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## 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  $\omega 6$  PUFA, our understanding of the corresponding  $\omega 3$  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  $\omega 3$  polyunsaturated fatty acids (PUFA), which show

protective effects against colon, breast, and prostate cancer in a number of experimental systems [1–5]. Since  $\omega$ 3 and  $\omega$ 6 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  $\omega$ 6 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  $\omega$ 3 PUFA oppose these actions, but their generation is still poorly understood. In this review, we highlight the interplay between dietary PUFA intake, elongation,  $\beta$ -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  $\omega$ 6 PUFA metabolism to the relative scarcity of knowledge on  $\omega$ 3 PUFA metabolism.

## 2 Source of $\omega$ 6 and $\omega$ 3 PUFA and conversion within each series

$\omega$ 6 and  $\omega$ 3 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  $\omega$ 6 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  $\omega$ 3 series, alpha linolenic acid ( $\alpha$ -LNA, 18:3n-3), found at moderate levels in most terrestrial plants, is not converted efficiently to long-chain  $\omega$ 3 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  $\omega$ 3 PUFA is through dietary intake of fish or supplementation with fish oil.

During  $\omega$ 6 PUFA conversion, fatty acid desaturase 2 (FADS2) or delta-6 desaturase converts LA to gamma linolenic acid ( $\gamma$ -LNA, 18:3 n-6). This enzyme represents a rate-limiting step in the synthesis of AA from dietary LA [7] (Fig. 1).  $\gamma$ -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  $\omega$ 3 PUFA conversion. However, conversion of  $\alpha$ -LNA to DHA in humans appears to be very inefficient. Both  $\alpha$ -LNA-feeding studies and stable isotope studies have consistently demonstrated that increased consumption of  $\alpha$ -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  $\alpha$ -LNA is subject to  $\beta$ -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  $\alpha$ -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  $\alpha$ -LNA would only represent 0.13% and 0.05% of the starting  $\alpha$ -LNA amount, respectively. These data suggest

that FADS2, the first enzyme in the conversion sequence, is rate-limiting. Recently, it was proposed that the limited conversion of  $\alpha$ -LNA to DHA in HepG2 cells was in part due to a competition of  $\alpha$ -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  $\omega$ 3 and  $\omega$ 6 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  $\omega$ 3 and  $\omega$ 6 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 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.

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)  $\alpha$  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 PPAR $\alpha$  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 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  $\omega$ 6 PUFA appears to be more efficient than that of  $\omega$ 3 PUFA, it is tempting to speculate that ACC1 and ACLY inhibitors may preferentially reduce the formation of AA and consequently that of the  $\omega$ 6-series eicosanoids.

## 6 PUFA oxidation and cycling

Human beings first evolved while consuming a diet containing roughly equivalent amounts of  $\omega$ 6 and  $\omega$ 3 PUFA [76]. During the last two centuries, however, the consumption of  $\omega$ 6 PUFA has increased dramatically due to the increased intake of vegetable oils. Today, the ratio of  $\omega$ 6 and  $\omega$ 3 PUFA in western diets is approximately 30:1. The low intake of  $\alpha$ -LNA from the diet is consistent with the observation that  $\alpha$ -LNA is underrepresented relative to LA in various tissues and organs in the body [77–79]. Even with an equal amount of  $\omega$ 6 and  $\omega$ 3 PUFA intake, some evidence suggests that this phenomenon may also be the result of rapid  $\beta$ -oxidation of  $\alpha$ -LNA relative to other fatty acids [80, 81]. Indeed, carnitine palmitoyltransferase (CPT1), a key enzyme in fatty acid  $\beta$ -oxidation, exhibits the fastest maximum turnover capacity with  $\alpha$ -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  $\omega$ 6 and  $\omega$ 3 PUFA [83], data indicate that the release of fatty acids from phospholipids could be quite different. Three

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  $\omega$ 3 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  $\omega$ 3 and  $\omega$ 6 PUFA are released from phospholipids would be expected to depend on the relative expression of the various phospholipases.

To date, it is unclear whether  $\omega$ 6 and  $\omega$ 3 PUFA are differently  $\beta$ -oxidized and how  $\omega$ 6 and  $\omega$ 3 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 hydroxyicosatetraenoic 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  $\omega$ 3 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  $\omega$ 6 counterpart [94]. However, in contrast to  $\omega$ 6 PUFA, the metabolism of  $\omega$ 3 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 studied of which are LOX5 (ALOX5), LOX12 (ALOX12) and LOX15 (ALOX15), where the names reflect 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

