NIH Public Access

Author Manuscript

Cancer Metastasis Rev. Author manuscript; available in PMC 2013 December 17.

Published in final edited form as:

Cancer Metastasis Rev. 2011 December ; 30(0): . doi:10.1007/s10555-011-9299-7.

Polyunsaturated fatty acid metabolism in prostate cancer

Isabelle M. Berquin,
Department of Cancer Biology, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA

Comprehensive Cancer Center, Wake Forest School of Medicine, Winston-Salem, NC, USA

Iris J. Edwards,
Department of Pathology, Wake Forest School of Medicine, Winston-Salem, NC, USA

Comprehensive Cancer Center, Wake Forest School of Medicine, Winston-Salem, NC, USA

Steven J. Kridel, and
Department of Cancer Biology, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA

Comprehensive Cancer Center, Wake Forest School of Medicine, Winston-Salem, NC, USA

Yong Q. Chen
Department of Cancer Biology, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA

Comprehensive Cancer Center, Wake Forest School of Medicine, Winston-Salem, NC, USA

Yong Q. Chen: yqchen@wfubmc.edu

Abstract

Polyunsaturated fatty acids (PUFA) play important roles in the normal physiology and in pathological states including inflammation and cancer. While much is known about the biosynthesis and biological activities of eicosanoids derived from ω6 PUFA, our understanding of the corresponding ω3 series lipid mediators is still rudimentary. The purpose of this review is not to offer a comprehensive summary of the literature on fatty acids in prostate cancer but rather to highlight some of the areas where key questions remain to be addressed. These include substrate preference and polymorphic variants of enzymes involved in the metabolism of PUFA, the relationship between *de novo* lipid synthesis and dietary lipid metabolism pathways, the contribution of cyclooxygenases and lipoxygenases as well as terminal synthases and prostanoid receptors in prostate cancer, and the potential role of PUFA in angiogenesis and cell surface receptor signaling.

Keywords

Prostate cancer; Polyunsaturated fatty acids; Metabolism; Cyclooxygenase; Eicosanoids

1 Introduction

Consumption of high levels of dietary lipids is usually associated with increased risk of cancer, with the notable exception of ω3 polyunsaturated fatty acids (PUFA), which show

© Springer Science+Business Media, LLC 2011

Correspondence to: Yong Q. Chen, yqchen@wfubmc.edu.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

protective effects against colon, breast, and prostate cancer in a number of experimental systems [1–5]. Since ω3 and ω6 PUFA cannot be synthesized *de novo*, they are essential fatty acids and must be taken in from the diet. However, PUFA elongation to longer chain species shares malonyl-CoA as a common substrate with *de novo* fatty acid synthesis. Hence, levels of specific PUFA in an organism depend on dietary intake and on metabolism of these fatty acids by desaturases, elongases, cyclooxygenases (COXs), lipoxygenases (LOXs), and other enzymes [5]. In turn, metabolism shows interindividual differences due to polymorphism in the genes encoding the various metabolic enzymes [6]. Bioactive metabolites of ω6 PUFA generated by COXs and LOXs (eicosanoids) have been extensively investigated and play various roles in inflammation, cancer cell proliferation, and metastasis. Overall, metabolites of ω3 PUFA oppose these actions, but their generation is still poorly understood. In this review, we highlight the interplay between dietary PUFA intake, elongation, β-oxidation, storage, and eicosanoid synthesis and *de novo* fatty acid synthesis. We further discuss the potential roles of PUFA and their metabolites in prostate cancer, with an emphasis on angiogenesis and cell surface receptors, and contrast the wealth of information available on ω6 PUFA metabolism to the relative scarcity of knowledge on ω3 PUFA metabolism.

2 Source of ω6 and ω3 PUFA and conversion within each series

ω6 and ω3 PUFA cannot be interconverted in mammals, but within each series, metabolism can produce various lipids that differ in chain lengths and number of unsaturated bonds. Linoleic acid (LA, 18:2n-6) is an ω6 PUFA found in abundant supply in vegetable oils; it is metabolized primarily to arachidonic acid (AA, 20:4n-6) through a series of alternating oxidative desaturation and elongation steps. In the ω3 series, alpha linolenic acid (α-LNA, 18:3n-3), found at moderate levels in most terrestrial plants, is not converted efficiently to long-chain ω3 PUFA such as eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3; see below). Therefore, in humans the main source for these long-chain ω3 PUFA is through dietary intake of fish or supplementation with fish oil.

During ω6 PUFA conversion, fatty acid desaturase 2 (FADS2) or delta-6 desaturase converts LA to gamma linolenic acid (γ-LNA, 18:3 n-6). This enzyme represents a rate-limiting step in the synthesis of AA from dietary LA [7] (Fig. 1). γ-LNA is elongated to dihomo-gammalinolenic acid (DGLA, 20:3 n-6) through a process of four enzymatic reactions. The first of these is condensation of the fatty acyl chain with malonyl-CoA, catalyzed by an enzyme encoded by the *ELOVL5* gene (elongation of very long-chain fatty acids, family member 5). This is followed by a reduction reaction mediated by 3-ketoacyl-CoA reductase (KAR, also known as HSD17B12), a dehydration reaction catalyzed by 3-hydroxyacyl-CoA dehydratase (HACD), and finally a second reduction reaction catalyzed by *trans*-2,3-enoyl-CoA reductase (TECR). After chain elongation, fatty acid desaturase 1 (FADS1) or delta-5 desaturase converts DGLA to AA. Again, this step is relatively inefficient [7] (Fig. 1).

The same enzymes are involved in ω3 PUFA conversion. However, conversion of α-LNA to DHA in humans appears to be very inefficient. Both α-LNA-feeding studies and stable isotope studies have consistently demonstrated that increased consumption of α-LNA does not result in increased DHA in plasma or cell lipids (reviewed in [8, 9]). Instead of being further anabolized, most of the ingested α-LNA is subject to β-oxidation to provide energy and only a small fraction is converted to EPA. From kinetic analyses of fatty acid conversion, it was estimated that conversion of α-LNA to EPA might be as low as 0.2%, conversion of EPA to DPA was estimated at 64%, and conversion of DPA to DHA at 37% [10]. Therefore, the overall amount of DPA and DHA made from α-LNA would only represent 0.13% and 0.05% of the starting α-LNA amount, respectively. These data suggest

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

that FADS2, the first enzyme in the conversion sequence, is rate-limiting. Recently, it was proposed that the limited conversion of α-LNA to DHA in HepG2 cells was in part due to a competition of α-LNA and tetracosapentaenoic acid (24:5n-3) for FADS2 [11]. There is some evidence of gender differences in efficiency of the elongation–desaturation pathway suggesting that sex hormones may play a regulatory role [9, 12, 13].

3 Polymorphism of the FADS gene cluster and potential impact on PUFA conversion

The human FADS gene cluster (*FADS1, FADS2*, and *FADS3*) is located on chromosome 11q12–13.1. Approximately 207 single-nucleotide polymorphisms (SNPs) were identified on *FADS1*, 610 SNPs on *FADS2*, and 246 SNPs on *FADS3* (http://www.ncbi.nlm.nih.gov/snp/). Interestingly, microRNA hsa-mir-1908, which is expressed in embryonic stem cells, cancer, and the female reproductive tract [14–16], is located in the first intron of the *FADS1*. One SNP (rs174561) is present within the miRNA, and two additional SNPs (rs73487465 and rs75810419) flank it. Whether these SNPs have an effect on hsa-mir-1908 expression is currently unclear.

Schaeffer et al. [17] first reported an association between genetic variants of the *FADS* gene cluster and PUFA composition in phospholipids. Several SNP studies [18–28] and a genome-wide association study [29] have replicated the observation. *FADS* polymorphisms may affect both ω3 and ω6 PUFA desaturation–elongation. The topic has been the subject of multiple reviews [30–34]. Recent evidence suggests that polymorphisms in the *FADS* gene cluster which alters desaturase activity might differ between Caucasians and Asians [35]. An intriguing question is whether this polymorphic difference, if confirmed, has an impact on the effect of ω3 and ω6 PUFA on cancer risk among different populations.

4 Dependence of tumor cells on de novo fatty acid synthesis

Although fatty acids are consumed at high levels in a typical western diet, tumor cells display an obligate requirement to synthesize fatty acid *de novo* [36, 37]. This is evidenced by high expression levels of enzymes in the pathway in multiple types of cancer, including prostate cancer. For example, fatty acid synthase (FASN), the enzyme that catalyzes the synthesis of fatty acid, is expressed at high levels in prostate cancer and its expression is correlated with disease progression and outcome [36, 38–43]. The fatty acid synthesis pathway is turned on early in prostate cancer development and is regulated by androgen [44–46]. In addition, the pathway is driven by the same processes that drive prostate cancer. As one example, the PI3-kinase pathway is the primary driver of *FASN* expression in prostate cancer [47]. Pharmacological blockade of the PI3-kinase pathway reduces *FASN* expression, as does reexpression of *PTEN* in *PTEN*-null cells [48]. Moreover, patients with tumors that are *PTEN* negative and express high levels of *FASN* have decreased disease-free survival [38]. Conversely, the prostate-specific expression of *FASN* is sufficient to induce prostatic intraepithelial neoplasia (PIN) lesions in mice [49]. Collectively, these findings strongly suggest that that the *de novo* pathway of fatty acid synthesis is not only required for prostate cancer but may have a role in promoting disease progression.

There are other enzymes upstream of FASN that are involved in fatty acid synthesis. Fatty acid synthesis primarily uses glucose as the primary carbon source, although recent evidence demonstrates that glutamine also serves as a carbon source in tumor cells [50–52]. To generate the substrates for fatty acid synthesis, several enzymatic steps are required. First, citrate is shunted out of the TCA cycle into the cytoplasm and converted to acetyl-CoA by ATP-citrate lyase (ACLY) [50–52]. The resulting acetyl-CoA is converted to malonyl-CoA by the cytosolic acetyl-CoA carboxylase 1 (ACC1) through an ATP-dependent

carboxylation reaction [53, 54]. Generation of malonyl-CoA is the rate-limiting step of fatty acid synthesis. The ultimate steps of fatty acid synthesis are performed by FASN, which also resides in the cytosol, by combining 1 acetyl-CoA with 7 malonyl-CoA to synthesize the 16-carbon fatty acid palmitate [55–58]. FASN also synthesizes the 14-carbon fatty acid myristate and the 18-carbon fatty acid stearate, albeit to lesser degrees. Palmitate can undergo a series of modifications before it is utilized in the cells. It can be elongated by two carbons to stearate using malonyl-CoA as the elongation substrate, just as it is for PUFA. Palmitate and stearate can also be desaturated by stearoyl-CoA desaturase-1 to form the monounsaturated palmitoleate and oleate, respectively. Thus, the fatty acid synthesis pathway generates the saturated fatty acid component of the cell but also provides the precursor for the monounsaturated component of the cell.

The ubiquitous expression of *FASN* in tumor cells is paralleled by an absolute requirement for *de novo* fatty acid synthesis to proliferate and survive [36, 43]. Because of the cellular dependence on fatty acid synthesis to facilitate membrane biogenesis and other aspects of cell biology, fatty acid synthesis impacts on virtually every aspect of cellular activity. For example, it is required for cell cycle progression, protein synthesis, mitochondrial function, and protein targeting [59–63]. Accordingly, blocking the activity of ACLY, ACC1 and FASN reduces proliferation or induces cell death *in vitro* and inhibits tumor growth *in vivo* [51, 59, 64–69].

5 Relationship between *de novo* lipid synthesis and dietary lipid metabolism pathways

The dependence of tumor cells on *de novo* fatty acid synthesis suggests that these cells have different requirements for fatty acid compared to normal cells. Some portion of the increased demand can be attributed to increased proliferation of tumor cells compared to normal cells. It may also be possible that dietary and *de novo* fatty acids are subject to different fates in a cell. In such a case, it may be that dietary fatty acid is unable to meet to demands of the tumor cell. The fate of newly synthesized fatty acid in a tumor cells has been well defined. Most of it is used to support membrane biogenesis in the form of phospholipids, although some portion is used for protein palmitoylation and protein targeting [63, 70]. Interestingly, recent evidence demonstrates that *de novo* synthesized fatty acid is primarily used to support phosphatidylcholine (PC) synthesis [71]. Blockade of the pathway has little effect on phosphatidylserine, phosphatidylethanolamine, and phosphatidylinositol. It is tempting to speculate that dietary fat is required to support the non-PC portion of tumor cell membranes. The pool of newly synthesized fatty acid used for membrane biogenesis is preferentially enriched into detergent-insoluble microdomains known as lipid rafts [70]. This is consistent with the finding that lipid rafts are rich in lipids containing saturated fatty acid. It also suggests that fatty acid synthesis supports signaling functions that are associated with lipid rafts.

