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Cyclooxygenase, lipoxygenase and tumor angiogenesis

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Abstract. Arachidonic acid metabolism through cyclooxygenase (COX) and lipoxygenase (LOX) pathways generates various biologically active lipids that play important roles in inflammation, thrombosis and tumor progression. Angiogenesis, the formation of new capillary vessels from preexisting ones, underpins a number of physiological processes and participates in the development of several pathological conditions such as arthritis, cancer and various eye diseases. The formation of new capillary vessels is a multistep process that involves endothelial cell proliferation, migration and tube formation. In the present review, we survey the literature on the regulation of angiogenesis by arachidonate metabolites, especially those from the COX and 12-LOX pathways in the context of tumor growth, and put forward some unanswered but important questions for future studies.

Key words. Cyclooxygenase; lipooxygenase; angiogenesis; eicosanoid; tumor.

Introduction

Bioactive lipids generated from arachidonic acid via cyclooxygenase (COX) and lipooxygenase (LOX) pathways have been of great interest due to their potent and diverse biological activities. The involvement of these bioactive lipids in tumor progression is implicated by the increased expression of COX and LOX in various cancers. For example, COX-2 has been found upregulated in a variety of cancers, including pancreatic cancer [1, 2], lung [3–5], gastric adenocarcinoma [6], breast cancer [7], colon [8–11], prostate cancer [12–14], and head and neck cancer [15–17]. The expression of 12-LOX also has been found in prostate cancer [18], pancreatic cancer [19], breast cancer [20–22] and lung cancer [23], among others [24]. Recently, a number of studies imp licated COX and LOX in modulation of tumor angiogenesis [25–26], raising the exciting possibility of using nonsteroidal antiinflammatory drugs (NSAIDs) and LOX inhibitors as anti-angiogenesis agents for cancer treatment.

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Angiogenesis

Overview

Angiogenesis, the formation of new capillary blood vessels from preexisting vasculature, involves complex interactions among endothelial cells, matrix proteins and soluble factors, which lead to endothelial cell proliferation, migration and tube formation. It is an integral process for embryonic development and other physiological conditions such as the female menstrual cycle. However, in adults, angiogenesis is usually related to various diseases, including tumor growth and metastasis, arthritis and various eye diseases. Interrupting the blood supply of tumors, termed anti-angiogenesis therapy, is one of most promising approaches to treat cancers and various other angiogenic diseases.

Anatomy of angiogenesis

The adult vasculature is usually quiescent. Under proper stimulation from angiogenic factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), endothelial cells exit from quiescence and undergo the following steps to form new capillary vessels. These steps include (i) dissolution of basement membrane by proteases, (ii) endothelial cell migration and proliferation, (iii) formation of capillary tubes

and (iv) survival of newly formed blood vessels. Essentially every phase of angiogenesis is regulated by angiogenesis inhibitors and inducers. Disruption of one of these steps can potentially inhibit angiogenesis. Here we describe each of these steps in more detail.

Dissolution of basement membrane by proteases

For endothelial cells to enter avascular tissue, they must first detach themselves from basement membrane through limited, focal proteolysis. Matrix metalloproteinases (MMPs) including MMP-2 and MMP-9 are induced [27] and secreted [28]. Activation of MMP has been suggested to facilitate endothelial cells to invade through basement membrane [29] and enter avascular tissue in response to angiogenic stimuli [30]. Blockade of this focal proteolysis with tissue inhibitors of MMP (TIMPs) or synthetic MMP inhibitors is found to inhibit angiogenesis [31–32]. Overexpression of TIMP in tumor cells also blocked tumor angiogenesis as well as tumor cell invasion [33].

Endothelial cell proliferation

Once endothelial cells leave their original sites, they proliferate, and in the process of proliferation, invade avascular tissue. Angiogenic factors such as VEGF and bFGF can stimulate endothelial cell proliferation. A number of angiogenesis inhibitors such as angiostatin and endostatin were found based on the inhibition of endothelial cell proliferation [34–35].

