Leukotrienes and Inflammation –A Review

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Abstract

Leukotrienes, together with the prostaglandins and other related compounds, are derived from 20 carbon (eicosa) fatty acids that contain double bonds (enoic). Hence this group of substances is called the eicosanoids. The name leukotriene derives from the original discovery of these substances in white blood cells (polymorphonuclear leucocytes) and the fact that they all have in common 4 double bonds (hence the 4 subscript), 3 of which are in a conjugated triene structure. Leukotrienes do not exist preformed in cells. They are formed from the breakdown of arachidonic acid, a polyunsaturated 20 carbon fatty acid. In its esterified form, arachidonic acid is bound to the phospholipids of the cell membranes. Both immunological and non-immunological stimuli can release arachidonic acid from membrane phospholipids by activating phospholipase A_2. The glucocorticosteroid drugs can inhibit phospholipase A_2 and thereby decrease the production of all the leukotrienes and hence leukotriene-mediated responses. Generally, inflammation leads to vasodilation, vascular hyperpermeability, increased blood flow and recruitment of leukocytes to inflamed sites. These events cause enhanced production of cytokines, chemokines, chemical mediators and lipid mediators such as LTs and prostaglandins. Acute inflammation occurs over a short time (seconds, minutes and hours). In contrast, chronic inflammation is a long-lasting inflammatory and immune response that occurs over months to years and results in diverse diseases including asthma, allergies, atherosclerosis, arthritis, obesity, cancer and other age-related diseases such as AMD. In this review article we aimed to highlight the evidence that implicates LTs in physiological function and also in disease processes.

Keywords – *Leukotrienes, Inflammation, Cardiovascular Disease, Asthma, Rheumatoid Arthritis.*

Introduction

The name "leukotriene" is referring to the cellular source (leukocytes are one of the major sources) as well as the conjugated triene that characterizes their structure. Lipid mediators, which denote bioactive mediators derived from lipids, play roles in immune regulation, self-defense, and the maintenance of homeostasis in living systems. They include prostaglandins (PGs) and leukotrienes (LTs), lysophospholipids (including sphingosine 1-phosphate), and endocannabinoids. Leukotrienes, together with prostaglandins, thromboxanes, and lipoxins, are the major constituents of a group of biologicallyactive oxygenated fatty acids known as eicosanoids [1] and constituent family of lipid mediators with potent biological activities.[2] Because myeloid cells contain substantial amounts of esterified arachidonic acid (AA)[3] and constitutively express all of the enzymes necessary to hydrolyze it and metabolize it via the5- lipoxygenase (5-LO) pathway, they are capable of generating large quantities of products termed leukotrienes (LTs) within seconds to minutes after encountering an activating stimulus. The systemic name of arachidonic acid is 5,8,11,14- eicosatetraenoic acid, symbolized as C20:4, indicating a total of 20 carbons (twenty in greek is eicosi) and presence of four

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doubal bonds at the indicated positions.[4] LTs, which are derived from arachidonic acid (5Z,8Z,11Z,14Z-eicosatetraenoic acid; AA) through two steps catalyzed by 5-lipoxygenase (5-LO), are inflammatory mediators that function in normal host defense and play roles in inflammatory diseases.[5,6] Leukotrienes (LTs) are short-lived lipid mediators, which act in an autocrine and paracrine manner. They can be subdivided into two groups: the first group is represented by leukotriene B4 (LTB4) alone. The second group is constituted by the cysteinyl leukotrienes (cys-LTs), namely leukotriene C4 (LTC4), leukotriene D4 (LTD4) and leukotriene E4 (LTE4).[7,8]

Inflammation is the response of living tissue to damage. The inflammatory process is the reaction of blood vessel, which brings about an accumulation of fluid and white blood cell in the extravascular tissue.1 The acute inflammatory response has functions of destroying and eliminating the components of exudate. The damaged tissue can be broken down and partially liquefied, and the debris removed from the site of damage.[9]1 Inflammation is caused by release of chemicals from tissues and migrating cells after injury. Most strongly implicated are the prostaglandins (PGs), leukotrienes (LTs), histamine, bradykinin, more recently, platelet activating factor (PAF) and interleukin-1 and other various mediators.[10]

DISEASES THAT HAVE ROLE OF LEUKOTRIENE

Allergic diseases: Asthma, Allergic rhinitis, Rhino sinusitis, Atopic dermatitis, Urticaria, Allergic fungal sinusitis.

