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ALOX15 as a Suppressor of Inflammation and Cancer: Lost in the Link

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Abstract

Mounting evidence supports a mechanistic link between inflammation and cancer, especially colon cancer. ALOX15 (15-lipoxygenase-1) plays an important role in the formation of key lipid mediators (e.g., lipoxins and resolvins) to terminate inflammation. ALOX15 expression is downregulated in colorectal cancer (CRC). Intestinally-targeted transgenic expression of ALOX15 in mice inhibited dextran sodium sulfate-induced colitis from promoting azoxymethane- induced colorectal tumorigenesis, demonstrating that ALOX15 can suppress inflammation-driven promotion of carcinogen-induced colorectal tumorigenesis and therefore ALOX15 downregulation during tumorigenesis is likely to enhance the link between colitis and colorectal tumorigenesis. ALOX15 suppressed the TNF-α, IL-1β/NF-κB, and IL-6/STAT3 signaling pathways, which play major roles in promotion of colorectal cancer by chronic inflammation. Defining ALOX15's regulatory role in colitis-associated colorectal cancer could identify important molecular regulatory events that could be targeted to suppress promotion of tumorigenesis by chronic inflammation.

Keywords

ALOX15; Colon Cancer; Colitis-Associated Colorectal Cancer

Introduction

Evidence is mounting that a mechanistic link exists between inflammation and cancer [1], especially colonic cancer [2]. Colitis induced chemically in mice by dextran sodium sulfate strongly enhances colorectal carcinogenesis [3]. Similarly, mouse models of genetically-induced colitis, e.g., through IL-10 knock-out [4] or glutathione peroxidase-1 and peroxidase-2 isozyme knock-out [5], also show enhanced colorectal carcinogenesis [6]. In humans, inflammatory bowel diseases (ulcerative colitis and Crohn's disease) markedly increase colorectal cancer risk [6, 7], and colon cancer accounts for an estimated 15% of

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deaths in patients with ulcerative colitis [8]. Although differences in molecular pathogenesis exist between colitis-associated colorectal cancer and the more common sporadic colorectal cancer [2], some chronic inflammatory mechanisms (e.g., cyclooxygenase-2 overexpression) contribute significantly to both [6]. Thus, studying the mechanisms by which chronic inflammation promotes colonic tumorigenesis could also provide insights into the pathogenesis of sporadic colorectal tumorigenesis.

The development and maintenance of chronic inflammation is strongly influenced by oxidative metabolism of polyunsaturated fatty acids (PUFAs) [9]. PUFA oxidative metabolism is enzymatically regulated in cells via several groups of enzymes, the best known of which are the cyclooxygenases (COXs), lipoxygenases (LOXs), and cytochrome p450s (CYP450s) [10]. The roles of cyclooxygenases and cytochrome p450 enzymes in inflammation and cancer have been studied extensively in the literature [10, 11]. The current review will focus on the role of LOXs, especially ALOX15 (human 15-lipoxygenase-1; mouse 12/15-lipoxygenase), in chronic inflammation and cancer.

LOXs metabolize PUFAs and thereby regulate inflammation and its resolution

LOXs are dioxygenase enzymes that incorporate oxygen into PUFAs (e.g., arachidonic acid (AA) or linoleic acid (LA)) to form biologically-active peroxide products (e.g., hydroperoxyeicosatetraenoic acids (HpETEs) or hydroperoxyoctadecadienoic acid HpODEs) [12, 13]. LOXs are named according to the specific location in the arachidonic acid carbon chain where the enzyme catalyzes lipid peroxidation (e.g., ALOX12 oxygenates arachidonic acid at the 12th carbon). Human LOX genes include *ALOX5, ALOXE3, ALOX12, ALOX12B, ALOX15*, and *ALOX15B*; mice share these 6 genes, and an additional skin-specific 12-LOX (*Alox12e*), which is a pseudogene in humans [12, 14].

While products of LOX-mediated AA metabolism (e.g., 5-HETE and leukotriene B_4 (LTB_4) from 5-LOX-mediated metabolism) contribute to the initiation of acute inflammation [15], other products of LOX-mediated metabolism of PUFAs (lipoxins (from AA), resolvins (from docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), protectins (DHA), and maresins (DHA)) are critical to the active process of inflammation resolution, failure of which allows for the development of chronic inflammation [9].

