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Review Article

BLT2 is a pro-tumorigenic mediator during cancer progression and a therapeutic target for anti-cancer drug development

Nam-Kyu Cho, Young-Chul Joo, Jun Dong Wei, Jae In Park, Jae-Hong Kim

College of Life Sciences and Biotechnology, Korea University, Seoul 136-701, Korea

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Abstract: Cancer is a leading cause of death worldwide and has been linked to inflammation. Leukotriene B_4 (LTB_4) is synthesized from arachidonic acid via the 5-lipoxygenase pathway and is a potent chemoattractant for inflammatory cells. LTB_4 was recently shown to be associated with the pathogenesis of inflammatory diseases, including cancer. Of the two known LTB_4 receptors, BLT1 and BLT2, the biological roles of the low-affinity LTB_4 receptor 2, BLT2, have only recently been elucidated. This review focuses on recent discoveries regarding BLT2 and its roles in cancer progression and the downstream signaling mechanisms of the BLT2-linked signaling cascade in cancer cells. We believe that these findings will facilitate the development of new cancer treatments.

Keywords: Leukotriene B_4 receptor 2 (BLT2), leukotriene B_4, NADPH oxidase, reactive oxygen species, nuclear factor-kB, cancer progression

Introduction

Cancer caused the deaths of 8 million people worldwide in 2010, a 38% increase from 1990 according to the Global Burden of Disease Study 2010 [1]. The development of cancer requires a series of distinct but interconnected properties that allow cancer cells to survive, proliferate, and spread. These characteristics were described as the “Hallmarks of Cancer” by Hanahan and Weinberg [2]. A newly recognized characteristic of cancer is tumor-promoting inflammation [2]. The inflammatory microenvironment creates a local environment suitable for tumor initiation and growth and is hypothesized to be involved in the majority of tumors, even tumors in which a causal relationship with inflammation has not yet been confirmed [3-6].

A pro-inflammatory lipid mediator, LTB_4, plays a particularly important role in the tumor microenvironment because it is a very potent chemoattractant involved in neutrophil migration [7-9]. In addition, LTB_4 helps attract and activate other leukocytes at the inflammation site, including macrophages [10], eosinophils [11], immature mast cells [12], dendritic cells [13], and T cells [14]. LTB_4 is synthesized from arachidonic acid (AA), which is released from membrane phospholipids via the activity of cytosolic phospholipase A_2 ($cPLA_2$) (**Figure 1**) [15]. Free AA is subsequently metabolized to LTA_4 by 5-lipoxygenase (5-LOX) in conjunction with 5-LOX-activating protein (FLAP). LTA_4 is then hydrolyzed by LTA_4 hydrolase (LTA_4H) to LTB_4 [16, 17]. Many studies have demonstrated that LTB_4 is involved in numerous inflammatory diseases [18, 19], including asthma [20], atherosclerosis [21], arthritis [22], chronic obstructive pulmonary disease [23], and inflammatory bowel disease [24]. More recently, LTB_4 has been shown to be involved in numerous aspects of cancer. Treatment with 5-LOX, FLAP, and LTA_4H inhibitors decreases cancer cell survival and reduces both the number and volume of tumors in mouse models [10, 19].

LTB_4 mediates biological functions via the G-protein-coupled receptors (GPCRs) LTB_4 receptor-1 (BLT1) and LTB_4 receptor-2 (BLT2) [25]. Until recently, the majority of studies on LTB_4 receptors focused on BLT1, a high-affinity LTB_4 receptor first discovered in 1996 as a

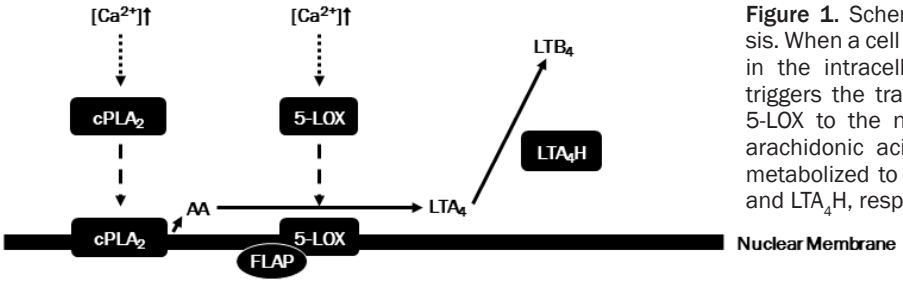

Figure 1. Schematic of LTB_4 Biosynthesis. When a cell is activated, the increase in the intracellular Ca^{2+} concentration triggers the translocation of $cPLA_2$ and 5-LOX to the nuclear membrane. Free arachidonic acid released by $cPLA_2$ is metabolized to LTA_4 and LTB_4 via 5-LOX and LTA_4H, respectively.