cancer, we knocked out *Cox1*, *Cox2*, *Lox5*, *Lox12*, or *Lox15* in prostate-specific *Pten*-null mice. We have previously demonstrate that  $\omega$ 3 and  $\omega$ 6 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  $\omega$ 3 diet compared to *Pten*-null, *Cox1*-positive mice on the same diet, essentially negating the protective effects of  $\omega$ 3 PUFA. In other words, *Cox1* appears to be required for the protective effects of  $\omega$ 3 PUFA, suggesting that  $\omega$ 3 metabolites of *Cox1* reduce cancer formation. On the other hand, tumor growth was decreased in mice on  $\omega$ 6 diet compared to *Pten*-null, *Cox1*-positive mice on the same diet, suggesting that  $\omega$ 6 metabolites of *Cox1* (e.g., PGE<sub>2</sub>) 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  $\omega$ 3 PUFA do not depend upon *Cox2*. Loss of *Lox5* reduced prostate tumor growth on  $\omega$ 6 diet but had no effect on  $\omega$ 3 diet, suggesting that  $\omega$ 6 metabolites of *Lox5* promote tumor growth, and protective effects of  $\omega$ 3 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<sub>2</sub>, which undergoes conversion to PGH<sub>2</sub> through the peroxidase activity of COX. In turn, PGH<sub>2</sub> 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<sub>2</sub> from COX-derived PGH<sub>2</sub> 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<sub>2</sub> synthase responsible for converting PGH<sub>2</sub> to PGD<sub>2</sub> has been described in the brain, whereas in immune cells this conversion is catalyzed by hematopoietic prostaglandin D synthase. Prostaglandin I<sub>2</sub> (prostacyclin) synthase (PTGIS) is involved in the conversion of PGH<sub>2</sub> to PGI<sub>2</sub>. In platelets, thromboxane A synthase 1 (TBXAS1) converts PGH<sub>2</sub> to TXA<sub>2</sub>.  $\omega$ 3 PUFA EPA is thought to serve as a substrate of the same set of enzymes to generate 3-series eicosanoids (PGH<sub>3</sub>, PGE<sub>3</sub>, etc.) [115]. However, for many of these enzymes, the extent to which  $\omega$ 3 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,

described as an HSP90 co-chaperone involved in the stabilization of the glucocorticoid receptor complex. A role for cPEGS in PGE<sub>2</sub> 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<sub>2</sub>. *mPGES-1* knockdown also decreased the tumorigenic potential of xenograft tumors in nude mice [121]. Polymorphisms in the *mPGES-2* and leukotriene A<sub>4</sub> 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<sub>2</sub> and PGE<sub>2</sub> appear to play antagonistic roles: *PTGIS* and PGI<sub>2</sub> are downregulated, whereas PGE<sub>2</sub> synthase and PGE<sub>2</sub> 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<sub>4</sub> 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 increase 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<sub>2</sub> 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<sub>2</sub> receptor (PTGIR or IP), and one TXA<sub>2</sub> 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<sub>2</sub> 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



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]).  $\omega$ 3 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  $\omega$ 3 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<sub>2</sub>, and HIF-1 $\alpha$  [152]. However, in a mouse model of hypoxia-induced retinal angiogenesis, an  $\omega$ 3 PUFA diet or expression of the *Caenorhabditis elegans fat-1* gene to endogenously enrich tissues in  $\omega$ 3 PUFA was shown to reduce pathological neovascularization without suppression of VEGF [153–155]. Likewise, an  $\omega$ 3 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  $\omega$ 3 PUFA was compared to an ordinary Swedish diet for the ability to reduce indices of inflammation [157]. A 45% reduction in the  $\omega$ 6 to  $\omega$ 3 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  $\omega$ 3 PUFA almost completely eliminated endothelial cell production of PDGF *in vitro* [158]. Further, in human volunteers fed with dietary fish oil, increased monocyte  $\omega$ 3 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  $\omega$ 3 PUFA, enrichment of tumor cells with the  $\omega$ 6 PUFA linoleic acid was shown to convert the growth-promoting activity of FGF from a transient to a sustained effect [171].

## 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  $\omega$ 3 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-1 $\alpha$  [180]. Effects of  $\omega$ 3 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 dietary  $\omega$ 3 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  $\omega$ 3 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  $\omega$ 3 PUFA modulation of angiogenesis may involve

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*<sup>-/-</sup>) demonstrated increased leukocyte adhesion to endothelial cells and increased inflammation-mediated corneal angiogenesis [203, 204]. The inflammatory cytokine, tumor necrosis factor (TNF) $\alpha$  promotes retinal angiogenesis [205]. TNF $\alpha$  was shown to also suppress endothelial cell syndecan-1 expression [206]. Dietary  $\omega$ 3 PUFA reduced retinal TNF $\alpha$  and protected against retinal neovascularization [153]. Further the antiangiogenic effect of  $\omega$ 3 PUFA was shown to be mediated by activation of the nuclear receptor PPAR $\gamma$  [154]. *SDC1* is a PPAR $\gamma$ -responsive gene, and we have shown that DHA upregulates syndecan-1 in prostate cancer cells through activation of PPAR $\gamma$  [197]. Critical experiments confirming a role for syndecan-1 in  $\omega$ 3 PUFA suppression of angiogenesis have yet to be conducted.