ALOX15 regulates inflammation through multiple pathways

Mammalian ALOX15 is an inducible and highly regulated enzyme in normal cells and evidence reveals it can counterregulate pro-inflammatory signaling via multiple mechanisms [16]. ALOX15 is most commonly known as the rate-limiting enzyme for production of 13-S-HODE from LA [17, 18]. 13-S-HODE is an activating ligand of peroxisome proliferator-activated receptor gamma (PPARγ) and suppressor of PPAR delta (PPARδ) [19–21]. PPARγ inhibits inflammation [22], while PPARδ promotes inflammation, especially colitis [23]. Studies with 12/15-LOX, the mouse homolog of human ALOX15, have suggested that 12/15-LOX plays both pro-inflammatory and anti-inflammatory roles due to its higher ratio of 12- to 15-lipoxygenase activity, and therefore higher levels of the pro-inflammatory

mediator 12-S-HETE [24]. In humans, however, several lines of evidence suggest that ALOX15 plays an anti-inflammatory role. Overexpression of human ALOX15 inhibits polymorphonuclear-cell-mediated tissue destruction in rabbits [25] and glomerulonephritis in rats [26]. ALOX15 activates PPARγ through 13-S-HODE [20, 27]. PPARγ activation inhibits colitis [22] and colitis-associated colonic tumorigenesis [28]. Further evidence of an anti-inflammatory role of human ALOX15 comes from studies of its impact on interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α). These molecules are major pro-inflammatory cytokines that contribute to the pathogenesis of human colitis; TNF-α-blocking agents are used to treat ulcerative colitis [29, 30]. Downregulation of ALOX15 expression in human colorectal cancer cells is associated with upregulation of IL-1β, and re-expression of ALOX15 in colon cancer cells suppresses IL-1β expression [31]. Furthermore, transgenic expression of human ALOX15 in mouse colonic epithelial cells inhibits TNF-α and nuclear factor kappa B (NF-κB) signaling [32].

While the role of 13-S-HODE in inhibiting inflammation is less established, resolvins and lipoxins, which are products of ALOX15-mediated metabolism of EPA or DHA and AA, respectively, have been demonstrated to play critical roles in resolution of inflammation [9]. Termination of the acute inflammatory phase has been shown to involve lipid mediator class switching of arachidonic acid metabolites from pro-inflammatory eicosanoids (e.g., prostaglandin E_2 and leukotriene B_4) to pro-resolving mediators such as lipoxins (e.g., lipoxin A_4 and lipoxin B_4) [9]. This shift in eicosanoid biosynthesis is dependent upon upregulation of ALOX15, which is critical to lipoxin biosynthesis [33, 34].

ALOX15 also contributes to the generation of resolvins, which are among the best-known pro-resolving mediators. The resolvins are oxidative metabolites of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA): the D-series resolvins (e.g., RvD1) are derived from DHA; the E-series resolvins (e.g., RvE1) are derived from EPA [35] (Figure 1). ALOX15 enzymatic function is critical to the generation of the RvD precursor 17-S-HpDHA from DHA [36, 37]. 15-LOX-like function of aspirin-acetylated COX-2 catalyzes generation of the RvE precursor 18-HEPE from EPA [37, 38]. Resolvins have demonstrated strong anti-inflammatory impacts (picomolar to nanomolar range) in various *in vivo* preclinical models of chronic inflammatory disease, including colitis [39, 40]. For example, RvE1, RvD1, and RvD2 inhibit chemically-induced colitis in mice [41, 42]. RvD1 markedly reduces IL-6, IL-1β, and TNF-α expression in various experimental models [36].

While ALOX15 is known to be expressed in the epithelial compartment, it is also present in other cells types, including leukocytes (e.g., neutrophils, macrophages) and vascular endothelial cells (reviewed in [43, 44]). Macrophages show a great deal of heterogeneity in terms of their biomarkers and actions within different tissues, dependent upon host status (healthy, injured, malignant, etc.) [45, 46], and the role of ALOX15 has been investigated in the context of macrophage phenotype [47–49]. The subsets of macrophages involved in resolution of acute inflammatory responses actively remove apoptotic cells and debris, and promote repair of damaged tissues [45, 50, 51]. Resolution-phase macrophages from resolving murine peritonitis were described as “M2-like”, expressing high IL-10, TGF-β, and arginase-1, low IL-12, and increased 12/15-LOX [50, 52]. Additional work using the peritonitis model uncovered distinctions between early and late resolution-phase

