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TOPIC HIGHLIGHT

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Cysteinyl leukotrienes and their receptors: Bridging inflammation and colorectal cancer

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Abstract

Long-standing inflammation has emerged as a hallmark of neoplastic transformation of epithelial cells and may be a limiting factor of successful conventional tumor therapies. A complex milieu composed of distinct stromal and immune cells, soluble factors and inflammatory mediators plays a crucial role in supporting and promoting various types of cancers. An augmented inflammatory response can predispose a patient to colorectal cancer (CRC). Common risk factors associated with CRC development include diet and lifestyle, altered intestinal microbiota and commensals, and chronic inflammatory bowel diseases. Cysteinyl leukotrienes are potent inflammatory metabolites synthesized from arachidonic acid and have a broad range of functions involved in the etiology of various pathologies. This review discusses the important role of cysteinyl leukotriene signaling in linking inflammation and CRC.

Key words: Eicosanoids; Cysteinyl leukotrienes; CysLT$_1$R; CysLT$_2$R; Inflammation; Colorectal cancer

Core tip: Despite several advances in diagnostic and therapeutic options, colorectal cancer (CRC) continues to be a major health problem and one of the leading causes of cancer-related deaths. The inflammatory milieu has been widely recognized as one of the enabling characteristics of cancer development. Cysteinyl leukotrienes are pro-inflammatory eicosanoids implicated in chronic inflammatory bowel diseases and CRC development. Hence, targeting cysteinyl leukotrienes and their receptors could provide alternative therapeutic approaches or be used in combination with existing therapies for more efficient treatment of CRC.

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INTRODUCTION

Colorectal cancer (CRC) is a global health care burden, with more than 1 million new cases diagnosed every year. It is the third most common malignancy and the fourth leading cause of cancer-related deaths worldwide[1]. A diet high in fat but low in fiber, excessive alcohol consumption, obesity and lack of physical activity, disruption of normal gut microbiota and the presence of long-term inflammatory bowel diseases (IBDs) such as ulcerative colitis (UC) and Crohn's disease (CD) predispose to CRC. Inflammation is a host-driven response to internal and external stimuli to counter non-self or self-molecules and maintain tissue homeostasis. However, chronic inflamma-

tion can be a major health problem in allergic, cardiovascular, fibrotic, local and systemic inflammatory diseases and several cancers[2-9]. In 1863, Rudolf Virchow was the first to speculate about the role of long-term inflammation in cancer based on his observations that cancerous tissues were frequently infiltrated by leukocytes[10]. Current epidemiological data indicate that more than 25% of all cancers are related to long-term infections and other types of unresolved inflammation[11-13]. Evidence from observational studies and randomized trials concerning the protective action of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin have indicated not only a reduced long-term risk of esophageal, gastric, biliary, breast, prostate, lung, and CRC but also a lowered risk of metastasis[14-18]. Inflammation present in the tumor microenvironment is characterized by high leukocyte infiltration, ranging in size, distribution and composition, such as tumor-associated macrophages (TAMs), mast cells, dendritic cells (DCs), natural killer cells (NKs), neutrophils, eosinophils and lymphocytes[19-21]. These cells produce a variety of cytotoxic mediators such as reactive oxygen and nitrogen species, serine and cysteine proteases, membrane-perforating agents, matrix metalloproteinases, pro-inflammatory cytokines, interferons (IFNs) and increased levels of enzymes such as cyclooxygenase-2 (COX-2), 5-lipoxygenase (5-LOX) and phospholipase A_2 (PLA_2), hence contributing to carcinogenesis[22-25]. This review addresses the role of cysteinyl leukotrienes in inflammation-induced colorectal carcinogenesis.

