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Commentary

New aspects of the role of hydroxyeicosatetraenoic acids in cell growth and cancer development

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ARTICLE INFO

Keywords:
HETE
Lipoxygenase
Cytochrome P-450
Cell proliferation
Angiogenesis
Apoptosis

ABSTRACT

Lipoxygenase (LOX) pathway leads to the formation of leukotrienes and also catalyses the conversion of arachidonic acid (AA) to hydroperoxyeicosatetraenoic acids that are then reduced to hydroxyeicosatetraenoic acids (HETE) by glutathione peroxidase. There are four mammalian LOXs that produce 5-, 8-, 12- and 15-HETE, respectively. Cytochrome P-450 isozymes are also capable of metabolising AA to HETEs either by bis-allylic oxidation (lipoxygenase-like reaction) to generate 5-, 8-, 9-, 11-, 12- and 15-HETE; or by ω/ω-1 hydroxylation to yield 16-, 17-, 18-, 19- and 20-HETEs.

It is now widely recognised that HETEs have important physiological and pathological functions that modulate ion transport, renal and pulmonary functions, vascular tone and reactivity, and inflammatory and growth responses. They can be released during the action of growth factors and cytokines, reaching physiological concentrations higher than that of prostanoids and modulating the functions of these factors. Their effects can occur through receptor or non-receptor mechanisms. Recent reviews have summarised the effects of HETEs in vascular homeostasis or lung and renal physiology. The present review focuses on the emerging effects of HETEs on cell signalling and physiological cell growth. It also discusses current observations regarding the role of HETEs in apoptosis, angiogenesis, the proliferation of cancer cells and metastasis, which constitute a potential area for successful therapeutic intervention.

1. Enzymes involved in HETE generation

Polyunsaturated fatty acids, such as arachidonic acid (AA) are found esterified at the sn-2 position of membrane phospholipids. These fatty acids have been regarded as structural components of cell membranes whose main function is to regulate membrane permeability. However, AA is released following activation of phospholipase A_2s and subsequent

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Abbreviations: AA, arachidonic acid; COX, cyclooxygenase; CYP, cytochrome P-450; DiHETE, dihydroxyeicosatetraenoic acids; EGF, epidermal-growth factor; ERK, extracellular signal-regulated kinases; HETE, hydroxyeicosatetraenoic acid; HETrE, hydroxyeicosatrienoic acids; HEPE, hydroxyeicosapentaenoic acids; HPETE, hydroperoxyeicosatetraenoic acid; LOX, lipoxygenase; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NDGA, nordihydroguaiaretic acid; PKC, protein kinase C; PG, prostaglandin; PDGF, platelet-derived growth factor; PI-3-kinase, phosphatidylinositol-3-kinase; PPAR, peroxisome proliferation-activated receptor; VEGF, vascular endothelial growth factor.

0006-2952/$ – see front matter
doi:10.1016/j.bcp.2008.07.033

metabolisation by cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P-450 (CYP) pathways [1,2]. These enzymes insert oxygen at different positions in AA to generate a major family of biologically active mediators called eicosanoids.

The four mammalian LOXs form hydroperoxyeicosatetraenoic acids (HPETEs) which are subsequently converted to hydroxyeicosatetraenoic acid (HETE) by glutathione peroxidase. Thus, 5-LOX induces to the formation of 5(S)-HETE and leukotrienes. The 12- and 15-LOXs can form 12(S)- and 15(S)-HETE from AA. Functionally distinct isoforms of 12-LOX have been cloned, including platelet, leukocyte and epidermal 12-LOXs [3]. Mammalian cells express two 15-LOXs: 15-LOX-1 and 15-LOX-2. Human 15-LOX-1 and the leukocyte 12-LOX have high homology and are classified as 12/15-LOXs because they can form both 12(S)-HETE and 15(S)-HETE [4] (Fig. 1). While 15-LOX-2 exclusively metabolises AA to produce 15-HETE, 15-LOX-1 can also metabolise linoleic acid to synthesise hydroxy octadecadienoic acids [5]. Based on the amino acid sequence, it appears that 15-LOX-2 is homologous to an 8-LOX found in the mouse [6].

The production of LOX metabolites has been observed in several tissues and cells, including epithelial cells, vascular smooth muscle cells, endothelial cells, monocytes and leukocytes. Interestingly, considerable species-specific variations have been observed in terms of the LOX products formed. For example, rabbit and bovine corneal epithelial cells primarily display 12-HETE [7], while 15-HETE predominates in monkey and human cells [8].