Endothelial cell migration and invasion

For endothelial cells to establish a network within avascular tissue, they must migrate toward and within the avascular tissue, facilitated by focal protease activity. Both VEGF and bFGF, as well as other angiogenic factors, have been found to stimulate endothelial cell migration. It has been found that the angiogenesis inhibitors angiostatin and endostatin not only inhibit endothelial cell proliferation but also attenuate endothelial cell migration [36–37].

Formation of capillary tubular structures by endothelial cells

Endothelial cells have the intrinsic ability to form tubelike structures in tissue culture. The process involves endothelial cell-cell interaction as well cell-matrix protein interaction. There are several assays currently used by researchers in the angiogenesis field. The first one is to plate endothelial cells such as human umbilical vein endothelial cell (HUVEC) onto a layer of Matrigel. Upon plating, endothelial cells form an interconnecting network of tubes within several hours. The structures can last days until the endothelial cells go apoptotic. This assay is widely used. In our opinion, the process of tube formation in this assay is passive and more stress related. The second assay for tube formation of endothelial cells is collagen culture in which endothelial cells are embedded in a collagen matrix. After a period of time, they begin to differentiate into tubelike structures. This assay also is widely and successfully used. The third assay is to use a unique endothelial cell line, tube-forming rat brain resistance vessel endothelial cells (RV-ECT), that can form tubelike structures spontaneously [38]. This process requires active participation of endothelial cell proliferation and migration and can be greatly facilitated by culturing within Matrigel [39].

Survival and maturation of newly formed blood vessels

Newly formed blood vessels are extremely vulnerable, partly because endothelial cells can easily unergo apoptosis. It has been suggested that maturation of newly formed blood vessels involves the deposition of matrix proteins and downregulation of proteolytic activity [40]. VEGF has been found to promote endothelial cell survival in vivo [41] and in vitro [42, 43]. Induction of endothelial cell apoptosis has been attributed to the ability of $\alpha_v\beta_3$ intergrin function blocking antibody (LM609) or peptides to inhibit bFGF-induced angiogenesis [44]. Angiostatin has also been found to induce endothelial cell apoptosis [45–46]. Endostatin also induces endothelial cell apoptosis [47].

Regulation of Angiogenesis

Angiogenesis is controlled by a balance between angiogenic and angiostatic factors. When Folkman first postulated that tumor growth is angiogenesis dependent, a search for tumor angiogenesis factors (TAF) was initiated which led to the discovery of angiogenin [48]. Now, an array of angiogenic factors have been found. Although a majority of them are proteins, some lipids also have been found to possess pro-angiogenic activities. Some stimulate vascular endothelial cells directly to either migrate, or proliferate, or form tubes or a combination of these effects, while others act indirectly by mobilizing host cells (macrophages, mast cells and, occasionally, lymphocytes) to release endothelial cell growth factors. The direct-acting factors include acidic and basic fibroblast growth factor (aFGF and bFGF), vascular endothelial growth factor (VEGF) and angiopoietin [49]. Examples of the indirect-acting factors are tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β) and platelet-derived endothelial cell growth factor/thymidine phosphorylase (PD-ECGF/TP).

The activity of angiogenic factors is counterbalanced by naturally occurring angiogenesis inhibitors which include, but are not limited to, thrombospondin [53], interferon, TIMPs, angiostatin, endostatin, METH1 [50] and platelet factor-4. Interferon-γ is the first example of the successful

application of angiogenesis inhibitors for the treatment of cancer in humans [51]. There are a number of synthetic or pharmarcologic angiogenesis inhibitors in clinical trials or in preclinical development [52 for review].

Thromspondin (TSP) is a well-studied endogenous inhibitor of angiogenesis. TSP-1 inhibits angiogenesis through induction of apoptosis [53], and the domains responsible for its angi-angiogenesis activity are two independent regions with type I repeats [54]. Similar to TSP-1, TSP-2 also inhibits tumor growth and angiogenesis [55].

