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Review Article

Targeting the eicosanoid pathway in hepatocellular carcinoma

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Abstract: Liver cancer has variable incidence worldwide and high mortality. Histologically, the most common subtype of liver cancer is hepatocellular carcinoma (HCC). Approximately 30-40% of HCC patients are diagnosed at an advanced stage, and at present, there are limited treatment options for such patients. The current first-line therapy with tyrosine kinase inhibitors, sorafenib or lenvatinib, prolongs survival by a median of about 2.5-3 months after which the disease normally progresses. Additionally, many patients discontinue the use of tyrosine kinase inhibitors due to toxicity or may not be suitable candidates due to co-morbidity or frailty. It is, therefore, imperative to identify novel therapeutic targets for advanced HCC patients. Persistent injury to the liver as a result of insults such as hepatitis B or C viral (HBV or HCV) infections, alcohol abuse, and non-alcoholic fatty liver disease (NAFLD), results in chronic inflammation, which progresses to hepatic fibrosis and later, cirrhosis, provides the conditions for initiation of HCC. One of the key pathways studied for its role in inflammation and carcinogenesis is the eicosanoid pathway. In this review, we briefly outline the eicosanoid pathway, describe the mechanisms by which some pathway members either facilitate or counter the development of liver diseases, with the focus on NAFLD/hepatic fibrosis/cirrhosis, and HCC. We describe the link between the eicosanoid pathway, inflammation and these liver diseases, and identify components of the eicosanoid pathway that may be used as potential therapeutic targets in HCC.

Keywords: Hepatocellular carcinoma, inflammation, eicosanoids, NAFLD, fibrosis, cirrhosis, phospholipase A_2, cyclooxygenase, lipoxygenase, cytochrome P450

Introduction

Liver cancer is the sixth most common malignancy worldwide and the fourth leading cause of cancer-related deaths [1]. The aggressive nature of the cancer results in a poor survival rate, especially for patients who have underlying chronic liver diseases. Unfortunately, the incidence and mortality rates are expected to show an unprecedented rise in the near future, essentially because of the increased incidence of obesity, diabetes [2], alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD) and HBV and HCV infections [3], all of which are the most common risk factors for liver cancer development. Histologically, the most common subtype of liver cancer is hepatocellular carcinoma (HCC), also known as hepatoma, which accounts for approximately 75-85% of total liver cancer cases [1]. Treatment options for HCC patients are based on the Barcelona Clinic Liver Cancer (BCLC) staging and guidelines [4]. A number of treatment modalities are available for early to intermediate HCC patients (BCLC stages A-B) with possible curative intent, including surgical resection, liver transplantation, radiofrequency ablation, and percutaneous ethanol injection. However, there is still a high risk of recurrence after curative treatment, resulting in a 5-year survival rate of 19.5% [5]. For advanced HCC patients (BCLC stage C) which comprise approximately 40% of all HCC patients, the most widely used first line therapy is multityrosine kinase inhibitors *viz.* sorafenib or lenvatinib.

The treatment of advanced HCC patients is challenging, as the majority of patients have underlying liver diseases such as cirrhosis and are less tolerant to various commonly used cytotoxic drugs. As an additional challenge, treatment with tyrosine kinase inhibitors such as sorafenib only prolongs patient survival by a median of 2.5-3 months for sorafenib (vs placebo) in SHARP and Asia-Pacific trials [6, 7] and 1.3 months for lenvatinib (vs sorafenib, where it was concluded to be non-inferior to sorafenib) in the REFLECT trial [8] after which resistance develops invariably and the disease progresses. The clinical response to sorafenib is highly variable, and can cause multiple adverse events in patients, with the most common being hand-foot syndrome, diarrhea, alopecia, abdominal pain, nausea, increased risk of cardiac arrest, hypertension, drug-induced hepatitis and perforation of the bowel [9]. These treatment-related toxicities are frequently a reason for discontinuation in many patients. Moreover, approximately 30% of HCC patients are known to have either inherent or acquired resistance to sorafenib treatment [6, 7, 10]. In recent times, numerous second-line therapies have been approved for advanced HCC patients whose disease have progressed from sorafenib, including small multikinase inhibitors, regorafenib [11] and cabozantinib [12], and immune checkpoint inhibitors, nivolumab [13] and pembrolizumab [14]. The potential of combinination immunotherapy with anti-vascular and multikinase inhibitors as potential first-line therapy has also been discussed [15]. Although these candidates have shown promising results, there are many drugs, either alone or in combination, that have failed to improve clinical outcomes in patients when compared with sorafenib in the first-line settings, including sunitinib [16], brivanib [17], linifanib [18], sorafenib plus erlotinib [19], and sorafenib plus doxorubicin [20]. Therefore, there remains a need to find treatment options as first-line therapy which have a better efficacy and tolerability profile to improve outcomes, either as monotherapy or in combination with the already existing drugs, sorafenib or lenvatinib.

Chronic inflammation resulting from chronic liver injury plays a pivotal role in the development and progression of HCC [21]. Progression from normal liver to HCC encompasses the development of hepatic fibrosis due to various etiologies, of which the most common have been infections with HBV & HCV, ALD, and NAFLD [22, 23]. Hepatic fibrosis results from the excessive accumulation of extracellular matrix (ECM) proteins, of which collagen I and III are the most common types [24, 25], leading to scar formation and distortion of hepatic architecture [26, 27]. Excessive deposition of ECM as a result of chronic liver injury is known to occur when hepatic stellate cells (HSCs) become activated from their usual quiescent state and start proliferating rapidly and acquire myofibroblast-like characteristics [28, 29]. If the liver injury persists, there is development of nodules of regenerating hepatocytes and altered hepatic function leading to liver cirrhosis. Therefore, it is essential to understand the mechanisms by which inflammatory mediators contribute to hepatocarcinogenesis, and to evaluate whether these mediators could be targeted to develop drugs against HCC. One of the most studied pathways related to inflammation is the eicosanoid pathway [30]. Many members of the eicosanoid pathway have pro-inflammatory properties and have been identified as potential treatment targets. For example, the cyclooxygenase (COX) enzyme is the principal target of the most common non-steroidal anti-inflammatory drug (NSAID), aspirin, which has been shown to reduce the risk of developing numerous tumors, including HCC [31]. In recent years, several members of the eicosanoid pathway have been implicated in the promotion of various solid and non-solid malignancies [32].

In this review, we briefly describe the eicosanoid pathway and examine its role in non-alcoholic fatty liver disease (NAFLD), hepatic fibrosis and cirrhosis, which are the pre-malignant conditions of HCC. Further, we will discuss the role of eicosanoids in the development and progression of HCC and whether targeting these eicosanoids could potentially be a useful therapeutic strategy in the treatment of advanced HCC.