CYP proteins also metabolise AA to produce HETEs by one or more of the following reactions: bis-allylic oxidation (lipoxygenase-like reaction) to generate 5-, 8-, 9-, 11-, 12- and 15-HETEs, or ω/ω-1 hydroxylation to afford 16-, 17-, 18-, 19- and 20-HETEs. Most CYPs are primarily expressed in the liver. However, some CYPs are predominantly detected in the heart, vasculature, gastrointestinal tract, kidney, and lung [9], and recent data indicate that specific CYPs are localised in vascular smooth muscle cells and endothelium [10]. Thus, 5-, 8-, 12- and 15-HETEs can be synthesised by LOXs and CYPs, whereas 9-, 11-, 16-, 17-, 18-, 19- and 20-HETEs appear to be synthesised exclusively by CYPs (Fig. 1).

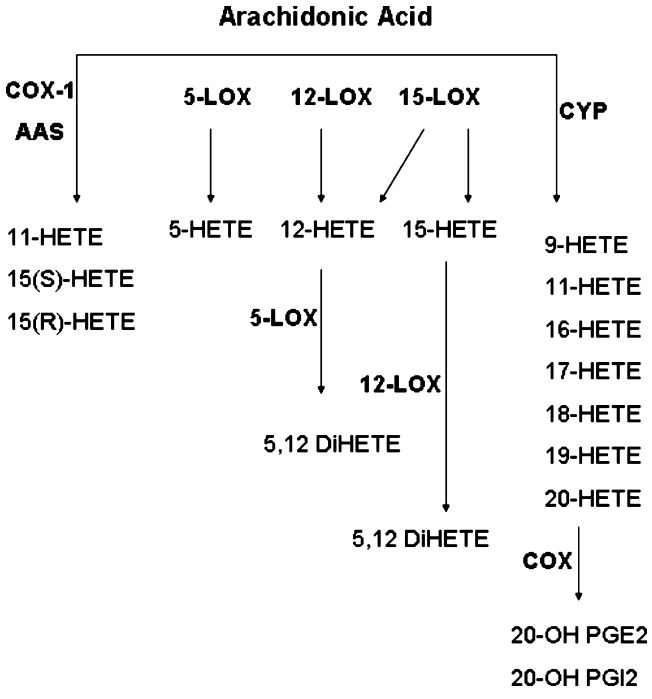

Fig. 1 – The main pathways to HETE synthesis and HETE metabolism. 5-, 12- and 15-HETE were synthesised by 5-, 12- and 15-LOX. These HETEs together with 9-, 11-HETE can be also produced by bis allylic oxidation by CYPs, whereas 16-, 17-, 18-, 19- and 20-HETE were synthesise by ω/ω-1 hydroxylation by CYPs. Finally, HETEs were metabolised by LOX or COX pathways.

The appearance of both HETE enantiomers (R and S) cannot attributed mainly to autoxidation. Although formation of the (S)-HETEs enantiomers can be accounted by LOXs, it is still unclear whether the enzyme responsible for (R)-HETE synthesis is a CYP or LOX. In this regard, the CYP-catalysed synthesis of (R)-HETEs has been demonstrated using purified CYPs [11,12]. Controversy on this issue increased when Boeglin et al. [13] cloned and characterised a 12(R)-LOX from human keratinocytes, thus demonstrating the presence of (R)-LOXs in mammals. Finally, it should be noted that acetylsalicylate treatment of COX-1 was found to induce time-dependent inactivation of oxygenated activity, and consequently, COX-1 exclusively formed 15(R)-HETE [14]. More recently, Thuresson et al. [15] reported that COX-1 primarily produced PGG_2, although is also produced several HETEs such as 11(R)-HETE, 15(S) and 15(R)-HETE. Thus, HETEs might be produced through the three pathways of the AA cascade, even though LOX and CYP pathways are the main source of HETEs.

After HETE formation these AA metabolites can be incorporated into membrane phospholipids and released in response to hormonal stimuli [16]. Thus, preformed HETEs bound to lipids represent a significant reservoir in tissues. In addition, HETEs can be metabolised by COX or LOX/CYP pathways. The most extensively studied HETE in term of metabolism by COX is 20-HETE, which is converted by COX into a 20-OH prostaglandin (PG) H_2 and then undergoes additional metabolism by isomerases to 20-OH PGE_2 or 20-OH PGI_2 [17]. Furthermore, HETEs can also be metabolised by LOX/CYP pathways to produce dihydroxyeicosatetraenoic acids (DiHETEs). Thus, 12(S)-HETE or 15(S)-HETE may be oxidised by 5-LOX to produce 5,12-DiHETE or 5,15-DiHETE respectively [18] (Fig. 1).