receptor involved in human B cell lymphoblast chemoattraction [26]. BLT1 is expressed primarily on leukocytes and plays an important role in inflammatory processes [27]. A second GPCR for LTB_4, BLT2, was not discovered until it was cloned and characterized in a BLT1 gene cluster by Yokomizo et al. in 2000 [28, 29]. The low-affinity BLT2 is stimulated by several ligands. In addition to LTB_4, its ligands include 12 (*S*)-hydroxy-5 (*Z*), 8 (*Z*), 10 (*E*), 14 (*Z*)-eicosatetraenoic acid (12 (*S*)-HETE) and 12 (*S*)-hydroxy-5 (*Z*), 8 (*E*), 10 (*E*)-heptadecatrienoic acid (12-HHT) [25, 30]. Recent studies of BLT2 indicate that BLT2 is involved in various aspects of cancer progression. In particular, the generation of ROS via NADPH oxidases (NOXs) has been associated with BLT2-mediated cancer progression (**Table 1**). This review focuses on the recently discovered roles of BLT2 and BLT2-mediated generation of ROS and the downstream signaling cascade involved in cancer progression.

The relationship between BLT2 and cancer progression

The role of BLT2 in cancer progression was first recognized when we demonstrated that BLT2 is upregulated in a variety of human cancers and that BLT2 blockade significantly attenuates Ras-induced transformation [31]. Because Ras signaling pathways are associated with various aspects of cancer progression [32], the proposed link between BLT2 and Ras signaling suggested new roles for BLT2 in human cancer. Increasing evidence indicates that BLT2 plays a critical role in mediating different aspects of cancer development, such as proliferation, survival, angiogenesis, invasion, and metastasis (**Table 1**) [33-41]. Consequently, elucidating the function of BLT2 may be relevant to cancer therapy.

For example, treatment with the BLT2-specific antagonist LY255283 or transfection with BLT2 siRNA induces cell cycle arrest and apoptosis in androgen receptor (AR)-positive prostate cancer cells [37], bladder cancer cells [38], and estrogen receptor (ER)-negative breast cancer cells [35], suggesting that BLT2 plays a role in mediating cancer cell survival. In addition, BLT2 may be important in angiogenesis because it is involved in the signaling pathways of angiogenic factors such as vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8) [42, 43]. VEGF is a very potent angiogenic factor that is involved in tumor growth. VEGF/VEGFR signaling results in vascular permeability and endothelial cell survival, mitogenesis, migration, and differentiation [44]. Activation of BLT2 by its ligands significantly enhances VEGF-mediated angiogenesis *in vitro* as well as *in vivo* [42]. Furthermore, in mast cells, IL-8 synthesis by IL-1β appears to be mediated by BLT2-induced activation of nuclear factor-κB (NF-κB) [43]. In these studies, inhibition of BLT2 by LY255283 or siRNA markedly attenuated angiogenic activity.

We have also demonstrated the significance of BLT2 in mediating cancer invasiveness and metastasis. For example, in aggressive bladder cancer cells, BLT2 markedly enhances invasiveness by upregulating matrix metalloproteinase-9 (MMP-9) [36]. BLT2 also increases the invasiveness of ovarian cancer cells via a different pathway, with MMP-2 as the effector [39]. In aggressive breast cancer cells, BLT2 confers invasiveness via IL-8 regulation [40]. In these studies, metastatic nodule formation in mice was induced by the injection of cancer cells and was significantly attenuated by BLT2 inhibition with either an antagonist or by siRNA transfection. In addition, we recently demonstrated that BLT2-ROS signaling through MMP-9 is involved in Ras-induced invasiveness because inhibition of BLT2 function results in a significant decrease in Ras-induced invasiveness [33].

Table 1. Stress-type- and cell-type-specific BLT2 downstream signaling cascades

BLT2 downstream	NOX isoform	BLT2 ligands	Stress type	Cell type	Phenotype	Refs
ERK/AKT	NOX1/4	LTB_4, 12 (S)-HETE	Tumor	Bladder cancer	Survival	[38]
		LTB_4, 12 (S)-HETE	UV	Keratinocyte (HaCaT)	MMP-1, photo-aging	[69]
JAK/STAT3	NOX4	LTB_4, 12 (S)-HETE	Tumor	Ovarian cancer	Invasion, MMP-2	[39]
NF-κB	NOX4	12 (S)-HETE	Tumor	Prostate cancer (LNCaP)	AR expression, survival	[37]
	NOX1	LTB_4	Tumor	Breast cancer (MDA231, 453)	IL-8 synthesis, invasion	[40]
	NOX1/4	LTB_4, 12 (S)-HETE	Tumor	Bladder cancer (253J-BV)	Invasion, MMP-9	[36]
	NOX1	LTB_4, 12 (S)-HETE	Allergen	Mast cell	Th2 cytokine synthesis	[72]
	NOX1	LTB_4	IL-1β	Mast cell (HMC-1)	IL-8 synthesis, angiogenesis	[43]
JNK/p38	NOX1	LTB_4, 12 (S)-HETE	UV	Keratinocyte	Apoptosis (sunburn)	[73]
	NOX1	12-HHT	UV	Keratinocyte	IL-6 synthesis suppression	[74]

Another group recently reported that BLT2 might be involved in the metastasis of pancreatic cells [45]. These studies demonstrate the importance of BLT2 in mediating invasion and metastasis in cancer, thereby presenting new opportunities for the treatment of malignant tumors.