Eicosanoid pathway: a brief overview

Eicosanoids are biologically active lipid mediators that have been implicated in diverse physiological and pathological processes (reviewed in [32]). The classical eicosanoid pathway is initiated when the precursor, arachidonic acid (AA), a 20-carbon chain fatty acid having four

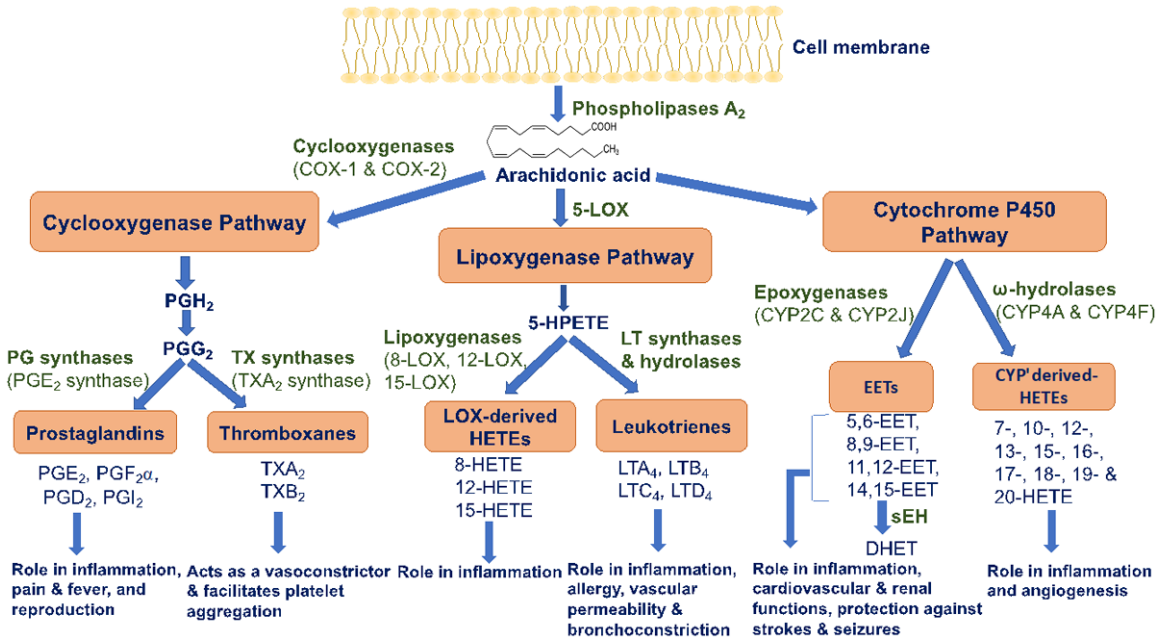

Figure 1. Brief overview of the eicosanoid pathway. Membrane phospholipids are acted upon by members of the PLA_2 family, most commonly $cPLA_2\alpha$, which then releases AA. Once released, AA can undergo metabolism by three major pathways, the COX pathway, LOX pathway, or CYP pathway to release various different types of eicosanoids, including PGs, TXs, LTs, HETEs, and EETs. Some of the major eicosanoids produced and the enzymes responsible for their synthesis have been shown here. PLA_2: phospholipase A_2, AA: arachidonic acid, COX: cyclooxygenase, LOX: lipoxygenase, CYP: cytochrome P450, PGs: prostaglandins, TXs: thromboxanes, LTs: leukotrienes, HETEs: hydroxyeicosatetraenoic acids, EETs: epoxyeicosatrienoic acids.

double bonds (20:4), is mobilized from cellular membranes, typically by phospholipase A_2 (PLA_2) enzymes (**Figure 1**). AA is an essential omega-6 (ω-6) polyunsaturated fatty acid, which must be provided through the diet and together with its dietary precursor linoleic acid, is abundantly present in animal fats. In recent years, a second class of eicosanoids derived from the ω-3 unsaturated fatty acid eicosapentaenoic acid have been defined. They are metabolized by the same pathways as AA, generally act to resolve inflammation, have not been well-studied in the cancer setting and will not be considered further here. The identification and function of these resolving eicosanoids have been well reviewed [33].

There are over 30 types of PLA_2 enzymes known at present, which are categorized into six major groups based on both structural and functional characteristics: Ca^{2+}-dependent cytosolic PLA_2 ($cPLA_2$) enzymes, secreted PLA_2 ($sPLA_2$) enzymes, Ca^{2+}-independent PLA_2 ($iPLA_2$) enzymes, platelet-activating factor acetylhydrolase (PAF-AH) enzymes, lysosomal PLA_2 enzymes, and adipose-PLA_2 [34]. However, one particular PLA_2, $cPLA_2\alpha$ (Group IVA PLA_2, PLA_2-GIVA or IVA-PLA_2), encoded by the PLA2G4A gene, is known to specifically mediate AA release for eicosanoid production in cells under most circumstances [35]. Upon release, AA may undergo further metabolism by three major tissue and/or cell-type specific pathways to release eicosanoids, *viz*. the cyclooxygenase (COX), lipoxygenase (LOX), or cytochrome P450 (CYP) pathways.

The COX pathway comprises two isoforms of the enzyme cyclooxygenase (prostaglandin G/H synthase, PTGS). COX-1, encoded by the PTGS-1 gene, is constitutively expressed in most cells whereas the expression of COX-2, encoded by PTGS-2, increases substantially in response to inflammatory injury [36]. In the COX pathway, free AA is acted upon by the cyclooxygenase function of COX enzymes to produce a short-lived intermediate prostaglandin H_2, which is acted on by the peroxidase function of COX to release prostaglandin G_2 (PGG_2). PGG_2 is then further metabolized into prostaglandins PGE_2, PGD_2, $PGF_2\alpha$, or PGI_2 by cell-type specific synthases, PGE synthase-1 or

-2, PGD synthase, PGF synthase or PGI synthase or to thromboxanes (TXA_2 or TXB_2) by TXA_2 synthase, together referred to as prostanoids. Once released, prostaglandins mediate their paracrine and autocrine effects by binding to specific receptors. PGE_2 binds to its G-protein coupled E prostanoid (EP) receptors present on the cell surface, which are categorized as EP1, EP2, EP3, and EP4 [37, 38]. Binding of PGE_2 to these receptors results in the activation of different signaling pathways and can potentially have different outcomes. Known cell surface receptors for PGD_2 are DP and GPR44, $PGF_2\alpha$ binds to the FP receptor, PGI_2 binds to IP receptor, and TXA_2 binds to TP receptor (reviewed in [32]).