Fibrotic diseases: Airway remodeling in asthma, Bronchiolitis obliterans after lung transplantation, Idiopathic pulmonary fibrosis, Scleroderma, Asbestosis.

Other pulmonary syndromes: Acute lung injury or adult respiratory distress syndrome, Viral bronchiolitis, Obstructive sleep apnea, Chronic obstructive pulmonary disease, Cystic fibrosis and other forms of bronchiectasis, Bronchopulmonary dysplasia.

Other local inflammatory diseases: Arthritis (including osteoarthritis and gout), Glomerulonephritis, Interstitial cystitis, Psoriasis, Inflammatory bowel disease.

Systemic inflammatory diseases: Rheumatoid arthritis, Vasculitides (systemic lupus erythematosus, Churg–Strauss syndrome, Henoch–Schonlein purpura), Transplant rejection.

Cancer: Solid tumors (including melanoma, mesothelioma, and pancreatic, lung, esophageal, prostate, and colon cancers), Leukemias, Lymphomas, etc.

Cardiovascular disease: Atherosclerosis, Aortic aneurysm, Sickle cell crisis, Ischemia–reperfusion injury, Pulmonary arterial hypertension, Sepsis.[11,12]

Biosynthesis of Leukotrienes

In response to a hormonal or other stimulus a specific phospholipase-A2 present in most types of cells attacks membrane phospholipids releasing arachidonic acid. Phospholipase-A2 is specific for the carbon-2 position of the phospholipids, to which arachidonic acid is attached. After the release of arachonic acid is released into the cytosol, it can follow on of the 2 pathways. One is cyclooxygenease pathway (Produces prostaglandins and thromboxanes), and other is Lipooxygenease pathway (Produces Leukotrienes).

Lipooxygenease Pathway For Synthesis of Leukotrienes.

Lipooygenease catalyzes the addition of a single oxygen molecule in the arachidonic acid to form Hydroperoxyeicosatetraenoic acids (HPETEs). Three Lipooxygenases are present in human cells-5-Lipooxygenase, 12-Lipooxygenase and 15-Lipooxygenase. They operate in same manner but insert the oxygen at different places in the arachidionic acid chains. Different cells contains different lipooxygenease, like 5-Lipooxygenase is rich in Neutrophil and leukocytes. Platelets are rich in 12-lipooxygenase. Eosinophil leukocytes are rich in 12-lipooxygenase. Only 5-lipooxygenase forms leukotrienes and they are present in leukocytes and converts arachidonic acid to 5-hydroxyperoxyeicosatetraenoic acid. This is converted to leukotriene-A4, the precursor of other leukotrienes.[13]