Downstream signaling mechanisms of BLT2 in cancer cells

NF-kB downstream of BLT2

NF-kB is a pleiotropic transcription factor that is activated by a broad range of stimuli and is an integral protein in a number of cell signaling pathways. It induces the expression of genes involved in the regulation of biological responses such as immune responses, inflammation, and cell survival [46, 47]. NF-kB plays a critical role in the progression of the majority of cancers [48-50]. In normal resting cells, NF-kB is usually inactive. In this state, NF-kB is bound to inhibitors of kappa B (IkB) in the cytosol until it is activated by a wide array of stimuli. However, in cancer cells, NF-kB is often constitutively active, not as a result of either an IkB loss-of-function mutation or an IkB kinase (IKK) gain-of-function mutation but as a result of persistent "normal" activation in most cases [50, 51]. Our recent studies have indicated that BLT2 stimulates NF-kB activity in prostate, breast, and bladder cancer cells (**Table 1** and **Figure 2**). BLT2 appears to mediate the activation of MMP-9 by stimulating NF-kB activity through ROS production via NOXs. This appears to promote an aggressive cancer phenotype, suggesting a critical role for BLT2 in mediating invasion and metastasis. For example, in Ras-transformed cells, NF-kB activation by the BLT2-NOX1-ROS-linked signaling cascade is involved in the upregulation of MMP-9, which leads to invasion and metastasis [33]. In aggressive 253J-BV bladder cancer cells, the BLT2-NOX1/4-ROS-NF-kB-linked signaling cascade also appears to play a role in invasion and metastasis by controlling MMP-9 [36].

Another downstream component of NF-kB is IL-8, which is a key factor in cancer invasion and angiogenesis [52, 53]. IL-8 binds to its receptors CXCR1 and CXCR2 and activates signaling pathways involving phosphatidyl-inositol-3-kinase (PI3K), phospholipase C, Akt, and mitogen-activated protein kinase (MAPK), resulting in the activation of various transcription factors that promote cell survival, angiogenesis, and invasion [54]. In the highly aggressive human breast cancer cell lines MDA-MB-231 and MDA-MB-435 and the mast cell line HMC-1, the activation of BLT2 markedly upregulates NOX1-dependent ROS generation, which in turn induces NF-kB-dependent IL-8 synthesis [40, 43]. In aggressive breast cancer cells, IL-8 synthesis via the BLT2-NOX1-ROS-NF-kB-linked signaling cascade contributes to invasiveness and metastasis [40]. For mast cells, the pro-inflammatory cytokine IL-1β mediates IL-8 synthesis in part through the upregulation of BLT2 expression and LTB_4 synthesis, which leads to NF-kB activation and significantly contributes to angiogenic activities [43].

The androgen receptor (AR) was previously reported to be upregulated by NF-kB in prostate cancer [55]. AR is a nuclear transcription factor that belongs to the steroid receptor superfamily and is activated by androgen to