macrophages [47]. Here, populations of F4/80+ macrophages from resolving exudates were distinguished in part on the basis of CD11b expression; $CD11b^{high}$ macrophages had low levels of M1 markers, moderate expression of pro-inflammatory cytokines and chemokines, and low 12/15-LOX, while $CD11b^{low}$ macrophages showed reduced pro-inflammatory cytokines/chemokines, low IL-10, and higher 12/15-LOX and TGFβ. In addition to differences in markers, $CD11b^{high}$ macrophages were efficient phagocytic cells, whereas $CD11b^{low}$ macrophages ceased phagocytosing apoptotic PMN, and were described as "satiated". Satiated macrophages were also more likely to emigrate to draining lymph nodes, where they are involved in modulation or termination of adaptive immune responses [47] [49]. Interestingly, satiated efferocytosis was promoted in the peritonitis model by addition of resolvins E1 and D1 (a 12/15-LOX metabolite). ALOX15 expression can be induced in macrophages through interactions with/engulfment of apoptotic cells; it is also inducible by IL-4 and IL-13 [52–54], and galectin-1 [55]. Interestingly, mouse ALOX15 (12/15-LOX) has been shown to control uptake of apoptotic cells by different macrophage subsets, helping to limit inappropriate immune responses [56]. Alterations in the IL-10 signaling pathway have also been implicated in development of chronic inflammatory states in the colon [57];reviewed in [58, 59]. IL-10 is considered an important anti-inflammatory mediator and macrophage-specific deficits in IL-10 signaling can lead to severe inflammation in the colon [58, 60, 61]. Evidence has shown that specialized pro-resolving mediators (e.g., RvD1) requiring ALOX15 for biosynthesis have been shown to increase IL-10 levels in models of acute inflammation [36, 62]. More specifically, both DHA and RvD1 have been shown to drive adipose tissue macrophages towards an M2-like phenotype [63]. Given the accumulating data on ALOX15 expression, SPM biosynthesis and/or responsiveness in macrophage subpopulations, more attention should be placed on how ALOX15/SPMs may influence IL-10 signaling in the intestine under normal and pathological states.

Under homeostatic conditions, gut macrophages have an anti-inflammatory or M2 polarization, playing a key role in maintaining a tolerogenic environment [64, 65]. In the setting of chronic inflammatory disease (UC, Crohn's) or neoplastic progression, macrophage phenotype can be altered [65]. Although tumor-associated macrophages (TAMs) are considered to act in a protumorigenic manner, in part through proangiogenic and immunosuppressive mechanisms [66], there is controversy over whether macrophages in CRC represent a good prognostic indicator or not [65, 67, 68]. Many issues still surround TAMs, for example, the precise origin (e.g., tissue resident or monocyte-derived) of these cells at earlier stages of tumor development is unclear, and whether these cells can act to control early stages of cancer (preneoplastic lesions) remains to be determined [66]. In the context of CRC, macrophage populations may differ depending on whether the cancer arose in a chronically inflamed tissue or represents a sporadic lesion. To date, the ALOX15 status of macrophages (and other stromal cell types) associated with tumor development in colon has not been studied in depth, but given that M2-like or pro-resolving macrophages express ALOX15 and M2-like macrophages are key in regulating the intestinal microenvironment, there is support for the concept that ALOX15+ macrophages have regulatory functions limiting colitis and subsequent promotion of colorectal tumorigenesis. Mechanistic studies to clearly confirm this role are needed.