Both angiostatin and endostatin are tumor-derived angiogenesis inhibitors which are implicated in concomitant tumor dormancy [34–35]. Angiostatin is an internal fragment generated from cleavage of plasminogen. Angiostatin, but not plasminogen, specifically inhibited endothelial cell proliferation and, upon systemic administration, significantly blocked angiogenesis and growth of metastasis [34, 56]. Angiostatin itself is not produced by tumor cells, rather, certain tumors can produce or activate proteases capable of generating angiostatin from circulating plasminogen. A serine protease that specifically cleaves angiostatin from plasminogen is produced by prostate cancer cells [57–58].

Endostatin is a fragment of collagen XVIII, a novel collagen frequently found near blood vessels [35]. Endostatin is reported to be a highly active endothelial-specific inhibitor that inhibits microvascular endothelial cell proliferation at doses of 100–500 ng/ml. Endostatin inhibits primary tumor growth as well as establishment and growth of metastasis. A recent study found that after mice bearing Lewis lung carcinoma, T241 fibrosarcoma or B16F10 melanoma were treated with endostatin at 20 mg/kg per day to regress tumors for 6, 4 and 2 cycles, respectively, tumor dormancy was achieved indefinitely even after therapy was discontinued for 11 months [59].

The anti-angiogenesis therapy as exemplified by angiostatin and endostatin illustrates an important conceptual framework for the treatment of cancer. If angiogenesis inhibitors specifically target normal endothelial cells which are genetically stable, anti-angiogenesis will not induce drug resistance and thus may be valuable for long-term maintenance therapy [59]. A recent study demonstrated that combination of anti-angiogenesis therapy with conventional radiation therapy had a combined anti-tumor effect without increased resistance or toxicity [60].

How do tumors become angiogenic?

It is well recognized that a rate-limiting step in solid tumor growth is the recruitment of new capillary blood vessels from the host vasculature [61]. The ability of tumors to stimulate neovascularization is determined by its 'angiogenic switch' whose on/off is dictated by the net balance of angiogenic stimulators and natural inhibitors [61]. Tumors can secrete or mobilize various angiogenic factors such as VEGF, bFGF and interleukin (IL)-8 to tip the balance in favor of angiogenesis. Tumors also can downregulate the level of angiogenesis inhibitors such as TSP to promote tumor progression [62–63]. On the other hand, tumors can generate angiostatin [34], endostatin [35] or TSP [64] to suppress the growth of other tumor nodules, a phenomenon known as concomitant resistance.

The angiogenic switch is regulated by the genetic makeup of tumor cells. Activated oncogenes or inactivated tumor suppressor genes not only increase mitogenesis and prevent apoptosis, but also lead to the development of an angiogenic phenotype [62]. Mutation of the p53 tumor suppressor gene in human fibroblasts is associated with a sharp decrease in the expression of TSP-1 and an increase in VEGF secretion, which causes the cells to switch from an anti-angiogenic to an angiogenic phenotype [65–66]. The activated ras oncogene is a potent stimulator of VEGF secretion in many tumor types [67–68]. Other nononcogenic genes such as PEG-3 also stimulate VEGF gene expression in transformed cells [69].

The angiogenic switch can also be regulated by the tumor microenvironment. Hypoxia and hypoglycemia, as often experienced by prevascular tumors, can enhance the ability of tumor cells to stimulate angiogenesis by stimulating VEGF expression [70–73]. Hypoxia also stimulates the secretion of angiogenin [74].

The tumor angiogenic switch is further regulated by hormones. In prostate cancer, androgen stimulates VEGF expression in hormone-dependent cancer cells [75] and capillary vessel regression precedes tumor shrinkage upon hormone withdrawal in vivo [76]. Similar activities also have been observed with estrogen in breast cancer [77].