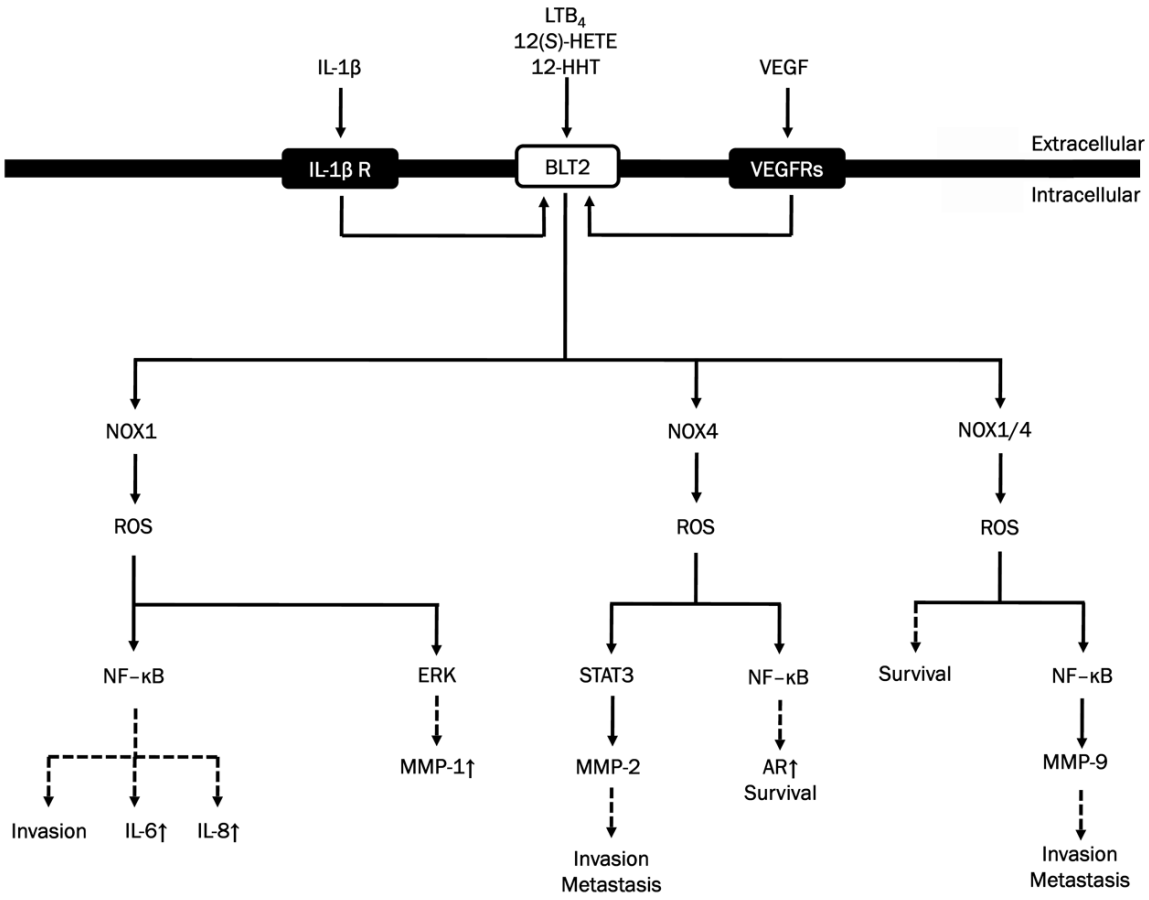

Figure 2. A Comprehensive Overview of BLT2 Signaling Pathways. For details, see text.

mediate normal development and survival of the prostate [56, 57]. However, in androgen-responsive and more progressed castration-resistant prostate cancer, AR mediates the aberrant survival and proliferation of cancer cells [57, 58]. We observed that ROS produced by BLT2-mediated NOX4 activation stimulated NF-kB-mediated AR expression. Moreover, treatment with the inhibitor 12-LOX decreased AR expression and the survival of AR-positive LNCaP prostate cancer cells, indicating that 12 (S)-HETE is the ligand that activates BLT2. In conclusion, the 12 (S)-HETE-BLT2-NOX4-ROS-NF-kB-linked signaling cascade upregulates AR expression to positively affect the survival of AR-positive prostate cancer cells [37].

JAK/STAT3 downstream of BLT2

The downstream pathways of BLT2 also involve other downstream components in addition to NF-kB (**Table 1** and **Figure 2**). For example, we have established that BLT2 confers MMP-2-mediated invasiveness by regulating Tyr^{705} phosphorylation-induced activation of signal transducer and activator of transcription-3 (STAT3) in ovarian cancer [39]. Janus kinase 2 (JAK2) is phosphorylated when a membrane receptor is dimerized by a ligand and phosphorylates STAT3 at Tyr^{705} for activation [59, 60]. Constitutive activation of STAT3 has been reported to mediate cancer development in different types of ovarian cancer [62, 63]. Previous studies have also established a link between STAT3 and MMP-2 in promoting cancer cell invasiveness [64, 65]. Therefore, BLT2 and NOX4 inhibition were used to demonstrate that the STAT3-MMP-2 pathway lies downstream of the BLT2-NOX4-ROS pathway. There is also evidence suggesting that the ROS produced by NOXs activate the signaling pathway leading from JAK by inhibiting tyrosine phosphatases (PTPs) that dephosphorylate JAK [66]. We propose that the BLT2-NOX4-ROS pathway activates the JAK2-STAT3-MMP-2 pathway in ovarian cancer cells to promote invasiveness and

metastasis by inhibiting PTPs [39]. However, the details of this mechanism must be further elucidated.