Although the expression and activity of enzymes in the fatty acid synthesis pathway is highly correlated with cancer, there are several examples of normal biology in which the pathway is active. Embryonic development is an example of when the pathway appears to be active and required as *Fasn*- and *Acc1*-deficient mice display an embryonic mutant phenotype [53, 55]. *Fasn*-deficient embryos display lethality prior to implantation and heterozygotes die at multiple stages during development [55]. Similarly, *Acc1*-deficient embryos display lethality at around day 8.5 [53]. It is interesting to note that placing pregnant mothers on a diet enriched in saturated fatty acid is not sufficient to protect embryos from the effects of *Fasn* deletion. Whether this is because of differential utilization of dietary fat compared to synthesized fat or from having to cross the placenta is unknown.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

The liver and adipose tissue are two other examples in which the fatty acid synthesis pathway is active. In these tissues, fatty acid is generated and, following excessive caloric consumption, stored as triglyceride for future energy. Mice with liver-specific deletion of *Acc1* and *Fasn* have also been generated [54, 72]. Mice engineered to have targeted *Fasn* deletion in the liver display a phenotype that can be reversed with a peroxisome proliferator-activated receptor (PPAR) α agonist, but not with a high-fat diet [72, 73]. It was subsequently demonstrated that *Fasn*-dependent fatty acid synthesis was responsible for the formation of the PPARα ligand 1-palmitoyl-2-oleoyl-*sn*-glycerol-3-phosphocholine (16:0/18:1-GPC) [73]. Of note, this lipid is among the most abundant of all lipid species. That a high-fat diet could not recapitulate the wild-type liver phenotype of the wild-type mice suggests that dietary fat may be utilized differently than *de novo* synthesized fat in cells.

Unlike what has been a demonstrated *in vivo* using total or tissue-specific knockout of *Fasn*, exogenous fatty acid is able to protect cells from the effects of inhibiting FASN and ACC1 in tumor cell lines *in vitro*. As discussed earlier, when tumor cell lines are treated with FASN and ACC1 inhibitors or transfected with siRNA against either of the two enzymes, cell cycle blockade and cell death ensue. Many of the cellular effects can be delayed or ameliorated by supplementing cells with exogenous fatty acid in their culture medium. Palmitate supplementation can restore cell cycle progression and survival following siRNA knockdown of *FASN* and *ACC1* [59, 65, 74]. Recent studies also suggest that tumor cells may obtain fatty acid from the circulation through a lipoprotein lipase and CD36-dependent mechanism [75]. Moreover, it appears that this mechanism has the potential to protect tumor cells from the effects of inhibitors of *de novo* fatty acid synthesis. Although *in vitro* experimentation does not always adequately reflect *in vivo* biology, it is interesting to consider that dietary fat may have a different influence on tumor cells than on normal cells. This could be related to the fact that tumor cells have an absolute requirement for the synthesis of saturated fatty acid.

Development of FASN, ACC1, and ACLY inhibitors is the subject of intense investigation. Because PUFA elongation requires malonyl-CoA, one interesting possibility is that inhibition of ACC1 or ACLY could reduce cellular malonyl-CoA level and consequently diminish the LA to AA conversion. Since elongation of dietary ω6 PUFA appears to be more efficient than that of ω3 PUFA, it is tempting to speculate that ACC1 and ACLY inhibitors may preferentially reduce the formation of AA and consequently that of the ω6-series eicosanoids.

6 PUFA oxidation and cycling

Human beings first evolved while consuming a diet containing roughly equivalent amounts of ω6 and ω3 PUFA [76]. During the last two centuries, however, the consumption of ω6 PUFA has increased dramatically due to the increased intake of vegetable oils. Today, the ratio of ω6 and ω3 PUFA in western diets is approximately 30:1. The low intake of α-LNA from the diet is consistent with the observation that α-LNA is underrepresented relative to LA in various tissues and organs in the body [77–79]. Even with an equal amount of ω6 and ω3 PUFA intake, some evidence suggests that this phenomenon may also be the result of rapid β-oxidation of α-LNA relative to other fatty acids [80, 81]. Indeed, carnitine palmitoyltransferase (CPT1), a key enzyme in fatty acid β-oxidation, exhibits the fastest maximum turnover capacity with α-LNA as substrate relative to other fatty acids, whether the substrates are presented as nonesterified fatty acids or as acyl-CoA esters [82].

Although the rate of esterification may be comparable between ω6 and ω3 PUFA [83], data indicate that the release of fatty acids from phospholipids could be quite different. Three

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

major groups of phospholipase A2 (PLA2) enzymes have been identified: secreted PLA2 or sPLA2, cytosolic PLA2 or cPLA2, and calcium-independent PLA2 or iPLA2. sPLA2 and cPLA2 can selectively release AA from the *sn*-2 position of phospholipids and the released AA is then the substrate of oxygenases. Interestingly, phospholipids with ω3 PUFA (EPA or DHA) in the *sn*-2 position are poor substrates for cPLA2 [84, 85]. In contrast, iPLA2 may selectively release DHA [86]. Therefore, the extent to which ω3 and ω6 PUFA are released from phospholipids would be expected to depend on the relative expression of the various phospholipases.

To date, it is unclear whether ω6 and ω3 PUFA are differently β-oxidized and how ω6 and ω3 PUFA are cycled in tumor cells. The role of cPLA2 and sPLA2 in cancer has been discussed previously [87–89]. A study found that sPLA2 was upregulated and that endogenous inhibitors of cPLA2 were downregulated in prostate cancer, with resulting effects on cancer cell growth [90]. In another study, the mRNA and protein levels of sPLA2 were significantly higher in Gleason pattern grade 2–4 carcinomas than benign prostate samples and correlated with proliferation, but the expression was lower in metastases [91]. Compared to cytosolic and secreted phospholipases, little is known about the expression and function of iPLA2 enzymes in prostate cancer.

7 Relative contribution of oxygenases in prostate cancer

AA is metabolized by a number of enzymes belonging to the COX and LOX families as well as cytochrome P450 epoxygenases. COXs catalyze the first reaction in the conversion of AA to prostaglandins (PG) G and H, which are further metabolized into other prostaglandins (PGE, PGF, PGJ), prostacyclins (PGI), and thromboxanes (TXA, TXB), whereas LOXs mediate the first step in the conversion of AA to leukotrienes and hydroxyeicosatetraenoic acids (HETEs). Cytochrome P450 oxygenases convert AA to HETEs by the action of omega-hydroxylase activity and to epoxyeicosatrienoic acids (EETs) by epoxygenase activity. The resulting lipid metabolites have multiple biological activities and have been implicated in various pathological processes, including inflammation, autoimmunity, and cancer [92, 93]. Long-chain ω3 fatty acids are also believed to be substrates of COX, LOX, and P450 enzymes, and the resulting products tend to have opposing effects to their ω6 counterpart [94]. However, in contrast to ω6 PUFA, the metabolism of ω3 PUFA is not well understood.

COXs (also known as prostaglandin G/H synthases, PTGS) have two well-characterized isoforms, namely COX1 or PTGS1 and COX2 or PTGS2. *COX1* is a constitutively expressed gene in most tissues whereas *COX2* is an immediate-early response gene, highly induced during tumor progression [95]. A third isoform, COX3, appears to be a splice variant of the *COX1* gene. Due to its induction in inflammation and cancer, COX2 has been the object of intense study and proposed as a target for cancer therapy. Numerous review articles have been written on this topic [96–99]. There are several types of LOXs in mammals, the most widely studies of which are LOX5 (ALOX5), LOX12 (ALOX12) and LOX15 (ALOX15), where the names reflects the substrate specificity in terms of the carbon number [100]. LOXs have been suggested to play roles in cancer as well [101].

Due to the existence of multiple oxygenases, the role of specific enzymes in the development of prostate cancer has not been studied systematically in a single system or animal model. In addition, studies performed in animals rarely take diet into account for the design and interpretation of the experiments. For this reason, it is still unclear whether all oxygenases play an important role or some oxygenases are more critical in the development of prostate cancer in animals consuming different diets. To systematically assess the interaction between oxygenases and dietary PUFA in a single *in vivo* model of prostate

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

cancer, we knocked out *Cox1, Cox2, Lox5, Lox12*, or *Lox15* in prostate-specific *Pten*-null mice. We have previously demonstrate that ω3 and ω6 PUFA differentially modulate the growth and progression of prostate tumors in this model [3]. Preliminary results indicate that loss of *Cox1* had significant effects on prostate tumor growth in a PUFA-dependent manner; namely, tumor growth was significantly increased in *Cox1* knockout mice on ω3 diet compared to *Pten*-null, *Cox1*-positive mice on the same diet, essentially negating the protective effects of ω3 PUFA. In other words, *Cox1* appears to be required for the protective effects of ω3 PUFA, suggesting that ω3 metabolites of *Cox1* reduce cancer formation. On the other hand, tumor growth was decreased in mice on ω6 diet compared to *Pten*-null, *Cox1*-positive mice on the same diet, suggesting that ω6 metabolites of *Cox1* (e.g., PGE_2) play a promoting role on tumor formation. Loss of *Cox2* reduced prostate tumor growth regardless of diet, suggesting that metabolites of *Cox2* promote tumor growth and that suppressive effects of ω3 PUFA do not depend upon *Cox2*. Loss of *Lox5* reduced prostate tumor growth on ω6 diet but had no effect on ω3 diet, suggesting that ω6 metabolites of *Lox5* promote tumor growth, and protective effects of ω3 PUFA are independent of *Lox5*. Loss of *Lox12* or *Lox15* did not affect prostate tumor growth on either diet, suggesting that either PUFA metabolites are not generated from these two enzymes, or metabolites generated are not critical for prostate tumor in this animal model (Chen et al., unpublished). It is clear from these studies that the interaction between diet and metabolic genes can play an important role in determining cancer risk and response of cancer to dietary PUFA.

Substantial evidence from human studies supports the important role of COXs in PUFA metabolism and cancer [92]. *LOX5* has also been implicated in the progression of several types of human cancers [102–106] including that of the prostate [107–110]. Interestingly, interactions between dietary intake of PUFA and polymorphisms in *COX2* and *LOX5* genes may determine cancer risk [111–114]. Such reports are consistent with our animal studies, but the role of *COX1* as well as specific polymorphisms of eicosanoid metabolic enzymes in human prostate cancer warrants further investigations.

8 Role of prostaglandin, prostacyclin and thromboxane synthases, and prostanoid receptors in cancer

As mentioned above, COX1 and COX2 convert arachidonic acid into prostaglandin G_2, which undergoes conversion to PGH_2 through the peroxidase activity of COX. In turn, PGH_2 is converted to other prostaglandins, prostacyclin, and thromboxanes by the action of several isomerases also called terminal synthases (Fig. 2). Three terminal synthases capable of producing PGE_2 from COX-derived PGH_2 have been reported: prostaglandin E synthase (PTGES) or microsomal PGES-1 (mPGES-1), PTGES2 or mPGES-2, and PTGES-3 or cPGES. A prostaglandin D_2 synthase responsible for converting PGH_2 to PGD_2 has been described in the brain, whereas in immune cells this conversion is catalyzed by hematopoietic prostaglandin D synthase. Prostaglandin I_2 (prostacyclin) synthase (PTGIS) is involved in the conversion of PGH_2 to PGI_2. In platelets, thromboxane A synthase 1 (TBXAS1) converts PGH_2 to TXA_2. ω3 PUFA EPA is thought to serve as a substrate of the same set of enzymes to generate 3-series eicosanoids (PGH_3, PGE_3, etc.) [115]. However, for many of these enzymes, the extent to which ω3 PUFA can serve as substrates is unclear.

mPGES-1 is a microsomal glutathione-dependent prostaglandin E synthase that can be induced by LPS, the proinflammatory cytokine interleukin 1 beta, by tumor suppressor protein TP53, as well as in pathological conditions such as cancer. Therefore, mPGES-1 has been proposed as a therapeutic target in cancer [116, 117]. mPGES-2 is also a microsomal prostaglandin E synthase, but its expression seems to be independent of inflammation and there is less evidence linking it to cancer. cPGES is a cytosolic protein also known as p23,

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

described as an HSP90 co-chaperone involved in the stabilization of the glucocorticoid receptor complex. A role for cPEGS in PGE_2 synthesis has been suggested experimentally [118, 119], but the results of mouse knockout studies failed to support this function [120].

