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The yin and yang of leukotriene B₄ mediated inflammation in cancer

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Abstract

The high affinity leukotriene B₄ receptor, BLT1 mediates chemotaxis of diverse leukocyte subsets to the sites of infection or inflammation. Whereas the pathological functions of LTB₄/BLT1 axis in allergy, autoimmunity and cardiovascular disorders are well established; its role in cancer is only beginning to emerge. In this review, we summarize recent findings on LTB₄/BLT1 axis enabling distinct outcomes toward tumor progression. In a mouse lung tumor model promoted by silicosis-induced inflammation, genetic deletion of BLT1 attenuated neutrophilic inflammation and tumor promotion. In contrast, in a spontaneous model of intestinal tumorigenesis, absence of BLT1 led to defective mucosal host response, altered microbiota and bacteria dependent colon tumor progression. Furthermore, BLT1 mediated CD8⁺ T cell recruitment was shown to be essential for initiating anti-tumor immunity in number of xenograft models and is critical for effective PD1 based immunotherapy. BLT2 mediated chemotherapy resistance, tumor promotion and metastasis are also discussed. This new information points to a paradigm shift in our understanding of the LTB₄ pathways in cancer.

Keywords

Leukotriene B₄; BLT1; BLT2; Neutrophils; CD8⁺ T cells; Inflammation; Cancer; Immune surveillance

1. Introduction

Leukotriene B₄ (LTB₄), a potent lipid chemoattractant, derived from arachidonic acid pathway exerts its functions via the activation of G-protein coupled receptors, BLT1 (high affinity) [1] and BLT2 (low affinity) [2] and implicated in inflammation in many chronic diseases [3–8]. The pathways activated by these receptors control not only leukocyte migration by chemotaxis but also cell activation pathways including changes in gene expression leading to increased inflammation. Over three decades, studies have associated

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leukotrienes with several inflammatory diseases including asthma, colitis, dermatitis, rheumatoid arthritis, septic peritonitis among others [9–13]. Evidence of their importance in disease development was often obtained from detection of these mediators in inflammatory exudates as well as the efficacy of leukotriene antagonists in abolishing or reducing the inflammatory conditions. An important development in this area is the generation of mice that are deficient in leukotriene biosynthesis or leukotriene receptors as well as transgenic animals expressing specific receptors. Several independent lines of BLT1 and/or BLT2 deficient mice as well as a transgenic over expressing BLT1 were generated in different laboratories [14–21]. These gene targeted mice have been instrumental in defining a critical role for these receptors in diverse inflammatory diseases such as atherosclerosis [22,23] asthma [16,24] autoimmune diseases [25–27] inflammatory arthritis [17,20,28,29] diet induced obesity [30], sleep apnea [31], bone resorption [32] and colitis [18].

Although BLT1 was long known to be a neutrophil chemoattractant receptor, recent studies identified BLT1 expression on macrophages, smooth muscle cells [22,23,33], endothelial cells [34], activated T-cells [35,36] and mast cells [37], considerably expanding the potential roles of LTB₄. Our experiments demonstrated functional expression of BLT1 on both mature and immature dendritic cells and having a direct effect in the control of adaptive immune responses [38]. This diversity of expression has led to the current concepts of *yin and yang* regulation of cancer as the activity of immune cells that influence both pro (neutrophils, MDSC) and anti-tumor (effector CD8⁺ T cells) outcomes may be controlled by LTB₄/BLT1 axis (Fig. 1). In this review, we will focus on discussing the role of leukotriene B₄ and its receptors in cancer.