COX and 5-LOX pathways that catalyse AA metabolism to produce prostaglandins and leukotrienes are well characterised, and both of them are targets of approved drugs. In contrast, our knowledge of HETEs produced by LOXs and/or CYPs is more limited, although recent efforts in this area may lead to new drug targets emerging from these pathways. A number of excellent recent reviews have summarised the effect of HETEs on vascular homeostasis, lung and renal vasculature, and renal function [19–21]. The present paper attempts to provide an overview of the differing roles of HETEs in the context of cell proliferation and cancer progression.

2. Effect of HETEs on cell signalling involved in cell growth

HETEs are involved in the cell signalling induced by several growth factors such as neurotensin, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), serum, angio-

tensin II and insulin. As summarised in Table 1 these growth factors induce HETE synthesis by enhancing the expression/activity of LOXs or CYPs until they reach physiological concentrations higher than that of prostanoids [22,23]. Consequently, LOX and CYP inhibitors modulate cell growth induced by numerous growth factors. This demonstrates that HETEs have important co-mitogenic effects on cells such as macrophages [24], lens epithelial cells [25], corneal cells [26], proximal tubule epithelial cells [27], fibroblasts [23] and smooth muscle cells [28]. Thus, growth factors released after tissue injury could increase cell proliferation and wound repair by inducing HETE synthesis [29]. In this regard, HETEs are predominantly synthesised in the cornea after injury and in rejected corneal grafts [30]. These findings explain why LOX inhibitors delay corneal epithelial migration and wound closure in rat cornea [31]. Furthermore, HETEs also modulate the effects of the growth factors on cancer cells such as PC3/DU145 prostate cancer cells [32,33] or U251 glioma cells [34] as well as many others as summarised Table 1.

On the other hand, HETEs might also be mitogenic agonists in the absence of another growth factor. Thus, Zeng et al. [40] recently reported that 5-HETE induced DNA synthesis in endothelial cells. 12-HETE also regulates DNA synthesis in human lens epithelial cells [25], endothelial cells [41] and smooth muscle cells [42]. Additionally, Palmberg et al. [43] reported that 15-HETE, but not 5-HETE, induced DNA synthesis in arterial smooth muscle cells. 20-HETE also induced cell proliferation and DNA synthesis in vascular smooth muscle [44] and proximal tubule cell [27] cultures, and several HETEs such as 5-, 12-, 15- and 20-HETE can be mitogenic on the same cell, fibroblast [24,45].

Understanding the mechanism by which HETEs are involved in cell growth could be a critical issue in cell growth/wound repair, cancer and lipid homeostasis. However, these molecular mechanisms have not been fully elucidated, and no cellular receptors for HETEs have yet been identified. However, subcellular HETE binding sites have been reported, for example, binding sites for 12(S)-HETE in cytosol, nuclei, and mitochondria of lung carcinoma cells [46]. Actin and the alpha subunit of the mitochondrial ATP synthase have also been identified as potential binding sites for HETEs. These mechanisms could be involved in the effects of HETEs on cell migration/cell proliferation. Some potential pathways by which these AA metabolites may stimulate cellular growth have also been explored. Thus, 5-HETE activates extracellular signal-regulated kinase (ERK) and AKT pathways. These effects are pertussis-toxin dependent, which implicates G-protein and probably a plasma membrane receptor in these events [47]. Moreover, Zeng et al. [40] reported that 5-HETE stimulates endothelial growth via Jak-2 and phosphatidylinositol-3-kinase (PI-3-kinase)-dependent induction of the expression of fibroblast growth factor-2. Similar effects have been reported with 12-HETE [48,49]. Furthermore, 12-HETE can induce p38MAPK, the transactivation of the transcription factor cAMP response element (CRE) binding protein [50] and the expression of c-fos/c-myc by proliferative epithelial cells [25]. Recently, Nieves and Moreno [51] reported that 12(S)-HETE activated ERK 1/2 and p38 MAPK pathways in 3T6 fibroblast cultures. In this way, 20-HETE also induced Ras/MAPK pathway in vascular smooth muscle cells [28]. Thus, HETEs can modulate the main cell signalling pathways involved in the control of the cell cycle and, consequently, cell growth. In this context, cyclin D_1 assembled with cdk4/6 in the early G_1 phase limits the rate of cellular proliferation induced by a number of stimuli. Over-expression of cyclin D_1 has been observed in several tumours. In turn, cyclin D_1 is regulated by the Ras/ERK signalling cascade. The first link between HETEs, cyclin levels and cell proliferation was suggested by Pidgeon et al. [52]. They connected the suppression of cyclin D_1 and cyclin D_3 levels and the impairment of phosphorylated retinoblastoma protein levels when 12-HETE synthesis was inhibited by baicalein (Fig. 2). Cell cycle arrest has also been reported following 12-LOX inhibition by S-phase arrest [53]. The induction of 15-LOX-1 decreased expression of p21, an inhibitor of cyclin E/cdk 2 complex in colon cancer cells [54] (Fig. 2).