ERK/AKT downstream of BLT2

In bladder cancer cells, the BLT2-NOX1/4-ROS signaling cascade-induced survival of cancer cells appears to involve ERK and Akt phosphorylation [38]. ERK, which is a MAPK, and the PI3K/Akt signaling pathway have been implicated in the promotion of cell survival under mild oxidative stress conditions [67, 68]. BLT2 may mediate ERK phosphorylation in pancreatic cancer [45], and ERK appears to function downstream of the BLT2-ROS cascade in keratinocytes [69]. There are also reports indicating that Akt and BLT2 phosphorylate each other [38, 70], further demonstrating the relationship between BLT2, ERK, and Akt. BLT2 and NOX1/4 knockdown significantly reduce ERK and Akt phosphorylation [39], indicating that ERK and Akt are critically involved in the BLT2 signaling pathway that promotes cell survival in bladder cancer. The detailed signaling mechanisms, however, remain to be characterized.

Cross-talk exists between signaling pathways, such as between the RAS/RAF/ERK and RAS/PI3K/AKT pathways or between the PI3K/AKT and stress-activated protein kinase (SAPK) pathways [67, 68, 71]. BLT2 may be involved in this cross-talk because it is involved in Ras-mediated activities, Akt-mediated cell survival, and SAPK pathway-mediated apoptosis. There is also evidence that NF-kB and STAT-3 cooperate during tumorigenesis [50]. Studies are needed to determine if and the mechanism by which these signaling pathways are interconnected through BLT2; these signaling pathways could behave differently depending on the cell type and stress type.

Conclusions and future perspectives

In this review, we have elucidated the effects of the low-affinity LTB_4 receptor BLT2 on cancer progression. In the process of evolving into a neoplastic state and becoming malignant, cells acquire hallmark characteristics of cancer, including sustainment of proliferative signals, activation of invasion and metastasis, induction of angiogenesis, and evasion of cell death [2]. The studies reviewed here demonstrate that these characteristics are likely to be mediated, at least in part, by BLT2 activity. As shown in **Figure 2**, activation of BLT2 by its ligands activates a number of signaling pathways that lead to cancer phenotypes for a variety of cancers. By controlling ROS production through NOXs, BLT2 mediates the actions of critical components of intracellular signaling pathways such as Akt, JAK2, STAT3, ERK, and NF-kB, which help confer cancer phenotypes to normal cells. The exact mechanisms by which BLT2-induced ROS controls those proteins remain to be determined. Because studies of the role of BLT2 as an integral part of cancer progression have only recently begun, the mechanism by which BLT2 interacts with other signaling pathways must be further elucidated in future studies. Nonetheless, BLT2-mediated ROS production and subsequent cross-talk among the different signaling pathways may hold enormous potential for the treatment of cancer.

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Address correspondence to: Dr. Jae-Hong Kim, College of Life Sciences and Biotechnology, Korea University, 5-1 Anam-dong, Sungbuk-gu, Seoul, 136-701, Korea. Tel: 82-2-3290-3452; Fax: 82-2-927-9028; E-mail: jhongkim@korea.ac.kr

References

[1] Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC,

Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA 3rd, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De Leon FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA and Memish ZA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2095-2128.

[2] Hanahan D and Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144: 646-674.

[3] Coussens LM and Werb Z. Inflammation and cancer. Nature 2002; 420: 860-867.

[4] Dinarello CA. The paradox of pro-inflammatory cytokines in cancer. Cancer Metastasis Rev 2006; 25: 307-313.

[5] Grivennikov SI, Greten FR and Karin M. Immunity, inflammation, and cancer. Cell 2010; 140: 883-899.

[6] Mantovani A, Allavena P, Sica A and Balkwill F. Cancer-related inflammation. Nature 2008; 454: 436-444.

[7] Afonso PV, Janka-Junttila M, Lee YJ, McCann CP, Oliver CM, Aamer KA, Losert W, Cicerone MT and Parent CA. LTB4 Is a Signal-Relay Molecule during Neutrophil Chemotaxis. Developmental Cell 2012; 22: 1079-1091.

[8] Palmblad J, Uden AM, Lindgren JA, Radmark O, Hansson G and Malmsten CL. Effects of novel leukotrienes on neutrophil migration. Febs Letters 1982; 144: 81-84.

[9] Yokomizo T, Izumi T and Shimizu T. Leukotriene B4: Metabolism and signal transduction. Arch Biochem Biophys 2001; 385: 231-241.

[10] Wang DZ and Dubois RN. Eicosanoids and cancer. Nat Rev Cancer 2010; 10: 181-193.

[11] Luna-Gomes T, Bozza PT and Bandeira-Melo C. Eosinophil recruitment and activation: the role of lipid mediators. Front Pharmacol 2013; 4: 27.

[12] Weller CL, Collington SJ, Brown JK, Miller HR, Al-Kashi A, Clark P, Jose PJ, Hartnell A and Williams TJ. Leukotriene B4, an activation product of mast cells, is a chemoattractant for their progenitors. J Exp Med 2005; 201: 1961-1971.

[13] Del Prete A, Shao WH, Mitola S, Santoro G, Sozzani S and Haribabu B. Regulation of dendritic cell migration and adaptive immune response by leukotriene B4 receptors: a role for LTB4 in up-regulation of CCR7 expression and function. Blood 2007; 109: 626-631.

