



5-Lipoxygenase: Its involvement in gastrointestinal malignancies

Neha Merchant^{a,1}, Lakkakula V.K.S. Bhaskar^{b,1}, Saimila Momin^{a,1}, Peela Sujatha^{c,1},
Aramati B.M. Reddy^{d,1}, Ganji Purnachandra Nagaraju^{a,*,1}

^a Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, 30322, USA

^b Sickle Cell Institute Chhattisgarh, Raipur, Chhattisgarh, 492001, India

^c Department of Biotechnology, Dr. B.R. Ambedkar University, Etcherla, Srikakulam, Andhra Pradesh, 532410, India

^d Department of Animal Biology, School of Life Sciences, University of Hyderabad, Hyderabad, 500046, India

ARTICLE INFO

Keywords:

Leukotrienes
5-Lipoxygenase
GI cancer

ABSTRACT

Lipoxygenases (LOXs) are dioxygenases that catalyze the peroxidation of linoleic acid (LA) or arachidonic acid (AA), in the presence of molecular oxygen. The existence of inflammatory component in the tumor micro-environment intimately links the LOXs to gastrointestinal (GI) cancer progression. Amongst the six-different human LOX-isoforms, 5-LOX is the most vital enzyme for leukotriene (LT) biosynthesis, which is the main inflammation intermediaries. As recent investigations have shown the association of 5-LOX with tumor metastasis, there has also been significant progress in discovering the function of 5-LOX pathway in GI cancer. Studies on GI cancer cells using the pharmacological drugs targeting 5-LOX pathway have shown antiproliferative and proapoptotic effects. Pharmacogenetic discoveries in other diseases have revealed strong heritable basis for the leukotriene pathway, which helps in exploring the mechanistic source of genetic alteration within the leukotriene pathway and offer insights into GI cancer pathogenesis and future prospects for treatment and prevention. This review recapitulates the current research status of 5-LOX activity in GI malignancies.

1. Introduction

Chronic inflammation is increasingly known as one of the most critical etiological factors in gastrointestinal (GI) cancers (Lee et al., 2016; Wang and Cho, 2015). Overexpression of 5-lipoxygenase (5-LOX), 5-LOX-activating protein (FLAP), as well as other leukotriene (LT) biosynthetic enzymes have been reported in many malignant cells of the GI tract including the colon, rectum, esophagus, and pancreas (Chen et al., 2004; Li et al., 2005; Melstrom et al., 2008; Wasilewicz et al., 2010). There are several pieces of evidence suggesting that 5-LOX triggers the progression and initiation of GI malignancies (Moore and Pidgeon, 2017; Ringleb et al., 2018). For example, a study by Hoque et al. (Hoque et al., 2005a, 2005b) revealed that 5-LOX inhibitors in esophageal tumor cell lines, led to a time and dose dependent decrease in cell viability as well as induced apoptosis, which is linked to the 5-LOX expression levels and LTB4 production in these tumor cell lines. Another study by Romano et al. (Romano et al., 2001a, 2001b) showed that an important mechanism of 5-LOX expression on apoptosis and cell proliferation is associated with the modulation of VEGF and the levels of mRNA by 5-LOX in malignant mesothelial cells. Likewise, an inflammation-related colon cancer development model investigation

found that the expression of 5-LOX is accompanied by the up-regulation of matrix metalloproteinase (MMP) – 2 as well as VEGF expression, which are two most important features of angiogenesis in GI malignancies (Ye et al., 2004). Another study revealed that the inhibition of 5-LOX induces the cell death (apoptosis) in pancreatic cancer (PC) cell lines (Zhou et al., 2015).

Cysteinyl LT 1 receptor (CysLT1R) antagonists and 5-LOX inhibitors are known to modulate the LT pathway (Boudreau et al., 2017; Csandl et al., 2016). Overexpression of CysLT1R in various GI cancers suggests that LT might play an essential function in the pathogenesis of these malignancies (Bengtsson et al., 2013; Osman et al., 2017; Ozkan et al., 2010; Sun et al., 2015). In addition, CysLT1R antagonists, montelukast have also been reported to inhibit tumor progression by inducing apoptosis (Tsai et al., 2017, 2016). Increased expression of 5-LOX in various GI cancers indicates that 5-LOX is a possible target for GI cancer (Hoque et al., 2005a, 2005b). Quantitative messenger (transcript) and protein analysis reported that amplified expression of 5-LOX in PC tissues is associated with TNM stage and lymph node metastasis (Zhou et al., 2015). Additionally, 5-LOX inhibitors showed cytotoxic effects independent of 5-LOX activity (Fischer et al., 2010). 5-LOX gene silencing methods and 5-LOX inhibitor trials revealed suppression of

* Corresponding author.

