Urinary leukotriene E_4 as a Biomarker of Exposure, Susceptibility and Risk in Asthma

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KEYWORDS

• Urinary leukotriene E_4 • Montelukast • Cysteinyl leukotriene • Second hand smoke

KEY POINTS

- Measurement of urinary LTE_4 ($uLTE_4$) can be a useful noninvasive method to assess changes in the rate of total body cysteinyl leukotriene levels.
- The P2Y12 receptor may be important in mediating LTE_4- related airway inflammation.
- $uLTE_4$ is a biomarker of exposure to both atopic and non-atopic asthma triggers such as air pollution and second hand smoke (SHS).
- High $uLTE_4$ levels may be a marker of increased susceptibility to SHS in children with asthma.
- The ratio of $uLTE_4$ to fractional exhaled nitric oxide is associated with a better response to leukotriene receptor antagonist than to inhaled corticosteroid treatment in children with mild to moderate asthma.

LEUKOTRIENE E_4 SYNTHESIS

Urinary leukotriene E_4 ($uLTE_4$) is a biomarker of total body cysteinyl leukotriene (CysLT) production and excretion. Leukotrienes are a family of lipid mediators derived from arachidonic acid through the 5-lipoxygenase pathway. They are produced by various leukocytes, hence the first part of their name (leuko). The triene part of the name refers to the number (3) of conjugated double bonds (alkenes). The first leukotriene to be synthesized, leukotriene A4 (LTA_4), is formed through the conversion of arachidonic acid, located in membrane phospholipids, to 5-hydroperoxyeicosatetraenoic and LTA_4 through membrane-bound 5-lipoxygenase (5-LO) and 5-lipoxygenase–activating protein (FLAP). The 5-LO inhibitor zileuton blocks this conversion step. In human mast cells, basophils, eosinophils, and macrophages, LTA_4 converts quickly either to LTB_4 (through leukotriene hydrolase) or LTC_4 by LTC_4 synthase with the incorporation of glutathione (g-glutamyl-cysteinyl-glycine). LTC_4 is subsequently converted to LTD_4 and then to the stable end product LTE_4. Because of the incorporation of cysteine, LTC_4, LTD_4, and LTE_4 are called cysteinyl leukotrienes (CysLTs) (**Fig. 1**).[1]

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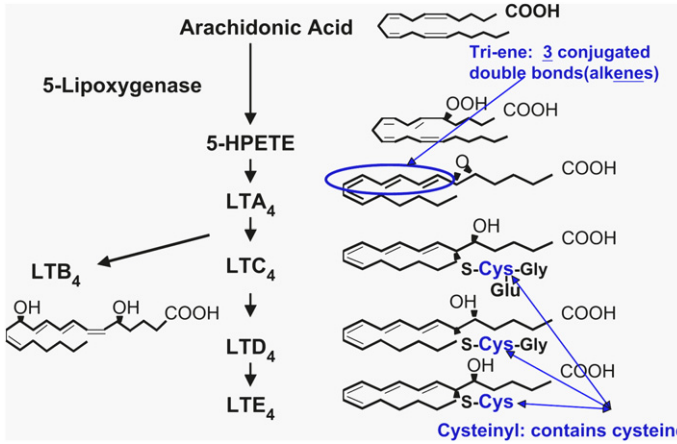

Fig. 1. The major steps in CysLT formation. 5-HPETE, 5-hydroperoxyeicosatetraenoic acid.

CYSTEINYL LEUKOTRIENE RECEPTORS

Both the cysteinyl leukotriene 1 receptor (CysLTR1) and CysLTR2 are constitutively expressed and unregulated in milieus with high cytokine levels.[2–6] CysLTR1 is expressed primarily on blood leukocytes such as monocytes/macrophages, eosinophils, basophils, mast cells, neutrophils, T and B lymphocytes, and on interstitial cells of the nasal mucosa and airway smooth muscle (**Fig. 2**).[3–5] The cellular distribution of CysLTR1 suggests a positive feedback loop because many cells that express CysLT1R also synthesize CysLTs. Leukotriene receptor antagonists (LTRA) such as montelukast block CysLTR1 but not CysLTR2. CysLTR2 is highly expressed in heart

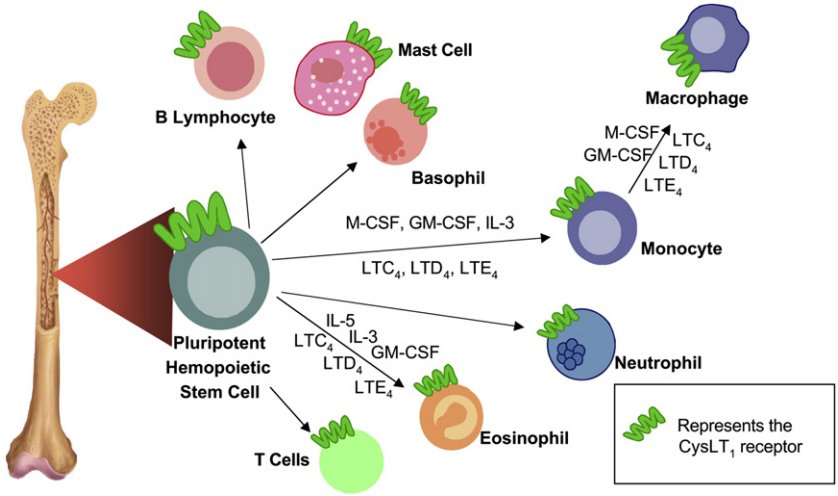

Fig. 2. The wide expression of the CysLT1 receptor on blood leukocytes. GM-CSF, granulocyte-macrophage colony-stimulating factor; M-CSF, macrophage-specific colony-stimulating factor. (*Adapted from* Figueroa DJ, Breyer RM, Defoe SK, et al. Expression of the cysteinyl leukotriene 1 receptor in normal human lung and peripheral blood leukocytes. Am J Respir Crit Care Med 2001;163:232, and Merck Inc; with permission.)