Although 5-, 12-, 15- and 20-HETE have mitogenic action on various cell types, it should also be noted that HETEs can present anti-mitogenic action. For example, 8-HETE caused CH72 cell cycle arrest in the G_1 phase, and consequently blocked cell growth [55], 11-HETE reduces smooth muscle cell proliferation [56] and 15-HETE caused G_0/G_1 arrest of PC3 cells [57]. The 15-LOX-2 metabolite, 15-HETE, has been shown to activate peroxisome proliferator-activated receptor gamma

Table 1 – Growth factors induced HETE synthesis in different cells

Growth factor	Cell	HETE	Synthesised by	References
Neurotensin/EGF	Prostate cancer cells	5-HETE	5-LOX	[33]
Neurotensin/EGF	Prostate cancer cells	12-HETE	12-LOX	[33]
EGF/insulin	Lens epithelial cells	12-HETE	12-LOX	[25]
EGF	Epidermoid carcinoma	12-HETE	12-LOX	[35]
EGF/HGF/KGF	Corneal cells	12-HETE	12-LOX	[26]
PDGF	Smooth muscle cells	12-HETE	12-LOX	[36]
Angiotensin-II	Mesangial cells	12-HETE	12-LOX	[37]
Angiotensin-II	CHO cells	12-HETE	12-LOX	[38]
Foetal serum	Smooth muscle cells	12-HETE	12-LOX	[39]
Foetal serum	Fibroblast	12-HETE	CYP	[23]
EGF	Proximal tubule cells	20-HETE	CYP	[27]
NE/Angiotensin-II	Smooth muscle cells	20-HETE	CYP	[28]

EGF: epidermal-growth factor; HGF: hepatocyte-growth factor; KGF: keratinocyte-growth factor; PDGF: platelet-derived growth factor; NE: norepinephrine.

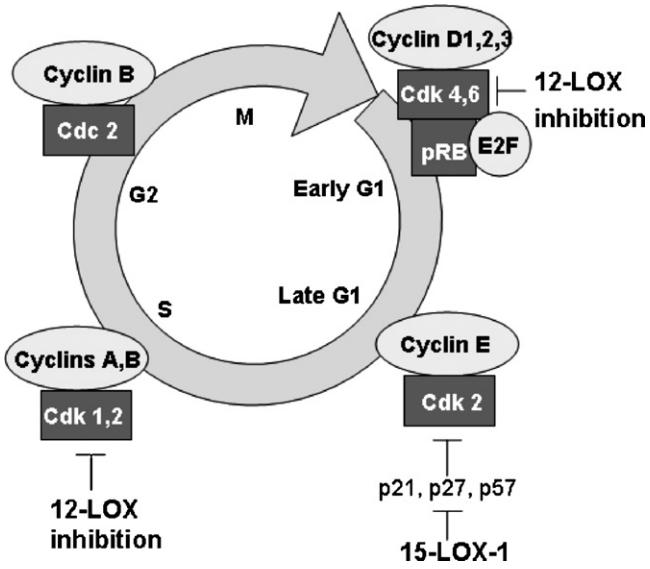

Fig. 2 – Effects of LOX pathway and LOX inhibition on cell cycle. LOX pathway regulates pRB phosphorylation and the expression of p21, p27 or p57 and consequently G_1 phase. On the other hand, LOX pathway is also involved in the control of the complex cyclin A, B/Cdk 1,2 during S phase.

(PPARγ) [57] a nuclear transcription factor involved in epithelial differentiation and consequently the arrest of cell growth. The interaction of 15-HETE with PPARγ would explain its anti-proliferative action on prostate cancer cells, synoviocyte [58] or keratinocyte [59] growth. Table 2 summarised the main mitogenic/anti-mitogenic effects of HETEs.

There is no information about the biological effects of HETE metabolites (DiHETEs) on cell growth. However, LOX/CYP metabolism of gammalinolenic acid or eicosapentaenoic acid produce biological active molecules such as hydroxyeicosatrienoic acids (HETrEs) and hydroxyeicosapentaenoic acid (HEPEs), respectively, metabolites (15-HETrE and 15-HEPE) that markedly inhibited prostate cancer cell growth [76].

