Editorial

Unraveling the complexity of leukotriene and prostaglandin inflammatory signaling

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Cysteinyl leukotrienes are primarily made by inflammatory leukocytes, such as eosinophils, basophils, mast cells, macrophages, and monocytes, through oxidation of arachidonic acid by means of the enzyme 5-lipoxygenase to generate leukotriene (LT) A_4, an unstable intermediary.[1] The enzyme LTC_4 synthase converts LTA_4 to LTC_4 in mast cells, basophils, eosinophils, and monocytes.[1] LTC_4 is exported from the cell and converted to LTD_4 and LTE_4. LTC_4 synthase is expressed in inflammatory leukocytes, endothelial cells, platelets, and lung and vascular smooth muscle cells; however, platelets lack 5-lipoxygenase.[1]

A remarkable cellular communication network exists whereby activated neutrophils overproducing LTA_4 can generate LTC_4 with platelet help, creating a model for LT production in the setting of neutrophil-platelet transcellular conversion and potentially linking multiple inflammatory processes requiring neutrophil and platelet responses.

LT production can subsequently lead to infiltration of biologically active mediators, allergic cell recruitment, and bystander cell activation, which are dependent on cognate receptor activation. LTs are known to bind 5 receptors designated LTB_4 receptor 1 and 2, cysteinyl leukotriene receptor (CysLTR) 1 and 2, and G-protein coupled receptor 99 (GPR99). $CysLT_1R$ binds LTD_4 with greater affinity than LTC_4 and with equal affinity to $CysLT_2R$.

LT blockade with $CysLT_1R$ antagonists provides benefit in the treatment of asthma phenotypes, such as aspirin-exacerbated respiratory disease and exercise-induced asthma, in patients with chronic rhinosinusitis with nasal polyposis and, to a variable degree, in patients with allergic rhinitis.

LTs, along with prostaglandins (PGs), lipoxins, resolvins, and thromboxanes, are downstream molecules to arachidonic acid metabolism.[2] Cross-talk between arachidonic acid metabolite signaling is incompletely understood.

Arachidonic acid released from lipid membranes on cellular activation from cytokines, growth factors, trauma, infection, and inflammation, with the help of COX-1 or COX-2, leads to generation of PGH_2. PGH_2 is subsequently metabolized in a cell-specific pattern into variable metabolites, such as thromboxanes, and PG metabolites, such as PGE_2.[2] PGE_2 can have important effects in modulating inflammation and tissue repair and might contribute to the development of nasal polyps.[3]

PGE_2 can bind 4 prostaglandin E receptors (EP), designated EP1 to EP4. EP3 signaling in response to PGE_2 is primarily coupled to Gαi protein, which decreases cyclic AMP formation.[4,5] In addition to potential treatments for asthma, chronic rhinosinusitis with nasal polyposis, and allergic rhinitis, EP3 receptor antagonists can potentially be used to treat type 2 diabetes mellitus, bladder overactivity, cerebrovascular disease, coronary artery disease, hypertension, neurodegenerative disorders, pain, premature labor, restenosis, and thrombosis.[6]

The article by Kondeti et al[7] in this issue of the *Journal* demonstrates in a mouse model that LTD_4 synergizes with PGE_2 to activate mast cells *in vitro* and vascular inflammation *in vivo* through $CysLT_1R$ and EP3 (Fig 1). The article, through an elegant series of experiments, demonstrates LTD_4-PGE_2 synergy after blockade of $CysLT_1R$ and $CysLT_2R$ and EP1 to EP4. Stimulation experiments with LTD_4 and PGE_2 demonstrate inflammatory gene transcript upregulation of macrophage inflammatory protein 1β, TNF-α, IL-8, and COX-2; increased COX-2 expression; PGD_2 secretion; and enhanced phosphorylation of extracellular signal-regulated kinase, as well as that LTD_4-PGE_2 signals through protein kinase G. This article revealing extracellular signal-regulated kinase–protein kinase G pathway convergence opens up new interesting questions into convergence of the growing complexity of LT-PG synergy. It is interesting to speculate whether this pathway might be antigen independent, given other research on EP3 signaling in mast cells.[8]

The article by Kondeti et al[7] looks at mast cells in a mouse model. Given that human mast cell subsets have different functions, additional research assessing these subsets and other cell types that also signal through $CysLT_1R$ and EP3 could increase the scope of the current findings. Modulation of this pathway is likely, given that other cell types signal through EP3 and LTs.[9] It is unclear how fine tuning of this pathway occurs at the tissue level, given that there are 8 known human splice variants of EP3 versus 3 splice variants in the mouse, as well as splice variants of the enzyme PGE synthase, which is responsible for production of PGE_2.[10]

EP3 can be important in temperature regulation and might play a critical role in islet cell function and reduction of lipolysis in adipose tissue, suggesting overlap between allergic inflammation and a more broad inflammatory pathway involved in other disease states, such as infection response, obesity, and diabetes.[10,11]