COX and tumor angiogenesis

COX: overview

COX catalyzes a key step in the conversion of arachidonic acid to prostaglandin H2, the immediate substrate for a series of cell-specific prostaglandin and thromboxane synthases. Prostaglandins possess potent biological activities and play critical roles in the regulation of immune function, kidney development, reproductive biology and gastrointestinal integrity [78]. There are two COX isoforms, which differ mainly in their pattern of expression. COX-1 is usually expressed in most tissues. In contrast, COX-2 is usually absent in most tissues, but is induced by numerous physiological or pathological stimuli.

Expression of COX in cancer

The expression of COX-2 is regulated by the genetic makeup of tumor cells. Oncogenes such as ras stimulate COX-2 expression [79], while tumor suppressors such as p53 downregulate COX-2 expression [80]. Elevation in COX-2 expression has been documented in various cancers, including pancreatic cancer [1–2], lung cancer [3–5], gastric adenocarcinoma [6], breast cancer [7], colon cancer [8–11], prostate cancer [12–14], and head and neck cancer [15–17].

The role of COX in tumor progression has been investigated in more detail in colon cancer. Clinical and epidemiological data indicate that NSAIDs, inhibitors of cyclooxygenase, induce a siginificant and often complete regression of colonic polyps in patients with familial adenomatous polyposis and also are chemopreventive for colon cancer in nonfamilial adenomatous polyposis subjects [81–86]. Oshima et al. demonstrated that the formation of interestinal polyps in $Apc^{\Delta 716}$ knockout mice was dramatically suppressed by crossing with COX-2 knockout mice [87], indicating that induction of COX-2 represents an early rate-limiting step.

Increased COX-2 expression in cancer cells may confer on them increased tumorigenic and metastatic potentials. Rat intestinal epithelial (RIE) cells that expressed elevated COX-2 protein levels have increased adhesion to extracellular matrix (ECM) proteins, decreased E-cadherin levels and are resistant to butyrate-induced apoptosis, which are reversed by sulindac sulfide (a COX inhibitor) [88], suggesting that overexpression of COX-2 leads to phenotypic changes in intestinal epithelial cells that could enhance their tumorigenic potential. When human colon cancer cells (Caco-2) were permanently transfected with a COX-2 expression vector, they acquired increased invasiveness compared with the parental Caco-2 cells or the vector-transfected control cells [89]. Biochemical changes associated with this phenotypic change included activation of metalloproteinase-2 and increased RNA levels for the membrane-type metalloproteinase, demonstrating that constitutive expression of COX-2 can lead to phenotypic changes that alter the metastatic potential of colorectal cancer cells [89].

Modulation of tumor angiogenesis by COX

In colon carcinoma, COX-2-overexpressing cells produce prostaglandins and pro-angiogenic factors to stimulate endothelial cell migration and tube formation [25]. Inhibitors of COX have anti-angiogenesis activity [90]. Treatment with a select COX-2 inhibitor NS398 decreased expression of VEGF and bFGF in colon cancer cells that overexpress COX-2 and inhibited tumor angiogenesis [91], suggesting that COX-2 can increase the expression of VEGF and bFGF in colon cancer cells.

It has been suggested that while COX-2 regulates angiogenesis in color cancer cells, COX-1 modulates angiogenesis in endothelial cells [25, 91]. Recently, however, several lines of evidence suggest that COX-2 is also involved in angiogenic process of endothelial cells. First, the expression of COX-2 was associated with angiogenesis by human gastric endothelial cells in vitro, and both COX-1 and COX-2 activities are required for angiogenesis during ulcer healing [92]. Second, COX-2 activity in human microvascular endothelial cells is required for angiogenic activity of oncostatin M [93]. Third, in endothelial cells, both COX-2 selective and nonselective NSAIDs inhibit P42/44 MAP kinase activity and interfere with extracellular signal-related kinase (ERK) nuclear translocation in both prostaglandin-dependent and -independent manners [94]. Therefore, both COX-1 and COX-2 regulate angiogenesis. NSAIDs are promising agents that have been shown to inhibit unwanted angiogenesis such as in cornea [95] and cancer [91].