3. Inhibition of apoptosis by HETEs

The induction of cell death is often preceded by an arrest in the cell cycle. Indeed there are substantial evidences that critical regulatory steps occur during the G_1 phase. As pointed out in the previous section, the impairment of HETE synthesis by LOX inhibitors induces cell arrest and apoptosis, whereas HETEs inhibit programmed cell death. Thus, LOX inhibitors induce apoptosis in vascular smooth muscle cells [77], W256 carcinosarcoma cells [78], prostate cancer cells [52], breast cancer cell lines [62] and neuroblastoma cells [79]. Moreover, these events were reverted by exogenous addition of HETEs. In this regard, tumour cells in which 5-LOX is constitutively active are highly resistant to anti-neoplasic drugs or ionising radiation, and inhibition of 5-LOX greatly increases their sensitivity to such treatments [80]. In addition, geotaxis stress, induced by DNA damaging agents, was shown to increase 5-LOX in human fibroblasts [80]. Recent findings indicate that the exclusive inhibition of 5-LOX did not induce apoptosis in RAW 264.7 macrophage. In contrast, non-specific LOX inhibition increased apoptotic cells [24]. In human breast cancer cells, specific inhibition of both 5-LOX and 12-LOX resulted in significant apoptosis of cells associated with induced cytochrome c release, activation of many caspase family members and resultant poly ADP ribose polymerase cleavage [79].

HETEs could prevent apoptosis, since the down-regulated bcl-2 and up-regulated bax [77] affect the expression and localisation of alpha(v)beta(5)integrin, vitronectin receptors, and actin microfilaments [32]. Therefore, it is clear that 12-LOX inhibitors alter the expression of Bcl-family proteins, resulting

Table 2 – Mitogenic and anti-mitogenic effects of HETEs

HETE	Cells	References
Mitogenics		
5-HETE	Microvascular endothelial cells	[40]
	Mesangial cells	[60]
	Mammary epithelial cells	[22]
	Smooth muscle cells	[61]
	Fibroblasts	[23]
	Breast cancer cells	[62]
	Prostate cancer cells	[33]
	Colon cancer cells	[63]
	Pancreatic cancer cells	[64]
	Lung cancer cells	[65]
12-HETE	Endothelial cells	[41]
	Vascular smooth muscle cells	[42]
	Lens epithelial cells	[25]
	Mesangial cells	[60]
	Mammary epithelial cells	[61]
	Cardiomyocytes	[66]
	Keratinocytes	[67]
	Fibroblasts	[23]
	Epidermoid carcinoma cells	[49]
	Pancreatic cancer cells	[68]
	Colorectal cancer cells	[63]
	Prostate cancer cells	[69]
	Gastric cancer cells	[70]
15-HETE	Mammary epithelial cells	[61]
	Smooth muscle cells	[43]
	Fibroblasts	[23]
	20-HETE	
	Vascular smooth muscle cells	[42]
	Proximal tubule epithelial cells	[27]
	Fibroblasts	[45]
Anti-mitogenic		
8-HETE	CH72 cells	[55]
11-HETE	Vascular smooth muscle cells	[71]
12-HETE	Liver epithelial cells	[72]
15-HETE	Synoviocytes	[58]
	Keratinocytes	[59]
	Prostate epithelial cells	[73]
	Chronic myeloid leukemia cells	[74]
	Prostate cancer cells	[57]
	Lung cancer cells	[75]
15-HETrE/15-HEPE	Prostate cancer cells	[76]

in a shift in their ratios that favours apoptosis. Moreover, the survival signalling mediated by HETEs can be operated via activation of the PI-3-kinase/AKT route through the inactivation of a series of pro-apoptotic proteins, such as p21WAF, Bad and glycogen synthase kinase 3. In this regard, Pidgeon et al. [52] observed that the inhibition of HETE synthesis reduced phosphorylated AKT levels and consequently decreased survivin and increased caspase 3 activity, important elements involved in the development of apoptosis.

In cancer cells, the triggering of apoptosis is due to a disturbance of the balance between pro- and anti-apoptotic proteins promoting pro-apoptotic signalling. The anti-apoptotic activity of HETEs could have an important role in the emergence of neoplasm by preventing the death of cells that have undergone chromosomal rearrangements or other types of DNA damage. Such cells are normally eliminated by means of check-point controls, such as the p53 pathway. However, there is no clear evidence of transcriptional antagonism between HETEs and the p53 pathway. Even though the role of 15-LOX in mediating anti-carcinogenic effects was established, the mechanisms mediating these effects are still unclear. Recently, Mahipal et al. [74] reported that 15-HETE trigger cell death through the release of cytochrome c and activation of caspase-3 induced by HETE stimulated reactive oxygen species production.