## 11 Conclusions

Dietary  $\omega$ 3 and  $\omega$ 6 PUFA are subjected to complex metabolic processes involving genes for lipid release from glycerolipids, elongation,  $\beta$ -oxidation, storage, eicosanoid synthesis and signaling. Much of the knowledge is derived from the study of  $\omega$ 6 PUFA. Relatively little is known about  $\omega$ 3 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  $\alpha$ -LNA?
2. Is the low conversion rate of  $\alpha$ -LNA to EPA primarily due to low bioavailability of  $\alpha$ -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?**

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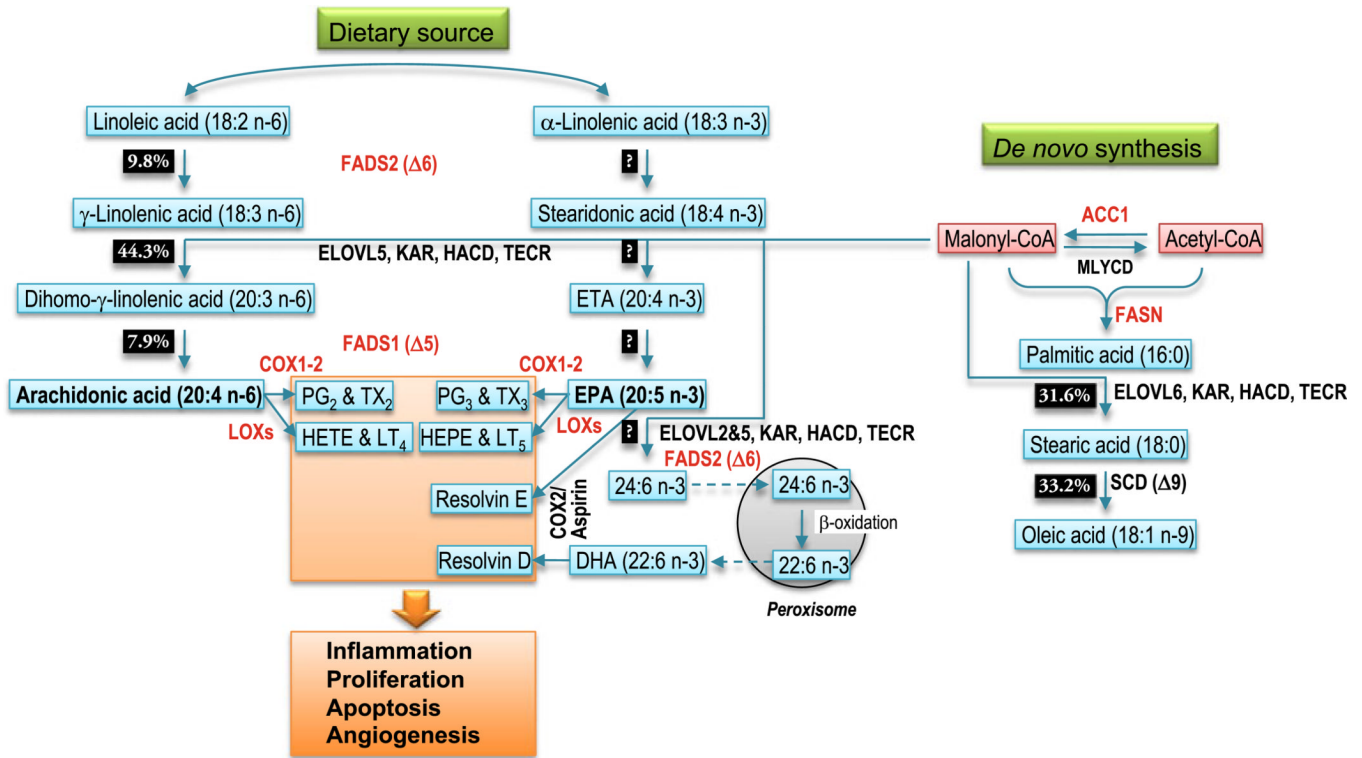
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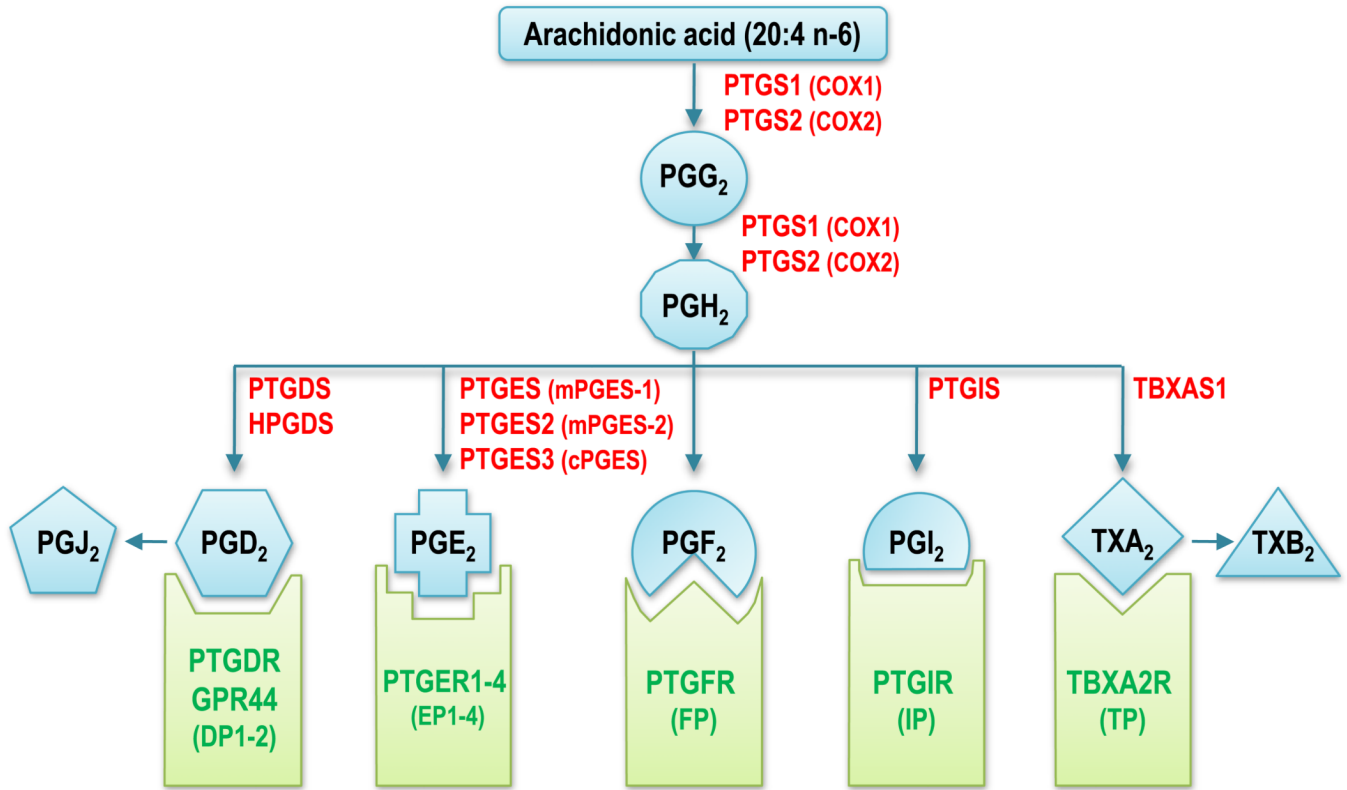
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**Fig. 1.**