One report showed that *mPGES-1* is expressed at high levels in DU145 human prostate cancer cells and in human prostate cancer tissues compared with benign hyperplasia. Short hairpin RNA-mediated *mPGES-1* knockdown in DU145 decreased clonogenic survival and increased sensitivity to adriamycin-induced apoptosis, which could be rescued by exogenous PGE_2. *mPGES-1* knockdown also decreased the tumorigenic potential of xenograft tumors in nude mice [121]. Polymorphisms in the *mPGES-2* and leukotriene A_4 hydrolase (*LTA4H*) genes were found to be inversely associated with prostate cancer risk [122].

In contrast with other prostaglandin synthases, PTGIS may reduce cancer risk (reviewed in [123]). The *PTGIS* gene promoter was identified as being hypermethylated in 43 out of 100 colorectal cancers and in colorectal cancer cell lines [124]. Promoter repeat polymorphism in *PTGIS* has also been found to be associated with risk of adenomas in a case–control study of individual with colorectal polyps versus polyp-free controls [125]. In human lung cancer, PGI_2 and PGE_2 appear to play antagonistic roles: *PTGIS* and PGI_2 are downregulated, whereas PGE_2 synthase and PGE_2 are upregulated [126, 127]. Moreover, transgenic mice with selective pulmonary prostacyclin synthase overexpression are protected from carcinogen-induced lung tumor formation [128]. The role of prostacyclin and PTGIS in prostate cancer is less clear.

Thromboxane A_4 synthase (TBXAS1) is overexpressed in a number of cancers and has been proposed to contribute to tumor development and progression by modulating tumor growth, angiogenesis, thrombosis, invasion, and metastasis and by inhibiting apoptosis. The balance in the expression of *PTGIS* and *TBXAS1* has been suggested to be clinically relevant [123]. In prostate cancer, immunohistochemical analysis of tumor samples showed significantly elevated TBXAS1 expression in prostate tumors compared to normal luminal or secretory cells, with a marked increased in tumors presenting perineural invasion [129]. In addition, migration of PC-3 cells, which express high levels of TBXAS1, was reduced by inhibition of this enzyme, whereas motility of *TBXAS1*-negative DU145 cells was stimulated by its overexpression.

Nine prostanoid receptors have been identified, which belong to the G protein-coupled receptor family and are conserved from mouse to human (Fig. 2). There are two PGD_2 receptors, called PTGDR or DP1 and GPR44 or DP2, four subtypes of PGE receptors, named PTGER1–4 or EP1–4, one PGF receptor (PTGFR or FP), one PGI_2 receptor (PTGIR or IP), and one TXA_2 receptor (TBXA2R or TP) [130]. In mouse prostate cells, expression of *Ep1*, *Ep2*, and *Ep4* is detectable (Chen et al., unpublished). Only *EP2* and *EP4* were detected in PC3, DU145, and LNCaP human prostate tumor cells, which is consistent with the literature [131, 132]. Aberrant TXA_2 signaling and *TP* expression is associated with prostate cancer, where a direct correlation was observed with tumor Gleason score and pathological state [133, 134]. However, much remains to be learnt about the expression of these prostanoid receptors and their activation by ω6 and, especially, ω3 prostanoids in cancer cells.

9 Role of PUFA in tumor angiogenesis

Nonsteroidal anti-inflammatory drugs (NSAIDs) exert some of their anti-inflammatory and antitumor effects by reducing prostanoid production through the inhibition of COX enzyme activity. NSAIDs have been reported to have beneficial effects on reducing the risk of developing prostate cancer [135–138]. The role of eicosanoids in tumor inflammation and

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

proliferation has been reviewed extensively [92, 93, 139–143]. Here we will focus on the potential role of PUFA in angiogenesis and cell surface receptor signaling.

Angiogenesis plays a major role in tumor progression by providing a blood supply to the growing tumor and facilitating its dissemination [144, 145]. The significance of angiogenesis in human prostate cancer progression is evidenced by correlations of microvessel density with Gleason score, pathologic stage of disease, and patient survival [146, 147]. The most investigated stimulator of angiogenesis is VEGF (reviewed in [148]). ω3 PUFA were shown to suppress VEGF-stimulated endothelial cell proliferation, migration, and tube formation during sprouting angiogenesis [149, 150], and endothelial cell expression of the VEGF receptor FLK-1 was reduced by EPA [151]. Effects of ω3 PUFA on *in vivo* models of VEGF-induced angiogenesis are inconsistent. Both EPA and DHA inhibited VEGF expression and reduced microvessels in tumors arising from HT-29 colon cancer cell transplants in nude mice. This involved inhibition of a pathway comprising COX2, PGE_2, and HIF-1α [152]. However, in a mouse model of hypoxia-induced retinal angiogenesis, an ω3 PUFA diet or expression of the *Caenorhabditis elegans fat-1* gene to endogenously enrich tissues in ω3 PUFA was shown to reduce pathological neovascularization without suppression of VEGF [153–155]. Likewise, an ω3 PUFA diet-induced decrease in tumor microvessel density in a mouse breast cancer xenograft model was not accompanied by a reduction in *VEGF* mRNA [156]. Using a random crossover design, a Mediterranean diet enriched in ω3 PUFA was compared to an ordinary Swedish diet for the ability to reduce indices of inflammation [157]. A 45% reduction in the ω6 to ω3 PUFA ratio in serum was accompanied by a significant decrease in VEGF following the Mediterranean diet phase.

PDGF is another key regulator of angiogenesis. Studies examining the role of fish oil in reducing risk of cardiovascular disease showed that ω3 PUFA almost completely eliminated endothelial cell production of PDGF *in vitro* [158]. Further, in human volunteers fed with dietary fish oil, increased monocyte ω3 PUFA levels were associated with a 66% and 70% decrease in mRNA for *PDGF-A* and *PDGF-B*, respectively [159]. Similar studies have yet to be conducted with cancer patients.

The FGF family in vertebrates consists of 22 proteins that range in size from 17 to 34 kDa and share 17–31% sequence identity [160, 161]. FGFs display variable affinities for four cognate tyrosine kinase receptors, designated FGFR1–4, and all of which are upregulated in prostate cancer [162]. FGF1, FGF2, FGF6, FGF8, FGF9, and FGF17 show elevated expression in prostate tumors compared to normal human prostate [162–164]. Of these, FGF1 and FGF2 are well-defined promoters of angiogenesis [165]. Over 80% of prostate cancers express FGF1, and expression was shown to positively correlate with Gleason score [166]. The biological significance of FGF2 in prostate cancer was demonstrated in the transgenic adenocarcinoma of the mouse prostate mouse model, in which elimination of one or both *Fgf2* alleles reduced metastasis and increased survival [167]. FGF8 has also emerged as an important promoter of angiogenesis. An alternatively spliced isoform, FGF8b is the major isoform of FGF8 present in human prostate cancer and is strongly associated with stage and grade of disease [168]. Xenografts of PC3 cells overexpressing FGF8b in mice demonstrated an extensive capillary network and metastases [169]. Targeted prostate expression of *Fgf8b* in transgenic mice was shown to induce a hypercellular reactive stroma enriched in vasculature, prior to the development of PIN [170]. Although there is no evidence to date for regulation of any FGF by ω3 PUFA, enrichment of tumor cells with the ω6 PUFA linoleic acid was shown to convert the growth-promoting activity of FGF from a transient to a sustained effect [171].

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

10 Effects of PUFA on cell surface receptor signaling

Toll-like receptors (TLRs) are a family of transmembrane receptors that mediate an innate immune response through recognition of conserved patterns of microbial and viral components. They play a major role in defense against pathogens, particularly at mucosal surfaces. Although TLRs were originally detected only on immune cells [172], it is now known that tumor cells express functional TLRs that are stimulated by endogenous ligands in addition to those of microbial origin [173–175]. The physiological functions of TLRs in relation to cancer have been reviewed [175]. In prostate cancer, increased risk has been linked to sequence variations in *TLR4* [176] and the *TLR6–10* cluster [177]. Although the biological consequences of these polymorphisms are not understood, they are consistent with a major role of inflammation in prostate cancer and suppression of TLR activity may be one of the anti-inflammatory roles of ω3 PUFA. Dietary fish oil was shown to inhibit TLR4 activity in peripheral blood monocytes from human volunteers [178], and DHA acted as a pan inhibitor of TLRs in a macrophage cell line [179]. In prostate cancer cells, *TLR3* activation was shown to trigger apoptosis and promote angiogenesis through upregulation of HIF-1α [180]. Effects of ω3 PUFA on prostate cancer cell TLRs remain to be determined.

The syndecan family of cell surface proteoglycans consists of four members with a shared structure of small conserved cytoplasmic and transmembrane domains and larger, distinct ectodomains. The ectodomains are substituted predominantly with heparan sulfate glycosaminoglycan chains, but syndecan-1 can also exist as a hybrid bearing both heparan sulfate and chondroitin sulfate chains [181]. A biologically active ectodomain can be shed by the action of matrix metalloproteinases (reviewed in [182]). Syndecan-1 is the most widely studied in relation to cancer, but its role is complex and far from clear. Its heparan sulfate chains interact with a variety of extracellular matrix components, growth factors, cytokines, and enzymes to facilitate a role in regulation of cell proliferation, apoptosis, adhesion, and migration. Syndecan-1 is expressed primarily by epithelial cells, but with malignant conversion and tumor progression, syndecan-1 expression is reduced and this reduction is associated with poor prognosis in various epithelial-derived tumors [183–186]. However this may be tumor or stage specific, since syndecan-1 increases have been associated with unfavorable prognosis in some cancers [187–189]. Mounting evidence indicates that tumor progression is accompanied by a shift from an epithelial to stromal distribution for syndecan-1 [190–192]. This may result in changes in the fine structure of syndecan-1 that lead to altered function. Syndecan-1 has not been well studied in prostate cancer. An inverse relationship was reported between syndecan-1 and Gleason score [193, 194], but a tissue microarray analysis showed an increase in syndecan-1 with tumor progression [195]. *In vitro* studies have shown reduced expression of syndecan-1 in prostate cancer cell lines compared to normal prostate epithelial cells and lower expression in androgen-dependent LNCaP cells compared to androgen independent PC3 and DU145 cells [196].

Our studies have shown that in a mouse model of prostate cancer, the reduction in tumor growth as a result of dietaryω3 PUFA [3] is accompanied by an increase in the expression of syndecan-1 [196, 197]. Moreover, in human and mouse prostate cancer cells lines, syndecan-1 was upregulated by DHA but not EPA. This led to increased apoptosis through syndecan-1-dependent suppression of the PDK-1/AKT/BAD signaling pathway [196]. Syndecan-1 upregulation by DHA has also been demonstrated in human breast cancer cells [2, 198, 199] and in ω3 PUFA-enriched mammary glands and liver of *Fat-1* mice (Sun et al., in press).

New evidence points to an important role for syndecan-1 as a negative regulator of angiogenesis and suggests that ω3 PUFA modulation of angiogenesis may involve

NIH-PA Author Manuscript

syndecan-1. Shedding of the syndecan-1 ectodomain is triggered by inflammatory conditions [200, 201]. In a mouse model of lung injury, binding of the chemokine CXCL1 to syndecan-1 was shown to induce enzymatic shedding of the ectodomain-CXCL1 complex by MMP-7. This generated a transepithelial chemokine gradient to direct neutrophils to the injury site [201]. In addition, syndecan-1 is a negative regulator of leukocyte-mediated inflammatory responses by binding chemokines CCL7, CCL11, and CCL17 to inhibit CC chemokine-mediated T cell migration [202]. Mice with a deletion of the gene encoding syndecan-1 (*Sdc1*−/−) demonstrated increased leukocyte adhesion to endothelial cells and increased inflammation-mediated corneal angiogenesis [203, 204]. The inflammatory cytokine, tumor necrosis factor (TNF)α promotes retinal angiogenesis [205]. TNFα was shown to also suppress endothelial cell syndecan-1 expression [206]. Dietary ω3 PUFA reduced retinal TNFα and protected against retinal neovascularization [153]. Further the antiangiogenic effect of ω3 PUFA was shown to be mediated by activation of the nuclear receptor PPARγ [154]. *SDC1* is a PPARγ-responsive gene, and we have shown that DHA upregulates syndecan-1 in prostate cancer cells through activation of PPARγ [197]. Critical experiments confirming a role for syndecan-1 in ω3 PUFA suppression of angiogenesis have yet to be conducted.