4. HETEs are involved in angiogenesis

Growth factors and hypoxia converge in the regulation of key angiogenic genes. The cellular expansion of tumours progressively distances cells from the vasculature, and thus from oxygen and nutrients. Consequently, tumour cells, like growing tissues or embryonic cells, emit signals that initiate the formation of new blood vessels. This adaptive process, termed angiogenesis, is a general feature of every tissue, mainly in the wound repair process, and is a prerequisite for tumour expansion beyond a limiting size of 2–3 mm^3. Angiogenesis is an intricate stepwise process, that is mediated by the interplay of a variety of factors including tumour and endothelial cells, the balance between pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and anti-angiogenic factors, proteolytic enzymes, and cell surface molecules. VEGF is the most potent tumour angiogenic factor identified to date, and seems critical for initiating vessel sprouting. Recently, 5-HETE was found to stimulate angiogenesis by inducing expression of VEGF [81]. 12-HETE also has direct stimulatory effects on multiple processes associated with angiogenesis. For example, it has been shown to be a mitogenic factor for microvascular endothelial cells [82] and to stimulate endothelial cell migration [83]. It also up-regulates the surface expression of integrin alpha(v)beta(3), an integrin predominantly associated with angiogenic blood vessels in tumours and human wound granulation tissue [84].

The potential of 12-HETE to stimulate pathological angiogenesis may lie in its ability to induce the expression of VEGF [48]. Moreover, pharmacological 12-LOX inhibition reduced VEGF expression, confirming that the enzymatic activity of 12-LOX plays a significant role in the regulation of VEGF gene expression. Thus, transient transfection with a 12-LOX expression construct enhanced VEGF promoter activity [69]. Research has also shown that, HETEs exclusively synthesised by the cytochrome P-450 pathway, such as 20-HETE, have been reported to have similar effects on VEGF production [85]. These authors proposed that ERK/AKT pathways are involved in enhancing the VEGF expression induced by HETEs. However, it should be noted that VEGF can also induce HETE synthesis, and that this event is involved in endothelial cell proliferation [83].

5. Regulation of adhesion, migration and invasion by HETEs

The ability of tumour to invade new tissues requires the complex interplay of various cell surface-associated elements that regulate the proteolytic disruption of the extracellular matrix (ECM) and the modification of cell adhesion properties. These cell–ECM interactions, necessary for metastasis, are mediated by integrins. Several studies have reported the role of HETEs, in particular 12-HETE, in the regulation of surface integrin expression. Thus, adhesion of B16 murine melanoma cell to microvascular endothelial cells was enhanced by 12-HETE, via up-regulation of alpha(v)beta(3) integrin expression [84]. In a study by Pidgeon et al. [52], over-expression of 12-LOX increased membrane expression of alpha(v)beta(3) and alpha(v)beta(5) in both prostate and epidermoid cancer cell lines, with respect to wild-type or non-transfected cells [32]. These authors also reported a relationship between the increased surface integrin expression and survival. The fact that over-expression of 12-LOX in different tumour cell lines resulted in enhanced expression of integrins implies a general phenomenon of 12-LOX regulating a specific subset of integrins. The above events can be related to the role of 12-HETE in tumour invasiveness. 12-LOX transfected prostate cancer cells were reported to be more adhesive toward vitronectin and type I and IV collagen, and were more invasive through matrigel than were control cells [86]. In this study, when the cells were subcutaneously grown in nude mice, invasion to the surrounding tissue was more frequently observed in the 12-LOX transfected cells.

There are also evidences for the role of 5-HETE in cell adhesion and invasiveness though ECM destruction. Matrix metalloproteinases (MMP) are involved in the degradation of matrix components and they play an important role in the invasion of tumour cells through basement membrane barriers. Ye et al. [87] reported that 5-HETE induced the expression of MMP-2 and that this mechanism could be involved in the metastatic effect of 5-HETE. HETEs such as 12-HETE can modulate several another parameters related to the metastatic potential of tumour cells, such as motility [88], secretion of lysosomal proteinases [89], expression of integrin receptors [90], tumour cell adhesion to endothelium and spreading on the subendothelial matrix [91]. Nony et al. [92] reported that addition of exogenous 15-HETE to breast cancer cells stimulated cell adhesion to type IV collagen and activated the p38 MAPK pathway; this is an unusual finding, given the postulated ''anti-carcinogenic'' role for 15-LOX-2 and 15-HETE in cancer. Thus, in addition to survival and proliferation, HETEs are linked to angiogenesis and several biochemical processes involved in the spreading and migration mechanisms that regulate metastasis (Fig. 3).

