Role of lipid mediators and control of lymphocyte responses in type 2 immunopathology

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Type 2 immunopathology is a cardinal feature of allergic diseases and involves cooperation between adaptive immunity and innate effector responses. Virtually all cell types relevant to this pathology generate leukotriene and/or prostaglandin mediators that derive from arachidonic acid, express receptors for such mediators, or both. Recent studies highlight prominent functions for these mediators in communication between the innate and adaptive immune systems, as well as amplification or suppression of type 2 effector responses. This review focuses on recent advances and insights, and highlights existing and potential therapeutic applications of drugs that target these mediators or their receptors, with a special emphasis on their regulation of the innate and adaptive lymphocytes relevant to type 2 immunopathology. (J Allergy Clin Immunol 2018;141:1182-90.)

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Asthma, eosinophilic esophagitis (EoE), and chronic rhinosinusitis have become markedly more common in Western societies in the past half century. These diseases all involve end-organ dysfunction caused by persistent activation of the immune system, resulting in eosinophil-rich (type 2) immunopathology. Because these diseases cause substantial morbidity, developing new therapeutics and preventive strategies is a high priority. Such development requires an in-depth understanding of the underlying molecular and cellular mechanisms.

Abbreviations used

AA:	Arachidonic acid
AERD:	Aspirin-exacerbated respiratory disease
BAL:	Bronchoalveolar lavage
CRTH2:	Chemoattractant receptor-homologous molecule expressed on T_H2 cells
cysLT:	Cysteinyl leukotriene
$CysLT_1R$:	Cysteinyl leukotriene receptor type 1
$CysLT_2R$:	Cysteinyl leukotriene receptor type 2
$CysLT_3R$:	Cysteinyl leukotriene receptor type 3
DC:	Dendritic cell
DP:	D prostanoid
EoE:	Eosinophilic esophagitis
EP:	E-prostanoid receptor
EpC:	Epithelial cell
GPCR:	G protein–coupled receptor
5-HETE:	5-Hydroxytetraenoic acid
hPGDS:	Hematopoietic prostaglandin D synthase
ILC2:	Group 2 innate lymphoid cell
IP:	I prostanoid
5-LO:	5-Lipoxygenase
LT:	Leukotriene
LTC_4S:	Leukotriene C_4 synthase
LX:	Lipoxin
mPGES-1:	Microsomal prostaglandin E_2 synthase 1
OVA:	Ovalbumin
PG:	Prostaglandin
TSLP:	Thymic stromal lymphopoietin
TX:	Thromboxane
WT:	Wild-type

Allergic diseases involve prominent contributions from both the innate and adaptive immune systems. Thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 are generated primarily by barrier epithelial cells (EpCs) and released in the innate response to pathogens, antigens, and local injury (Fig 1). Their expression can also be persistently upregulated with severe disease, resulting in sustained pathology. Of their target cells, group 2 innate lymphoid cells (ILC2s) generate especially large quantities of type 2 cytokines (IL-5, IL-13, and IL-9)[1-3] when stimulated with barrier-derived cytokines,[4] as do mast cells, basophils, and certain populations of T_H2 cells. In mouse models of helminth infection, ILC2s are sufficient to induce mucosal eosinophilia and goblet cell hyperplasia, even in mice lacking adaptive immune systems.[5] Although less is known about the role of ILC2s in human disease, recent studies implicate ILC2s as potentially important sources of type 2 cytokines in patients with asthma, chronic rhinosinusitis, and EoE.[6-8]