2. Leukotriene B₄ in cancer

Chronic inflammation mediated through myeloid cells promotes tumor progression whereas immune surveillance mediated by the cytotoxic T lymphocytes (CTL) suppresses tumor growth [39–43]. Eicosanoids, including prostaglandins and leukotrienes have been linked to regulating tumor microenvironment and tumor promoting inflammation [44]. Since BLT1 is a well-established pro-inflammatory mediator much of the early studies are focused on the role of BLT1 in tumor promotion. Tumor promoting effect of 5-Lipoxygenase (5-LO) pathway has been implicated in various forms of cancer including those of pancreas, colon, stomach, prostate, ovaries and lungs [45]. High levels of 5-LO or its metabolites have been observed in various cancers which may directly correlate to the density of tumor infiltrating inflammatory cells [46,47]. Yokota et al. found in the absence of LTB₄/BLT1 signaling, injection of GM-CSF-based tumor vaccine led to rejection of subcutaneous tumors attributed to reduced MDSC recruitment into the tumors [48]. Moreover, a transcriptome analysis of human ovarian carcinoma ascites indicated that LTB₄ along with other arachidonic acid metabolites PGE₂, PGI₂ to be associated with early cancer relapse [49]. It was reported that enhanced levels of LTB₄ in human colon cancer specimens and colon dysplastic lesions [50]. Treating mice with Zileuton, an inhibitor of 5-LO was found to reduce systemic inflammation and polyp burden of small intestine/colon in a murine model of polyposis supporting above human studies [50]. Deletion of the key enzymes in LTB₄ biosynthesis, 5-LO or LTA₄H significantly abrogated tumor burden in K-ras–driven pancreatic ductal adenocarcinoma [51] or in xenograft mouse model of human pancreatic cancer [52].

Interestingly, an inhibitor of 5-LO was also shown to induce differentiation of glioma-stem-like cells thereby reducing the tumorigenicity of the xenografts [53]. Hepatitis B virus X protein, a crucial player in development of hepatocellular carcinoma increased the expression of 5-LO and LTB₄ leading to ERK1/2 activation in hepatocytes [54] providing evidence for the pathway to modulate tumor promoting inflammation.

Though LTB₄ by virtue of orchestrating a pro-inflammatory microenvironment can promote tumors, it can also directly impact the proliferative capacity of cancer cells [55,56]. Jeon et al. have shown that Leukotriene B₄ signaling in cancer cells confers resistance to transforming growth factor- β 1 (TGF- β 1)-induced cytostatic response through pSmad3L activation [57]. This was further validated by a positive correlation of BLT1 expression to pSmad3L expression in human breast cancer tissues. LTB₄ is also known to activate NF- κ B transcription factor [58] as well as produce reactive-oxygen species [59], both of which are known to have tumor promoting effects. However, these direct effects do not appear to be a common occurrence for any tissue type but rather specific for individual cancers due to specific acquired mutations.

2.1. LTB₄-BLT1 axis in silicosis promoted lung cancers

Lung cancers are the leading cause of cancer related deaths and inflammation is a major component of the tumor promoting effect of cigarette smoke [60]. In an orthotropic lung tumor model, tumor-associated neutrophils and macrophages were found to secrete high levels of LTB₄ [61]. Interestingly, BALF and exhaled breath condensate from lung cancer patients displayed significantly higher concentrations of LTB₄ as compared to smoker/non-smoker healthy controls [62,63]. Furthermore, levels of LTB₄ in these NSCLC patients were found to increase with progression of NSCLC stages I through IV, indicating the importance of LTB₄ in promoting lung tumors. Repeated exposure of crystalline silica (CS) in various occupational settings is known to induce chronic lung inflammation and silicosis. Although experimental evidence was lacking, epidemiological evidence indicated such exposure can eventually lead to lung cancer [64]. Our recent studies demonstrated that in both K-ras-activation-induced lung tumor model and an implantable lung tumor model, CS exposure substantially enhanced tumor burden [65]. In both the models, LTB₄-induced neutrophilic inflammation was found to be the key driver of tumor growth, as in the absence of BLT1, neutrophilic influx and subsequent tumor promotion were halted. Such pro-tumorigenic activity of tumor-associated neutrophils is increasingly being appreciated in lung and other forms of cancers [43,66]. Positive correlation exists between neutrophil numbers within the tumors and poor prognosis in NSCLC patients, indicating a strong association of neutrophils in the tumor to rapid tumor growth. Further, using a variety of *in vitro* and *in vivo* models of CS-induced inflammation, we described a complex cellular-molecular interaction initiated by mast-cell-derived-LTB₄ that orchestrates tumorpromoting neutrophilic inflammatory loop, perpetuated by IL-1 β and CXC/CC chemokines (Fig. 2). Although IL-1 β has been implicated in CS-induced lung neutrophil influx [67], production of LTB₄, an early mediator of CS-induced neutrophilic inflammation is independent of inflammasome activation and IL-1 β production [65] indicating the LTB₄/BLT1 pathway may be targeted in silicosis and associated lung cancers.