6. HETEs in normal and malignant tissue

The role of HETEs produced by LOX and CYP in the development and progression of cancer is complex due both to the variety of genes identified and the different profiles of LOX/CYP observed in tumour biopsies. 15-LOX-1 and 15-LOX-2 are usually preferentially expressed in normal tissue and benign lesions, whereas 5-LOX and 12-LOX are absent in normal epithelia, can be induced by pro-inflammatory stimuli, and are often expressed in epithelial cancers. Thus, 15-LOX-1 and 15-LOX-2 were found to be poorly expressed in breast cancer compared to normal epithelium [93], while elevated levels of both 5-LOX and 12-LOX were identified [94]. Similarly, 15-LOX-1 expression was down-regulated in colorectal adenomas [95] and 12-LOX expression was elevated in prostate cancer tissue compared with their corresponding normal tissues. Consequently, urinary levels of 12-HETE have been reported to be significantly elevated in prostate cancer patients [96]. Quantitative eicosanoid analysis of tumour peritoneum respect to benign peritoneum from patients with advanced epithelial ovarian cancer shown that 5-HETE and 12-HETE levels increased fourfold whereas 15-HETE concentrations moved in the opposite direction [97].

Recently, Piao et al. [98] reported that platelet-type 12-LOX is induced by inflammatory cytokines in the early stage of tumorigenesis, and is required for tumour promotion in mouse epidermal cell transformation. Moreover, it is possible that the production of HETEs functions as a rate-limiting factor for tumour promotion in epidermal cell transformation.

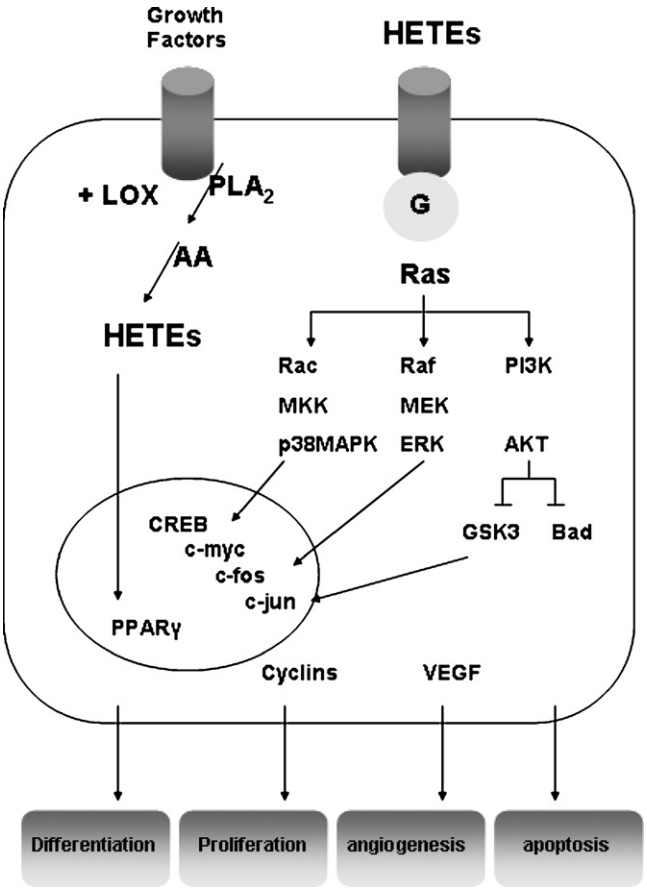

Fig. 3 – Cell signalling pathways involve in the effect of HETEs on cell proliferation/angiogenesis and apoptosis. Binding of HETEs to plasma membrane receptors (did not identify) results in the activation of the Ras/p38MAPK/ERK/AKT pathways, which are implicated in proliferation, angiogenesis and survival. The action of HETEs on differentiation/cell growth can be also mediated though the interaction with nuclear receptor such as PPARγ.

7. Implications and future directions

This review aims to present a conceptual framework for integrative signalling and proposes HETEs as some of the mediators behind this process. The findings presented strengthen the hypothesis that not all lipid derived from AA are exclusively pro-inflammatory mediators. In addition, HETEs could be protective mediators involved in the resolution of inflammation and in promoting cell proliferation and wound healing though the activation of several mitogenic signal pathways. Indeed, there is mounting evidence that HETEs are central mediators in the wound repair process and they are therefore potential targets in these events. As a result, a number of synthetic agonists have been developed for example WIT003 (20-hydroxyeicosa-6(Z) 15(Z)-dienoic acid), a stable 20-HETE agonist.