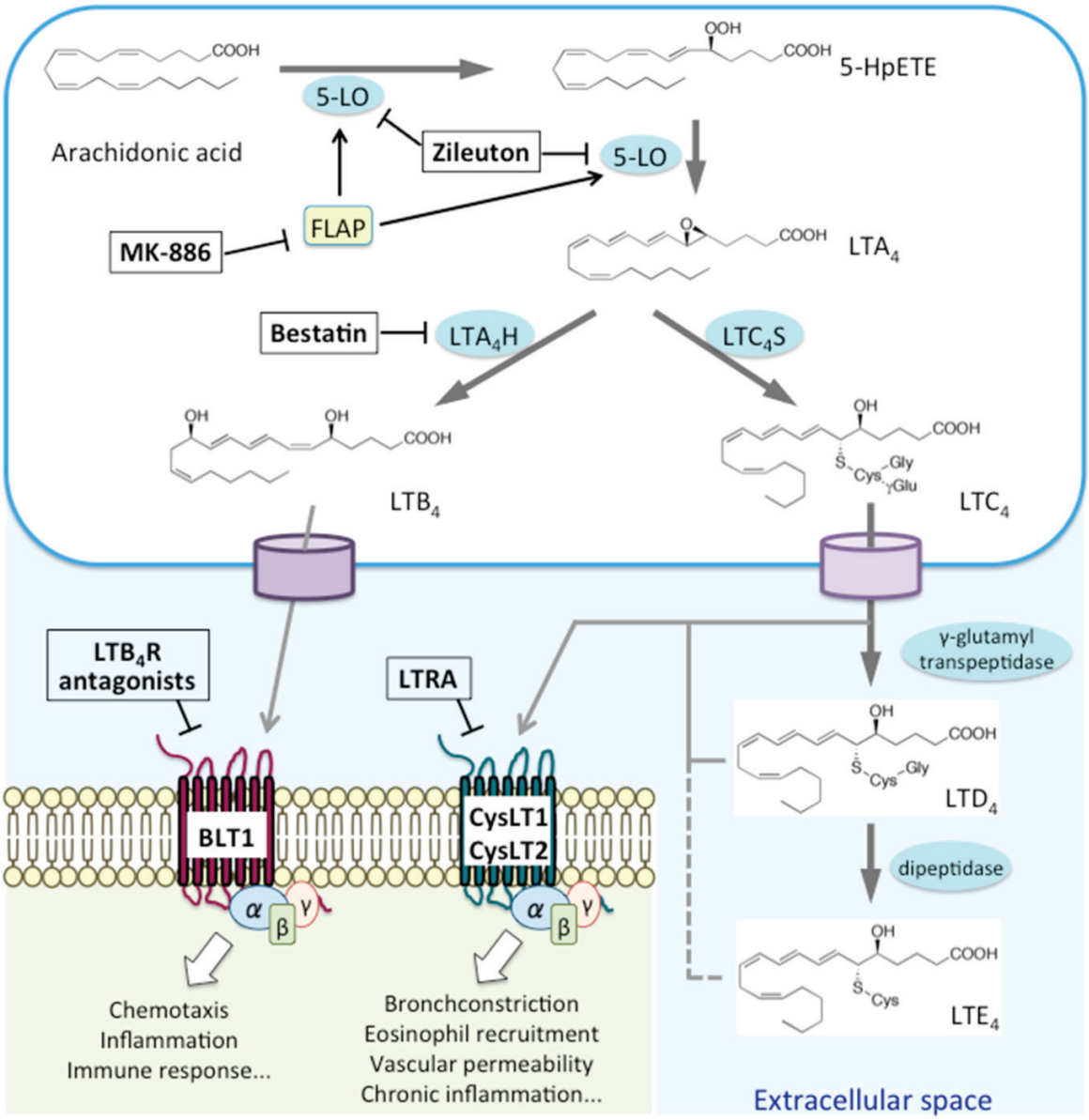

Figure 1- Receptors and Biosynthetic pathway of Leukotrienes[14]

Source of Figure - Jo-Watanabe A, Okuno T, Yokomizo T. The role of leukotrienes as potential therapeutic targets in allergic disorders. International journal of molecular sciences. 2019 Jan;20(14):3580.

Mechanism

Leukotrienes exert their effects in an autocrine or paracrine manner by binding receptors. These receptors are G protein-coupled (GPCR) receptors that activate a G protein once it is bound. Either the Gq protein, which leads to increases in intracellular calcium, is activated by leukotriene receptors, or the Gi protein, which leads to decreases in intracellular cAMP. A cascade of kinase reactions is then signalled by each of these G proteins, leading to changes in both transcriptional activity and cellular motility. There are both typical and distinctive effects of the various forms of leukotriene. In general, LTB and cysteinyl leukotrienes exert various effects across different receptor binding groups.LTB binds to receptors 1 and 2 (BLT1 and BLT2) of B leukotriene, respectively. Most importantly, LTB functions as a potent chemotactic neutrophil receptor. This activity highlights the inflammatory propellant aspect of leukotrienes, as the main LTB products are also neutrophils. Cysteinyl leukotrienes bind to cysteinyl leukotriene receptors type 1 and type 2 (cysLT1 and cysLT2), respectively). Airway

shifts, including bronchoconstriction, airway edema, and mucus secretion, are mainly regulated by cysLT1. On the other side, cysLT2, as it evokes increases in vascular permeability and tissue fibrosis but has no effect on the airways, is primarily an inflammatory stimulator. It is worth noting that increases in vascular permeability induced by leukotriene are 3 to 4 times more potent than histamine.[15]