11 Conclusions

Dietary ω3 and ω6 PUFA are subjected to complex metabolic processes involving genes for lipid release from glycerolipids, elongation, β-oxidation, storage, eicosanoid synthesis and signaling. Much of the knowledge is derived from the study of ω6 PUFA. Relatively little is known about ω3 PUFA metabolism. Moreover, the interplay between dietary fat and *de novo* synthesis is not fully understood, especially in cancer. We will end this review by posing a series of questions, which we believe are some of the key challenges in the field of PUFA research.

12 Key unanswered questions

1. Does FADS2 have the same activity towards LA and α-LNA?
2. Is the low conversion rate of α-LNA to EPA primarily due to low bioavailability of α-LNA or low activity of FADS?
3. Are there differences in *FADS* polymorphisms between Caucasians, Asians, and African-American populations, and do these differences have an impact on the effect of PUFA on cancer risk?
4. Considering the amount of fat in a typical diet, why do tumor cells require *de novo* fatty acid synthesis?
5. Are dietary and *de novo* synthesized fatty acids utilized differently in tumors compared to normal tissues and *in vivo* compared to cell culture?
6. Are *ACC1* and *FASN* good cancer therapeutic targets, and can dietary fat compensate for the loss of ACC1 or FASN in tumor tissue?
7. Can ACC1 inhibition affect arachidonic acid formation and metabolism?
8. What are the relative contributions of cyclooxygenases and lipoxygenases during human prostate cancer development, and what is the influence of diet?
9. How do polymorphic variants of lipid metabolizing enzymes interact with dietary fat to modify cancer risk and progression?

10. Which metabolites of EPA and DHA are found in prostate tissues and play a major role in suppression of prostate cancer?

References

1. Calviello G, Serini S, Piccioni E. n-3 polyunsaturated fatty acids and the prevention of colorectal cancer: molecular mechanisms involved. Current Medicinal Chemistry. 2007; 14(29):3059–3069. [PubMed: 18220742]
2. Sun H, Berquin IM, Owens RT, O'Flaherty JT, Edwards IJ. Peroxisome proliferator-activated receptor gamma-mediated up-regulation of syndecan-1 by n-3 fatty acids promotes apoptosis of human breast cancer cells. Cancer Research. 2008; 68(8):2912–2919. [PubMed: 18413760]
3. Berquin IM, Min Y, Wu R, et al. Modulation of prostate cancer genetic risk by omega-3 and omega-6 fatty acids. The Journal of Clinical Investigation. 2007; 117(7):1866–1875. [PubMed: 17607361]
4. Berquin IM, Edwards IJ, Chen YQ. Multi-targeted therapy of cancer by omega-3 fatty acids. Cancer Letters. 2008; 269(2):363–377. [PubMed: 18479809]
5. Chen YQ, Edwards IJ, Kridel SJ, Thornburg T, Berquin IM. Dietary fat–gene interactions in cancer. Cancer Metastasis Reviews. 2007; 26(3–4):535–551. [PubMed: 17849170]
6. Simopoulos AP. Genetic variants in the metabolism of omega-6 and omega-3 fatty acids: their role in the determination of nutritional requirements and chronic disease risk. Experimental Biology and Medicine. 2010; 235(7):785–795. [PubMed: 20558833]
7. Bernert JT Jr, Sprecher H. Studies to determine the role rates of chain elongation and desaturation play in regulating the unsaturated fatty acid composition of rat liver lipids. Biochimica et Biophysica Acta. 1975; 398(3):354–363. [PubMed: 1174521]
8. Burdge GC, Calder PC. Conversion of alphalinolenic acid to longer-chain polyunsaturated fatty acids in human adults. Reproduction Nutrition Development. 2005; 45(5):581–597.
9. Williams CM, Burdge G. Long-chain *n*-3 PUFA: plant *v.* marine sources. Proceedings of the Nutrition Society. 2006; 65(1):42–50. [PubMed: 16441943]
10. Pawlosky RJ, Hibbeln JR, Novotny JA, Salem N Jr. Physiological compartmental analysis of alpha-linolenic acid metabolism in adult humans. Journal of Lipid Research. 2001; 42(8):1257–1265. [PubMed: 11483627]
11. Portolesi R, Powell BC, Gibson RA. Competition between 24:5n-3 and ALA for Delta 6 desaturase may limit the accumulation of DHA in HepG2 cell membranes. Journal of Lipid Research. 2007; 48(7):1592–1598. [PubMed: 17409318]
12. Childs CE, Romeu-Nadal M, Burdge GC, Calder PC. Gender differences in the *n*-3 fatty acid content of tissues. Proceedings of the Nutrition Society. 2008; 67(1):19–27. [PubMed: 18234128]
13. Kitson AP, Stroud CK, Stark KD. Elevated production of docosahexaenoic acid in females: potential molecular mechanisms. Lipids. 2010; 45(3):209–224. [PubMed: 20151220]
14. Bar M, Wyman SK, Fritz BR, et al. MicroRNA discovery and profiling in human embryonic stem cells by deep sequencing of small RNA libraries. Stem Cells. 2008; 26(10):2496–2505. [PubMed: 18583537]
15. Nygaard S, Jacobsen A, Lindow M, et al. Identification and analysis of miRNAs in human breast cancer and teratoma samples using deep sequencing. BMC Medical Genomics. 2009; 2:35. [PubMed: 19508715]
16. Creighton CJ, Benham AL, Zhu H, et al. Discovery of novel microRNAs in female reproductive tract using next generation sequencing. PLoS One. 2010; 5(3):e9637. [PubMed: 20224791]
17. Schaeffer L, Gohlke H, Muller M, et al. Common genetic variants of the *FADS1 FADS2* gene cluster and their reconstructed haplotypes are associated with the fatty acid composition in phospholipids. Human Molecular Genetics. 2006; 15(11):1745–1756. [PubMed: 16670158]
18. Xie L, Innis SM. Genetic variants of the FADS1 FADS2 gene cluster are associated with altered (n-6) and (n-3) essential fatty acids in plasma and erythrocyte phospholipids in women during pregnancy and in breast milk during lactation. Journal of Nutrition. 2008; 138(11):2222–2228. [PubMed: 18936223]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

19. Martinelli N, Girelli D, Malerba G, et al. FADS genotypes and desaturase activity estimated by the ratio of arachidonic acid to linoleic acid are associated with inflammation and coronary artery disease. American Journal of Clinical Nutrition. 2008; 88(4):941–949. [PubMed: 18842780]
20. Malerba G, Schaeffer L, Xumerle L, et al. SNPs of the FADS gene cluster are associated with polyunsaturated fatty acids in a cohort of patients with cardiovascular disease. Lipids. 2008; 43(4): 289–299. [PubMed: 18320251]
21. Rzehak P, Heinrich J, Klopp N, et al. Evidence for an association between genetic variants of the *fatty acid desaturase 1 fatty acid desaturase 2* (*FADS1 FADS2*) gene cluster and the fatty acid composition of erythrocyte membranes. British Journal of Nutrition. 2009; 101(1):20–26. [PubMed: 18479586]
22. Bokor S, Dumont J, Spinneker A, et al. Single nucleotide polymorphisms in the *FADS* gene cluster are associated with delta-5 and delta-6 desaturase activities estimated by serum fatty acid ratios. Journal of Lipid Research. 2010; 51(8):2325–2333. [PubMed: 20427696]
23. Lu Y, Feskens EJ, Dolle ME, et al. Dietary n-3 and n-6 polyunsaturated fatty acid intake interacts with *FADS1* genetic variation to affect total and HDL-cholesterol concentrations in the Doetinchem Cohort Study. American Journal of Clinical Nutrition. 2010; 92(1):258–265. [PubMed: 20484448]
24. Mathias RA, Vergara C, Gao L, et al. *FADS* genetic variants and omega-6 polyunsaturated fatty acid metabolism in a homogeneous island population. Journal of Lipid Research. 2010; 51(9): 2766–2774. [PubMed: 20562440]
25. Molto-Puigmarti C, Plat J, Mensink RP, et al. *FADS1 FADS2* gene variants modify the association between fish intake and the docosahexaenoic acid proportions in human milk. American Journal of Clinical Nutrition. 2010; 91(5):1368–1376. [PubMed: 20335541]
26. Zietemann V, Kroger J, Enzenbach C, et al. Genetic variation of the FADS1 FADS2 gene cluster and n-6 PUFA composition in erythrocyte membranes in the European Prospective Investigation into Cancer and Nutrition-Potsdam study. British Journal of Nutrition. 2010; 104(12):1748–1759. [PubMed: 20691134]
27. Koletzko B, Lattka E, Zeilinger S, Illig T, Steer C. Genetic variants of the fatty acid desaturase gene cluster predict amounts of red blood cell docosahexaenoic and other polyunsaturated fatty acids in pregnant women: findings from the Avon Longitudinal Study of Parents and Children. American Journal of Clinical Nutrition. 2011; 93(1):211–219. [PubMed: 21106917]
28. Kwak JH, Paik JK, Kim OY, et al. FADS gene polymorphisms in Koreans: association with omega6 polyunsaturated fatty acids in serum phospholipids, lipid peroxides, and coronary artery disease. Atherosclerosis. 2011; 214(1):94–100. [PubMed: 21040914]
29. Tanaka T, Shen J, Abecasis GR, et al. Genome-wide association study of plasma polyunsaturated fatty acids in the InCHIANTI Study. PLoS Genetics. 2009; 5(1):e1000338. [PubMed: 19148276]
30. Lattka E, Illig T, Heinrich J, Koletzko B. FADS gene cluster polymorphisms: important modulators of fatty acid levels and their impact on atopic diseases. Journal of Nutrigenetics and Nutrigenomics. 2009; 2(3):119–128. [PubMed: 19776639]
31. Lattka E, Illig T, Heinrich J, Koletzko B. Do FADS genotypes enhance our knowledge about fatty acid related phenotypes? Clinical Nutrition. 2010; 29(3):277–287. [PubMed: 19948371]
32. Martinelli N, Consoli L, Olivieri O. A ‘desaturase hypothesis’ for atherosclerosis: Janus-faced enzymes in omega-6 and omega-3 polyunsaturated fatty acid metabolism. Journal of Nutrigenetics and Nutrigenomics. 2009; 2(3):129–139. [PubMed: 19776640]
33. Lattka E, Illig T, Koletzko B, Heinrich J. Genetic variants of the *FADS1 FADS2* gene cluster as related to essential fatty acid metabolism. Current Opinion in Lipidology. 2010; 21(1):64–69. [PubMed: 19809313]
34. Merino DM, Ma DW, Mutch DM. Genetic variation in lipid desaturases and its impact on the development of human disease. Lipids in Health and Disease. 2010; 9:63. [PubMed: 20565855]
35. Merino DM, Johnston H, Clarke S, et al. Polymorphisms in *FADS1* and *FADS2* alter desaturase activity in young Caucasian and Asian adults. Molecular Genetics and Metabolism. 2011; 103(2): 171–178. [PubMed: 21414826]
36. Kuhajda FP. Fatty acid synthase and cancer: new application of an old pathway. Cancer Research. 2006; 66(12):5977–5980. [PubMed: 16778164]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