Although a large body of scientific evidence outlined above suggests that LTB₄ signaling to be a key component in tumor promotion, so far clinical trials with LTB₄ antagonists LY293111 have not yielded promising results [68]. In a phase II study, treatment of stage-III/IV NSCLC patients with LY293111 along with cisplatin-gemcitabine did not increase median progression-free survival over placebo plus cisplatingemcitabine group [69]. Two key confounding factors might be effecting the efficacy of these treatments. First, inhibition of LTB₄-BLT1 axis could alter the host response and thereby inducing bacteria mediated tumor promoting inflammation. Alternatively, inhibition of BLT1 mediated CTL-migration could block anti-tumor immune response. Both these outcomes are discussed in the following sections.

2.2. LTB₄-BLT1 axis protects from progression of colon tumorigenesis

Colorectal cancer (CRC) is a major global health problem with more than one million new cases diagnosed every year and is the fourth leading cause of cancer-related deaths worldwide [70]. CRC has been associated with chronic inflammation and inflammatory bowel disease patients are 30% more at risk of developing CRC than population [71,72]. Therefore, it is not surprising that eicosanoids including leukotrienes are implicated in CRC. Increased levels of LTB₄ have been reported in colon cancer tissues and LTB₄-mediated proliferation of colon cancer cells [73,74]. In other studies, Dreyling et al. showed that LTB₄ levels are significantly increased in human gastrointestinal adenocarcinoma compared to normal colonic mucosa [75]. Most importantly, COX-2, PGE₂ as well as COX product of arachidonic acid (20:4 *n*-6) metabolism are significantly elevated in human colonic tumors [76,77]. Apc^{Min/+} mice carrying a germ-line mutation in the *APC* gene develop multiple polyps in the small intestine that produced significantly higher levels of LTB₄ relative to colonic mucosa [78,79]. It was shown that members of eicosanoid pathways such as cPLA₂, COX2 and prostaglandin E2 receptor (EP2) play a critical role in promoting intestinal tumors in Apc^{Min/+} mice [80–83]. Treatment with dual 5-LOX/COX inhibitor, licofelone significantly reduced overall tumorigenesis in Apc^{Min/+} mouse model indicating importance of leukotriene pathway in intestinal tumor development [84]. Deletion of 5-LO in APC⁴⁶⁸ background also led to a dramatic reduction in the number and size of intestinal polyps [85] suggesting a tumor promoting role for COX2 and 5-LO products. However, recent findings suggest a novel tumor protective role for LTB₄/BLT1 mediated host response in CRC.

Our recent work with Apc^{Min/+} mice in the context of BLT1^{-/-}, 5-LO^{-/-}, MyD88^{-/-} and BLT1^{-/-} MyD88^{-/-} mice led to several important observations [86]. The BLT1^{-/-}Apc^{Min/+} developed significantly increased colon tumor burden reminiscent of human *APC* mutations. Furthermore, these mice displayed significantly decreased survival, increase in total intestinal tumor burden and anemia. This was coincidental with a paradoxical increase in tumor promoting inflammatory mediators such as IL-6, IL-1β, TNF-α, CXCL1 *etc*. In the BLT1^{-/-} mice, a significant increase in colon tumor burden was also observed in azoxymethane/dextran sodium sulfate induced colon tumor model. These unexpected results suggested that LTB₄-BLT1 pathway is protective in Apc^{Min/+} mice from developing colon tumors. In a series of experiments, host response to infection was identified as the basis for these observations. Absence of BLT1 decreased multiple antibacterial proteins at the mucosal surfaces and in intestinal tumors in BLT1^{-/-}Apc^{Min/+} mice. BLT1^{-/-} mice were