EICOSANOIDS

Eicosanoids, from the Greek word "eicosa" meaning "20," are biologically active lipophilic molecules predominantly metabolized from arachidonic acid (AA), a 20-carbon polyunsaturated essential fatty acid, that are involved in physiological processes such as inflammation[14]. AA belongs to the ω-6 family of polyunsaturated fatty acids and is usually found esterified at the second carbon position in the phospholipids of membranes. It serves as a precursor to several lipid pro-inflammatory mediators such as prostaglandins (PGs), prostacyclins, thromboxanes (TXAs), lipoxins and leukotrienes (LTs), which have individual as well as overlapping functions in acute and chronic inflammation[26]. Aberrant AA metabolism is often linked to production of pro-inflammatory eicosanoids, chronic inflammatory diseases and carcinogenesis. The first eicosanoids were discovered in the 1960s, although in 1930 scientists had found that certain substances present in biological fluids such as sputum had the potential to induce contraction and relaxation in smooth muscles; they termed them"slow-reacting substances of anaphylaxis." Despite these early observations, it was not until 1979 that "leukotrienes" were identified and defined by Samuelsson and co-workers for their biological effects in inflammatory processes[27]. On account of their fundamental and seminal work on different eicosanoids, mainly the prostaglandins, and for their discovery of the role of anti-inflammatory compounds such as aspirin on prostaglandin metabolism, the scientists Bengt Samuelsson, John Vane and Sune Bergström were awarded the Nobel Prize for Physiology and Medicine in 1982.

AA, which is stored as diacylglycerol (DAG), is released from the phosphatidylinositol 4,5-bisphosphate (PIP_2) present in the outer nuclear envelope of cells, from which it is mobilized into the cytoplasm either by activation of calcium-dependent cytosolic PLA_2 or by the combined action of phospholipase C (PLC) and DAG lipase[26,28]. Once in the cytosol, AA can be enzymatically metabolized in a three-directional manner either by cytochrome P450 or by the COX pathway into prostaglandins, prostacyclins or thromboxanes, or through the 5-LOX pathway into leukotrienes A_4 (LTA_4), B_4 (LTB_4), C_4 (LTC_4), D_4 (LTD_4) and E_4 (LTE_4) (Figure 1). The last three alternative derivatives to LTA_4 are collectively termed "cysteinyl leukotrienes" (CysLTs) owing to the presence of a cysteine residue and are structurally similar but functionally distinct. The role of these eicosanoids in maintaining intestinal epithelial cell homeostasis is well documented[29-32]. Various epidemiological, clinical, and laboratory studies have shown that dysregulation of the COX and LOX pathways results in chronic inflammation and subsequently cancer[14,29].

LEUKOTRIENES AND THEIR RECEPTORS

The term leukotriene is derived from the two words *leuko* for white blood cells and *trienes*, meaning three conjugated double bonds, indicating that the ability to generate LTs from AA is largely restricted to leukocytes[28].

Synthesis of LTs is initiated by 5-LOX in concert with 5-lipoxygenase-activating protein (FLAP). The latter does not exhibit any enzymatic activity but facilitates the interaction between 5-LOX and its substrate AA. The first step in this pathway is oxygenation of AA to yield unstable 5-hydroperoxyeicosatetraenoic acid (5-HPETE), which immediately undergoes dehydration to form LTA_4. Further metabolism of LTA_4 either generates LTB_4 by the action of LTA_4 hydrolase (LTA_4-H) or leads to conjugation with glutathione in the presence of LTC_4 synthase (LTC_4-S) or glutathione S-transferase to yield LTC_4. After carrier-mediated transport of LTB_4 and LTC_4 to the extracellular milieu, LTC_4 can be further metabolized to LTD_4 through the cleavage of glutamic acid from the glutathione moiety, and additional glycine cleavage yields LTE_4[28,33] (Figure 1).

5-LOX is expressed predominantly by neutrophils, eosinophils, monocytes, macrophages and mast cells. Although nonleukocytes express 5-LOX and FLAP to a lesser extent and are not believed to synthesize appreciable amounts of LTs, expression of LTA_4-H and/or LTC_4-S, uptake of exogenous LTA_4 and further metabolization is possible, *via* a process referred to as transcellular biosynthesis[34].