[14] Goodarzi K, Goodarzi M, Tager AM, Luster AD and von Andrian UH. Leukotriene B4 and BLT1 control cytotoxic effector T cell recruitment to inflamed tissues. Nat Immunol 2003; 4: 965-973.

[15] Harizi H, Corcuff JB and Gualde N. Arachidonic-acid-derived eicosanoids: roles in biology and immunopathology. Trends Mol Med 2008; 14: 461-469.

[16] Cho KJ, Seo JM and Kim JH. Bioactive lipoxygenase metabolites stimulation of NADPH oxidases and reactive oxygen species. Mol Cells 2011; 32: 1-5.

[17] Joo YC and Oh DK. Lipoxygenases: Potential starting biocatalysts for the synthesis of signaling compounds. Biotechnol Adv 2012; 30: 1524-1532.

[18] Di Gennaro A and Haeggstrom JZ. The leukotrienes: immune-modulating lipid mediators of disease. Adv Immunol 2012; 116: 51-92.

[19] Peters-Golden M and Henderson WR. Mechanisms of disease: Leukotrienes. N Engl J Med 2007; 357: 1841-1854.

[20] Miyahara N, Miyahara S, Takeda K and Gelfand EW. Role of the LTB4/BLT1 pathway in allergen-induced airway hyperresponsiveness and inflammation. Allergol Int 2006; 55: 91-97.

[21] Sanchez-Galan E, Gomez-Hernandez A, Vidal C, Martin-Ventura JL, Blanco-Colio LM, Munoz-Garcia B, Ortega L, Egido J and Tunon J. Leukotriene B4 enhances the activity of nucle-

ar factor-kappaB pathway through BLT1 and BLT2 receptors in atherosclerosis. Cardiovasc Res 2009; 81: 216-225.

[22] Chen M, Lam BK, Kanaoka Y, Nigrovic PA, Audoly LP, Austen KF and Lee DM. Neutrophil-derived leukotriene B4 is required for inflammatory arthritis. J Exp Med 2006; 203: 837-842.

[23] Beeh KM, Kornmann O, Buhl R, Culpitt SV, Giembycz MA and Barnes PJ. Neutrophil chemotactic activity of sputum from patients with COPD: role of interleukin 8 and leukotriene B4. Chest 2003; 123: 1240-1247.

[24] Sharon P and Stenson WF. Enhanced synthesis of leukotriene B4 by colonic mucosa in inflammatory bowel disease. Gastroenterology 1984; 86: 453-460.

[25] Tager AM and Luster AD. BLT1 and BLT2: the leukotriene B4 receptors. Prostaglandins Leukot Essent Fatty Acids 2003; 69: 123-134.

[26] Owman C, Nilsson C and Lolait SJ. Cloning of cDNA encoding a putative chemoattractant receptor. Genomics 1996; 37: 187-194.

[27] Toda A, Yokomizo T and Shimizu T. Leukotriene B4 receptors. Prostaglandins Other Lipid Mediat 2002; 68-9: 575-585.

[28] Tryselius Y, Nilsson NE, Kotarsky K, Olde B and Owman C. Cloning and characterization of cDNA encoding a novel human leukotriene B4 receptor. Biochem Biophys Res Commun 2000; 274: 377-382.

[29] Yokomizo T, Kato K, Terawaki K, Izumi T and Shimizu T. A Second Leukotriene B4 Receptor, Blt2 A New Therapeutic Target in Inflammation and Immunological Disorders. J Exp Med 2000; 192: 421-432.

[30] Okuno T, Iizuka Y, Okazaki H, Yokomizo T, Taguchi R and Shimizu T. 12 (S)-hydroxyheptadeca-5Z, 8E, 10E-trienoic acid is a natural ligand for leukotriene B4 receptor 2. J Exp Med 2008; 205: 759-766.

[31] Yoo MH, Song H, Woo CH, Kim H and Kim JH. Role of the BLT2, a leukotriene B4 receptor, in Ras transformation. Oncogene 2004; 23: 9259-9268.

[32] Campbell PM and Der CJ. Oncogenic Ras and its role in tumor cell invasion and metastasis. Semin Cancer Biol 2004; 14: 105-114.

[33] Kim EY, Seo JM, Cho KJ and Kim JH. Ras-induced invasion and metastasis are regulated by a leukotriene B4 receptor BLT2-linked pathway. Oncogene 2010; 29: 1167-1178.

[34] Lopez-Otin C and Matrisian LM. Emerging roles of proteases in tumour suppression. Nat Rev Cancer 2007; 7: 800-808.