E-mail address: pganji@emory.edu (G.P. Nagaraju).

¹ All authors equally contributed

tumorigenic Wnt signaling and impaired tumor cell growth (Roos et al., 2016, 2014). Although, the pharmacological drugs targeting 5-LOX have shown antitumorigenic effects on GI cancer, clinical trials using these agents appear to be prone to significant off-target effects. The emphasis of this review is to understand the role of 5-LOX in GI cancers.

2. 5-lipoxygenase

Arachidonate 5-LOX or oxygen 5-LOX is a dioxygenase enzyme rich in non-heme iron (Needleman et al., 1986). This dioxygenase enzyme catalyzes LT from arachidonic acid (AA) (Sundaram and Ghosh, 2006). In general, AA is rich in polyunsaturated fatty acids and initiates the progression of many cancers (Cianchi et al., 2006). Cancer progression is also associated with AA metabolites such as eicosanoids that perform as mitogens (Anderson et al., 1998). The initial two steps in LT development are catalyzed by 5-LOX (Steinhilber et al., 2010), and the chemical reaction begins with in the cell production of AA. 5-LOX along with 5-LOX-activating proteins supports the catalysis of AA oxidation into 5(S)-hydroxy-6-trans-8,11,14-cis-eicosatetraenoic acid (5-HETE) (Sundaram and Ghosh, 2006), which is a direct result from the formation of epoxide LTA4 from dehydrated 5-HETE (Peters-Golden, 1998). LTA4 is further processed to form LTB4 or LTC4 either via LTA4 hydrolase enzymes through stereo-selective hydration or via glutathione conjugation catalyzed by LTC4 synthase (Avis et al., 2001). A series of consecutive metabolic reactions such as γ -glutamyltransferase is involved in the conversion of LTC4 to LTD4 and LTE4 (Steele et al., 1999). Activated 5-LOX enzymes translocate into the nucleoplasm where the activating proteins assist in the relocation of phospholipid-derived AA to 5-LOX. The efficient conversion of LTA4 from 5-HETE initiates 5-LOX development (Steinhilber et al., 2010). These oxidized molecules of 5-HETE and LTs induce tumor propagation and sustainability (Nieves and Moreno, 2006) by interacting with the G-protein-coupled transmembrane receptor OXER1 (Ghosh and Myers, 1997). Recent investigations have revealed that growth factors like epidermal growth factors (EGF) as well as neurotensin are involved in tumor progression facilitated by 5-LOX in various cancers (Hassan and Carraway, 2006; Karlage et al., 2010). 5-LOX can facilitate tumorigenesis directly by regulating the tumor cell and/or indirectly via modulating the tumor microenvironment. Studies including the genetic mutations (Baker et al., 2013) and certain inhibitors of 5-LOX (Cuendet and Pezzuto, 2000) (Fig. 1; Table 1) have shown the association of 5-LOX with tumor metastasis. Mutant studies suggested that catalytic activity is necessary for 5-LOX-associated effects on CRC cell line proliferation and metastasis (Baker et al., 2013). A study conducted on CRC patients revealed that 5-HETE, a metabolite of 5-LOX, elevated the VEGF expression levels and thereby initiated angiogenesis (Romano et al., 2001a, 2001b; Ye et al., 2005). Downstream activation of 5-LOX is known to be involved with AKT and ERK, which might play a vital role in advancing angiogenesis in cancer cells (Payne et al., 2007). Amplified 5-LOX as well as MMP activity is associated with the extracellular matrix (ECM) stiffness (Levental et al., 2009) and has induced invasion and metastasis in cancerous cells (Erler et al., 2009; Kirschmann et al., 2002). All of these discoveries reveal that 5-LOX plays an essential function in inducing tumor cell proliferation and metastasis including migration, invasion, adhesion and angiogenesis.