CysLT signaling is initiated upon binding of a li-

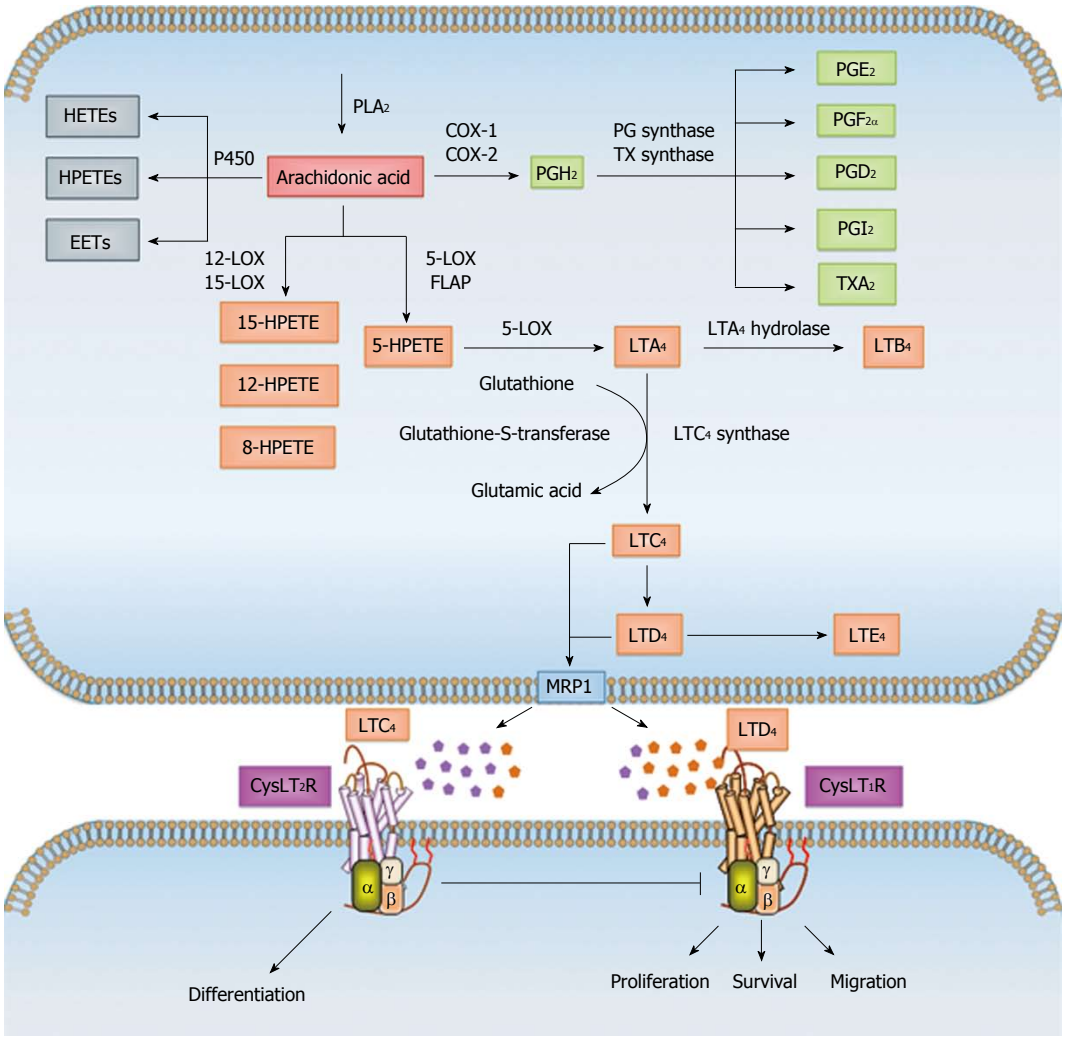

Figure 1 Overview of arachidonic acid metabolism. Arachidonic acid (AA) is a polyunsaturated fatty acid found in the phospholipids of cell membranes. AA is mobilized into the cytoplasm mostly by the activation of calcium-dependent cytosolic phospholipase A_2 (cPLA$_2$). Free AA in the cytosol can be enzymatically metabolized to eicosanoids through three major pathways: the cytochrome P450, cyclooxygenase (COX) and/or 5-lipoxygenase (5-LOX) pathways. In the P450 pathway, AA is metabolized to epoxyeicosatrienoic acids (EETs), hydroxyeicosatetraenoic acids (HETEs) and hydroperoxyeicosatetraenoic acids (HPETEs). In the COX pathway, AA is enzymatically converted to the intermediate prostaglandin H_2 (PGH$_2$), which is then sequentially metabolized to prostanoids, including prostaglandins (PGs), such as PGE$_2$, PGF$_2$, PGD$_2$ and PGI$_2$, and thromboxanes (TXs) such as TXA$_2$ by specific prostaglandin and thromboxane synthases. In the LOX pathway, AA is metabolized by 12- and 15-LOX to 8-, 12- and 15-HPETE or by 5-LOX and 5-lipoxygenase activating protein (FLAP) to intermediary 5-HPETE. 5-HPETE is further processed to form leukotrienes (LTs), the first of which is the unstable leukotriene A_4 (LTA$_4$). LTA$_4$ is subsequently converted to leukotriene B_4 (LTB$_4$) by LTA$_4$ hydrolase or together with glutathione to leukotriene C_4 (LTC$_4$) by LTC$_4$ synthase and glutathione-S-transferase. LTC$_4$ is converted by ubiquitous enzymes to form leukotriene D_4 (LTD$_4$) and leukotriene E_4 (LTE$_4$). The members of the multidrug resistance-associated protein (MRP) family are efflux transporters for both PGs and LTs. The cysteinyl leukotrienes (CysLTs) LTC$_4$, LTD$_4$ and LTE$_4$ act *via* G protein-coupled receptors CysLT$_1$R and CysLT$_2$R at the cell surface and induce different signaling mechanisms.