In the LOX pathway, AA may be acted upon by several cell-type-specific lipoxygenase enzymes. For example, 5-lipoxygenase (5-LOX), encoded by the ALOX5 gene, which is normally expressed in leukocytes and aberrantly expressed in several cancers [39, 40], produces the unstable intermediate hydroperoxyeicosatetraeoic acid (HPETE) with the involvement of 5-LOX-activating protein (FLAP). The intermediate may be converted to 5-hydroxyeicosatetraenoic acid (5-HETE) by cellular peroxidases. However, HPETE can also be converted to leukotrienes (LTs), of which the most commonly described ones are LTB_4, and the cysteinyl leukotrienes (cys-LTs) LTC_4, LTD_4, and LTE_4 in cells that express the appropriate LT synthases. To mediate their effects, these LTs bind to their cognate receptors; LTB_4 and LTD_4 bind to BLT1 and BLT2, and cys-LTs bind to cys-LT1 and cys-LT2. Over the years various types of HETEs have been described, including 8-HETE, 12-HETE, and 15-HETE, which are synthesized by their corresponding lipoxygenases i.e., 8-LOX, 12-LOX, and 15-LOX.

A third pathway by which AA is metabolized utilizes CYP enzymes, which are mainly associated with the detoxification of xenobiotics and various drugs in clinical use, including anti-cancer drugs like paclitaxel [41, 42]. Two distinct CYP families acting on AA are epoxygenases (CYP2C, CYP2J and CYP3A4) and omega (w)-hydrolases (CYP4A and CYP4F). The epoxygenase enzymes selectively carry out the epoxidation reaction at one of four double bond positions of AA to generate epoxyeicosatrienoic acids (EETs), namely, 5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET. Each of these regioisomers can be formed as either R,S or S,R enantiomers, resulting in eight possible compounds. EETs can further be catabolized to a lesser active compound dihydroxyeicosatrienoic acid (DHET) by the action of enzyme soluble epoxide hydrolase (sEH). The principal metabolic product of ω-hydrolases action is 20-HETE, however, numerous other CYP-derived HETEs have been defined, including 7-, 10-, 12-, 13-, 15-, 16-, 17-, 18-, and 19-HETEs [43]. It is interesting to note that HETEs can be generated by either LOX, or CYP pathways, so in this review we will distinguish these HETEs based on the enzymes that generate them, for example, LOX-derived HETEs or 20-HETE.

Eicosanoids: connecting inflammation and liver diseases

More than 80% of HCC cases have a background of cirrhosis, which develops as a result of various types of injuries such as chronic HBV or HCV infections, ALD, and NAFLD, among others [44, 45], whereas, approximately 20% of HCC cases develop directly from NAFLD, bypassing the cirrhosis stage [46], and it is likely to become the leading cause by 2030. NAFLD is described as the deposition of fat in the liver (hepatic steatosis), which is ≥5% of the liver weight and in absence of alcohol or other causes of hepatic steatosis [47]. NALFD progresses to the more severe form of fatty liver disease called non-alcoholic steatohepatitis (NASH), where inflammation and hepatocyte ballooning are present in addition to hepatic steatosis (**Figure 2**). NASH has been recognized as a major cause of hepatic fibrosis [48]. Historically, HBV or HCV infections have been the most common cause of cirrhosis, however, in recent years NAFLD has become a leading cause of chronic liver diseases including, cirrhosis in many countries [49-52]. This is not surprising since there has been an exponential rise in the incidence of obesity, type 2 diabetes mellitus (T2DM), insulin resistance [53], and dyslipidemia, which are the most common risk factors of NAFLD and part of the broader collection of conditions known as the metabolic syndrome, increase the risk of progression to NASH, cirrhosis and HCC [54-59]. Intriguingly, various members of the eicosanoid pathway have been shown to play a pivotal role in obesity [60, 61], insulin resistance [62, 63], and

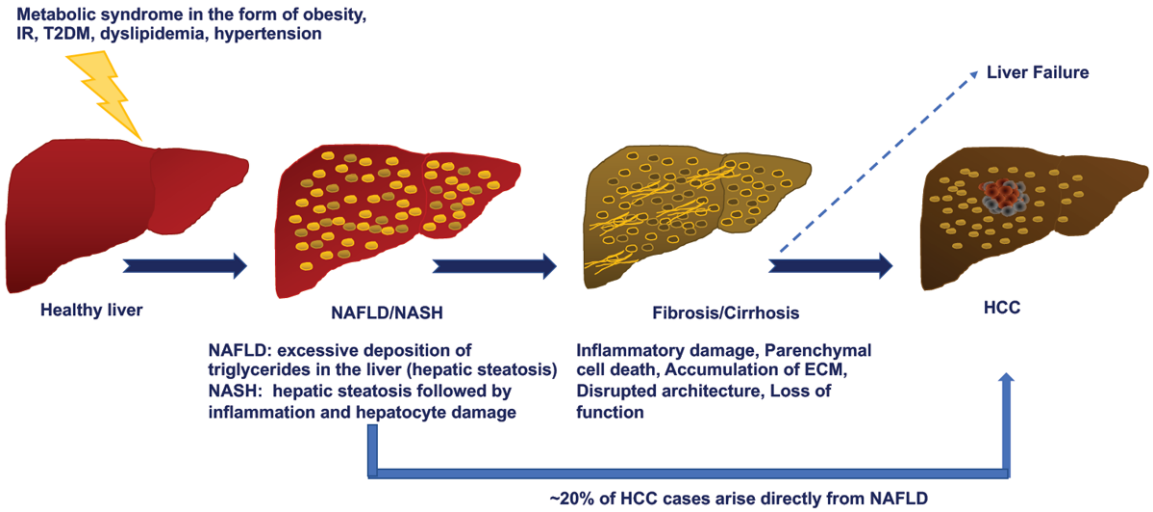

Figure 2. Stages of HCC progression from healthy liver. Healthy liver when persistently injured with factors like IR, T2DM, obesity, dyslipidemia, hypertension result in the deposition of fat in the liver (hepatic steatosis or NAFLD), and later, NASH, which is accompanied by hepatic inflammation. Under the conditions of persistent injury, NASH progresses to hepatic fibrosis and to its more severe form, cirrhosis, which is characterized by excessive deposition of the ECM as a result of activation of HSCs, inflammatory damage, parenchymal cell death, disruption of architecture and loss of function. Once the patient's condition develops further, it can either result in liver failure or development of HCC. Approximately 20% of all HCC cases arise directly from NAFLD, bypassing the fibrosis/cirrhosis stage. IR: insulin resistance, T2DM: type 2 diabetes mellitus, NAFLD: non-alcoholic fatty liver disease, NASH: non-alcoholic steatohepatitis, ECM: extracellular matrix, HSCs: hepatic stellate cells.