[35] Choi JA, Lee JW, Kim H, Kim EY, Seo JM, Ko J and Kim JH. Pro-survival of estrogen receptor-negative breast cancer cells is regulated by a BLT2-reactive oxygen species-linked signaling pathway. Carcinogenesis 2010; 31: 543-551.

[36] Kim EY, Seo JM, Kim C, Lee JE, Lee KM and Kim JH. BLT2 promotes the invasion and metastasis of aggressive bladder cancer cells through a reactive oxygen species-linked pathway. Free Radic Biol Med 2010; 49: 1072-1081.

[37] Lee JW, Kim GY and Kim JH. Androgen receptor is up-regulated by a BLT2-linked pathway to contribute to prostate cancer progression. Biochem Biophys Res Commun 2012; 420: 428-433.

[38] Seo JM, Cho KJ, Kim EY, Choi MH, Chung BC and Kim JH. Up-regulation of BLT2 is critical for the survival of bladder cancer cells. Exp Mol Me 2011; 43: 129-137.

[39] Seo JM, Park S and Kim JH. Leukotriene B4 receptor-2 promotes invasiveness and metastasis of ovarian cancer cells through signal transducer and activator of transcription 3 (STAT3)-dependent up-regulation of matrix metalloproteinase 2. J Biol Chem 2012; 287: 13840-13849.

[40] Kim H, Choi JA, Park GS and Kim JH. BLT2 up-regulates interleukin-8 production and promotes the invasiveness of breast cancer cells. PLoS One 2012; 7: e49186.

[41] Hennig R, Osman T, Esposito I, Giese N, Rao SM, Ding XZ, Tong WG, Buechler MW, Yokomizo T, Friess H and Adrian TE. BLT2 is expressed in PanINs, IPMNs, pancreatic cancer and stimulates tumour cell proliferation. Br J Cancer 2008; 99: 1064-1073.

[42] Kim GY, Lee JW, Cho SH, Seo JM and Kim JH. Role of the low-affinity leukotriene B4 receptor BLT2 in VEGF-induced angiogenesis. Arterioscler Thromb Vasc Biol 2009; 29: 915-920.

[43] Kim GY, Lee JW, Ryu HC, Wei JD, Seong CM and Kim JH. Proinflammatory cytokine IL-1beta stimulates IL-8 synthesis in mast cells via a leukotriene B4 receptor 2-linked pathway, contributing to angiogenesis. J Immunol 2010; 184: 3946-3954.

[44] Hicklin DJ and Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. J Clin Oncol 2005; 23: 1011-1027.

[45] Park MK, Park Y, Shim J, Lee HJ, Kim S and Lee CH. Novel involvement of leukotriene B (4) receptor 2 through ERK activation by PP2A down-regulation in leukotriene B (4)-induced keratin phosphorylation and reorganization of pancreatic cancer cells. Biochim Biophys Acta 2012; 1823: 2120-2129.

[46] Hiscott J, Kwon H and Genin P. Hostile takeovers: viral appropriation of the NF-kappa B pathway. J Clin Invest 2001; 107: 143-151.

[47] Wan F and Lenardo MJ. The nuclear signaling of NF-kappaB: current knowledge, new insights, and future perspectives. Cell Res 2010; 20: 24-33.

[48] Karin M. Nuclear factor-kappa B in cancer development and progression. Nature 2006; 441: 431-436.

[49] Bours V, Dejardin E, Goujon-Letawe F, Merville MP and Castronovo V. The NF-kappa B transcription factor and cancer: high expression of NF-kappa B- and I kappa B-related proteins in tumor cell lines. Biochem Pharmacol 1994; 47: 145-149.

[50] Grivennikov SI and Karin M. Dangerous liaisons: STAT3 and NF-kappa B collaboration and crosstalk in cancer. Cytokine Growth Factor Rev 2010; 21: 11-19.

[51] DiDonato JA, Mercurio F and Karin M. NF-kappa B and the link between inflammation and cancer. Immunological Reviews 2012; 246: 379-400.

[52] Lin Y, Huang RC, Chen LP, Li SY, Shi Q, Jordan C and Huang RP. Identification of interleukin-8 as estrogen receptor-regulated factor involved in breast cancer invasion and angiogenesis by protein arrays. Int J Cancer 2004; 109: 507-515.

[53] Karashima T, Sweeney P, Kamat A, Huang SY, Kim SJ, Bar-Eli M, McConkey DJ and Dinney CPN. Nuclear factor-kappa B mediates angiogenesis and metastasis of human bladder cancer through the regulation of interleukin-8. Clin Cancer Res 2003; 9: 2786-2797.

[54] Waugh DJJ and Wilson C. The Interleukin-8 Pathway in Cancer. Clin Cancer Res 2008; 14: 6735-6741.

[55] Zhang L, Altuwaijri S, Deng F, Chen L, Lal P, Bhanot UK, Korets R, Wenske S, Lilja HG, Chang C, Scher HI and Gerald WL. NF-kappaB regulates androgen receptor expression and prostate cancer growth. Am J Pathol 2009; 175: 489-499.