ALOX15 inhibits colorectal tumorigenesis

ALOX15 expression is lost early in colorectal tumorigenesis, starting at the premalignant adenoma phase [69–72]. In contrast, other LOXs do not appear to be significantly altered during colonic tumorigenesis [31, 73, 74]. Downregulation of ALOX15 expression has also been reported in various other human cancers, including lung [75], esophageal [76], breast [77], endometrial [78], urinary bladder [79] and pancreatic cancer [80]. Additionally, screening of 128 different human cancer cell lines representing 20 different human cancers, including all common human cancers, showed that ALOX15 expression was markedly repressed [75]. Loss of ALOX15 expression is transcriptionally mediated [81] and independent of substrate availability [31]. While some earlier studies suggested that ALOX15 might have a procarcinogenic role, several lines of evidence, including more recent evidence [32, 82] have demonstrated that ALOX15 has a tumor-suppressing role, especially in colorectal tumorigenesis [74, 83]. ALOX15 re-expression in human colorectal cancer cells via pharmaceutical agents [21, 84, 85] or plasmid or adenoviral vectors [20, 70, 73] inhibits the growth of those cells *in vitro* and *in vivo* [86]. Transgenic expression of human ALOX15 in mouse colonocytes (ALOX15-Gut mice) inhibits colorectal tumorigenesis [32]. ALOX15 expression in ALOX15-Gut mice inhibits NF-κB activation and azoxymethane-induced colorectal tumorigenesis [32] and colitis-associated colorectal tumorigenesis [82].

ALOX15 inhibits colitis-driven promotion of colorectal tumorigenesis

NF-κB and STAT3 cooperate to promote colitis-associated colorectal cancer [87]. We studied whether ALOX15 influenced STAT3 signaling in colitis-promoted colorectal tumorigenesis. We found that the acceleration of azoxymethane-induced colorectal tumorigenesis by dextran sodium sulfate-driven colitis was inhibited by ALOX15 transgenic expression in colonic epithelial cells [82]. Inhibition of tumor development/progression in this model was associated with suppression of both IL-6 expression and subsequent STAT3 phosphorylation and signaling, thereby limiting expression of protumorigenic STAT3-driven genes *Notch3* and *Muc1*. Similarly, in human colon cancer cells, re-expression of ALOX15 downregulated IL-6/STAT3 signaling [82], thus demonstrating the translational relevance of the ALOX15 transgenic mouse model results to human colonic tumorigenesis.

ALOX15 exerts important modulatory effects on PPARγ and PPARδ, which are lipid nuclear receptors that function as master regulators of various important cellular events [e.g. metabolism [88], inflammation [89], and tumorigenesis[90]]. While PPARγ is considered to have an antitumorigenic role, the role of PPARδ in tumorigenesis was felt to be controversial [90]. Nevertheless, PPARδ can play an antagonistic role to PPARγ during tumorigenesis [20], and mounting data are confirming the strong protumorigenic role for PPARδ [23, 91, 92]. As mentioned earlier, ALOX15, via 13-S-HODE production, downregulates PPARδ [21]. PPARδ promotes colitis and IL-6 expression [23]. However, prior results regarding the role of PPARδ in intestinal tumorigenesis were contradictory: *Ppard* germline knock-out in APC^{min} mice increased intestinal tumorigenesis in one mouse model [93] but inhibited it in another [94]. In contrast, in the azoxymethane-induced intestinal carcinogenesis model, which better simulates human colonic tumorigenesis, intestinally-targeted *Ppard* genetic deletion profoundly inhibited colonic tumorigenesis [95]. Moreover, intestinally-targeted

Ppard overexpression resulted in strong promotion of azoxymethane-induced tumorigenesis [91]. Cross-breeding of mice with intestinally-targeted *Ppard* overexpression with ALOX15 transgenic mice confirmed *in vivo* the ability of ALOX15-mediated signaling to suppress PPARδ and downstream signaling through IL-6/STAT3, thereby limiting the development of colitis-associated colon cancer [82]. ALOX15 suppression of PPARδ/IL-6/STAT3 signaling also strongly inhibited expression of MUC1 [82], which activates proinflammatory, protumorigenic pathways in colon cancer (e.g., NF-κB) [96] and promotes colitis-associated colon cancer [97].

On the basis of these findings and our prior findings of ALOX15 repression of TNF-α and IL-1β as drivers of NF-κB signaling [32], we propose a theoretical model in which ALOX15 interrupts positive feedback cycles between proinflammatory factors and NF-κB and STAT3 to inhibit tumorigenesis (Figure 2). These findings support the concept that ALOX15 downregulation during tumorigenesis further augments colitis promotion of colonic tumorigenesis, thus strengthening the link between these two pathological processes.