T2DM [64]. Together, they form an unholy nexus of eicosanoids-metabolic syndrome-inflammation-carcinogenesis, which is beyond the scope of this review. Instead, we will describe some of the most common eicosanoid pathway members that have been shown to play either promoting or protective (or both) roles in NAFLD/NASH and fibrosis/cirrhosis (**Table 1**) in the following section.

Phospholipases A_2

sPLA_2-IIA

The levels of sPLA_2-IIA were found to be significantly elevated in the sera of chronic hepatitis B and cirrhosis patients in comparison with healthy controls [65]. It was also shown that HBV promotes transcriptional activation of sPLA_2-IIA by binding to its promoter region.

c$PLA_2\alpha$

c$PLA_2\alpha$ knockout mice which were fed either normal chow or high-fat and cholesterol diet (HFCD) showed significantly lower hepatic fat deposition and cytoplasmic vacuolation of hepatocytes around the central vein and smaller epidermal fat pads compared to wild-type mice [66, 67]. Deficiency of c$PLA_2\alpha$ in mice also inhibited the development of hepatic fibrosis which was induced by either HFCD or by carbon tetrachloride (CCl_4) injection [68]. In c$PLA_2\alpha$ knockout mice, parenchymal collagen deposition in the liver was considerably reduced because of failure of HSC activation in comparison with the wild-type mice (**Figure 3**). It has also been demonstrated that c$PLA_2\alpha$ expression increases during spontaneous and transforming growth factor-beta (TGF-β)-induced activation of rat HSCs *via* induction of peroxisome proliferator-activated receptor-beta/delta [69]. Moreover, pharmacological inhibition of c$PLA_2\alpha$ using inhibitor AACOCF3 inhibited TGF-β-induced HSC activation. To demonstrate that c$PLA_2\alpha$ could be a potential therapeutic target in hepatic fibrosis, an orally bioavailable c$PLA_2\alpha$ inhibitor, ASB14780 was given to mice at early or advanced stages of hepatic fibrosis [70]. ASB14780 reduced CCl_4-induced hepatotoxicity and collagen deposition in a dose-dependent manner and was successful in ameliorating the symptoms of fatty liver induced by HFCD and hepatic fibrosis in an already established

Table 1. Role of eicosanoid pathway members in NAFLD/NASH, Fibrosis/Cirrhosis and HCC

Eicosanoid pathway member members	Role in NAFLD/NASH, Fibrosis/Cirrhosis	Role in HCC	References
Phospholipases A_2			
$sPLA_2$-IIA	Potentially promoting	Potentially oncogenic	[65, 113, 114, 190]
$cPLA_2\alpha$	Promoting	Oncogenic	[66-71, 127, 128]
COX-2	Promoting*	Oncogenic*	[56, 72-79, 138-149]
PGE_2	Promoting*	Oncogenic	[80-84, 150-159]
TXA_2	Potentially promoting	Insufficient data	[85-87]
Lipoxygenases			
(5-LOX, 8-LOX 12/15-LOX)	Promoting	Potentially oncogenic	[88-94, 97, 162, 163, 177]
Leukotrienes			
(LTB_4, Cys-LTs)	Promoting	Potentially oncogenic	[163-165]
LOX-derived HETEs			
(5-HETE, 8-HETE, 12-HETE, 15-HETE)	Potentially promoting	Potentially oncogenic	[98, 99, 178, 179]
Epoxygenases			
(CYP2C, CYP2J, CYP3A4)	Potentially promoting	Insufficient data	[100-102, 180-182]
ω-hydrolases			
(CYP4A, CYP4F)	Promoting	Insufficient data	[107-111, 185, 186]
EETs			
(5,6-EE, 8,9-EET, 11,12-EET, 14,15-EET)	Potentially promoting	Insufficient data	[100, 101, 103]
Soluble epoxide hydrolase	Promoting	Insufficient data	[104-106]
20-HETE	Insufficient data	Insufficient data	[101, 112]

*Both promoting and protective roles have been described.

model. Interestingly, the recruitment of hepatic monocytes/macrophages was markedly reduced in mice having either $cPLA_2\alpha$ deficiency or that were treated with ASB14780 compared to the control mice in CCl_4-induced fibrosis model [68, 70]. Furthermore, $cPLA_2\alpha$ has also been reported to mediate CCl_4-induced hepatotoxicity via inhibition of autophagy [71].

Cyclooxygenase (COX) pathway

Cyclooxygenase-2

The role of the COX-2 enzyme in fatty liver and steatohepatitis is controversial, with numerous studies indicating the enzyme to have a protective role while others support a steatosis-promoting role. COX-2 expression increased in liver tissues of mice that were fed HFCD which correlated with elevated levels of markers of liver dysfunction [72]. A number of selective and non-selective COX-2 inhibitors have been used in animal models of steatosis and fibrosis including NSAIDs celecoxib, meloxicam, and nimesulide [56, 72-75]. Treatment with celecoxib significantly reduces hepatic fat accumulation and progression to steatohepatitis along with the decreased expression of hepatic COX-2 [72, 73, 75]. Mice treated with nimesulide were shown to have reduced expression of tissue inhibitor of metalloproteinases-1, procollagen-1 and monocyte chemoattractant protein-1, as well as the number of F4/80-positive Kupffer cells (KCs) (resident hepatic macrophages) [56]. Moreover, treatment with meloxicam resulted in reduced collagen deposition, lower levels of TGF-β1 and matrix metallopeptidase-9 and alleviation of hepatic fibrosis [74].

Conversely, various studies have demonstrated that COX-2 plays a protective role against either high-fat diet (HFD) or chemically-induced hepatic fibrosis [76-78]. Celecoxib treatment was shown to increase severity of CCl_4-induced fibrosis in mice by activating HSCs [79]. Using a human COX-2 transgenic mouse model that constitutively overexpresses COX-2, with steatosis induced by either HFD or CCl_4, Martin-Sanz and colleagues have demonstrated that COX-2 provides protection against steatosis, insulin resistance, oxidative stress, apoptosis, proinflammatory cytokines and activation of HSCs [77, 78]. This discrepancy can be attributed to various factors, for example, different genetic background of mice or possibly, the age at which treatment was started.