[56] Brinkmann AO, Blok LJ, de Ruiter PE, Doesburg P, Steketee K, Berrevoets CA and Trapman J. Mechanisms of androgen receptor activation and function. J Steroid Biochem Mol Biol 1999; 69: 307-313.

[57] Heinlein CA and Chang C. Androgen receptor in prostate cancer. Endocr Rev 2004; 25: 276-308.

[58] Cohen MB and Rokhlin OW. Mechanisms of Prostate Cancer Cell Survival After Inhibition of AR Expression. J Cell Biochem 2009; 106: 363-371.

[59] Aggarwal BB, Kunnumakkara AB, Harikumar KB, Gupta SR, Tharakan ST, Koca C, Dey S and Sung B. Signal transducer and activator of transcription-3, inflammation, and cancer: how intimate is the relationship? Ann N Y Acad Sci 2009; 1171: 59-76.

[60] Buettner R, Mora LB and Jove R. Activated STAT signaling in human tumors provides novel molecular targets for therapeutic intervention. Clin Cancer Res 2002; 8: 945-954.

[61] Yu H, Pardoll D and Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. Nat Rev Cancer 2009; 9: 798-809.

[62] Yue P, Zhang X, Paladino D, Sengupta B, Ahmad S, Holloway RW, Ingersoll SB and Turkson J. Hyperactive EGF receptor, Jaks and Stat3 signaling promote enhanced colony-forming ability, motility and migration of cisplatin-resistant ovarian cancer cells. Oncogene 2012; 31: 2309-2322.

[63] Colomiere M, Ward AC, Riley C, Trenerry MK, Cameron-Smith D, Findlay J, Ackland L and Ahmed N. Cross talk of signals between EGFR and IL-6R through JAK2/STAT3 mediate epithelial-mesenchymal transition in ovarian carcinomas. Br J Cancer 2009; 100: 134-144.

[64] Xie TX, Wei D, Liu M, Gao AC, Ali-Osman F, Sawaya R and Huang S. Stat3 activation regulates the expression of matrix metalloproteinase-2 and tumor invasion and metastasis. Oncogene 2004; 23: 3550-3560.

[65] Landen CN Jr, Lin YG, Armaiz Pena GN, Das PD, Arevalo JM, Kamat AA, Han LY, Jennings NB, Spannuth WA, Thaker PH, Lutgendorf SK, Savary CA, Sanguino AM, Lopez-Berestein G, Cole SW and Sood AK. Neuroendocrine modulation of signal transducer and activator of transcription-3 in ovarian cancer. Cancer Res 2007; 67: 10389-10396.

[66] Lee JK, Edderkaoui M, Truong P, Ohno I, Jang KT, Berti A, Pandol SJ and Gukovskaya AS. NADPH oxidase promotes pancreatic cancer cell survival via inhibiting JAK2 dephosphorylation by tyrosine phosphatases. Gastroenterology 2007; 133: 1637-1648.

[67] Trachootham D, Lu W, Ogasawara MA, Nilsa RD and Huang P. Redox regulation of cell survival. Antioxid Redox Signal 2008; 10: 1343-1374.

[68] Wu WS. The signaling mechanism of ROS in tumor progression. Cancer Metastasis Rev 2006; 25: 695-705.

[69] Kim C, Ryu HC and Kim JH. Low-dose UVB irradiation stimulates matrix metalloproteinase-1 expression via a BLT2-linked pathway in HaCaT cells. Exp Mol Med 2010; 42: 833-841.

[70] Wei JD, Kim JY and Kim JH. BLT2 phosphorylation at Thr(355) by Akt is necessary for BLT2-mediated chemotaxis. Febs Letters 2011; 585: 3501-3506.

[71] Malumbres M and Barbacid M. To cycle or not to cycle: A critical decision in cancer. Nat Rev Cancer 2001; 1: 222-231.

[72] Cho KJ, Seo JM, Lee MG and Kim JH. BLT2 Is upregulated in allergen-stimulated mast cells and mediates the synthesis of Th2 cytokines. J Immunol 2010; 185: 6329-6337.

[73] Ryu HC, Kim C, Kim JY, Chung JH and Kim JH. UVB radiation induces apoptosis in keratinocytes by activating a pathway linked to "BLT2-reactive oxygen species". J Invest Dermatol 2010; 130: 1095-1106.

[74] Lee JW, Ryu HC, Ng YC, Kim C, Wei JD, Sabaratnam V and Kim JH. 12 (S)-Hydroxyheptadeca-5Z, 8E, 10E-trienoic acid suppresses UV-induced IL-6 synthesis in keratinocytes, exerting an anti-inflammatory activity. Exp Mol Med 2012; 44: 378-386.