gand to one of the two G-protein-coupled receptors (GPCRs), CysLT$_1$R and CysLT$_2$R located at the plasma membrane[35,36], although the presence of other CysLT receptors such as GPR17, P2Y$_{12}$, and CysLT$_E$R have also been suggested[37-39]. Both CysLT$_1$R and CysLT$_2$R can also be localized to the nuclear membrane, since CysLT$_1$R has a bipartite nuclear localization sequence and CysLT$_2$R possesses an interferon regulatory 7 (IRF7) site, which in turn carries a nuclear localization sequence domain[40-42]. While the affinity of CysLT$_1$R for LTD$_4$ is high, the CysLT$_2$R has a low but an equal affinity for LTD$_4$ and LTC$_4$[35,36]. Functionally, CysLTs induce smooth muscle contraction, vascular leakage, eosinophil recruitment in inflammatory diseases, mucus production and chemotaxis[43-46].

LTB$_4$ also plays a pivotal role in inflammatory processes such as leukocyte chemoattraction, particularly of granulocytes and T cells, induction of rapid invasion and recruitment of these cells to the plasma membrane of endothelial cells, production of reactive oxygen species, and induction of gene expression[47,48]. LTB$_4$ mediates its signaling *via* two GPCRs: BLT$_1$ and BLT$_2$[49,50]. BLT$_1$ binds to LTB$_4$ with an affinity higher than that of the BLT$_2$ receptor. The tissue distribution of the two receptors is quite different. Whereas BLT$_1$ expression in both mice and humans has been reported to be predominantly restricted to peripheral leukocytes, BLT$_2$ expression in humans appears to be fairly ubiquitous, with the highest

level observed in the spleen, liver, and lymphocytes[51].

CYSTEINYL LEUKOTRIENES AND THEIR RECEPTORS IN COLORECTAL CANCER

IBD and colorectal cancer

Inflammation and CRC initiation and dissemination go hand in hand[10,52]. The most well-established connection exists between IBD-both UC and CD- and CRC[53-55]. "IBD" is a name given to a group of prolonged inflammatory disorders of the intestinal tract associated with debilitating symptoms and epithelial damage. The risk of developing CRC is 30%-50% higher in patients with IBD[56,57]. IBDs are characterized by increased leukocyte infiltration into the intestinal wall, where they can induce non-specific inflammation through activation and production of AA-derived pro-inflammatory metabolites such as LTs and PGs and subsequent tissue injury. Thus, the gastrointestinal tract is richly supplied with these eicosanoids that mediate several gastrointestinal diseases, including cancers. High levels of LTs such as LTE_4 have been detected in the urine of patients with UC and CD[58,59]. Among CysLTs, the presence of LTD_4 at an IBD site increases the risk of consequential cancer development, and specific LTD_4 antagonists have been shown to reduce colonic inflammation[60]. Although UC is fundamentally similar to CD, a few differences exist, primarily the presentation of a cytokine profile with a T helper 2 (Th2) antibody-mediated response[61]. CD is an autoimmune disease associated with T helper 1 (Th1)-mediated cytokines such as interleukin-12 (IL-12), IFN-γ and tumor necrosis factor-alpha (TNF-α)[61,62].