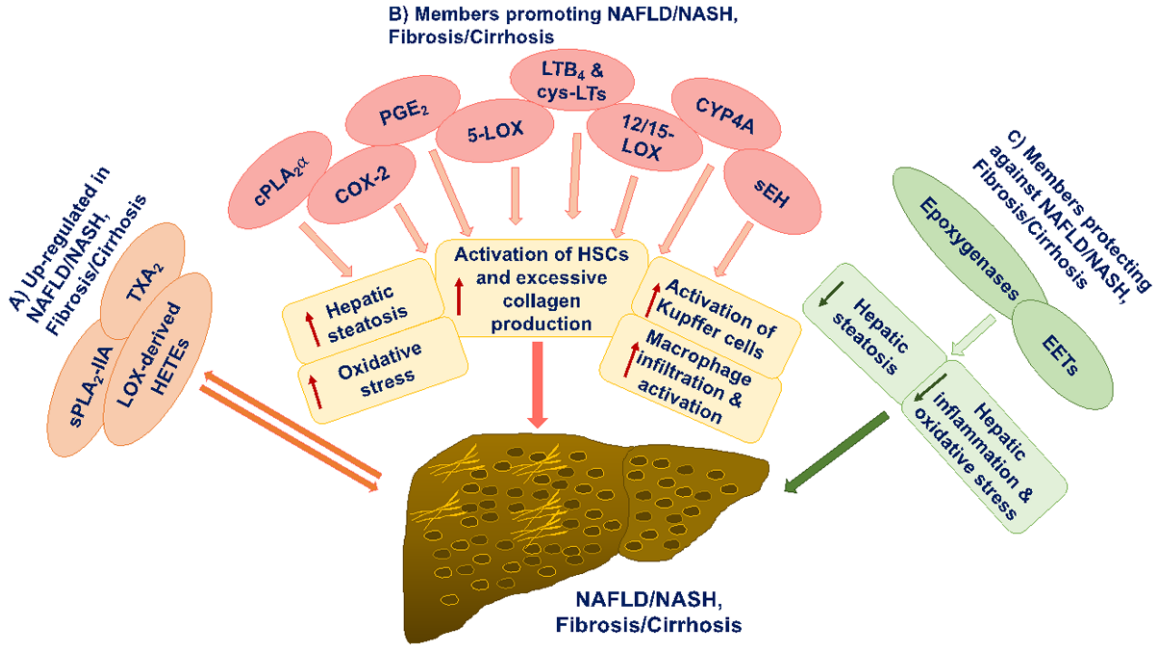

Figure 3. Eicosanoid pathway members as promoters or inhibitors of NAFLD/NASH/Fibrosis/Cirrhosis. Eicosanoid pathway members have bene categorized into three groups: A. Members whose levels are up-regulated in liver diseases, but no mechanism has been defined. These include $sPLA_2$-IIA, TXA_2, and LOX-derived HETEs. B. Members that promote liver diseases for which mechanisms have been described and these include $cPLA_2\alpha$, COX-2, PGE_2, 5-LOX, LTs & cys-LTs, sEH. Using *in vitro*, *in vivo* and clinical samples, these members have been demonstrated to contribute to NAFLD/Fibrosis progression by increasing hepatic steatosis, activation of Kupffer cells and HSCs, enabling infiltration of immune cells from circulation, and enhancing oxidative stress. C. Members which protect the liver from the development of NAFLD/Fibrosis by reducing hepatic fat accumulation and inflammation, and oxidative stress. These include epoxygenases and EETs.

Prostaglandin E_2

Similar to COX-2, the role of prostaglandins in NAFLD/NASH remains ambiguous. The levels of PGE_2 and COX-2 expression were reduced in HFD fed mice after administration of green tea extract and this was shown to provide protection against the development of NASH [80]. Mechanistically, PGE_2 has been shown to induce the production of oncostatin M (a member of the interleukin-6 family of cytokines) in KCs, which leads to insulin resistance and eventually, steatosis accompanied by inflammation [81]. Another study by the same group further corroborated the steatosis-promoting role of PGE_2 in mice [82].

On the contrary, addition of external PGE_2 reduced the TGF-β-induced expression of α-smooth muscle actin (α-SMA) and collagen a1(I), indicating that PGE_2 blocks the activation of HSCs [83, 84]. Moreover, it was shown that PGE_2 mediates these effects by reducing proliferation and promoting apoptosis in HSCs [84]. Use of different strains of mice and the design of experiments could be potential reasons of such conflicted results.

Thromboxane A_2

Circulating TXA_2 levels were found to be increased in mouse model of NAFLD induced by HFD [85]. It was further demonstrated that administration of genistein (an isoflavonoid derived from soybean) was effective in countering this increase in TXA_2 levels, which alleviated the symptoms NAFLD. Levels of circulating TXA_2 have been found to be increased at the time of liver transplantation in end-stage cirrhosis patients [86]. TXA_2 was also shown to increase the portal perfusion pressure in fibrotic rat livers [87].

Lipoxygenase (LOX) pathway

5-lipoxygenase and leukotrienes

A number of studies have demonstrated the steatosis promoting and pro-cirrhotic role of 5-LOX, which is essentially mediated by LTB_4

and cys-LTs [88-94]. The mRNA levels of 5-LOX were markedly upregulated in the liver tissue of cirrhotic rats compared to the control group and coincided with the higher tissue levels of cys-LTs [88]. In the liver, KCs are the only sinusoidal cell type which has all the components of functional 5-lipoxygenase pathway, and it has been demonstrated that KCs are the main source of LTB_4 and cys-LTs. Treatment with Bay-X-1005 (an inhibitor binding to FLAP and blocking the interaction between AA and 5-LOX resulting in inhibition of LTs) alleviated the symptoms of CCl_4-induced liver injury by reducing the expression of 5-LOX and FLAP, significantly lowering the levels of hepatic LTB_4 and cysLTs [90]. Cys-LTs are vital for the survival of KCs and blocking cys-LT production by Bay-X-1005 or AA861 (inhibitor of 5-LOX activity) induces the cell growth arrest in KCs [89]. Blocking of the 5-LOX pathway has also been shown to induce apoptosis in KCs. Treatment with cys-LT inhibitor, montelukast alleviated the features of hepatic fibrosis in rats induced by the bile duct ligation (BDL) method [95]. Montelukast successfully reduced the markers associated with hepatic fibrosis, including hydroxyproline, NF-κB, tissue inhibitor metalloproteinase-1, and vascular endothelial growth factor. In addition, montelukast treatment in cirrhotic rats was demonstrated to reduce the portal hypertension induced by LTC_4 and LTD_4 perfusion following BDL [87].