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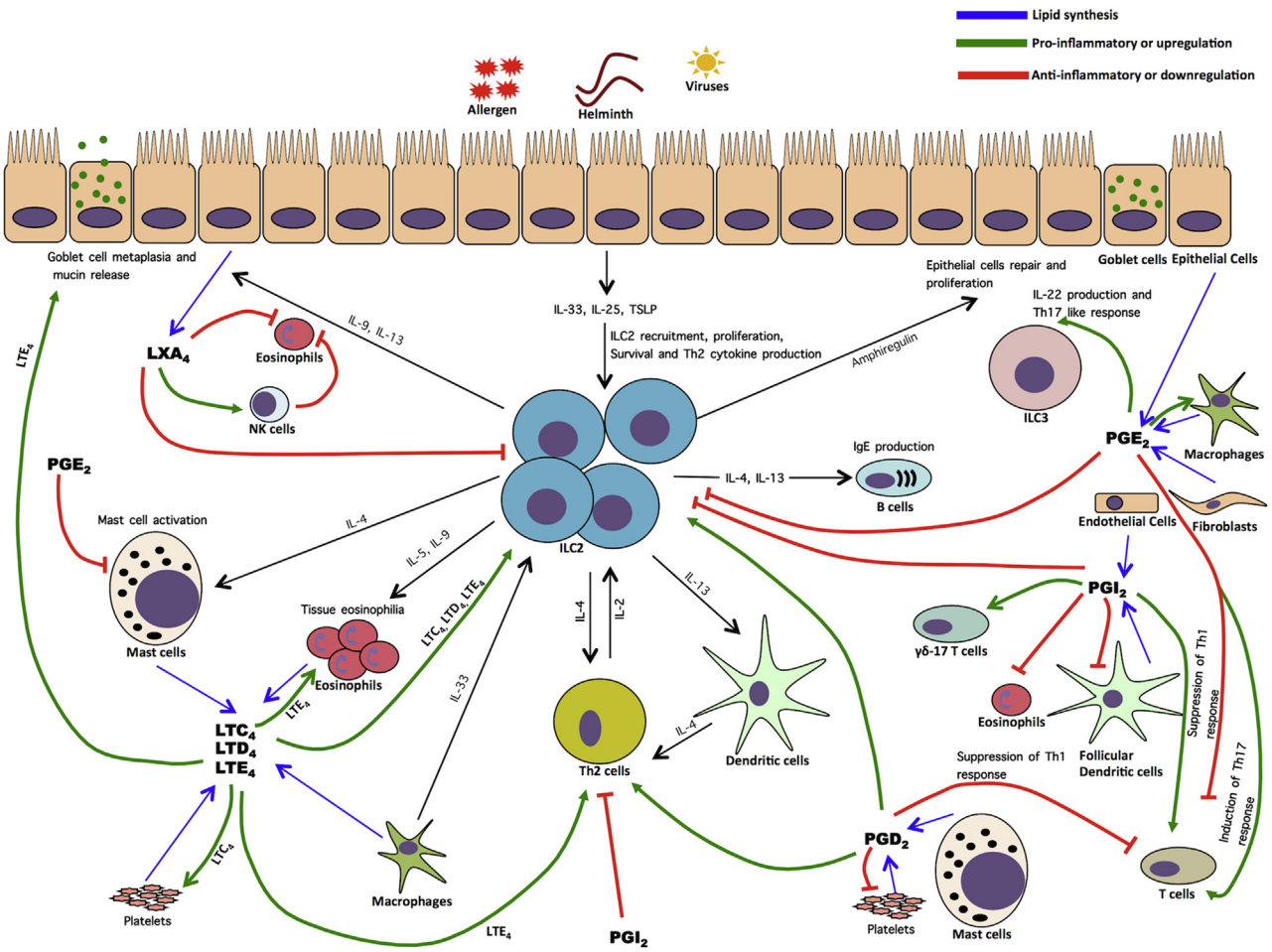

FIG 1. Production and effects of lipid mediators on type 2 inflammation. EpCs release IL-33, IL-25, and TSLP, which activate ILC2s and T_H2 cells and lead to T_H2 cytokine release. CysLTs, generated by mast cells, eosinophils, macrophages, and platelets, act on ILC2s and T_H2 cells. Mast cells and platelets are prime producers of PGD_2, which supports the type 2 response by activating ILC2s and T_H2 cells and suppresses the T_H1 response by inhibiting T-cell production of IFN-γ and IL-2. PGE_2, a product from EpCs, macrophages, and fibroblasts, suppresses activation of ILC2s but also enhances IL-33 synthesis by macrophages and potentiates a T_H17-like effector response from group 3 innate lymphoid cells *(ILC3)* and T cells. PGE_2 also has anti-inflammatory effects because it can block mast cell activation. PGI_2 has mostly anti-inflammatory roles on ILC2s, T_H2 cells, eosinophils, and follicular DCs. LXA_4 can also modulate the type 2 immune response by suppressing PGD_2-derived activation of ILC2s and promoting eosinophil apoptosis by natural killer *(NK)* cells.

Additionally, a population of conventional human T_H2 cells identified exclusively in subjects with allergic disease display ILC2-like features (including the expression and function of receptors for TSLP, IL-33, and IL-25). These cells, termed pathogenic effector T_H2 cells or "T_H2A" cells have innate-like functions such that they no longer require specific antigen exposure for activation and type 2 cytokine production.[9,10] They might account for the majority of cytokine-producing T cells in patients with allergic disease. Thus the mechanisms that control innate and adaptive lymphoid effectors, both positively and negatively, carry not only pathobiological significance but also potential therapeutic implications, especially in patients with severe disease.

Lipid mediators derived from arachidonic acid (AA) play substantial roles in the control of ILC2 and T_H2 cell function. AA is stored in membrane phospholipids and released at high levels on cell activation. AA is metabolized to prostaglandins (PGs), leukotrienes (LTs), and other bioactive mediators through specific synthetic enzyme pathways.[2,11] AA-derived bioactive lipids have receptor-specific inductive and suppressive effects that can influence the duration and magnitude of the immunopathology and end-organ dysfunction. This carries the potential for lipid mediator–targeted therapies to substantially affect allergic diseases.[12-15]

This review will cover our current understanding of the proinflammatory and anti-inflammatory functions of AA-derived lipids, their cells of origin, and their receptors. Although many cell types (including mast cells, basophils, and eosinophils) relevant to type 2 immunopathology express these receptors, we will focus primarily on the effects of lipid mediators on ILC2s and T_H2 cells, as well as their upstream cytokine sources, where applicable, because of the recent increase in published literature on this subject.