Colitis-associated cancer (CAC) is known to be highly infiltrated by several cells of the innate immune system, including neutrophils, mast cells, NKs, DCs and TAMs[63]. Moreover, recent evidence supports the concept that malignant tumors also recruit a specific subpopulation of myeloid cells called myeloid-derived suppressor cells[64]. These cells share some characteristics with monocytes, macrophages, neutrophils, and DCs and help suppress any potential anti-tumor immune response and tumor angiogenesis. As in several cancers, including CRC, in which the major inflammatory cellular components are macrophages, TAMs contribute immensely to cancer growth and expansion. TAMs are macrophages that display an M2 type (alternatively activated phenotype) and secrete high levels of Th2 cytokines, growth factors and inflammatory mediators that promote tumor growth, angiogenesis, and metastasis[65,66]. We have observed a high intra-tumoral density of TAMs in colon cancer tissue compared with the adjacent normal tissue, and M2 macrophages were required for effective colon cancer cell migration *via* factors derived from M2 macrophages and their association with signal regulatory protein alpha (SIRP-α) through CD47[67].

Eicosanoids and colorectal cancer

Apart from its role in inflammation-associated diseases such as asthma, psoriasis, rheumatoid arthritis and IBD[68], LTB_4 has pro-tumorigenic effects in breast cancer, melanoma, lymphoma, and head and neck carcinoma[69-72]. Increased expression of LTB_4 and its receptor BLT_1 have been demonstrated in human CRC tissue[73]. Ihara *et al*[73] demonstrated significant expression of BLT_1 in the colon cancer cell lines Caco-2 and HT-29. Using both the 5-LOX inhibitor AA-861 and selective BLT_1 antagonist U75302 in these cell lines, the authors showed induction of apoptosis and reduced proliferation[73]. LTB_4-stimulated extracellular signal-regulated kinase (Erk) activation in these cancer cells was also abrogated by U75302. A subsequent study investigated the effectiveness of another LTB_4 receptor antagonist (LY293111) in combination with gemcitabine, an anti-tumor adjuvant and radiosensitizer, on the proliferation rate of human colon cancer cell lines LoVo and HT-29 in an athymic heterotrophic xenograft mouse model and found a significant reduction in tumor growth due to apoptosis *via* the mitochondrial pathway[74]. The findings from these and several other studies emphasize the role of LTB_4 signaling in colon cancer cells and warrant the use of specific LTB_4 receptor antagonists to suppress CRC expansion.

Among the eicosanoids derived from the COX-pathway, PGE_2 is the most abundant and extensively studied in cancer, including CRC[29]. In both the spontaneous adenomatous polyposis coli $(Apc)^{Min/+}$ mouse model of intestinal cancer and the azoxymethane (AOM)-induced CRC mouse model, PGE_2 has been shown to increase the tumor burden[75,76]. Selective inhibition of PGE_2 synthesis, through genetic deletion of microsomal PGES (mPGES-1), significantly reduced tumor formation in an $Apc^{Min/+}$ and AOM-induced mouse model of intestinal and CRC, respectively, and further established the role of PGE_2 in tumorigenesis[77,78].

Increased expression of the enzymes responsible for production of PGs and LTs-COX-2 and 5-LOX, respectively has been documented in human colorectal adenocarcinomas compared with adjacent normal mucosa[79-81]. Various clinical trials over the past two decades have highlighted the use of eicosanoid-depressing and anti-inflammatory drugs in the prevention and treatment of CRC. Two groups of compounds have shown promising results: aspirin (NSAID) and celecoxib (COX-2 selective inhibitor)[82].

Cysteinyl leukotrienes, their receptors and colorectal cancer

Upregulated expression of $CysLT_1R$ has been observed in several human cancers, including transitional cell carcinoma (TCC) in the bladder, neuroblastomas, and brain, prostate, breast, and CRCs[6,80,83-86]. We have shown that high $CysLT_1R$ tumor expression is associated with a poor survival prognosis in breast and CRC patients[80,86], whereas concomitant low $CysLT_1R$ and high $CysLT_2R$ expression indicate a good prognosis in CRC patients[87]. We have also demonstrated high $CysLT_1R$ expression in established colon cancer cell lines[42,80]. The $CysLT_1R$ and