2.1. Pharmacogenetic relevance of 5-lipoxygenase genetic variations

5-LOX is an essential molecule in the synthesis of LTs, which are implicated in the modulation of inflammation in various disease including GI cancers. The gene encoding *ALOX5* is positioned on chromosome 10q11.2 and harbors several polymorphisms that affect its function (Funk et al., 1989). The Sp1 addition/deletion (5-prime-GGGCGG-3-prime) polymorphisms in promoter area of the *ALOX5* has been identified. Variation within repeats has been revealed to affect gene expression (Roberts et al., 2008). Different alleles involving

removals (1 or 2) or add-ons (1, 2, or 3) of Sp1 domains and/or linked with phenotypic variances in humans (Kalayci et al., 2006; Maznyczka et al., 2008; Schentrup et al., 2009; Telleria et al., 2008; Todur and Ashavaid, 2012). Although, much information is not available on this microsatellite polymorphism, anti-asthma treatment in patients with either of the two mutant alleles showed a drastic reduction in their FEV1 compared patients carrying only one wild-type allele (Drazen et al., 1999). Subsequently, cancer and inflammation are intimately linked due to enhanced leukotriene production (Wisastra and Dekker, 2014). As there is a strong heritable basis for the leukotriene pathway, exploring the mechanistic basis of genetic difference within this pathway will offer insights into GI cancer pathogenesis and future prospects for its treatment and prevention (Tantisira and Drazen, 2009).

3. 5-LOX in esophageal cancer

Various studies suggest that abnormal levels of AA metabolites play an essential role in human esophageal adenocarcinogenesis (EAC). The key AA derivatives of 5-LOX signaling molecules namely include, 5-HETE, LTB4, and cysteinyl LTs, which are well-known to initiate inflammatory pathways, proliferation, vascular absorptivity, and tightening of smooth muscle tissues in EAC patients (Hwang et al., 2002). Normal human esophageal tissues regulate 5-LOX function and produce adequate quantities of LTB4 (Chen and Yang, 2001). But, in the case of malignant EAC tissues, the levels of LTB4 increase remarkably (Hong et al., 2004a, 2004b), suggesting the involvement of the 5-LOX and AA pathways are vital biomarkers in EAC patients. Inhibiting AA metabolism by 5-LOX inhibitors is a key mechanism in restraining EAC (Zhi et al., 2003a, 2003b). The mixture of COX-2 inhibitor and 5-LOX inhibitor as advanced therapeutic strategies in the treatment regimen of EAC patients has exhibited some significant effects by inducing apoptosis. A recent study revealed that the combination of zileuton (5-LOX inhibitor) and celecoxib (COX-2 inhibitor) was successfully able to suppress LTB4 expression and regress EAC tumor progression *in vivo* (Chen et al., 2004). This study evidently indicates that targeting 5-LOX as well as COX-2 signaling pathway could be effective in inhibiting the EAC development. Another study revealed that LTB4, a 5-LOX metabolite, is capable of reversing the effects of inhibitors of 5-LOX, which induces apoptosis in EAC cells. PPAR- γ activation or LTB4R-1 inhibition by LY293111 allows for repression of LTB4 production by suppressing proliferation and inducing apoptosis in EAC cell lines (Budman and Calabro, 2004). This mechanism is linked to fewer EAC cases and hence is considered a new therapeutic approach in treating EAC (Zhi et al., 2003a, 2003b).

4. 5-LOX in gastric cancer

AA is cleaved by phospholipases from the membrane phospholipids. It is catalyzed by cyclooxygenase (COX) or by LOX. Human gastric cancer (GC) cell lines are known to metabolize AA, especially through the LOX signaling pathway instead of the COX pathway (Hong et al., 2001). AA is converted into HPTE (hydroperoxyeicosatetraenoic) acid and ultimately to either HETE or to LTs by lipoxygenase 5-LOX (Poff and Balazy, 2004). GC progression is inhibited by prostaglandins, PGD2 and PGE2, and it is stimulated by leukotrienes, LTC4 and LTD4 (Ye et al., 2005). 5-LOX expression is known to be elevated in GC tissues compared to other adjacent non-tumorous tissues (Ye et al., 2005). This study also revealed that inhibition of 5-LOX resulted a time and dose dependent stimulation of cell death, but no effect was observed on the 5-LOX messenger and protein expressions (Ye et al., 2005). Another study inspected the function of a 12-LOX metabolite, known as 12-HETE, in GC progression and instituted that 12-LOX inhibition reduced GC cell proliferation and induced apoptosis. 12-HETE also reversed the growth inhibition in GC cell lines (Wong et al., 2001). This suggests that the role of both 5-LOX and 12-LOX in GC development is crucial. It is

Download English Version:

<https://daneshyari.com/en/article/8733577>

Download Persian Version:

<https://daneshyari.com/article/8733577>

[Daneshyari.com](https://daneshyari.com)