Sites of Leukotrienes Biosynthesis

The cellular distribution of the enzymes regulating each stage of the biosynthetic pathway determines the locations in which the leukotrienes are synthesised. The distribution of 5-lipoxygenase is restricted to a specific number of myeloid cells: neutrophils, eosinophils, monocytes, macrophages, mast cells, basophils, and B lymphocytes. The distribution of 5-lipoxygenase is limited to a specific number of myeloid cells: neutrophils, eosinophils, monocytes, macrophages, mast cells, basophiles, and B lymphocytes. Most of these cells, with the exception of human monocytes and macrophages, contain large amounts of either LTB4 or LTC4, but not both. All other cells known as leukotriene secretors have been shown to almost exclusively release either LTB4 or C4.Neutrophils have been shown to synthesise significant quantities of LTB4, possessing 5-LO and LTA4-hydrolase, whereas eosinophils and mast cells preferentially synthesise LTC4, according to the presence within these cells of 5-LO and LTC4-synthase.[16,17]

Leukotrienes Receptors

The LTC4, LTD4, and LTE4 cysteinyl leukotrienes are lipid inflammation mediators that function through two G protein-coupled receptors (GPCRs), type 1 cysteinyl leukotriene receptor (CysLT1R) and type 2 (CysLT2R)1. Although LTD4 is CysLT1R2's preferred endogenous ligand, CysLT2R responds to LTC4 and LTD43 similarly. CysLTRs have bronchoconstrictive and pro-inflammatory effects and are also considered to play a role in asthma, allergic rhinitis, cardiovascular disease and cancer.Several selective CysLT1R antagonists have been approved as antiasthmatic drugs, such as zafirlukast, pranlukast, and montelukast, but a significant fraction of patients do not respond to this therapy. In physiology and pathology, the various expression profiles, tissue distribution, and endogenous ligand sensitivity for CysLTRs, their heterodimerization and cross-regulation, as well as the prevalence of asthma-associated polymorphisms in CysLT2R suggest different functions for each receptor subtype. On the basis of an animal asthma model induced by LTC4, it was proposed that CysLT2R-selective or dual antagonists can improve treatment of cases of severe asthma.[18]

Cysteinyl leukotrienes

Bioconversion of LTC4 into LTD4 and LTE4 does not seem to be a catabolic inactivation because for most biological activities, LTD4 is at least as potent as LTC4, and LTE4 seems to be only marginally less potent. Infusion of radio-labeled LTC4 and LTE4 in ordinary subjects results in rapid bloodstream disappearance along with identification of fractional quantities of LTE4 in the urine within the first 2 hours.[19] Later on, considerable quantities of omega- and betaoxidized LTE4 metabolites are found in urine.[20] A multiple increase in urinary LTE4 excretion reported in patients with severe liver dysfunction indicates that the liver could be the source of CysLT catabolism.[21]

Leukotriene B4

No urinary metabolites of LTB4 have been identified so far, unlike what has been observed for Cys-LTs. In purified polymorphonuclear leukocyte preparations, LTB4 undergoes rapid metabolism to deliver 20-hydroxy LTB4 and 20-carboxy LTB4 .[22] This conversion is catalysed by a particular enzyme called cytochrome P-450, but occurs primarily after the release of intact LTB4 and reuptake by adjacent cells.[23] In view of the decreased biological activity of the 20-carboxy metabolite, omega-oxidation may be a mechanism for the local inactivation of LTB4. On the other hand, in monocytes, eosinophils, and macrophages, this metabolism is not observed, and insufficient evidence exists that it can occur in vivo.