Future questions to be answered

The literature to date regarding the contribution of ALOX15 to colonic tumorigenesis has been focused on the role of ALOX15 in colonic epithelial cells. The likely reason for this focus is that ALOX15 loss has been observed in epithelial but not in stromal cells in cancer [69]. Given the demonstration that ALOX15 expression in leukocytes is critical in mediating the lipid mediator class switching to resolve acute inflammation, it is important to address the role of ALOX15 activity in populations of cells that make up the tumor microenvironment. It is currently unknown whether ALOX15 suppression in various leukocyte subclasses is involved in the tumor promotion by chronic inflammation or conversely, whether increasing ALOX15 expression or activity in these cells might help limit tumor development. Further studies to determine ALOX15's expression and actions in classes of tumor-associated leukocytes are therefore warranted. As the biosynthesis of many specialized pro-resolving mediators (e.g. lipoxins, resolvins) from PUFA precursors requires multiple enzymatic steps, and can involve transcellular mechanisms of biosynthesis, it will be important to address potential relationships between cell populations in order to fully understand ALOX15's roles in tumor biology. Additional studies are also needed to determine whether the regulatory role of ALOX15 in suppressing inflammation-driven tumorigenesis is specific to colon cancer or also applies to other cancers.

Conclusion

Emerging data show that ALOX15 is an important regulator of major signaling pathways (e.g., TNF-α, IL-1β/NF-κB, and IL-6/STAT3) that promote colitis-associated colon cancer. Further defining this role of ALOX15 could identify important molecular regulatory events that could be targeted to suppress colitis-associated colonic tumorigenesis in particular and possibly inflammation-driven promotion of tumorigenesis in general.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- ALOX15 plays an important role in the formation of key lipid mediators (e.g., lipoxins and resolvins) to terminate inflammation.
- ALOX15 expression is downregulated in colon cancer.
- ALOX15 most likely plays an important regulatory role in suppressing signaling pathways (e.g., NF-κB and STAT3) that promote colitis-associated colonic tumorigenesis.

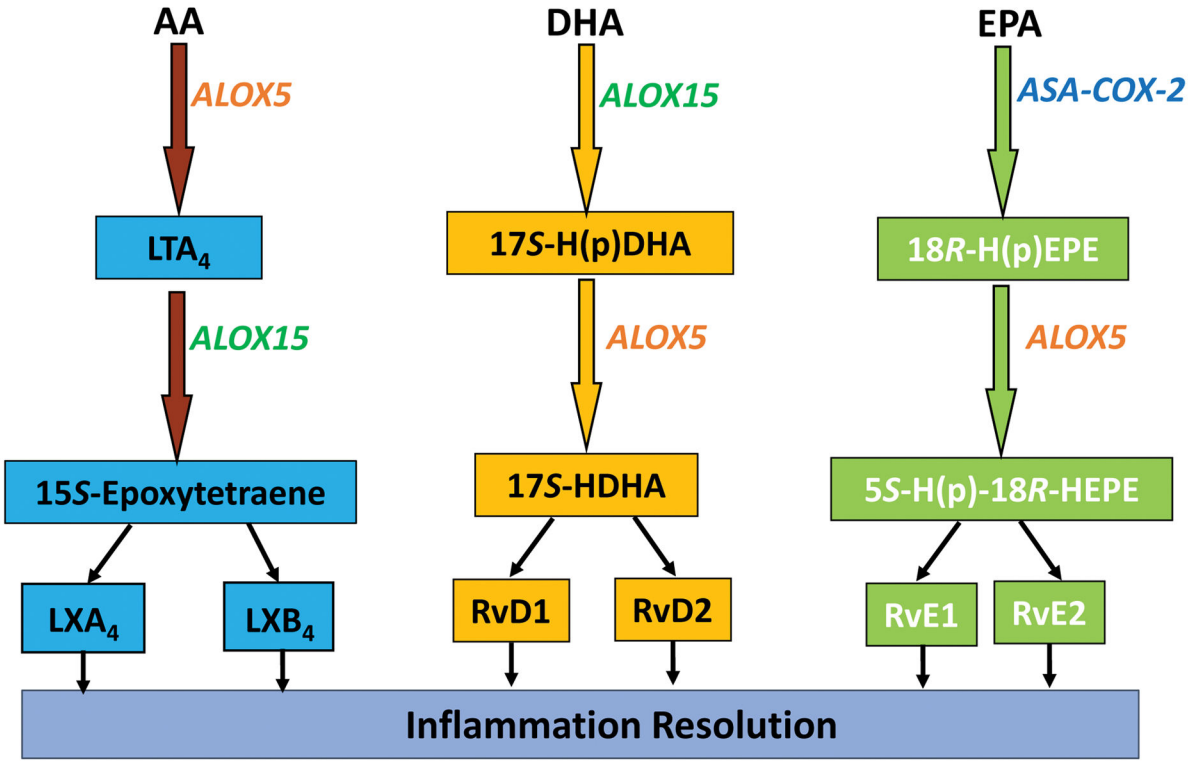

Figure 1. Enzymes involved in biosynthesis of lipoxins (LXs) and resolvins (Rvs) from long-chain PUFA