12/15-lipoxygenase and LOX-derived HETEs

Deficiency of Alox15 (the gene encoding 12/15-LOX in mice) is known to have a protective effect against development of obesity, insulin resistance, and inflammation in HFD fed mice [96]. Using hyperlipidaemia-prone apolipoprotein E (Apo E) knockout mice, Martinez-Clemente *et al.,* demonstrated that *Alox15* deficiency on an Apo $E^{-/-}$ background (Apo $E^{-/-}$/12/15$LOX^{-/-}$) provided protection against hepatic steatosis, insulin-resistance, and inflammatory injury and also improved glucose tolerance [97].

The levels of 5-HETE, 8-HETE, and 15-HETE were significantly elevated in NASH patients compared with the lean normal controls or NAFLD patients, suggesting a dysregulation of the LOX pathway is an important feature of progression from NAFLD to NASH [98]. 8-HETE, 15-HETE, and PGD_2 were also found to be dysregulated in mice that were fed a diet supplemented with 3,5-diethoxycarbonyl-1,4-dihydrocollidine to induce steatohepatitis [99].

Cytochrome P450 (CYP) pathway

Epoxygenases and EETs

CYP2J2 overexpressing mice on 24-week HFD exhibited lower levels of triglycerides in the plasma and liver, reduced hepatic inflammation and oxidative stress, and improved liver function compared to the control mice [100]. Wild-type mice fed an atherogenic diet demonstrated reduced expression of CYP2C29, CYP2C50, CYP2C55, and CYP2J5 in the liver [101]. Another study found higher mRNA expression of Cyp2c in the HFCD-fed mice compared to the normal chow fed mice, even though the activity of CYP2C was markedly lower in the HFCD group [102].

In HFD mice, treatment with EET analogs, 14,15-EE-8(Z)-E and NUDSA, markedly reduced weight-gain, adipose tissue expansion, pro-adipogenic gene expression, and glucose intolerance, suggesting a protective role of EETs [103]. A protective role of EETs has also been described by Schuck *et al.,* using a HFCD-fed NAFLD/NASH mouse model. Their study demonstrated that onset of steatosis greatly suppressed the levels of hepatic and circulating EETs, invariably due to loss in activity and expression of members of CYP2C and CYP2J family, including CYP2C29, CYP2C50, CYP2C-55, and CYP2J5 [101].

Soluble epoxide hydrolase

Since sEH is the enzyme hydrolysing EETs, it is completely plausible that the disruption of sEH would elevate the levels of EET thereby exerting protection against hepatic steatosis and related inflammation. This was indeed demonstrated by various studies, using an *in vivo* mouse model of hepatic steatosis or *in vitro* cell culture models [104-106].

ω-hydrolases and 20-HETE

The expression of various CYP4A enzymes is considerably increased in murine models of NASH [107, 108], and also in the livers of NAFLD patients [109]. CYP4A10 and CYP4A14 levels

were up-regulated in a mouse model of NASH, which acted as the initiators of hepatic oxidative stress [110]. Furthermore, forced expression of CYP4A14 resulted in enhanced fat accumulation in the livers of mice that were fed HFD or methionine-choline deficient diet [109]. Conversely, CYP4A14 null mice resisted fat deposition, hepatic inflammation and fibrosis. Pharmacological inhibition of CYP4A by a specific inhibitor HET0016 was shown to reduce the endoplasmic reticulum (ER) stress, apoptosis, insulin resistance, and steatosis in the livers of db/db diabetic mice models [108]. Recently, inhibition of CYP4A by HET0016 or genetic silencing was linked to reduce ER-stress and improved insulin signaling in an *in vitro* 3D hepatic steatosis model [111].

Not many studies have investigated the role of ω-hydrolases-derived 20-HETE is NAFLD/NASH. The levels of 20-HETE in the plasma, the liver and liver microsomes were found to be similar in mice that were fed either atherogenic or standard diets [101]. They were also found to be involved in the pathophysiology of portal hypertension related to cirrhosis [112].

Role of eicosanoid pathway members in HCC

sPLA$_2$-IIA

The mRNA and protein levels of sPLA$_2$-IIA were significantly elevated in HCC tissues compared with to normal-adjacent tissues and healthy controls [113]. The levels and enzymatic activity of sPLA$_2$-IIA were also enhanced in tumor tissues and serum samples of HCC patients [65, 113, 114]. Increased sPLA$_2$-IIA expression was shown to be an indicator of moderately differentiated tumors [115], however, another study found that elevated levels of serum sPLA$_2$-IIA correlated with lower TNM stage and less frequent lymph node metastasis [65]. *In vitro* studies have demonstrated that HBV infection leads to increased promoter activity of sPLA$_2$-IIA gene (PLA2G2A) [65].

Studies in other tumor types have provided strong evidence that sPLA$_2$-IIA plays an oncogenic role. The levels of sPLA$_2$-IIA were significantly elevated in the tumor tissues and plasma/serum samples of breast [116], lung [117], and prostate [118-121] cancer patients compared with non-tumor controls, which also correlated with the patient outcomes. It has been further shown that targeting sPLA$_2$-IIA reduces cell proliferation and tumor growth [121-124] and induces apoptosis [123], indicating that sPLA$_2$-IIA is a potential target (**Table 2**). Mechanistically, various studies have demonstrated that sPLA$_2$-IIA activates HER/HER2/PI3K/AKT/NF-κB pathway in different cell types [121-123, 125, 126].

cPLA$_2$α

Protein expression of cPLA$_2$α was increased in the tumor tissues of HCC patients compared to the normal adjacent liver tissues [127, 128]. This higher cPLA$_2$α expression correlated with poorer prognosis of HCC patients, and was associated with clinicopathological factors *viz*. macro- and micro-vascular invasion and cirrhosis [127, 128]. Mechanistically, it was demonstrated that cPLA$_2$α plays a role in mediating epithelial-to-mesenchymal transition (EMT) in HCC cells induced by epidermal growth factor and TGF-β via activation of the PI3K/AKT/ERK pathway [127]. Recently, cPLA$_2$α was shown to promote cell-matrix adhesion by activating proteins involved in cell-matrix interactions such as focal adhesion kinase and paxillin [128].

A number of studies have corroborated to the pro-tumorigenic role of cPLA$_2$α in breast [129-131], prostate [132], colon [133, 134], brain [135], and lung tumors [135, 136]. Interestingly, cPLA$_2$α activation has been shown to allow quiescent endothelial cells to enter the cell cycle and, conversely, inhibition of cPLA$_2$α reduced the angiogenic tubule formation *in vitro* suggesting that cPLA$_2$α may play an important role in angiogenesis [137]. The pro-angiogenic role of cPLA$_2$α has been demonstrated by other studies as well [135, 136].