more susceptible to peritoneal *E. coli* infection supporting critical nature of BLT1 in mediating host response. Most importantly, deletion of BLT1 in the MyD88^{-/-} mice resulted in neonatal lethality of the mice further supporting the role of BLT1 in host-response. Indeed, with broad spectrum antibiotic treatments, further analysis showed significant decrease in tumorigenesis in BLT1^{-/-}MyD88^{-/-}Apc^{Min/+} mice suggesting that BLT1 acts upstream of MyD88 promoted inflammation in colon tumorigenesis. In contrast to BLT1^{-/-}Apc^{Min/+}, the 5LO^{-/-}Apc^{Min/+} mice showed decreased polyp numbers and increased survival [86] suggesting that 5-LO might play a role in tumor initiation. It is possible that 5-LO derived products other than LTB₄ could have a direct promotional activity on intestinal tumors. Consistent with these observations, cystinyl leukotriene receptor 1 (CysLT1) deficient mice in the Apc^{Min/+} background were also shown to display reduced tumor burden [87].

Gut microbiota play an important role in modulating both the innate and adaptive immune systems and regulate human health as well as outcomes of several diseases [88–95]. Fecal microbiota analysis showed that BLT1^{-/-}Apc^{Min/+} mice harbor distinct microbial composition, with increased levels of *Akkermansia muciniphila* compared to Apc^{Min/+} mice. *A. muciniphila* (Verrucomicrobia phylum) is a mucin degrading bacteria present in the human intestines [96–98], and was reported to be present at increased levels in colon cancer patients [99], ulcerative colitis-associated pouchitis [100] compared to healthy individuals. The germ-free BLT1^{-/-}Apc^{Min/+} mice displayed complete absence of colon tumors that reappeared upon fecal transplantation suggesting critical nature of microbiota in promoting colon tumorigenesis (Fig. 3). Interestingly, small intestinal tumors are unaltered in germ-free BLT1^{-/-}Apc^{Min/+} mice suggesting microbiota independent tumor promoting mechanisms operate in the small intestines of these mice. BLT1 also plays an important role in immune surveillance by attracting cytotoxic CD8⁺ T cells (discussed in the following section). Defective host response due to deletion of BLT1 in Apc^{Min/+} mice likely resulted in reshaping of the gut microbiota leading to increased inflammation and colon tumorigenesis, where as in the small intestine, BLT1 might be critical for immune surveillance to recruit anti-tumor CTLs. Further studies will be required to address the mechanisms of actions of LTB₄/BLT1 axis in colorectal tumor microenvironment and cell-type specific requirement of BLT1 in mediating mucosal host defense.

2.3. BLT1 expression is critical for CD8⁺ T cell infiltration into tumors

Preclinical and clinical studies suggest a positive prognostic implication and prolonged survival advantage associated with the presence of tumor infiltrating CD8⁺ T cells [101,102]. CTL migration is a complex process that requires co-ordination among multiple entities such as adhesion molecules, chemokines/chemokine receptors and unique vasculature at the target site. Although, CTL accumulation during allergic inflammation was shown to require BLT1 [103], the anti-tumor role of BLT1 via CTL migration to tumors has not been examined until recently.

Our recent studies demonstrated a critical role for BLT1 in antitumor immunity in multiple solid tumor models in mice viz. TC1 cervical cancer, B16 melanoma and E0771 breast cancer [104,105]. In all these tumor models, implantation of cancer cells (s.c.) in BLT1^{-/-}