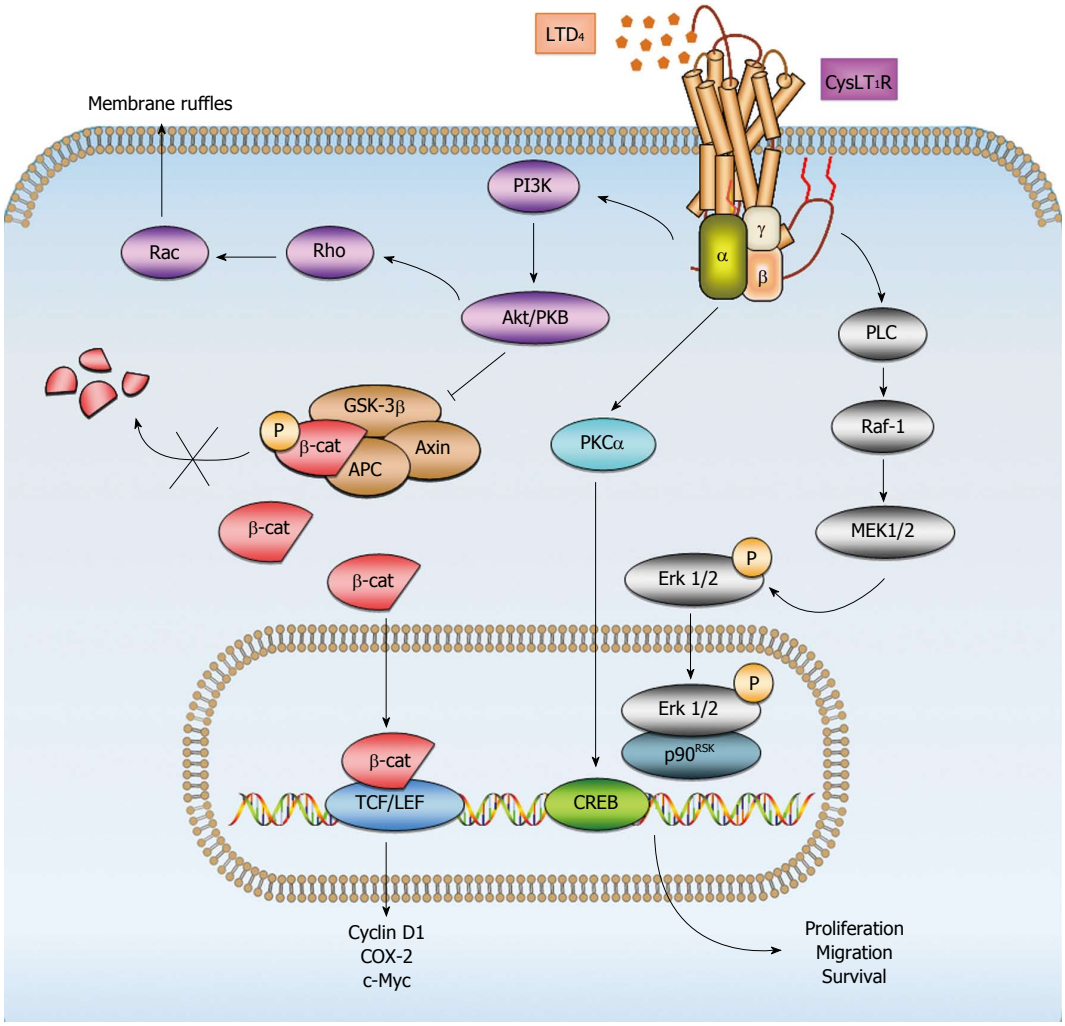

Figure 2 Signaling pathways of LTD_4 and $CysLT_1R$. Upon stimulation with LTD_4, various downstream signaling pathways become activated. LTD_4 induces cell membrane ruffles through phosphoinositide 3-kinase (PI3K) signaling, which in turn stimulates protein kinase Akt/PKB and the small GTPases Rho and Rac. Akt/PKB can inhibit glycogen synthase kinase-3 β (GSK-3β), which comprises the destruction complex for cytosolic β-catenin together with Axin and adenomatous polyposis coli (APC). Inhibition of the destruction complex leads to the accumulation of β-catenin in the cytosol and translocation to the nucleus. In the nucleus, β-catenin interacts primarily with members of the T-cell factor/lymphoid enhancer factor (TCF/LEF) family of transcription factors to activate target genes, leading to the expression of various proteins, such as cyclin D1, COX-2 and c-Myc, which contribute to diverse cellular processes, including proliferation and migration. LTD_4-$CysLT_1R$ signaling also regulates cell proliferation *via* mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (Erk) pathways. LTD_4-$CysLT_1R$ in turn activates phospholipase C (PLC), Raf-1 and mitogen-activated protein kinase kinase (MEK-1/2). This activation leads to the translocation of p-Erk from the cytosol to the nucleus and interaction with $p90^{RSK}$, which can activate various transcription factors. Conversely, LTD_4-$CysLT_1R$ mediates survival through protein kinase Cα (PKCα) and the transcription factor cAMP response element-binding protein (CREB). β-cat: β-catenin.