COX pathway

COX-2

COX-2 is one of the best studied enzymes of the eicosanoid pathway in HCC, and there is an overwhelming consensus that the COX-2 enzyme strongly contributes to hepatocarcinogenesis. In humans, COX-2 is overexpressed in HCC tissues compared to the non-tumor tissues [138, 139]. Although many published experimental studies and meta-analyses have correlated increased COX-2 expression with higher TNM stage of tumor, increased tumor

size, lymphovascular invasion, and in general, lower disease-free survival and overall survival [138, 140], not all have corroborated this observation [139, 141]. Polymorphisms in *PTGS2* (the gene encoding COX-2) have been reported (-1195G/A, -765G/C and +8473T/C) and are associated with an increased risk of HCC development [142]. Other studies did not find correlation between risk of HCC and -765G/C and/or +8473T/C [143, 144], although, -1195G/A was associated. COX-2 is expressed in most of the HCC cell lines and inhibition of COX-2 by its selective inhibitors (NS-398 or SC-58635 or celecoxib) or genetic knockdown has been found to inhibit tumor cell growth and proliferation *via* decreasing COX-2-mediated apoptosis resistance [139, 145-147]. Moreover, using a xenografted mouse model, it was demonstrated that treatment of mice using the selective COX-2 inhibitor, meloxicam, significantly reduced tumor growth and volume [148]. In addition, COX-2 has been shown to promote migration and invasion of the HCC cells, which was halted by celecoxib treatment [138, 149].

Prostaglandins

The vast majority of published literature provide strong evidence suggesting that PGE_2 plays a pro-carcinogenic role in HCC. PGE_2 levels are significantly elevated in human HCC tissues and peritumoral liver tissue compared to the normal liver tissues and correlated with advanced BCLC stage and absence of encapsulation [150]. Numerous mechanisms have been described by which PGE_2 mediates its tumor promoting effects, including increasing cell growth and proliferation [150], promoting migration and/or invasion of cancer cells [150-155], and mediating EMT [156]. PGE_2 has been shown to mediate all these effects by binding to its various EP receptors, EP1, EP2, EP3 and EP4. For example, PGE_2 was shown to upregulate the expression of Y box-binding protein 1, leading to activation of proto-oncogene Src and epidermal growth factor receptor, which led to further activation of p44/p42/MAPK/mTOR pathway and as a result, increased invasive ability of HCC cells *in vitro* [154].

PGE_2 is also well known to be immunosuppressive in cancer [32, 157] and recent evidence suggests that induction of the COX pathway in pancreatic tumors modifies the tumor microenvironment to exclude T-cells and enrich for myeloid-derived suppressor cells, resulting in resistance to immune checkpoint inhibitors [158]. In HCC, there is evidence that HCC-derived fibroblasts can induce natural killer (NK) cell dysfunction and that fibroblast-derived PGE_2 inhibits NK cell activation, thus aiding tumor progression [159].

Thromboxanes

The role of thromboxanes in HCC development has not been well-investigated, although its pro-carcinogenic role has been described for breast cancer, where the TXA_2 pathway was associated with cancer cell growth, and invasion and metastasis [160]. Additionally, TXA_2 is known to promote angiogenesis and metastasis in a lung carcinoma mouse model [161].

LOX pathway

5-LOX and LTs

The mRNA and protein levels of 5-LOX was elevated in rat and human tumor tissues compared with normal liver tissues [162]. Inhibition of 5-LOX by zileuton reduced the tumor burden in diethylnitrosamine (DEN)-induced HCC in male Wistar rats and cell viability in HepG2 by promoting apoptosis in the liver [162]. The mRNA levels and transcriptional activity of NF-κB p65 subunit was shown to be enhanced by 5-LOX in HepG2 cells *via* increase in phosphorylated IκBa [163]. In addition to 5-LOX, LTB_4 also increased the transcriptional activity of NF-κB p65. LTB_4 was shown to increase the proliferation of HCC cells of mouse (BNL 1ME A.7R.1) and human origin (Hep3B, Huh-7, and PLC/PRF/5), and use of LTB_4 receptor antagonists inhibited LTD_4-induced proliferation [164]. Moreover, treatment with the LTB_4 receptor antagonist ONO-4057 prevented the metastatic progression to the lungs. The levels of circulating LTD_4 was markedly higher in HCC patients compared with healthy controls, however, it did not correlate with increased tumor burden or inflammation [165]. It was further shown that HCC patients having chronic hepatitis B had considerably higher LTD_4 levels in comparison with non-hepatitis B infected HCC patients.

Besides HCC, the role of 5-LOX has been investigated in different tumor types, including prostate [166-170], gastric [171], colon [172] and pancreatic [173], whereby inhibition of 5-LOX

was shown to reduce cell proliferation *in vitro* and tumor growth *in vivo*, primarily by induction of apoptosis. The oncogenic role of Cyc-LTs and their utility as potential therapeutic targets have been described [174, 175].

Although the tumor-promoting effects of the 5-LOX pathway metabolites through increased proliferation are relatively clear, the effect of leukotrienes on the immune component of the tumor microenvironment is more complex. LTB_4 is a chemotactic agent for myeloid leukocytes, (granulocytes, monocytes, macrophage and dendritic cells). In addition, tumor-associated-macrophage-derived LTB_4, along with chemokines such as CXCL9 and CXCL10, is an important mediator of T-cell recruitment to tumors, although more work is required to confirm this in human tumors. It is however, possible that inhibition of LTB_4 production could result in decreased T cell recruitment to tumors and so promote tumor progression. While there is very little data in HCC, an LTB_4 antagonist trialed in lung cancer is reported to have worsened the disease [176].

12/15-Lipoxygenase and LOX-derived HETEs

The protein levels of 12-LOX were increased in hepatoma cell line, HepG2 and SMMC-7721 cells and DEN-induced male Wistar rat tumor tissues [177]. Treatment with 12-LOX inhibitor baicalein was successful in inhibiting proliferation in cell lines and inducing apoptosis in rat tissues and was shown to be mediated by ERK-1/2. Moreover, protective effects of baicalein were countered by exogenous 12-HETE in HepG2 and SMMC-7721 cells.