Among the products of the COX pathway, PGE_1 and PGE_2 are reported to promote angiogenesis [96–98]. In contrast, 15-deoxy-$\Delta^{12,14}$-PGJ_2, a product from PGD_2, induces endothelial cell apoptosis by activation of PPARγ [99] and inhibits angiogenesis [100]. It seems, therefore, that the actual profile of the downstream COX metabolites, rather than the level of COX protein or activity, is more relevant in angiogenesis regulation. Among them, thromboxane A_2 has been demonstrated as the mediator for COX-2-dependent angiogenesis and regulates endothelial cell migration [101–103].

Despite our better understanding of the role of COX in angiogenesis and tumor progression, many questions remain. For example, how does COX upregulate the angiogenic potentials of tumor cells? Are COX products angiogenic? If so, to what extent? Regarding the role of endogenous COX in endothelial cell angiogenic processes, how do endogenous COX activities regulate endothelial cell proliferation, migration, tube formation, survival and other angiogenic processes? How do they fit into the overall picture of the signalling events underlying endothelial cell angiogenic responses? Do VEGF and other angiogenic factors require COX activity to elicit angiogenic responses? Further research should focus on the mechanistic involvement of COX in endothelial cell angiogenic responses.

LOX and tumor angiogenesis

LOX: overview

Another important arm, in addition to the COX pathway, of arachidonic acid metabolism to bioactive eicosanoids is the LOX pathway. There are a number of members in the LOX family, including 5-, 8-, 12- and 15-LOX whose main products are 5(*S*)-, 8(*S*)-, 12(*S*)-,

and 15(*S*)-HETE, respectively [104]. Among them, 12(*S*)-HETE has a plethora of biological activities including stimulating tumor cell adhesion, invasion and metastasis [105]. Here we focus on 12-LOX and its role in tumor angiogenesis.

Expression of LOX in cancer

The expression of 12-LOX has been detected in various cancer cell lines as well as in tumor tissues. 12-LOX messengers RNAs (mRNA) have been detected in erythroleukemia, colon carcinoma, epidermoid carcinoma A431 cells, human glioma, prostate and breast cancer cells [105]. Rat and murine tumor cell lines also express 12-LOX [23, 106]. The sequences of reverse-transcriptase polymerase chain reaction (RT-PCR) 12-LOX products from human epidermoid A431 cells and human prostate cancer cells and tissues have complete homology to platelet-type 12-LOX [106]. The product of 12-LOX activity in tumor cells has been identified as predominantly the S enantiomer by chiral high-pressure liquid chromatography (HPLC) and its structure confirmed by gas chromatography-mass spectrometry (GC-MS) analysis [107]. In addition, 12-LOX mRNA has been found to be upregulated in some cancer cell lines by cytokines such as epidermal growth factor [108–110] and autocrine motility factor [111]. Oncogenes such as fos also stimulate the expression of 12-LOX in A431 cells [112].

In a study involving over 130 prostate cancer patients, Gao et al. found that the level of 12-LOX mRNA expression is correlated with tumor stage [18]. In this important clinical study, the expression level of 12-LOX and tumor stage, grade, positive surgical margins and lymph node positivity were evaluated. Overall, 38% of 122 evaluable patients demonstrated elevated levels of 12-LOX mRNA in prostate cancer tissue compared with their matching normal tissues. A statistically significantly greater number of cases were found to have an elevated level of 12-LOX among T3, high grade and surgical margin positive than T2, intermediate, and low grade and surgical margin negative prostatic adenocarcinomas. These data suggest that elevation of 12-LOX mRNA expression occurs more frequently in advanced-stage, high-grade prostate cancer [18]. These observations suggest that the 12-LOX activity may be associated with prostate cancer progression in vivo.