$CysLT_2R$ expression ratio seems to be important in the disease etiology of CRC. Accordingly, we have shown that these two receptors are co-localized and form hetero- and homodimers in a human intestinal epithelial cell line and that LTC_4 stimulation of $CysLT_2R$ negatively regulates the plasma membrane expression of $CysLT_1R$ by inducing internalization of the receptor heterodimer complex[88]. The expression of $CysLT_1R$ has also been positively correlated with the cell survival factors COX-2 and Bcl-x_L in tumor specimens from patients with CRC[80].

We have previously observed that LTD_4, *via* $CysLT_1R$, induces upregulation of proteins associated with CRC - such as COX-2, β-catenin, and Bcl-2 - in intestinal epithelial cells[89]. Upregulation of β-catenin expression was shown to be dependent on phosphoinositide 3 kinase (PI3K)-glycogen synthase kinase 3β (GSK-3β) signaling[30]. Moreover, our previous work has shown that LTD_4-induced $CysLT_1R$ signaling results in cell proliferation, survival, and migration through distinct signaling pathways. LTD_4-induced $CysLT_1R$-signaling through cAMP response element-binding protein (CREB) and p90 ribosomal s6 kinase ($p90^{RSK}$) was shown to induce survival and proliferation, respectively, while inducing migration *via* the PI3K-Rac signaling pathway[90,91] (Figure 2).

COX-2 expression has also been detected in various colon cancer cells[92], and we have shown that LTD_4 *via* $CysLT_1R$ enhances survival by activating the mitogen-activated protein kinase kinase (Mek)/Erk signaling pathway and increasing COX-2 and subsequent Bcl-2 expression in the colon cancer cell line Caco-2[93]. Furthermore, we have demonstrated that LTD_4 *via* $CysLT_1R$ induces

increased proliferation and migration in the colon cancer cell line HCT-116, probably *via* the GSK-3β/β-catenin pathway with subsequent increased transcription of the target genes *MYC* and *CCD1*[94]. By contrast, decreased expression of CysLT$_2$R has been observed in different colon cancer cell lines (Caco-2 and SW480) compared with an epithelial intestinal cell line, and LTC$_4$ stimulation of CysLT$_2$R has been shown to induce differentiation as demonstrated by increased intestinal alkaline phosphatase activity in Caco-2 cells[42]. In the same colon cancer cell line, anti-tumorigenic IFN-α was shown to induce CysLT$_2$R promoter activity and expression, whereas mitogenic epidermal growth factor (EGF) displayed the opposite effect, suppressing CysLT$_2$R promoter activity and expression. LTC$_4$-mediated CysLT$_2$R signaling suppressed EGF-induced cell migration, and IFN-α induced expression of the differentiation marker mucin-2 and alkaline phosphatase activity[95].

These results indicate potential pro- and anti-tumorigenic properties conveyed by CysLT$_1$R and CysLT$_2$R, respectively, in CRC.

LEUKOTRIENE RECEPTOR ANTAGONISTS AND LEUKOTRIENE SYNTHESIS INHIBITORS

CysLT$_1$R antagonists have been used in studies of inflammatory diseases such as rheumatoid arthritis and atherosclerosis[96,97]. The CysLT$_1$R antagonists pranlukast, zafirlukast and montelukast are commercially available and are currently in clinical use to treat asthmatic patients[98]. Emerging data suggest that the pro-inflammatory CysLTs might have an important role in solid tumors.

CysLT$_1$R antagonist treatment has been shown to inhibit tumor growth by inducing apoptosis in a variety of human urological cancer cell lines (*e.g.*, renal cell carcinoma, bladder cancer, prostate cancer, and testicular cancer)[99]. Montelukast has been shown to induce early apoptosis in a bladder transitional cell carcinoma (TCC) cell line, as well as in three different prostate cancer cell lines[6,83]. In addition, montelukast has been shown to induce the intrinsic apoptotic pathway, resulting in cleavage of caspases 3 and 9, and cell cycle arrest in neuroblastoma cell lines[84].