mice significantly increased tumor size and decreased the survival compared to WT mice. This phenotype was lost when TC1 cells were implanted in Rag2^{-/-} or Rag2^{-/-}BLT1^{-/-} mice underscoring the involvement of BLT1 on an adaptive immune population. Depletion of CD8⁺ T cells resulted in enhanced tumor growth in WT but not in BLT1^{-/-} mice, implicating the important role of BLT1 on CD8⁺ T cells in this model. In tumor bearing Rag2^{-/-} animals, adoptively transferred BLT1^{-/-} CTLs failed to reach the tumors and reduce tumor growth compared to WT CTLs. These studies highlighted the importance of BLT1 expression on CTLs for their migration into tumors for generation of anti-tumor immune response and effective immune surveillance (Fig. 4). Importantly, the tumors in BLT1^{-/-} mice had equal numbers of CD4⁺ T cells, MDSCs and myeloid cells suggesting specific recruitment of CTLs in tumors is dependent on expression of BLT1. A recent study in an orthotopic lung cancer model also showed rapid tumor growth in 5-LO mice compared to WT [106]. CD8⁺ T cell depletion eliminated these differences indicating that a 5-LO generated mediator, most likely LTB₄, facilitates CTL mediated tumor suppression further supporting the above conclusions. In contrast, in a GM-CSF gene transduced leukemia model [48] BLT1^{-/-} mice showed similar or better primary and recall immune responses that were attributed to a reduced MDSC population in the tumors of BLT1^{-/-} mice and robust CD4 dependent antitumor responses. The divergence in the results observed between the studies may be due to the differences in the mouse strains (BALB/c), tumor model (leukemia), and expression of GM-CSF in the tumor cells.

At what juncture of the multistep trafficking process is BLT1 required for CTL homing to tumors remains to be determined. Among the many chemokine receptors, CXCR3 expression was found to be critical for Ag-specific CD8⁺ T cells to traffic across the tumor vasculature [107]. CCR5 and CCR2 were not essential for CXCR3-mediated CTL extravasation across tumor vessels despite the presence of CCL2 and CCL5 chemokines in the tumor milieu. Interestingly, the BLT1^{-/-}CXCR3^{-/-} double knockout mice did not display further enhancement in tumor growth or decrease survival compared to either of the single knockout mice [105]. In co-transfer experiments, WT cells could not facilitate additional BLT1^{-/-} or CXCR3^{-/-} CTL infiltration to tumors suggesting that other cytokine and/or chemokine pathways cannot bypass requirement for either BLT1 or CXCR3 in *in vivo* trafficking to tumors.

Programmed cell death protein 1 (PD-1; check point) blockade has proven to be the most promising immunotherapy for human cancers [108–110]. Presence of TILs in tumors correlates with the response to PD-1 blockade therapy [111]. The PD-1 blockade based therapy completely failed to reduce melanoma growth in the BLT1 or CXCR3 deficient mice [105]. In the absence of either BLT1 or CXCR3, there is a defect in T cell infiltration leading to a non-T cell-inflamed tumor that fails to respond to PD-1 blockade therapy. These findings open avenues for exploring strategies to enhance LTB₄ levels in the tumor to facilitate CTL infiltration and anti-tumor immunity during checkpoint blockade based immunotherapy (Fig. 4).

3. BLT2 in cancer promotion and chemotherapy resistance

The low affinity LTB₄ receptor BLT2 is also activated by a natural ligand 12-HHT [112]. The characterization of BLT2 and its role in endothelial functions have been described elsewhere in this issue. It was reported that BLT2 play an important role in the generation of ROS via NADPH oxidases and modulates cancer progression [113,114]. Blocking BLT2 activity with its inhibitor (LY255283) or by siRNA induced cell cycle arrest and apoptosis in AR positive prostate, bladder and ER-negative breast cancer cells indicating that BLT2 may enhance survival signaling pathways [115–117]. In addition, activation of BLT2 by its ligands promoted VEGF-mediated angiogenesis both in *in vitro* and *in vivo* models [118]. BLT2 was also reported to increase the invasiveness of ovarian cancer cells and breast cancer cells through MMP-2 pathways [119] and IL-8 pathway respectively [120]. A novel function for BLT2 in cancer chemoresistance was recently reported [121]. This study demonstrated that platinum-induced fatty acids (PIFAs)- mediate chemoresistance through F4/80⁺/CD11b^{low} splenocytes. Furthermore, 12-S-HHT, but not 16:4(*n*-3) induced chemoresistance could be blocked by the BLT2 specific inhibitor LY255283 or in the BLT2 deficient mice. Overall these studies highlight the critical nature of BLT2 in cancer cell survival, invasiveness, chemoresistance and metastasis and its potential as a therapeutic target in certain cancers.