Pro-angiogenic activities of 12(*S*)-HETE

The arachidonate product of 12-LOX, 12(*S*)-HETE, has various effects on endothelial cells, ranging from integrin surface expression to retraction. First, it upregulates the surface expression of integrin $\alpha_v\beta_3$. Tang et al. illustrated that 12(*S*)-HETE increases the surface expression of $\alpha_v\beta_3$ in both rat aorta endothelial cells [113-114] and murine pulmonary microvascular endothelial cell (CD3 and CD4) [115–116], an integrin predominantly associated with angiogenic blood vessels in tumors and human wound granulation tissue [44]. Second, 12(*S*)-HETE can induce a reversible, nondestructive, time- and dose-dependent retraction of endothelial cells by stimulating cytoskeletal rearrangement [117–118]. It was demonstrated that tumor cells indeed can synthesize 12(*S*)-HETE in sufficient amounts to induce microvascular endothelial cell retraction [119]. Coincubation of Lewis lung carcinoma cells or B16 amelanotic cells melanoma (B16a) cells, but not 3T3 fibroblasts, with microvascular endothelial cells (CD3) resulted in a time-dependent retraction of the CD3 monolayers. Lewis lung carcinoma cell-induced endothelial cell retraction was blocked by a specific lipoxygenase inhibitor BHPP, but not by cycloxygenase inhibitors [119]. Fourth, 12(*S*)-HETE acts as a mitogen for microvasuclar endothelial cells [120], especially at low concentration of serum [121]. In murine pulmonary microvascular endothelial cells (CD4), 12(*S*)-HETE enhanced the growth and DNA synthesis in a time- and dose-dependent manner [120]. Fifth, 12(*S*)-HETE promotes wound healing in injured CD4 endothelial cell monolayer [120]. Finally, 12(*S*)-HETE stimulates endothelial cell migration, while 5(*S*)-HETE and 15(*S*)-HETE do not [26, 39].

Modulation of tumor angiogenesis by 12-LOX

The definitive proof that 12-LOX regulates tumor angiogenesis is from two independent studies. In the first study, Nie et al. [26] overexpressed 12-LOX in human prostate cancer PC3 cells by transfection with a platelet-type 12-LOX cDNA construct. Stable transfectants, which express constitutively high levels of 12-LOX in both mRNA and protein levels, were generated and cloned. These 12-LOX transfected PC3 cells produced more 12(*S*)-HETE than did the mock-transfected PC3 cells. In vitro, the growth rates of several 12-LOX-transfectant clones were similar to those of neo-controls and PC-3 wild type. However, following subcutaneous injection into nude mice, 12-LOX-transfected PC3 cells grew faster and formed larger tumors than neo-controls, and the increased tumor volume was positively correlated with enhanced tumor angiogenesis [26]. Another study involves breast cancer. Using a similar approach, Connolly and Rose overexpressed 12-LOX in breast cancer cells and found that 12-LOX enhanced tumor angiogenesis and growth in a fatpad animal model [22]. Taken together, these studies suggest that 12-LOX, when expressed in cancer cells, can enhance their angiogenic potential.

Since angiogenesis is required for continued tumor growth beyond 2 to 3 mm in diameter, and inhibition of angiogenesis has proven an effective approach to rein in tumor growth, inhibition of 12-LOX activity may be a novel approach to develop anticancer, antiangiogenesis therapy.

Summary and perspective

It has been observed that COX and LOX are expressed in a variety of cancers. Increased COX-2 levels likely influence the tumorigenic, angiogenic and metastatic potentials of cancer cells. In this regard, NSAIDs may present as promising chemopreventive and chemotherapeutic agents for various cancers. A number of studies have also suggested the involvement of LOX in tumor cell proliferation, apoptosis and angiogenesis. LOX inhibitors in many instances demonstrate potent anticancer effects. Manipulation of arachidonic acid metabolism therefore represents a promising approach to develop cancer therapy, and further vigorous translational investigation is warranted.

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