Studies in CysLT$_1$R-deficient mice have revealed its role in enhanced vascular permeability during an acute inflammatory response[100]. Pranlukast and montelukast have been shown to reduce vascular permeability by regulating vascular endothelial growth factor (VEGF) expression in allergen-induced asthmatic lungs of mice[101]. Furthermore, the two abovementioned CysLT$_1$R antagonists have been shown to inhibit the permeability of peripheral capillaries, thereby preventing tumor metastasis in a Lewis lung carcinoma metastasis model[102]. Proliferation and migration of endothelial cells are needed to form new vessels, a process required in cancer development. Montelukast has been shown to reduce LTD$_4$-CysLT$_1$R-mediated migration of the endothelial cell line EA.hy926 *via* the Erk1/2 pathway[103]. In line with aforementioned data, we have demonstrated in a nude mouse xenograft model of colon cancer that reduction of tumor growth can be accomplished with CysLT$_1$R antagonist treatment. The molecular mechanisms underlying the observed inhibition of tumor growth was attributed to the reduction in proliferation, induction of apoptosis and impairment of angiogenesis[104].

We have also shown that the CysLT$_1$R antagonist ZM198,615 reduces proliferation in the colon cancer cell lines Caco-2 and SW480[105]. Cianchi *et al*[106] reported the additive effects of the COX-2 selective inhibitor celecoxib, when combined with either the 5-LOX inhibitor MK886 or CysLT$_1$R antagonist LY171883, in reducing the proliferative ability of Caco-2 and HT29 cells. The combined treatment was also shown to induce apoptosis, whereas none of these compounds had any effect alone.

The COX pathway is the most extensively studied among eicosanoid pathways in CRC prevention and/or therapy. However, the cardiovascular side effects associated with long-term usage of NSAIDs and selective COX-2 inhibitors have raised some concerns. Other approaches are being explored, such as inhibition of 5-LOX activity. Simultaneous dual inhibition of COX-2 and 5-LOX activity could possibly provide a more effective and tolerable therapy than COX-inhibition alone. Accordingly, the anti-tumor effects of celecoxib in colon cancer cells were augmented when combined with inhibition of 5-LOX activity using the FLAP inhibitor MK886[106]. The combined inhibition of COX-2 and 5-LOX activity have also shown a more pronounced anti-tumor growth effect in a cigarette smoke-promoting mouse xenograft model of CRC[107]. However, targeting either the COX or LOX pathway alone resulted in a shunt toward the other pathway, except in the latter study, in which a shunt was observed when COX-2 activity was targeted with celecoxib. The abovementioned studies investigated the effects on CRC growth targeting the eicosanoid production in epithelial cells. However, the activity of 5-LOX of mast cells was also shown to be important in intestinal polyp formation in APCΔ^{468} mice. The mast cells were found to utilize 5-LOX to promote proliferation of intestinal epithelial cells and recruit myeloid-derived suppressor cells to the polyp site[108]. Another possible effective chemopreventive option against CRC could be the modification of AA metabolism. Apc$^{Min/+}$ mice with the fed diets containing highly purified ω-3 polyunsaturated fatty acids were shown to have their mucosal AA replaced, presumably with a reduction in the production of pro-inflammatory mediators. Reduced polyp formation could be observed in both the intestine and the colon of these mice. These effects were associated with significantly decreased proliferation, COX-2 expression, and nuclear β-catenin accumulation, as well as a concomitant increase in apoptosis in the intestinal epithelium[109]. A reduction in size and number of rectal polyps has also been observed in patients with hereditary CRC (familial adenomatous polyposis, FAP) who have undergone colectomy and received highly purified ω-3-polyunsaturated fatty acids[110].

CONCLUSION

Deregulated AA metabolism creates an imbalance in the tissue homeostatic events of proliferation, regeneration and repair, and host defense. Additionally, deregulated AA metabolism contributes to sustained inflammatory processes that could result in CRC development. Among the implicated inflammatory mediators are the eicosanoids, such as CysLTs. Thus, the modification of CysLT signaling could pave the way for the development of new personalized medicine for patients with CRC[104].

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