Role of Leukotrienes in Inflammation

Leukotrienes and Cardiovascular Disease

The potential participation of LTs in the production of damage caused by myocardial infarction has been of great concern in recent years. An increased risk of stroke and myocardial infarction (MI) is associated with the genetic variants within the 5-LO pathway; in addition,

the development of CysLTs increases in ischaemia-reperfusion injury in both patients and animal models. LTs are difficult to measure reliably in the blood because of their rapid metabolism and excretion, while elevated plasma concentrations of these mediators have been recorded after acute MI. They affect coronary vascular resistance, infarct size, pulmonary vascular resistance, bronchial tone, and renal vascular resistance directly or indirectly; in addition, they are main inflammatory regulators and thus potential targets to influence healing after MII.[24]

Leukotrienes and Asthma

LTs have been assessed in asthmatic patients' exhaled breath condensate (EBC), sputum, BAL fluid and urine. In patients with asthma, sputum CysLT concentrations are elevated, indicating asthma severity . In patients with asthma, particularly those with nocturnal asthma, LT concentrations are increased in the BAL fluid. Measurement of LTs is likely to indicate pulmonary synthesis of LTs in BAL fluid, sputum and EBC. To test the systemic synthesis of CysLTs, urinary measurement of LTE4, the most abundant CysLT excreted in the urine, is used as circulating concentrations of LTs are normally undetectable. No or only minor variations between healthy and atopic asthmatic subjects in urinary LTE4 concentrations have generally been documented under basal conditions. Urinary LTE4 excretion is elevated in atopic asthmatics after allergen challenge, in aspirin-sensitive asthmatics in nocturnal asthma.[25]

Rheumatoid arthritis and Leukotrienes

Rheumatoid arthritis (RA) is among the most prevalent autoimmune diseases (1-3% worldwide). RA is a prototypic inflammatory disease, characterized by a changed homeostasis state in which immunological stimulation and unwanted inflammation take precedence. The disordered inflammation has painful and deteriorating immediate effects while causing accumulated tissue damage that could contribute to symmetric polyarthritis leading to lifelong discomfort, impairment and shorter life expectancy.[26] LTs are allowed to play an increasingly significant role in the pathophysiology of Inflammatory disorders, particularly those events that occur in this includes activation of leukocytes and control by LTB4 of proinflammatory cytokines and suggests that this The receptor-ligand pair leads to the inflamed joint's recruitment of leukocytes. Leukocytes, immunocomplex, and rheumatoid factor are linked to RA synovium, At the stage of LTB4, and LTs, LTB4 in particular, RA bone remodelling was also involved. Local blood flow is regulated by Proinflammatory PGs and LTB4, Vascular dilation and changes in the permeability required at the Place for adhesion, diapedesis and recruitment of leukocytes. To date, drugs that inhibit 5-LOX have been approved for Diseases of the bones. Provided that LTB4 is also a strong inducer of Migration by neutrophils. In synovium, this effect may have wider functional significance.[27]

Allergic rhinitis and Leukotrienes

CysLTs are synthesised by mast cells and basophils during the early phase of antigen response and by eosinophils and macrophages during the late phase via the 5-lipoxygenase metabolism of arachidonic acid. In patients with allergic rhinitis, the levels of cysLT in nasal secretions are elevated after short-term allergen instillation and in the allergy season. By interacting with receptors, particularly the cysLT1 receptor, on target cells, these lipid mediators function locally and systemically. Evidence obtained from topical application of cysLTs in the nose and from the effects of LTRAs suggests that nasal mucous secretion, congestion, and inflammation are caused by cysLTs.By improving immune responses and the formation, adhesion, migration, and survival of inflammatory cells such as eosinophils, CysLTs promote allergic inflammation. They also increase the generation of a number of other proinflammatory mediators, such as cytokines, which in turn increase the development of cysLTs and receptors. CysLTs fulfil the requirements for relevant allergic rhinitis mediators through their various effects on the structural components of disease that are immune, inflammatory, and local. LTRAs provide a valuable approach to the treatment of this severe and widespread condition by blocking the cysLT1 receptor responsible for most of these symptoms.[28]

Conclusion

Leukotrienes are inflammatory chemicals, they released from body after coming into contact with an allergen. Leukotrienes cause airway muscles to contract and excess mucus and fluid to be created. By binding to unique G-protein-coupled receptors, they exert their biologic effects. In this review article we

aimed to highlight the evidence that implicates LTs in physiological function and also in disease processes.

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