37. Menendez JA, Lupu R. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. Nature Reviews. Cancer. 2007; 7(10):763–777.
38. Bandyopadhyay S, Pai SK, Watabe M, et al. FAS expression inversely correlates with PTEN level in prostate cancer and a PI 3-kinase inhibitor synergizes with FAS siRNA to induce apoptosis. Oncogene. 2005; 24(34):5389–5395. [PubMed: 15897909]
39. Milgraum LZ, Witters LA, Pasternack GR, Kuhajda FP. Enzymes of the fatty acid synthesis pathway are highly expressed in *in situ* breast carcinoma. Clinical Cancer Research. 1997; 3(11): 2115–2120. [PubMed: 9815604]
40. Pflug BR, Pecher SM, Brink AW, Nelson JB, Foster BA. Increased fatty acid synthase expression and activity during progression of prostate cancer in the TRAMP model. Prostate. 2003; 57(3): 245–254. [PubMed: 14518031]
41. Rossi S, Graner E, Febbo P, et al. Fatty acid synthase expression defines distinct molecular signatures in prostate cancer. Molecular Cancer Research. 2003; 1(10):707–715. [PubMed: 12939396]
42. Shah US, Dhir R, Gollin SM, et al. Fatty acid synthase gene overexpression and copy number gain in prostate adenocarcinoma. Human Pathology. 2006; 37(4):401–409. [PubMed: 16564913]
43. Kridel SJ, Lowther WT, Pemble CWt. Fatty acid synthase inhibitors: new directions for oncology. Expert Opin Investig Drugs. 2007; 16(11):1817–1829.
44. Swinnen JV, Esquenet M, Goossens K, Heyns W, Verhoeven G. Androgens stimulate fatty acid synthase in the human prostate cancer cell line LNCaP. Cancer Research. 1997; 57(6):1086–1090. [PubMed: 9067276]
45. Swinnen JV, Ulrix W, Heyns W, Verhoeven G. Coordinate regulation of lipogenic gene expression by androgens: evidence for a cascade mechanism involving sterol regulatory element binding proteins. Proceedings of the National Academy of Sciences of the United States of America. 1997; 94(24):12975–12980. [PubMed: 9371785]
46. Swinnen JV, Verhoeven G. Androgens and the control of lipid metabolism in human prostate cancer cells. The Journal of Steroid Biochemistry and Molecular Biology. 1998; 65(1–6):191–198. [PubMed: 9699873]
47. Swinnen JV, Roskams T, Joniau S, et al. Overexpression of fatty acid synthase is an early and common event in the development of prostate cancer. International Journal of Cancer. 2002; 98(1): 19–22.
48. Van de Sande T, De Schrijver E, Heyns W, Verhoeven G, Swinnen JV. Role of the phosphatidylinositol 3′-kinase/PTEN/Akt kinase pathway in the overexpression of fatty acid synthase in LNCaP prostate cancer cells. Cancer Research. 2002; 62(3):642–646. [PubMed: 11830512]
49. Migita T, Ruiz S, Fornari A, et al. Fatty acid synthase: a metabolic enzyme and candidate oncogene in prostate cancer. Journal of the National Cancer Institute. 2009; 101(7):519–532. [PubMed: 19318631]
50. Bauer DE, Hatzivassiliou G, Zhao F, Andreadis C, Thompson CB. ATP citrate lyase is an important component of cell growth and transformation. Oncogene. 2005; 24(41):6314–6322. [PubMed: 16007201]
51. Hatzivassiliou G, Zhao F, Bauer DE, et al. ATP citrate lyase inhibition can suppress tumor cell growth. Cancer Cell. 2005; 8(4):311–321. [PubMed: 16226706]
52. DeBerardinis RJ, Mancuso A, Daikhin E, et al. Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. Proceedings of the National Academy of Sciences. 2007; 104(49):19345–19350.
53. Abu-Elheiga L, Matzuk MM, Kordari P, et al. Mutant mice lacking acetyl-CoA carboxylase 1 are embryonically lethal. PNAS. 2005; 102(34):12011–12016. [PubMed: 16103361]
54. Mao J, DeMayo FJ, Li H, et al. Liver-specific deletion of acetyl-CoA carboxylase 1 reduces hepatic triglyceride accumulation without affecting glucose homeostasis. Proceedings of the National Academy of Sciences of the United States of America. 2006; 103(22):8552–8557. [PubMed: 16717184]
55. Chirala SS, Chang H, Matzuk M, et al. Fatty acid synthesis is essential in embryonic development: fatty acid synthase null mutants and most of the heterozygotes die in utero. Proceedings of the

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

National Academy of Sciences of the United States of America. 2003; 100(11):6358–6363. [PubMed: 12738878]

56. Wakil SJ. Fatty acid synthase, a proficient multifunctional enzyme. Biochemistry. 1989; 28(11): 4523–4530. [PubMed: 2669958]
57. Wakil SJ, Stoops JK, Joshi VC. Fatty acid synthesis and its regulation. Annual Review of Biochemistry. 1983; 52(1):537–579.
58. Smith S. The animal fatty acid synthase: one gene, one polypeptide, seven enzymes. The FASEB Journal. 1994; 8(15):1248–1259.
59. Chajes V, Cambot M, Moreau K, Lenoir GM, Joulin V. Acetyl-CoA carboxylase alpha is essential to breast cancer cell survival. Cancer Research. 2006; 66(10):5287–5294. [PubMed: 16707454]
60. Knowles LM, Axelrod F, Browne CD, Smith JW. A fatty acid synthase blockade induces tumor cell-cycle arrest by down-regulating Skp2. Journal of Biological Chemistry. 2004; 279(29):30540–30545. [PubMed: 15138278]
61. Little JL, Wheeler FB, Fels DR, Koumenis C, Kridel SJ. Inhibition of fatty acid synthase induces endoplasmic reticulum stress in tumor cells. Cancer Research. 2007; 67(3):1262–1269. [PubMed: 17283163]
62. Heiligtag SJ, Bredehorst R, David KA. Key role of mitochondria in cerulenin-mediated apoptosis. Cell Death and Differentiation. 2002; 9(9):1017–1025. [PubMed: 12181752]
63. Fiorentino M, Zadra G, Palescandolo E, et al. Overexpression of fatty acid synthase is associated with palmitoylation of Wnt1 and cytoplasmic stabilization of beta-catenin in prostate cancer. Laboratory Investigation. 2008; 88(12):1340–1348. [PubMed: 18838960]
64. Migita T, Narita T, Nomura K, et al. ATP citrate lyase: activation and therapeutic implications in non-small cell lung cancer. Cancer Research. 2008; 68(20):8547–8554. [PubMed: 18922930]
65. Brusselmans K, De Schrijver E, Verhoeven G, Swinnen JV. RNA interference-mediated silencing of the acetyl-CoA-carboxylase-alpha gene induces growth inhibition and apoptosis of prostate cancer cells. Cancer Research. 2005; 65(15):6719–6725. [PubMed: 16061653]
66. Kridel SJ, Axelrod F, Rozenkrantz N, Smith JW. Orlistat is a novel inhibitor of fatty acid synthase with antitumor activity. Cancer Research. 2004; 64(6):2070–2075. [PubMed: 15026345]
67. Alli PM, Pinn ML, Jaffee EM, McFadden JM, Kuhajda FP. Fatty acid synthase inhibitors are chemo-preventive for mammary cancer in neu-N transgenic mice. Oncogene. 2005; 24(1):39–46. [PubMed: 15489885]
68. Kuhajda FP, Jenner K, Wood FD, et al. Fatty acid synthesis: a potential selective target for antineoplastic therapy. Proceedings of the National Academy of Sciences of the United States of America. 1994; 91(14):6379–6383. [PubMed: 8022791]
69. Orita H, Coulter J, Tully E, Kuhajda FP, Gabrielson E. Inhibiting fatty acid synthase for chemoprevention of chemically induced lung tumors. Clinical Cancer Research. 2008; 14(8): 2458–2464. [PubMed: 18413838]
70. Swinnen JV, Van Veldhoven PP, Timmermans L, et al. Fatty acid synthase drives the synthesis of phospholipids partitioning into detergent-resistant membrane microdomains. Biochemical and Biophysical Research Communications. 2003; 302(4):898–903. [PubMed: 12646257]
71. Rysman E, Brusselmans K, Scheys K, et al. *De novo* lipogenesis protects cancer cells from free radicals and chemotherapeutics by promoting membrane lipid saturation. Cancer Research. 2010; 70(20):8117–8126. [PubMed: 20876798]
72. Chakravarthy MV, Pan Z, Zhu Y, et al. “New” hepatic fat activates PPAR[alpha] to maintain glucose, lipid, and cholesterol homeostasis. Cell Metabolism. 2005; 1(5):309–322. [PubMed: 16054078]
73. Chakravarthy MV, Lodhi IJ, Yin L, et al. Identification of a physiologically relevant endogenous ligand for PPAR[alpha] in liver. Cell. 2009; 138(3):476–488. [PubMed: 19646743]
74. De Schrijver E, Brusselmans K, Heyns W, Verhoeven G, Swinnen JV. RNA interference-mediated silencing of the fatty acid synthase gene attenuates growth and induces morphological changes and apoptosis of LNCaP prostate cancer cells. Cancer Research. 2003; 63(13):3799–3804. [PubMed: 12839976]
75. Kuemmerle NB, Rysman E, Lombardo PS, et al. Lipoprotein lipase links dietary fat to solid tumor cell proliferation. Molecular Cancer Therapeutics. 2011; 10(3):427–436. [PubMed: 21282354]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

76. Simopoulos AP. Essential fatty acids in health and chronic disease. American Journal of Clinical Nutrition. 1999; 70(3 Suppl):560S–569S. [PubMed: 10479232]
77. Crawford MA, Casperd NM, Sinclair AJ. The long chain metabolites of linoleic avid linolenic acids in liver and brain in herbivores and carnivores. Comparative Biochemistry and Physiology. B. 1976; 54(3):395–401.
78. Horrobin DF, Huang YS, Cunnane SC, Manku MS. Essential fatty acids in plasma, red blood cells and liver phospholipids in common laboratory animals as compared to humans. Lipids. 1984; 19(10):806–811. [PubMed: 6503624]
79. Fu Z, Sinclair AJ. Increased alpha-linolenic acid intake increases tissue alpha-linolenic acid content and apparent oxidation with little effect on tissue docosahexaenoic acid in the guinea pig. Lipids. 2000; 35(4):395–400. [PubMed: 10858024]
80. Leyton J, Drury PJ, Crawford MA. Differential oxidation of saturated and unsaturated fatty acids *in vivo* in the rat. British Journal of Nutrition. 1987; 57(3):383–393. [PubMed: 3109464]
81. DeLany JP, Windhauser MM, Champagne CM, Bray GA. Differential oxidation of individual dietary fatty acids in humans. American Journal of Clinical Nutrition. 2000; 72(4):905–911. [PubMed: 11010930]
82. Gavino VC, Cordeau S, Gavino G. Kinetic analysis of the selectivity of acylcarnitine synthesis in rat mitochondria. Lipids. 2003; 38(4):485–490. [PubMed: 12848298]
83. Bryan DL, Hart P, Forsyth K, Gibson R. Incorporation of alpha-linolenic acid and linoleic acid into human respiratory epithelial cell lines. Lipids. 2001; 36(7):713–717. [PubMed: 11521969]
84. Martin-Chouly CA, Menier V, Hichami A, et al. Modulation of PAF production by incorporation of arachidonic acid and eicosapentaenoic acid in phospholipids of human leukemic monocyte-like cells THP-1. Prostaglandins & Other Lipid Mediators. 2000; 60(4–6):127–135. [PubMed: 10751643]
85. Pickett WC, Ramesha CS. Ether phospholipids in control and 20:4-depleted rat PMN: additional evidence for a 1-O-alkyl-2-20:4-sn-glycerol-3-phosphocholine specific phospholipase A2. Agents and Actions. 1987; 21(3–4):390–392. [PubMed: 3120515]
86. Strokin M, Sergeeva M, Reiser G. Docosahexaenoic acid and arachidonic acid release in rat brain astrocytes is mediated by two separate isoforms of phospholipase A2 and is differently regulated by cyclic AMP and Ca2+ British Journal of Pharmacology. 2003; 139(5):1014–1022. [PubMed: 12839876]
87. Nakanishi M, Rosenberg DW. Roles of cPLA2alpha and arachidonic acid in cancer. Biochimica et Biophysica Acta. 2006; 1761(11):1335–1343. [PubMed: 17052951]
88. Murakami M, Taketomi Y, Girard C, Yamamoto K, Lambeau G. Emerging roles of secreted phospholipase A2 enzymes: lessons from transgenic and knockout mice. Biochimie. 2010; 92(6): 561–582. [PubMed: 20347923]
89. Scott KF, Sajinovic M, Hein J, et al. Emerging roles for phospholipase A2 enzymes in cancer. Biochimie. 2010; 92(6):601–610. [PubMed: 20362028]
90. Dong Q, Patel M, Scott KF, Graham GG, Russell PJ, Sved P. Oncogenic action of phospholipase A2 in prostate cancer. Cancer Letters. 2006; 240(1):9–16. [PubMed: 16182442]
91. Mirtti T, Laine VJ, Hiekkanen H, et al. Group IIA phospholipase A as a prognostic marker in prostate cancer: relevance to clinicopathological variables and disease-specific mortality. APMIS. 2009; 117(3):151–161. [PubMed: 19245588]
92. Wang D, Dubois RN. Eicosanoids and cancer. Nature Reviews Cancer. 2010; 10(3):181–193.
93. Panigrahy D, Kaipainen A, Greene ER, Huang S. Cytochrome P450-derived eicosanoids: the neglected pathway in cancer. Cancer Metastasis Reviews. 2010; 29(4):723–735. [PubMed: 20941528]
94. Chapkin RS, Kim W, Lupton JR, McMurray DN. Dietary docosahexaenoic and eicosapentaenoic acid: emerging mediators of inflammation. Prostaglandins, Leukotrienes, and Essential Fatty Acids. 2009; 81(2–3):187–191.
95. Dubois RN, Abramson SB, Crofford L, et al. Cyclooxygenase in biology and disease. The FASEB Journal. 1998; 12(12):1063–1073.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