Using a liquid chromatography-mass spectrometry (LC-MS/MS) approach, Gong *et al.,* identified a panel of serum eicosanoids that could differentiate between HCC patients and healthy controls, including 5-HETE, 12-HETE, and 15-HETE in addition to other eicosanoids ($PGF_2\alpha$, TXB_2, LTE_4, 5,6-EET, 14,15-EET, 14,15-DHET, and 5,6-DHET) [178]. When compared to cirrhosis patients with a hepatitis B background (HBV-cirrhosis), the levels of 5-HETE, and 15-HETE along with $PGF_2\alpha$, and TXB_2, were significantly higher in patients with HCC. Another study using the LC-MS/MS approach investigated the changes in the levels of various eicosanoids in the sera and liver tissues in a C57BL/6J HCC mouse model using overexpression of c-Met and activated b-catenin [179]. HETEs obtained from serum and the liver (5-HETE & 15-HETE) were significantly elevated compared to the control mice. Many other eicosanoids were found to be elevated in the sera (6-keto-PGF1-α, $PGF_2\alpha$, PGD_2, PGE_2, TXB_2, LTE_4, 9,10-DiHOME, 9,10-EpOME, 12,13-EpOME, 5,6-EET and 8,9-EET), and liver (6-Keto-$PGF_1\alpha$, $PGF_2\alpha$, PGE_2, TXB_2, 5-HEPE, 15-HEPE, 9,10-DiHOME 12,13-DiHOME, 9-HODE and 13-HODE).

CYP pathway

Epoxygenases and EETs

CYP2J2 expression has been found to be higher in tumor tissues than in paired non-tumor tissues at both the mRNA and protein levels, and expression negatively correlated with tumor differentiation, and positively correlates with tumor size and levels of alpha-fetoprotein [180]. CYP2C8 and CYP2C9 were also expressed at higher levels but could not distinguish tumor from non-tumor tissues. Overexpression of CYP2J2 was shown to increase the proliferation of the HCC cell line HepG2 via increased Akt phosphorylation, and this increased proliferation was reduced following treatment with a specific PI3K/Akt inhibitor, LY294002 [181]. Using The Cancer Genome Atlas database (n=360 HCC patients) and the Gene Expression Omnibus database (n=231 HCC patients) to investigate the role of CYP2C family members (CYP2C8, CYP2C9, CYP2C18, and CYP2C19) as potential prognostic HCC markers post-hepatectomy, it was found that low expression of CYP2C8, CYP2C9, and CYP2C19, alone or in combination, were indicative of short median survival in HCC patients [182].

The levels of 5,6-EET, 14,15-EET were significantly elevated in the sera of HCC patients compared with the healthy controls, including many other eicosanoids (as mentioned in LOX-derived HETEs section). An *in vitro* study using HepG2, revealed that 14,15-EET counters palmitic acid-induced inflammation and generation of oxidative stress by targeting the NF-κB/JNK signaling pathway [100].

sEH Not many studies have investigated the role of sEH in HCC, even though a number of studies have demonstrated that targeting sEH

Table 2. Eicosanoid pathway members as potential novel therapeutic targets in HCC/Oncogenic role of eicosanoid pathway members in various malignancies

Eicosanoid pathway member	Tumor type	Pathways implicated	Mechanisms	References
$sPLA_2$-IIA	Breast, Lung, Prostate	HER/HER2/PI3K/AKT/NF-κB, STAT-1	Cell proliferation, tumor growth, apoptosis	[116-126]
$cPLA_2\alpha$	Breast, Prostate, Colorectal, Brain, Lung	PI3K/AKT, EGFR/HER2, MAPK	Cell proliferation, tumor growth, angiogenesis, migration & invasion, EMT	[129-137]
5-LOX	Prostate, Gastric, Colorectal, Pancreatic, Prostate	PKC, c-Myc, c-JNK	Apoptosis, cell proliferation, tumor growth, cancer stem cells, metastasis	[166-173]

has potentially beneficial effects in different cancer types, including colorectal carcinoma [183]. Interestingly, pharmacological inhibition of sEH in addition to COX-2 had a synergistic effect in reducing the tumor angiogenesis and metastasis in Lewis lung carcinoma mouse model [184].

ω-hydrolases and 20-HETE

Expression of w-hydrolase enzyme CYP4A11 was shown to be higher in non-tumor liver tissues at both mRNA and protein levels compared to tumorigenic tissues and is positively correlated with better patient outcomes in terms of smaller tumor size, low histological grade and stage [185]. CYP4F2 mRNA and protein expression was found to be higher in non-tumor tissue in comparison with HCC tissue, and along with CYP4F12 was found to be an indicator of better overall survival for HCC patients [186].

The role of 20-HETE in HCC has not been investigated, although, the oncogenic role of 20-HETE in other tumors is emerging [187-189].

Conclusions

Although some eicosanoid pathway members (e.g. COX-2 and PGE_2) may have dual tumor protective and tumor promoting roles in NAFLD/NASH, studies in humans have consistently shown that COX-2 and PGE_2 play an oncogenic role in HCC. This rationale has supported the investigation of COX-2 inhibitors in clinical trials thus far, but none have been approved for clinical use. It is vital we reach a better understanding of this apparent paradox between eicosanoid pathway enzymes strongly implicated in the causation of HCC and the ineffectiveness of those enzyme inhibitors for treatment. The reasons for this are not clear, and may relate, in part to issues around enzyme specificity, enzyme duplicity of action, and off-target effects that produce unwanted toxicity before the primary endpoint can be met. One such example is the previous use of non-selective COX inhibitors, which target both COX-1 and COX-2. Since COX-1 plays a pivotal role in maintaining homeostasis and basal levels of PGE_2 required for normal physiology, imbalances in COX-1 levels may result in the adverse events associated with these non-specific inhibitors [171].

The role of inflammation has long been recognized as one of the major factors contributing to initiation and progression of various solid and non-solid malignancies, including hepatocellular carcinoma. Therefore, a timely opportunity exists to investigate specific inflammation targets in the development of HCC, and whether these are 'druggable'. As the number of HCC cases are projected to increase sharply in the future, the importance of developing novel therapeutics for HCC cannot be understated. In this context, certain members of the eicosanoid pathway seem to be good candidates, including $sPLA_2$-IIA, $cPLA_2\alpha$, and 5-LOX (**Table 2**), since not only have they been shown to contribute to the progression of liver diseases, but their oncogenic roles have already been well-documented for other tumor types.

In summary, various *in vitro*, animal, and human studies provide strong and overlapping evidence that eicosanoid pathway members play an important role in the development and progression of hepatic steatosis and inflammation related to it, and also, ultimately, hepatocellular carcinoma. However, the biology of the eicosanoid pathway is complex as it relates to the development and progression of cancer, given that some pathway members have contradictory roles, both tumor - inhibitory and tumor-promoting, so it is essential to further delineate

their actions. For other members of the pathway, the paucity of literature is striking, and warrants further study, particularly with a view to finding important therapeutic targets.

Disclosure of conflict of interest

None.

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