE is reduced by peroxidase to 5-HETE, then, 5-HETE is converted to 5-oxo-eicosatetraenoic acid (5-oxo-ETE). 5-HETE and 5-ox-ETE are tumorigenic. Role of 8-HETE in prostate cancer is not known while 12-HETE is tumorigenic. 15-LOX-1 metabolizes the major substrate, linoleic acid (LA) to 13-hydroxyoctadecadienoic acid (13-HODE) (inset). 15-LOX-1 is tumorigenic. 15-LOX-2 metabolizes AA to 15-HETE, which is antitumorigenic in prostate cancer.

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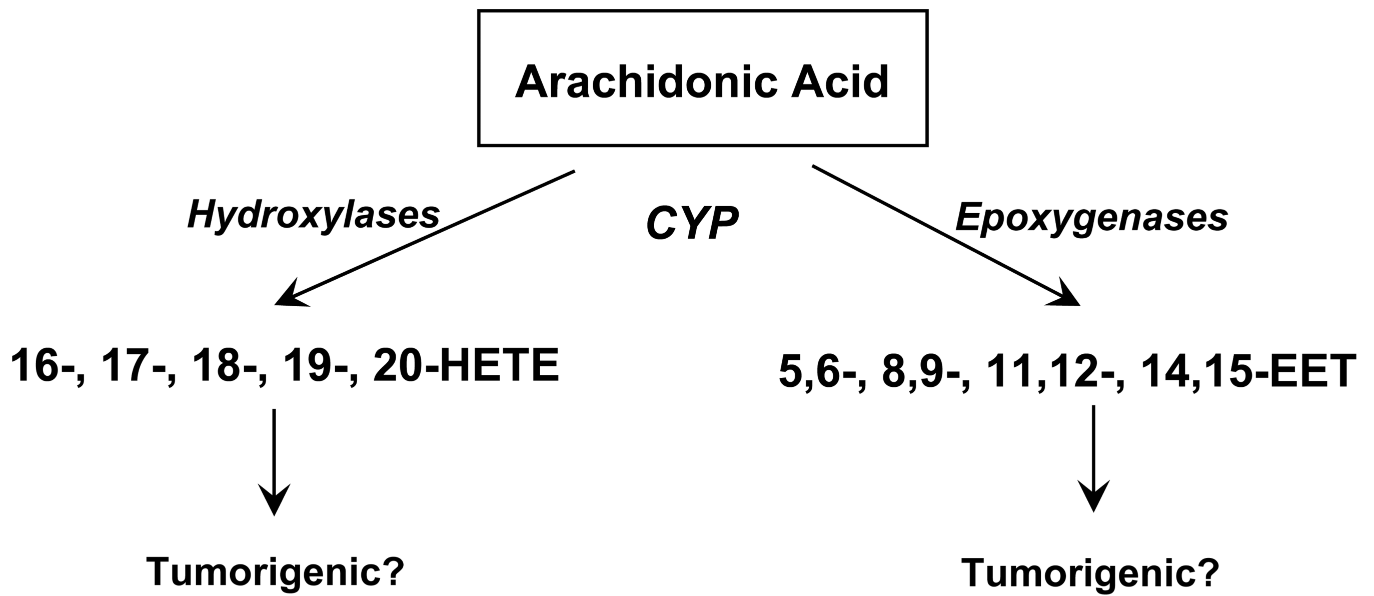

Figure 4.
Cytochrome P450 pathway of AA. CYP hydroxylases metabolize AA to HETEs and CYP epoxygenases metabolize AA to four regioisomeric epoxyeicosatrienoic acids (EETs). At present, roles of HETEs and EETs in prostate cancer are not known.

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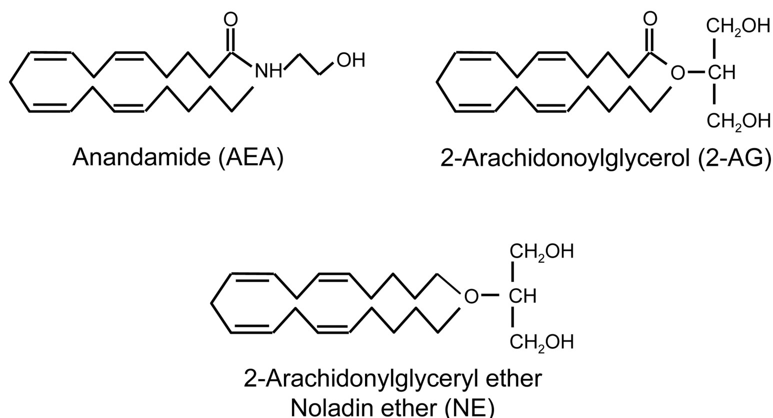

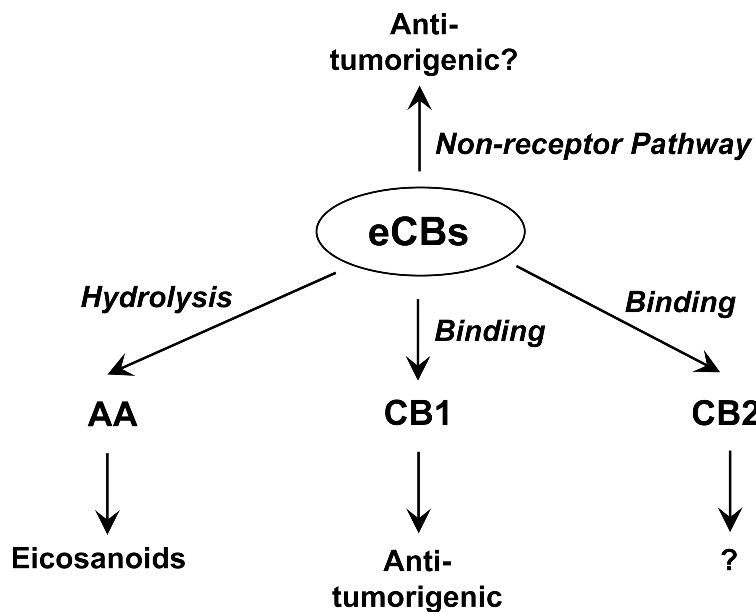

Figure 5.

Endocannabinoids (eCBs) in prostate cancer. (A) Structures of some of well-characterized endocannabinoids (shown are AA-derived eCBs), anandamide (AEA), 2-arachidonoylglycerol (2-AG), and noladin ether (NE). (B) Mechanistic pathways for eCBs. Hydrolysis of eCBs produces free AA which is further metabolized by oxygenases to eicosanoids in the AA pathways. The eCBs bind to cannabinoid receptor type 1 (CB1 receptor) to inhibit prostate caner cell proliferation and invasion/migration; however, the role of CB2 receptor is not clear. The eCBs can inhibit prostate cancer proliferation by a non-receptor-mediated pathway.