96. Sobolewski C, Cerella C, Dicato M, Ghibelli L, Diederich M. The role of cyclooxygenase-2 in cell proliferation and cell death in human malignancies. Int J Cell Biol. 2010; 2010:215158. [PubMed: 20339581]
97. Wang MT, Honn KV, Nie D. Cyclooxygenases, prostanoids, and tumor progression. Cancer Metastasis Reviews. 2007; 26(3–4):525–534. [PubMed: 17763971]
98. Reese AC, Fradet V, Witte JS. Omega-3 fatty acids, genetic variants in COX-2 and prostate cancer. Journal of Nutrigenetics and Nutrigenomics. 2009; 2(3):149–158. [PubMed: 19776642]
99. Menter DG, Schilsky RL, DuBois RN. Cyclooxygenase-2 and cancer treatment: understanding the risk should be worth the reward. Clinical Cancer Research. 2010; 16(5):1384–1390. [PubMed: 20179228]
100. Brash AR. Lipoxygenases: occurrence, functions, catalysis, and acquisition of substrate. Journal of Biological Chemistry. 1999; 274(34):23679–23682. [PubMed: 10446122]
101. Pidgeon GP, Lysaght J, Krishnamoorthy S, et al. Lipoxygenase metabolism: roles in tumor progression and survival. Cancer Metastasis Reviews. 2007; 26(3–4):503–524. [PubMed: 17943411]
102. Avis IM, Jett M, Boyle T, et al. Growth control of lung cancer by interruption of 5-lipoxygenase-mediated growth factor signaling. The Journal of Clinical Investigation. 1996; 97(3):806–813. [PubMed: 8609238]
103. Soumaoro LT, Iida S, Uetake H, et al. Expression of 5-lipoxygenase in human colorectal cancer. World Journal of Gastroenterology. 2006; 12(39):6355–6360. [PubMed: 17072961]
104. Ye YN, Wu WK, Shin VY, Bruce IC, Wong BC, Cho CH. Dual inhibition of 5-LOX and COX-2 suppresses colon cancer formation promoted by cigarette smoke. Carcinogenesis. 2005; 26(4): 827–834. [PubMed: 15637091]
105. Faronato M, Muzzonigro G, Milanese G, et al. Increased expression of 5-lipoxygenase is common in clear cell renal cell carcinoma. Histology and Histopathology. 2007; 22(10):1109–1118. [PubMed: 17616938]
106. Hayashi T, Nishiyama K, Shirahama T. Inhibition of 5-lipoxygenase pathway suppresses the growth of bladder cancer cells. International Journal of Urology. 2006; 13(8):1086–1091. [PubMed: 16903934]
107. Ghosh J. Inhibition of arachidonate 5-lipoxygenase triggers prostate cancer cell death through rapid activation of c-Jun N-terminal kinase. Biochemical and Biophysical Research Communications. 2003; 307(2):342–349. [PubMed: 12859962]
108. Ghosh J, Myers CE. Inhibition of arachidonate 5-lipoxygenase triggers massive apoptosis in human prostate cancer cells. Proceedings of the National Academy of Sciences of the United States of America. 1998; 95(22):13182–13187. [PubMed: 9789062]
109. Sharma BK, Pilania P, Singh P. Modeling of cyclooxygenase-2 and 5-lipooxygenase inhibitory activity of apoptosis-inducing agents potentially useful in prostate cancer chemotherapy: derivatives of diarylpyrazole. Journal of Enzyme Inhibition and Medicinal Chemistry. 2009; 24(2):607–615. [PubMed: 18825552]
110. Sundaram S, Ghosh J. Expression of 5-oxoETE receptor in prostate cancer cells: critical role in survival. Biochemical and Biophysical Research Communications. 2006; 339(1):93–98. [PubMed: 16289380]
111. Koh WP, Yuan JM, van den Berg D, Lee HP, Yu MC. Interaction between cyclooxygenase-2 gene polymorphism and dietary n-6 polyunsaturated fatty acids on colon cancer risk: the Singapore Chinese Health Study. British Journal of Cancer. 2004; 90(9):1760–1764. [PubMed: 15150618]
112. Siezen CL, van Leeuwen AI, Kram NR, Luken ME, van Kranen HJ, Kampman E. Colorectal adenoma risk is modified by the interplay between polymorphisms in arachidonic acid pathway genes and fish consumption. Carcinogenesis. 2005; 26(2):449–457. [PubMed: 15550453]
113. Hedelin M, Chang ET, Wiklund F, et al. Association of frequent consumption of fatty fish with prostate cancer risk is modified by COX-2 polymorphism. International Journal of Cancer. 2007; 120(2):398–405.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

114. Fradet V, Cheng I, Casey G, Witte JS. Dietary omega-3 fatty acids, cyclooxygenase-2 genetic variation, and aggressive prostate cancer risk. Clinical Cancer Research. 2009; 15(7):2559–2566. [PubMed: 19318492]

115. Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. American Journal of Clinical Nutrition. 2004; 79(6):935–945. [PubMed: 15159222]

116. Haeggstrom JZ, Rinaldo-Matthis A, Wheelock CE, Wetterholm A. Advances in eicosanoid research, novel therapeutic implications. Biochemical and Biophysical Research Communications. 2010; 396(1):135–139. [PubMed: 20494126]

117. Radmark O, Samuelsson B. Microsomal prostaglandin E synthase-1 and 5-lipoxygenase: potential drug targets in cancer. Journal of Internal Medicine. 2010; 268(1):5–14. [PubMed: 20497297]

118. Tanioka T, Nakatani Y, Semmyo N, Murakami M, Kudo I. Molecular identification of cytosolic prostaglandin E2 synthase that is functionally coupled with cyclooxygenase-1 in immediate prostaglandin E2 biosynthesis. Journal of Biological Chemistry. 2000; 275(42):32775–32782. [PubMed: 10922363]

119. Park JY, Pillinger MH, Abramson SB. Prostaglandin E2 synthesis and secretion: the role of PGE2 synthases. Clinical Immunology. 2006; 119(3):229–240. [PubMed: 16540375]

120. Lovgren AK, Kovarova M, Koller BH. cPGES/p23 is required for glucocorticoid receptor function and embryonic growth but not prostaglandin E2 synthesis. Molecular and Cellular Biology. 2007; 27(12):4416–4430. [PubMed: 17438133]

121. Hanaka H, Pawelzik SC, Johnsen JI, et al. Microsomal prostaglandin E synthase 1 determines tumor growth *in vivo* of prostate and lung cancer cells. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106(44):18757–18762. [PubMed: 19846775]

122. Amirian ES, Ittmann MM, Scheurer ME. Associations between arachidonic acid metabolism gene polymorphisms and prostate cancer risk. Prostate. 2011; 71(13):1382–1389. [PubMed: 21308720]

123. Cathcart MC, Reynolds JV, O'Byrne KJ, Pidgeon GP. The role of prostacyclin synthase and thromboxane synthase signaling in the development and progression of cancer. Biochimica et Biophysica Acta. 2010; 1805(2):153–166. [PubMed: 20122998]

124. Frigola J, Munoz M, Clark SJ, Moreno V, Capella G, Peinado MA. Hypermethylation of the prostacyclin synthase (PTGIS) promoter is a frequent event in colorectal cancer and associated with aneuploidy. Oncogene. 2005; 24(49):7320–7326. [PubMed: 16007128]

125. Poole EM, Bigler J, Whitton J, Sibert JG, Potter JD, Ulrich CM. Prostacyclin synthase and arachidonate 5-lipoxygenase polymorphisms and risk of colorectal polyps. Cancer Epidemiology, Biomarkers & Prevention. 2006; 15(3):502–508.

126. Ermert L, Dierkes C, Ermert M. Immunohistochemical expression of cyclooxygenase isoenzymes and downstream enzymes in human lung tumors. Clinical Cancer Research. 2003; 9(5):1604–1610. [PubMed: 12738712]

127. Nana-Sinkam P, Golpon H, Keith RL, et al. Prostacyclin in human non-small cell lung cancers. Chest. 2004; 125(5 Suppl):141S. [PubMed: 15136467]

128. Niknami M, Vignarajan S, Yao M, et al. Decrease in expression or activity of cytosolic phospholipase A2alpha increases cyclooxygenase-1 action: a cross-talk between key enzymes in arachidonic acid pathway in prostate cancer cells. Biochimica et Biophysica Acta. 2010; 1801(7):731–737. [PubMed: 20227521]

129. Nie D, Che M, Zacharek A, et al. Differential expression of thromboxane synthase in prostate carcinoma: role in tumor cell motility. American Journal of Pathology. 2004; 164(2):429–439. [PubMed: 14742249]

130. Narumiya S, Sugimoto Y, Ushikubi F. Prostanoid receptors: structures, properties, and functions. Physiological Reviews. 1999; 79(4):1193–1226. [PubMed: 10508233]

131. Chen Y, Hughes-Fulford M. Prostaglandin E2 and the protein kinase A pathway mediate arachidonic acid induction of *c-fos* in human prostate cancer cells. British Journal of Cancer. 2000; 82(12):2000–2006. [PubMed: 10864209]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

132. Wang X, Klein RD. Prostaglandin E2 induces vascular endothelial growth factor secretion in prostate cancer cells through EP2 receptor-mediated cAMP pathway. Molecular Carcinogenesis. 2007; 46(11):912–923. [PubMed: 17427962]

133. Dassesse T, de Leval X, de Leval L, Pirotte B, Castronovo V, Waltregny D. Activation of the thromboxane A2 pathway in human prostate cancer correlates with tumor Gleason score and pathologic stage. Eur Urol. 2006; 50(5):1021–1031. discussion 31. [PubMed: 16522350]

134. Nie D, Guo Y, Yang D, et al. Thromboxane A2 receptors in prostate carcinoma: expression and its role in regulating cell motility via small GTPase rho. Cancer Research. 2008; 68(1):115–121. [PubMed: 18172303]

135. Mahmud S, Franco E, Aprikian A. Prostate cancer and use of nonsteroidal anti-inflammatory drugs: systematic review and meta-analysis. British Journal of Cancer. 2004; 90(1):93–99. [PubMed: 14710213]

136. Platz EA, Rohrmann S, Pearson JD, et al. Nonsteroidal anti-inflammatory drugs and risk of prostate cancer in the Baltimore Longitudinal Study of Aging. Cancer Epidemiology, Biomarkers & Prevention. 2005; 14(2):390–396.