4. Summary and conclusions

The distinct results in different tumor models and human studies raise number of important questions about the role of leukotriene B₄ pathway in cancer. Although BLT2 may be directly involved in promoting tumor growth by virtue of expression on cancer cells, BLT1 appears to affect cancer progression mainly through immune modulation. Based on the observations outlined here, the major challenge is to address how the LTB₄/BLT1 pathway may be targeted to improve cancer patient outcomes? First, the classic inflammation promotion of cancer by LTB₄/BLT1 was clearly demonstrated in human lung cancers as well as CS promoted lung tumors. While targeting this pathway to prevent the progression of silicosis appears promising, treatment of lung tumors might not lead to optimal outcomes as other mechanisms including host response to infection and immune surveillance are also involved in tumorigenesis. The cell types that regulate the host response to infection, a major factor in the progression of colorectal cancer needs further investigation. Studies are also needed to better understand the cell types that produce LTB₄ during tumor progression. Most solid tumors that respond to PD1 based immunotherapy, however, could benefit from strategies to enhance LTB₄ production in tumors or BLT1 expression on tumor antigen specific CTLs.

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Fig. 1.

Yin-yang mechanism of LTB₄-BLT1 axis in control of cancer. LTB₄ is produced from arachidonic acid (AA) through the sequential actions of 5-Lipoxygenase (5-LO), 5-lipoxygenase-activating protein (FLAP) and Leukotriene A₄ hydrolase (LTA₄H). LTB₄ exerts its biological activities through G-protein coupled receptors, BLT1 (high affinity) and BLT2 (low affinity). BLT1 is expressed on variety of immune cells including granulocytes that mediate tumor promoting inflammation and CTLs that promote immune surveillance leading to anti-tumor immunity. Expression of BLT2 on epithelial cells has been implicated in pro-tumorigenic signaling by promoting chemotherapy resistance, angiogenesis, inflammation and metastasis.

Fig. 2.

Crystalline Silica (CS) promotes lung tumor progression through LTB₄-BLT1 pathway. Exposure of CS leads to production of LTB₄ predominantly from mast cells and macrophages. In lung epithelial cells exposure of CS leads to production of CXC chemokines. The sterile inflammation initiated by the mast cell produced LTB₄ is perpetuated by autocrine loop of neutrophil produced LTB₄. CS-induced cell death/phagocytosis loop of macrophages also contributes to production of LTB₄. Altogether, CS-induced LTB₄, IL-1β and CXC chemokines result in increased inflammation and recruitment of tumor promoting N2 neutrophils leading to enhanced tumorigenesis.

Fig. 3.

BLT1 influences gut microbiota to regulate colon tumorigenesis. *Apc^{Min/+}* mice develop spontaneous intestinal tumors. Deletion of BLT1 in the *Apc^{Min/+}* background led to defective host response (*e.g.*, decrease in host defense proteins such as angiogenins and Reg3 γ) and altered gut microbiota. *BLT1^{-/-}Apc^{Min/+}* mice displayed a significant increase in highly inflamed rapidly growing colonic tumors. *BLT1^{-/-}Apc^{Min/+}* mice raised under germ free condition are free of colon tumors that reappeared upon fecal transplantation.

Fig. 4.

Expression of BLT1 on CD8⁺ T cells is critical for immune surveillance. Tumor antigens are presented by dendritic cells (DC) to Naïve T cells at the draining lymph nodes (LN). The activated cytotoxic T cells (CTLs) acquire the expression of BLT1 and CXCR3 allowing them to enter the tumors resulting in regression. Absence of either BLT1 or CXCR3 results in failure of CTL migration to tumors leading to unchecked tumor growth and failure of PD1 based immunotherapy.