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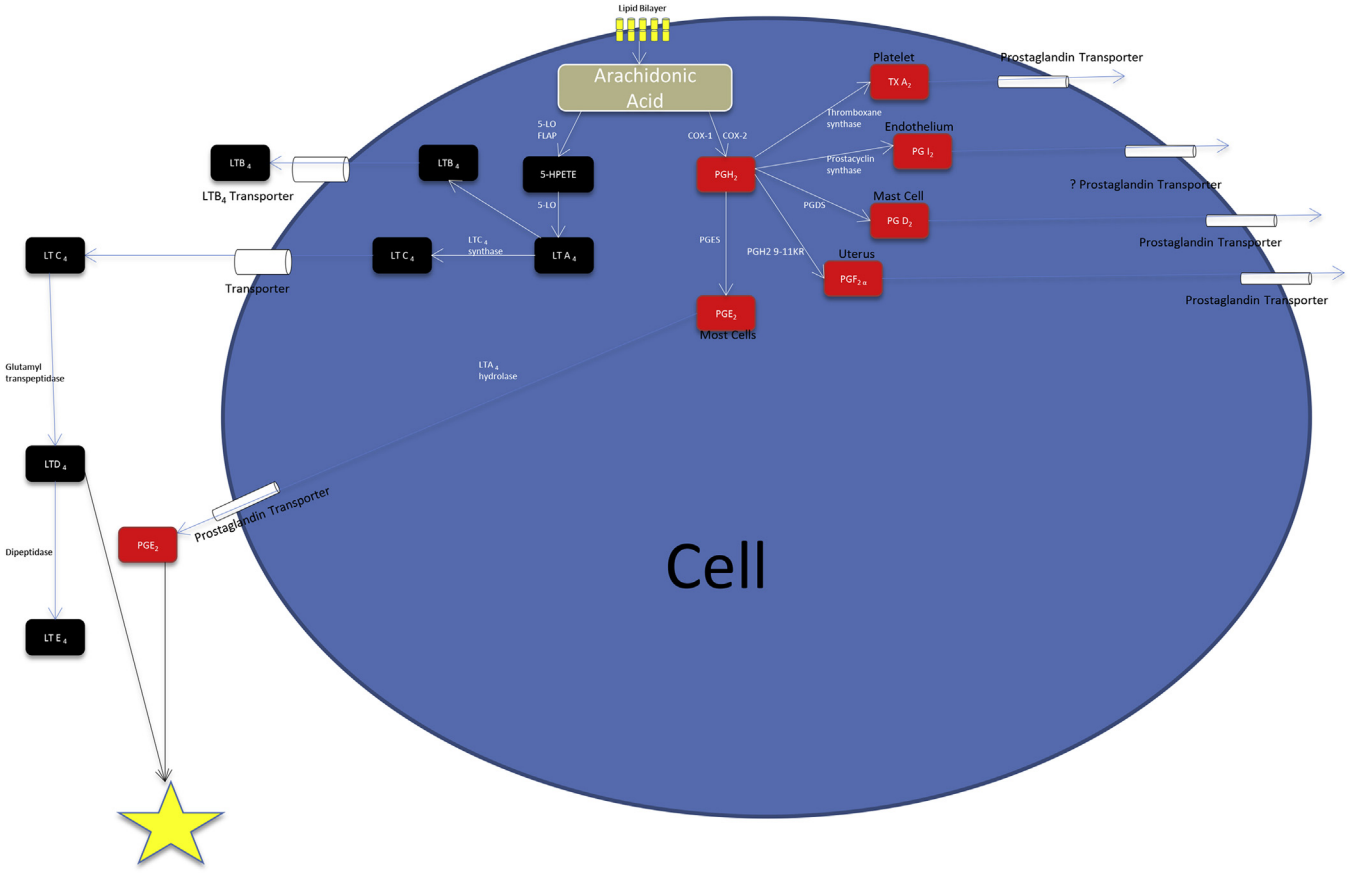

FIG 1. Synergy: mast cell activation, vascular inflammation through $CysLT_1R$, and EP3. *BLT*, Leukotriene B_4 receptor; *FLAP*, 5-lipoxygenase activating protein; *HPETE*, 5-hydroperoxyeicosatetraenoic acid; *5-LO*, 5-lipoxygenase; *LTC4S*, leukotriene C_4 synthase; *PGDS*, prostaglandin D_2 synthase; *PGES*, prostaglandin E synthase; *$PGF_{2\alpha}$*, prostaglandin $F_{2\alpha}$; *PGH2 9-11KR*, prostaglandin H_2 9-11-endoperoxide reductase; *PKG*, protein kinase G; *TXA_2*, thromboxane A_2.

Furthermore, in the setting of allergy, in conjunction with comorbid obesity and diabetes and studies showing a higher disease burden with comorbid conditions, this article provides new insights linking the laboratory with the clinical setting.[12,13] Although this study does not assess physiologic alterations to blocking EP3, further work is necessary to assess potential side effects of blocking this pathway.

The exciting questions that can be raised from this article make it of great interest. A more complete understanding of LT and PG pathways might provide novel therapeutic targets to guide precision health.

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