137. Chan JM, Feraco A, Shuman M, Hernandez-Diaz S. The epidemiology of prostate cancer—with a focus on nonsteroidal anti-inflammatory drugs. Hematology/Oncology Clinics of North America. 2006; 20(4):797–809. [PubMed: 16861115]

138. Salinas CA, Kwon EM, FitzGerald LM, et al. Use of aspirin and other nonsteroidal antiinflammatory medications in relation to prostate cancer risk. American Journal of Epidemiology. 2010; 172(5):578–590. [PubMed: 20688905]

139. Wang D, Dubois RN. The role of COX-2 in intestinal inflammation and colorectal cancer. Oncogene. 2010; 29(6):781–788. [PubMed: 19946329]

140. Chapkin RS, Seo J, McMurray DN, Lupton JR. Mechanisms by which docosahexaenoic acid and related fatty acids reduce colon cancer risk and inflammatory disorders of the intestine. Chemistry and Physics of Lipids. 2008; 153(1):14–23. [PubMed: 18346463]

141. Wall R, Ross RP, Fitzgerald GF, Stanton C. Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. Nutrition Reviews. 2010; 68(5):280–289. [PubMed: 20500789]

142. Wang D, DuBois RN. Pro-inflammatory prostaglandins and progression of colorectal cancer. Cancer Letters. 2008; 267(2):197–203. [PubMed: 18406516]

143. Wymann MP, Schneiter R. Lipid signalling in disease. Nature Reviews Molecular Cell Biology. 2008; 9(2):162–176.

144. Folkman J, Cole P, Zimmerman S. Tumor behavior in isolated perfused organs: *in vitro* growth and metastases of biopsy material in rabbit thyroid and canine intestinal segment. Annals of Surgery. 1966; 164(3):491–502. [PubMed: 5951515]

145. Gimbrone MA Jr, Leapman SB, Cotran RS, Folkman J. Tumor dormancy *in vivo* by prevention of neovascularization. The Journal of Experimental Medicine. 1972; 136(2):261–276. [PubMed: 5043412]

146. Borre M, Offersen BV, Nerstrom B, Overgaard J. Microvessel density predicts survival in prostate cancer patients subjected to watchful waiting. British Journal of Cancer. 1998; 78(7): 940–944. [PubMed: 9764587]

147. Bono AV, Celato N, Cova V, Salvadore M, Chinetti S, Novario R. Microvessel density in prostate carcinoma. Prostate Cancer and Prostatic Diseases. 2002; 5(2):123–127. [PubMed: 12497001]

148. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocrine Reviews. 2004; 25(4):581–611. [PubMed: 15294883]

149. Tsuzuki T, Shibata A, Kawakami Y, Nakagawa K, Miyazawa T. Conjugated eicosapentaenoic acid inhibits vascular endothelial growth factor-induced angiogenesis by suppressing the migration of human umbilical vein endothelial cells. Journal of Nutrition. 2007; 137(3):641–646. [PubMed: 17311953]

150. Tsuji M, Murota SI, Morita I. Docosapentaenoic acid (22:5, n-3) suppressed tube-forming activity in endothelial cells induced by vascular endothelial growth factor. Prostaglandins, Leukotrienes, and Essential Fatty Acids. 2003; 68(5):337–342.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

151. Yang SP, Morita I, Murota SI. Eicosapentaenoic acid attenuates vascular endothelial growth factor-induced proliferation via inhibiting Flk-1 receptor expression in bovine carotid artery endothelial cells. Journal of Cellular Physiology. 1998; 176(2):342–349. [PubMed: 9648921]
152. Calviello G, Di Nicuolo F, Gragnoli S, et al. n-3 PUFAs reduce VEGF expression in human colon cancer cells modulating the COX-2/PGE2 induced ERK-1 and-2 and HIF-1alpha induction pathway. Carcinogenesis. 2004; 25(12):2303–2310. [PubMed: 15358633]
153. Connor KM, SanGiovanni JP, Lofqvist C, et al. Increased dietary intake of omega-3-polyunsaturated fatty acids reduces pathological retinal angiogenesis. Nature Medicine. 2007; 13(7):868–873.
154. Stahl A, Sapieha P, Connor KM, et al. Short communication: PPAR gamma mediates a direct antiangiogenic effect of omega 3-PUFAs in proliferative retinopathy. Circulation Research. 2010; 107(4):495–500. [PubMed: 20634487]
155. Sapieha P, Stahl A, Chen J, et al. 5-Lipoxygenase metabolite 4-HDHA is a mediator of the antiangiogenic effect of {omega}-3 polyunsaturated fatty acids. Science Translational Medicine. 2011; 3(69):69ra12.
156. Rose DP, Connolly JM. Antiangiogenicity of docosahexaenoic acid and its role in the suppression of breast cancer cell growth in nude mice. International Journal of Oncology. 1999; 15(5):1011–1015. [PubMed: 10536186]
157. Ambring A, Johansson M, Axelsen M, Gan L, Strandvik B, Friberg P. Mediterranean-inspired diet lowers the ratio of serum phospholipid n-6 to n-3 fatty acids, the number of leukocytes and platelets, and vascular endothelial growth factor in healthy subjects. American Journal of Clinical Nutrition. 2006; 83(3):575–581. [PubMed: 16522903]
158. Fox PL, DiCorleto PE. Fish oils inhibit endothelial cell production of platelet-derived growth factor-like protein. Science. 1988; 241(4864):453–456. [PubMed: 3393911]
159. Kaminski WE, Jendraschak E, Kiefl R, von Schacky C. Dietary omega-3 fatty acids lower levels of platelet-derived growth factor mRNA in human mononuclear cells. Blood. 1993; 81(7):1871–1879. [PubMed: 8461472]
160. Powers CJ, McLeskey SW, Wellstein A. Fibroblast growth factors, their receptors and signaling. Endocrine-Related Cancer. 2000; 7(3):165–197. [PubMed: 11021964]
161. Ornitz DM, Itoh N. Fibroblast growth factors. Genome Biology. 2001; 2(3) REVIEWS3005.
162. Kwabi-Addo B, Ozen M, Ittmann M. The role of fibroblast growth factors and their receptors in prostate cancer. Endocrine-Related Cancer. 2004; 11(4):709–724. [PubMed: 15613447]
163. Li ZG, Mathew P, Yang J, et al. Androgen receptor-negative human prostate cancer cells induce osteogenesis in mice through FGF9-mediated mechanisms. The Journal of Clinical Investigation. 2008; 118(8):2697–2710. [PubMed: 18618013]
164. Heer R, Douglas D, Mathers ME, Robson CN, Leung HY. Fibroblast growth factor 17 is over-expressed in human prostate cancer. The Journal of Pathology. 2004; 204(5):578–586. [PubMed: 15538740]
165. Folkman J, Shing Y. Angiogenesis. Journal of Biological Chemistry. 1992; 267(16):10931–10934. [PubMed: 1375931]
166. Dorkin TJ, Robinson MC, Marsh C, Neal DE, Leung HY. aFGF immunoreactivity in prostate cancer and its co-localization with bFGF and FGF8. The Journal of Pathology. 1999; 189(4): 564–569. [PubMed: 10629559]
167. Polnaszek N, Kwabi-Addo B, Peterson LE, et al. Fibroblast growth factor 2 promotes tumor progression in an autochthonous mouse model of prostate cancer. Cancer Research. 2003; 63(18):5754–5760. [PubMed: 14522896]
168. Gnanapragasam VJ, Robinson MC, Marsh C, Robson CN, Hamdy FC, Leung HY. FGF8 isoform b expression in human prostate cancer. British Journal of Cancer. 2003; 88(9):1432–1438. [PubMed: 12778074]
169. Valta MP, Tuomela J, Vuorikoski H, et al. FGF-8b induces growth and rich vascularization in an orthotopic PC-3 model of prostate cancer. Journal of Cellular Biochemistry. 2009; 107(4):769–784. [PubMed: 19415685]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

170. Elo TD, Valve EM, Seppanen JA, et al. Stromal activation associated with development of prostate cancer in prostate-targeted fibroblast growth factor 8b transgenic mice. Neoplasia. 2010; 12(11):915–927. [PubMed: 21076617]

171. Kasayama S, Koga M, Kouhara H, et al. Unsaturated fatty acids are required for continuous proliferation of transformed androgen-dependent cells by fibroblast growth factor family proteins. Cancer Research. 1994; 54(24):6441–6445. [PubMed: 7987840]

172. Iwasaki A, Medzhitov R. Toll-like receptor control of the adaptive immune responses. Nature Immunology. 2004; 5(10):987–995. [PubMed: 15454922]

173. Huang B, Zhao J, Li H, et al. Toll-like receptors on tumor cells facilitate evasion of immune surveillance. Cancer Research. 2005; 65(12):5009–5014. [PubMed: 15958541]

174. Kelly MG, Alvero AB, Chen R, et al. TLR-4 signaling promotes tumor growth and paclitaxel chemoresistance in ovarian cancer. Cancer Research. 2006; 66(7):3859–3868. [PubMed: 16585214]

175. Rakoff-Nahoum S, Medzhitov R. Toll-like receptors and cancer. Nature Reviews Cancer. 2009; 9(1):57–63.

176. Zheng SL, Augustsson-Balter K, Chang B, et al. Sequence variants of toll-like receptor 4 are associated with prostate cancer risk: results from the Cancer Prostate in Sweden Study. Cancer Research. 2004; 64(8):2918–2922. [PubMed: 15087412]

177. Sun J, Wiklund F, Zheng SL, et al. Sequence variants in toll-like receptor gene cluster (TLR6-TLR1-TLR10) and prostate cancer risk. Journal of the National Cancer Institute. 2005; 97(7): 525–532. [PubMed: 15812078]

178. Lee JY, Plakidas A, Lee WH, et al. Differential modulation of toll-like receptors by fatty acids: preferential inhibition by n-3 polyunsaturated fatty acids. Journal of Lipid Research. 2003; 44(3): 479–486. [PubMed: 12562875]

179. Lee JY, Zhao L, Youn HS, et al. Saturated fatty acid activates but polyunsaturated fatty acid inhibits toll-like receptor 2 dimerized with toll-like receptor 6 or 1. Journal of Biological Chemistry. 2004; 279(17):16971–16979. [PubMed: 14966134]

180. Paone A, Galli R, Gabellini C, et al. Toll-like receptor 3 regulates angiogenesis and apoptosis in prostate cancer cell lines through hypoxia-inducible factor 1 alpha. Neoplasia. 2010; 12(7):539–549. [PubMed: 20651983]

181. Rapraeger A, Jalkanen M, Endo E, Koda J, Bernfield M. The cell surface proteoglycan from mouse mammary epithelial cells bears chondroitin sulfate and heparan sulfate glycosaminoglycans. Journal of Biological Chemistry. 1985; 260(20):11046–11052. [PubMed: 3161889]

182. Manon-Jensen T, Itoh Y, Couchman JR. Proteoglycans in health and disease: the multiple roles of syndecan shedding. The FEBS Journal. 2010; 277(19):3876–3889. [PubMed: 20840585]

183. Inki P, Jalkanen M. The role of syndecan-1 in malignancies. Annali Medici. 1996; 28(1):63–67.

184. Matsumoto A, Ono M, Fujimoto Y, Gallo RL, Bernfield M, Kohgo Y. Reduced expression of syndecan-1 in human hepatocellular carcinoma with high metastatic potential. International Journal of Cancer. 1997; 74(5):482–491.

185. Kumar-Singh S, Jacobs W, Dhaene K, et al. Syndecan-1 expression in malignant mesothelioma: correlation with cell differentiation, WT1 expression, and clinical outcome. The Journal of Pathology. 1998; 186(3):300–305. [PubMed: 10211120]

186. Loussouarn D, Campion L, Sagan C, et al. Prognostic impact of syndecan-1 expression in invasive ductal breast carcinomas. British Journal of Cancer. 2008; 98(12):1993–1998. [PubMed: 18542065]

187. Barbareschi M, Maisonneuve P, Aldovini D, et al. High syndecan-1 expression in breast carcinoma is related to an aggressive phenotype and to poorer prognosis. Cancer. 2003; 98(3): 474–483. [PubMed: 12879463]

188. Davies EJ, Blackhall FH, Shanks JH, et al. Distribution and clinical significance of heparan sulfate proteoglycans in ovarian cancer. Clinical Cancer Research. 2004; 10(15):5178–5186. [PubMed: 15297422]

189. Choi DS, Kim JH, Ryu HS, et al. Syndecan-1, a key regulator of cell viability in endometrial cancer. International Journal of Cancer. 2007; 121(4):741–750.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

190. Stanley MJ, Stanley MW, Sanderson RD, Zera R. Syndecan-1 expression is induced in the stroma of infiltrating breast carcinoma. American Journal of Clinical Pathology. 1999; 112(3):377–383. [PubMed: 10478144]

191. Mennerich D, Vogel A, Klaman I, et al. Shift of syndecan-1 expression from epithelial to stromal cells during progression of solid tumours. European Journal of Cancer. 2004; 40(9):1373–1382. [PubMed: 15177497]

192. Wiksten JP, Lundin J, Nordling S, et al. Epithelial and stromal syndecan-1 expression as predictor of outcome in patients with gastric cancer. International Journal of Cancer. 2001; 95(1):1–6.