Conversion of  $\omega$ 6 and  $\omega$ 3 series PUFA by metabolic enzymes and interaction with *de novo* fatty acid synthesis. The main dietary  $\omega$ 6 and  $\omega$ 3 PUFA (LA, 18:2 n-6 and  $\alpha$ LNA, 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  $\beta$ -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  $\omega$ 6 and  $\omega$ 3 PUFA



**Fig. 2.** Main enzymes and G protein-coupled receptors in the cyclooxygenase pathway. Arachidonic acid is converted to PGG<sub>2</sub> by cyclooxygenase 1 or 2 and PGG<sub>2</sub> then undergoes conversion to PGH<sub>2</sub> through the peroxidase activity of COX. Several isomerases convert PGH<sub>2</sub> 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<sub>3</sub>, PGE<sub>3</sub>, 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<sub>2</sub> synthase (brain), *HPGDS* hematopoietic PGD synthase, *PTGES1–3* PGE synthase 1–3, *PTGIS* PGI<sub>2</sub> (prostacyclin) synthase, *TBXAS1* TXA synthase 1, *PTGDR* PGD<sub>2</sub> receptor, *PTGER1–4* PGE receptor 1–4 (subtype EP1–4), *PTGFR* PG F receptor, *PTGIR* PGI<sub>2</sub> (prostacyclin) receptor, *TBXA2R* TXA<sub>2</sub> receptor