A causal connection between the AA cascade and cell proliferation and cancer has been proposed for many years, and the implication of the COX pathway in these events is well documented [99]. However, the mechanism linking other AA metabolites and tumorigenesis is not well understood. As HETE synthesis has been associated with several epithelial-derived malignancies [100], these AA metabolites might be the missing link between the two processes.

By virtue of its anti-apoptotic activity the presence of HETE might prevent the elimination of genetically altered precancerous cells. In addition, by activating numerous signalling pathways involved in cell growth and by stimulating the transcription of VEGF and other growth factors, HETEs might cause enhanced cell proliferation and tumour angiogenesis.

Until recently, chemoprevention research focused exclusively on the tumour-promoting effects of HETEs and on modulating HETE synthesis by LOX inhibition [101]. However, we now know that some HETEs and related metabolites such as hydroxyoctadecadienoic acids have a tumour-suppressor function [102]. Thus, elevated levels of certain eicosanoids such as 5-HETE and 12-HETE together with PGE_2 and LTB_4 might promote tumour progression, whereas others such as 15-HETE might interfere with the progression to malignancy. Therefore, a novel approach for cancer chemoprevention would involve LOX/CYP modulators thereby shifting the balance from pro-carcinogenic (5-, 12-, 20-HETE) to anti-carcinogenic (8-, 15-HETE) metabolism of AA [103] (Fig. 4).

While further studies are needed to resolve many unanswered questions regarding the role of HETEs in cancer progression, several lines of evidence suggest that the up-regulation of HETE synthesis in different types of adenocarcinomas are related to increased tumour growth and progression [104–106]. Thus, the effects of HETEs on tumour promotion may be similar to those of the COX/PGs pathway. Therefore, it is

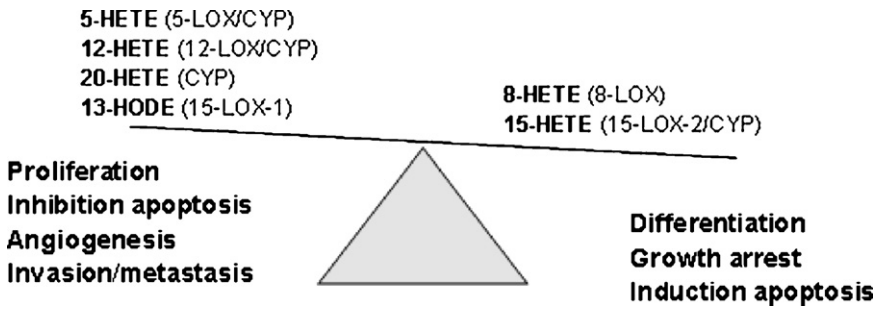

Fig. 4 – HETEs present pro-carcinogenic and anti-carcinogenic effects. LOX and cytochrome P-450 levels/activity shifting the balance of pro-carcinogenic (5-HETE, 12-HETE, 20-HETE) and anti-carcinogenic (8-HETE, 15-HETE) metabolism of polyunsaturated fatty acids.

possible that HETEs and PGs are two important elements for tumour progression in the early stages. This is consistent with the findings of recent reports in which the polymorphism of either COX-2 or platelet 12-LOX was shown to be associated with an increased risk of colon cancer development [107]. Therefore, inhibition of AA cascade pathways involved in HETE production may represent a promising approach for halting or reversing the progression of epithelial-derived malignancies. The main problem with this approach is that some types of cancer produce several HETEs and that several LOX and/or CYPs may be involved in the synthesis of the same HETE. However, this approach could be successfully used when a particular HETE release by a LOX or CYP was involved in adenocarcinoma development. In this regard, Guo et al. [108] observed that HET0016, a selective inhibitor of 20-HETE formation, reduced both volume and vascularisation in the glioblastomas, which are brain tumours that are resistant to conventional therapies.

In conclusion, identifying LOX/CYP target genes in normal cell and transformed cells is another important area for future research. As we begin to understand which genes are involved in HETE production, which receptors, transcription factors and signalling pathways are involved in HETE synthesis, and are able to determine the biological effects of HETEs, it should be possible to design new therapeutic strategies for modulating cell proliferation/wound repair and cancer progression.

Acknowledgments

Original works described in this review were supported by Spanish Ministry of Education and Science (BFI2001-3397) (BFU2004-04960) and (BFU2007-61727). We thank Robin Rycroft for valuable assistance in the preparation of the manuscript.

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