193. Kiviniemi J, Kallajoki M, Kujala I, et al. Altered expression of syndecan-1 in prostate cancer. APMIS. 2004; 112(2):89–97. [PubMed: 15056224]

194. Chen D, Adenekan B, Chen L, et al. Syndecan-1 expression in locally invasive and metastatic prostate cancer. Urology. 2004; 63(2):402–407. [PubMed: 14972511]

195. Zellweger T, Ninck C, Mirlacher M, et al. Tissue microarray analysis reveals prognostic significance of syndecan-1 expression in prostate cancer. Prostate. 2003; 55(1):20–29. [PubMed: 12640657]

196. Hu Y, Sun H, Owens RT, et al. Syndecan-1-dependent suppression of PDK1/Akt/bad signaling by docosahexaenoic acid induces apoptosis in prostate cancer. Neoplasia. 2010; 12(10):826–836. [PubMed: 20927321]

197. Edwards IJ, Sun H, Hu Y, et al. *In vivo* and *in vitro* regulation of syndecan 1 in prostate cells by N-3 polyunsaturated fatty acids. Journal of Biological Chemistry. 2008; 283(26):18441–18449. [PubMed: 18450755]

198. Edwards IJ, Berquin IM, Sun H, et al. Differential effects of delivery of omega-3 fatty acids to human cancer cells by low-density lipoproteins versus albumin. Clinical Cancer Research. 2004; 10(24):8275–8283. [PubMed: 15623603]

199. Sun H, Berquin IM, Edwards IJ. Omega-3 polyunsaturated fatty acids regulate syndecan-1 expression in human breast cancer cells. Cancer Research. 2005; 65(10):4442–4447. [PubMed: 15899837]

200. Park PW, Pier GB, Hinkes MT, Bernfield M. Exploitation of syndecan-1 shedding by *Pseudomonas aeruginosa* enhances virulence. Nature. 2001; 411(6833):98–102. [PubMed: 11333985]

201. Li Q, Park PW, Wilson CL, Parks WC. Matrilysin shedding of syndecan-1 regulates chemokine mobilization and transepithelial efflux of neutrophils in acute lung injury. Cell. 2002; 111(5): 635–646. [PubMed: 12464176]

202. Xu J, Park PW, Kheradmand F, Corry DB. Endogenous attenuation of allergic lung inflammation by syndecan-1. Journal of Immunology. 2005; 174(9):5758–5765.

203. Gotte M, Joussen AM, Klein C, et al. Role of syndecan-1 in leukocyte-endothelial interactions in the ocular vasculature. Investigative Ophthalmology & Visual Science. 2002; 43(4):1135–1141. [PubMed: 11923257]

204. Gotte M, Bernfield M, Joussen AM. Increased leukocyte-endothelial interactions in syndecan-1-deficient mice involve heparan sulfate-dependent and -independent steps. Current Eye Research. 2005; 30(6):417–422. [PubMed: 16020273]

205. Gardiner TA, Gibson DS, de Gooyer TE, de la Cruz VF, McDonald DM, Stitt AW. Inhibition of tumor necrosis factor-alpha improves physiological angiogenesis and reduces pathological neovascularization in ischemic retinopathy. American Journal of Pathology. 2005; 166(2):637–644. [PubMed: 15681845]

206. Kainulainen V, Nelimarkka L, Jarvelainen H, Laato M, Jalkanen M, Elenius K. Suppression of syndecan-1 expression in endothelial cells by tumor necrosis factor-alpha. Journal of Biological Chemistry. 1996; 271(31):18759–18766. [PubMed: 8702532]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

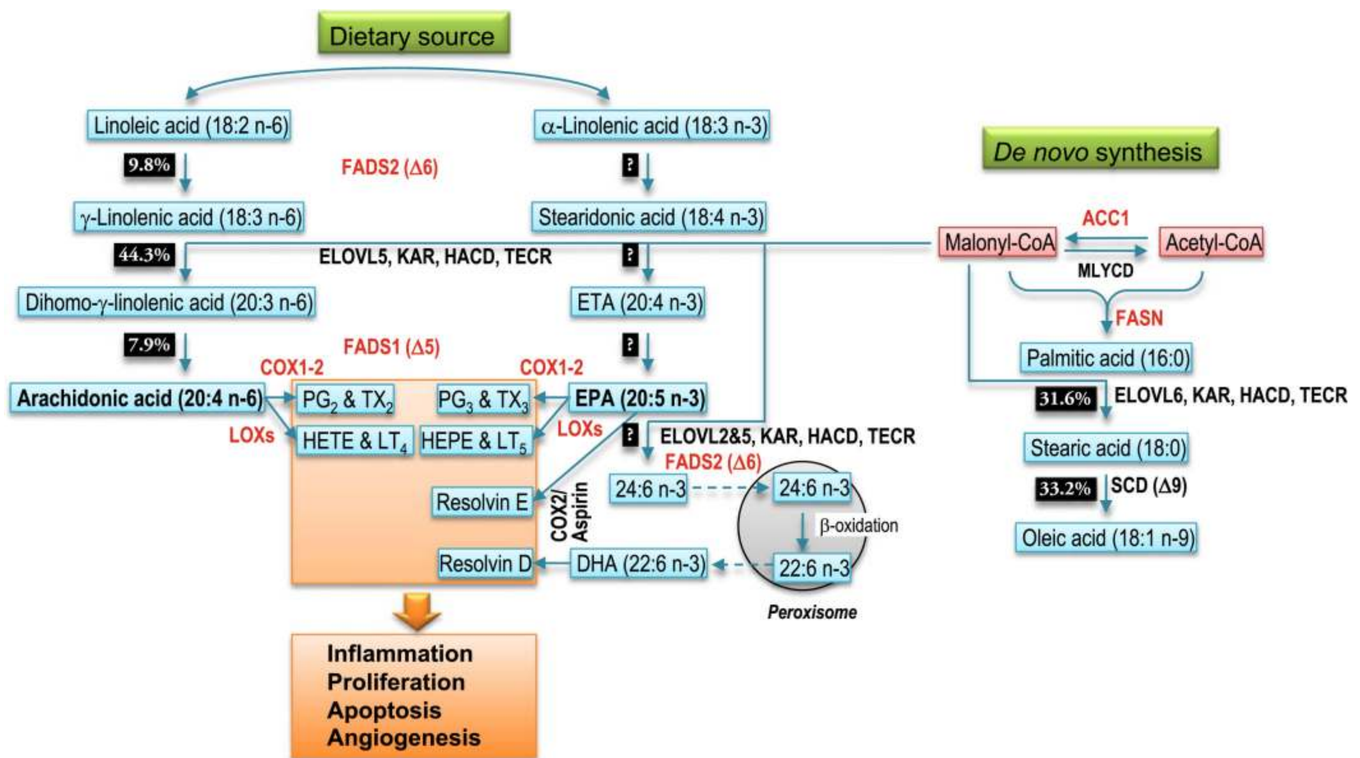

Fig. 1.

Conversion of ω6 and ω3 series PUFA by metabolic enzymes and interaction with *de novo* fatty acid synthesis. The main dietary ω6 and ω3 PUFA (LA, 18:2 n-6 and αLNA, 18:3 n-3) undergo a series of desaturation (FADS2, FADS1) and elongation (ELOVL5, KAR, HACD, TECR) steps converting them to AA and EPA, respectively. The *in vitro* conversion rates of these enzymatic steps are indicated as percent of product formed from 150 nmol substrate incubated with 5 mg of rat liver microsomal protein for 3 min [7]. Long-chain PUFA are converted to prostaglandins (*PG*) and thromboxanes (*TX*) by cyclooxygenases (*COX1–2*) or to leukotrienes (*LT*) and hydroxyeicosatetraenoic acids (*HETE*) by lipoxygenases (*LOX*). EPA can be further elongated and desaturated to DHA in a pathway involving β-oxidation in the peroxisome. In the presence of aspirin, COX2 metabolizes EPA and DHA to resolvins. The various products play important roles in inflammation, cell proliferation and apoptosis, and angiogenesis. In the *de novo* lipid synthesis pathway, acetyl-CoA and malonyl-CoA can be interconverted by acetyl-CoA carboxylase (*ACC1*) and malonyl-CoA decarboxylase (*MLYCD*). Acetyl-CoA and malonyl-CoA are used as substrates by fatty acid synthase (*FASN*) to generate long-chain saturated fatty acids, which can be elongated further (*ELOVL6*) or desaturated (*SCD*) to form monounsaturated fatty acids. Malonyl-CoA is also required for elongation of ω6 and ω3 PUFA

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

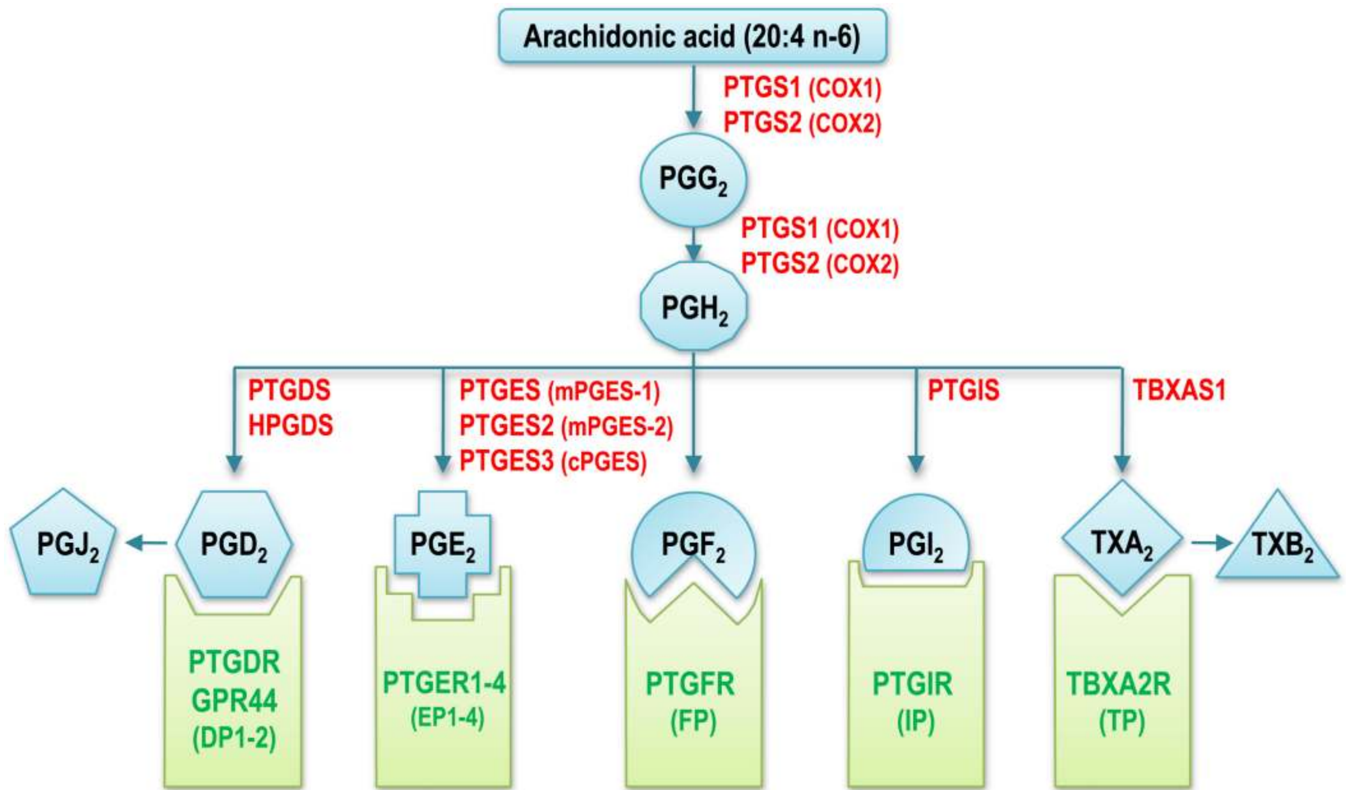

Fig. 2.

Main enzymes and G protein-coupled receptors in the cyclooxygenase pathway. Arachidonic acid is converted to PGG_2 by cyclooxygenase 1 or 2 and PGG_2 then undergoes conversion to PGH_2 through the peroxidase activity of COX. Several isomerases convert PGH_2 to other 2-series prostaglandins, prostacyclins or thromboxanes, which act in part by binding to specific prostanoid receptors (*green*). EPA is thought to serve as a substrate for the same set of enzymes to generate three-series eicosanoids (PGH_3, PGE_3, etc.). Some prostanoids have also been shown to bind to PPARs (not shown). Official protein symbols are shown in *red* for enzymes and in *green* for receptors, with common abbreviations in parenthesis. *PTGS1–2* prostaglandin-endoperoxide synthase 1–2, *PTGDS* PGD_2 synthase (brain), *HPGDS* hematopoietic PGD synthase, *PTGES1–3* PGE synthase 1–3, *PTGIS* PGI_2 (prostacyclin) synthase, *TBXAS1* TXA synthase 1, *PTGDR* PGD_2 receptor, *PTGER1–4* PGE receptor 1–4 (subtype EP1–4), *PTGFR* PG F receptor, *PTGIR* PGI_2 (prostacyclin) receptor, *TBXA2R* TXA_2 receptor