Multiple PUFA can be metabolized by lipoxygenases, including ALOX15. Shown here are the known pathways involved in biosynthesis of several key classes of SPMs from arachidonic acid (AA), docoahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). Note that the generation of bioactive mediators can involve multiple enzymatic steps and transcellular modes of biosynthesis have been described for SPM [35].

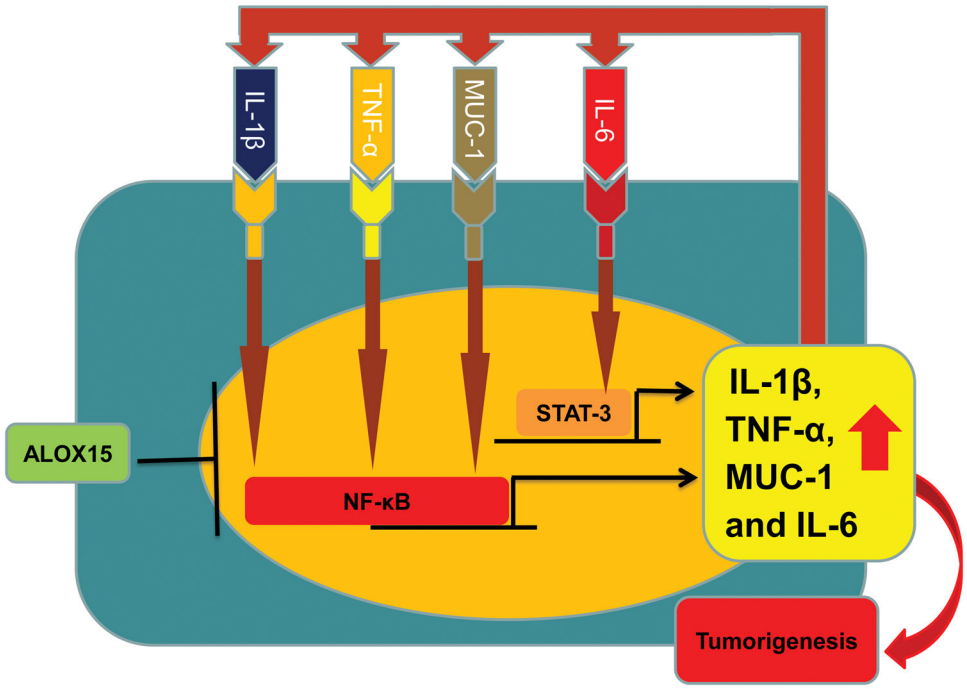

Figure 2. Schematic representation of proposed theoretical model for ALOX15 inhibition of cytokine-driven NF-κB and STAT3 enhancement of IL-6, IL-1β, MUC1 and TNF-α transcription and tumorigenesis promotion

As shown here and discussed in the text, ALOX15 impacts pro-tumorigenic signaling via multiple pathways including suppression of IL-6, IL-1β, TNF-α, STAT3 and NFκB signaling. STAT3 and NFκB are both key transcription factors associated with promotion of inflammation-driven tumorigenesis in the gut [87]. NFκB activity is enhanced by a number of cytokines, such IL-1β, TNF-α, as well as the glycoprotein MUC1. IL-6, an NFκB-responsive gene, can lead to upregulation of STAT3 signaling. In epithelial cancer cells as well as in the tumor microenvironment, dysregulation of these pathways leads to sustained inflammation through feed-forward mechanisms. While detailed mechanisms involved in ALOX15's ability to act as a brake on colorectal tumorigenesis by suppressing these pathways have not been worked out, they likely involve pro-resolving ALOX15 metabolites (e.g., lipoxins, resolvins, etc.) signaling.