Eosinophils are effector cells that migrate toward several mediators released at inflammatory sites to perform their multiple functions. The mechanisms driving eosinophil selective accumulation in sites of allergic inflammation are well-established and involve several steps controlled by adhesion molecules, priming agents, chemotactic, and activating factors. Even though the majority of studies focused on role of protein mediators like IL-5 and eotaxins, lipid mediators also participate in eosinophil recruitment and activation. Among the lipid mediators with distinguish eosinophil recruitment and activation capabilities are platelet activating factor and the eicosanoids, including leukotriene B4, cysteinyl leukotrienes, and prostaglandin D2. In this review, we focused on the role of these four lipid mediators in eosinophil recruitment and activation, since they are recognized as key mediators of eosinophilic inflammatory responses.

**Keywords:** eosinophil, chemotaxis, lipid mediators, prostaglandins, leukotrienes

Eosinophils are nowadays considered as multifunctional cells that have long been associated with allergy and parasitic infections. They are immunomodulatory cells that participate both in innate and adaptive immune response via expression of various receptors and secretion of a variety of mediators. To perform their functional activities, first eosinophils must migrate to sites of inflammatory reaction. Over the last years, a number of mediators and receptors involved in the regulation of eosinophil recruitment have been identified. Besides adhesion molecules and cytokines, eosinophil mobilization is mostly coordinated by a broad range of bioactive mediators known as chemokines. These molecules are an increasing family of small proteins with common structural motifs that via activation of their specific receptors play an important role not only in selective recruitment of eosinophils but also in subsequent eosinophil activation in sites of eosinophilic inflammation. Even though the main efforts in this research area are directed toward peptidic mediators, like chemokines, a growing body of data has unveiled key functional activities, first eosinophils must migrate to sites of inflammatory focus is a critical stage in the processes of chronic inflammation that affect, for instance, asthmatic airways. Eosinophilia is a classical feature of allergic inflammatory responses, therefore regulation of eosinophil migration to the inflammatory focus is a critical stage in the processes of chronic inflammation that affect, for instance, asthmatic airways. Eosinophilic recruitment into the tissues after immune or chemical stimuli requires the production of chemoattractants by several cells such as macrophages, mast cells, or lymphocytes. Briefly, local increase in the secretion of eosinophilostatic molecules, leads to eosinophil adhesion to the endothelium through interaction with selectins expressed on the vascular endothelium followed by firm adhesion through interaction with integrins. Subsequent transmigration through the endothelial cell monolayer is followed by chemotaxis in the tissue, a process known to be largely controlled by chemokines such eotaxin-1, 2, 3, and RANTES and their specific receptors, especially CCR3 (Simson and Foster, 2000). However, both in vivo and in vitro, eosinophils

**HOW DO LIPID MEDIATORS IMPACT EOSINOPHIL MIGRATION?**

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also migrate toward different factors distinct from chemokines such as C5a (Klebanoff et al., 1977), interleukin-5 (IL-5; Wang et al., 1989), granulocyte-macrophage colony-stimulating factor (GM-CSF; Scocer et al., 1990), and lipid mediators. Indeed, AA metabolites as leukotrienes and prostaglandins (PGs), as well as, platelet activating factor (PAF) are considered major players in the pathogenesis of asthma and other forms of allergic inflammation, in part because they control eosinophil influx and activation. Within a variety of cell types, phospholipase A$_2$-driven AA mobilization followed by the oxidative metabolism of free AA mediated by either two cyclooxygenases (COX; PGH synthase) or a family of lipoxygenase (LO) enzymes culminate with the generation of bioactive lipid mediators with roles in eosinophilic inflammation. Specifically concerning those with ability to elicit eosinophil recruitment, newly synthesized lipid mediators may comprise:

**LEUKOTRIENES $\text{LT}_4$**

Leukotriene $\text{LT}_4$ ($\text{LT}_{4\alpha}$) is a lipid mediator with potent chemoattractant properties that is rapidly generated from activated innate immune cells such as neutrophils, macrophages, and mast cells. Elevated levels of $\text{LT}_{4\alpha}$ have been reported in various allergic diseases and those levels have been related to disease activity and eosinophilia (O’Driscoll et al., 1984; Wardlaw et al., 1989; Shindo et al., 1993). $\text{LT}_{4\alpha}$ can bind to two highly conserved G protein-coupled receptors (GPCRs), $\text{LT}_{4\alpha}$ receptor 1 (BLT1) and the considered low-affinity BLT2 (Toda et al., 2002; Yokomizo, 2011). $\text{LT}_{4\alpha}$ serves as a potent chemoattractant through ligation of BLT1 on target cells. Expression and function of BLT$_1$ receptors on eosinophils remained for long time controversial, in part because $\text{LT}_{4\alpha}$-driven activity seemed to have some selectivity toward neutrophils. However, while strong demonstration of BLT$_1$ expression in human eosinophils is still pending, functional assays using LT$_{4\alpha}$ as agonist and specific BLT$_1$ antagonists have provided evidences of expression of active BLT$_1$ on human eosinophils. For instance, it has been shown a BLT$_1$-driven LT$_{4\alpha}$ ability to trigger calcium influx in human eosinophils (Murray et al., 2003a). On the other hand, murine (m)BLTR was cloned while searching for novel chemoattractant receptors in murine eosinophils and demonstrated that it encodes a functional receptor for LT$_{4\alpha}$ which are able to trigger chemotaxis of mouse eosinophils (Figure 1, left panel; Spada et al., 1997; Huang et al., 1998). Reinforcing both in vitro data and in vivo assays with BLT1 antagonists, in vivo studies using BLT1-deficient mice have confirmed that ligation of BLT1 by LT$_{4\alpha}$ is a key event for recruitment of eosinophils (Tager et al., 2000). However, it is noteworthy that while mouse eosinophils may generate only negligible amounts of LT$_{4\alpha}$, human eosinophils are not LT$_{4\alpha}$ producers, representing major cellular sources of cysteinyl LTs (Wellner et al., 1983). Based on the prominent eosinophil feature of recurrently depend on autocrine/paracrine stimulation to regulate their own functions, it seemed to be potentially more important the role of cysteinyl LTs in inducing eosinophilic responses, including autocrine/paracrine roles in induction of eosinophil chemotaxis and activation.

**CYSTEINYL LEUKOTRIENES**

Leukotriene C$_4$ and its extracellular derivatives LT$_{D4}$ and LT$_{E4}$ have many well recognized actions as mediators of allergic response, causing bronchoconstriction, mucous hypersecretion, increased microvascular permeability, and bronchial hyperresponsiveness. Additional but not as well-established effect is the ability of cysteinyl LTs to control eosinophil activities, including those related to tissue infiltration. Involvement of cysteinyl LTs in eosinophil influx is an in vivo phenomenon which was firstly demonstrated in guinea-pigs (Chan et al., 1990), but also observed in human (Laitinen et al., 1993) and reinforced by the anti-allergic effects of CysLT1 antagonists which, in addition to inhibiting allergic symptoms, also inhibit eosinophil recruitment during airway allergic inflammation (Peters-Golden, 2008). Even though cysteinyl LTs display negligible eosinophilic atactic activity in vitro (Figure 1, left panel; Fregonese et al., 2002), cysteinyl LTs contribute to several mechanisms involved in mouting tissue inflammatory response, including autocrine/paracrine stimulation to regulate their own functions, and paracrine roles in induction of eosinophil chemotaxis and activation.

![Figure 1](image-url)

**Figure 1** Schematic mechanisms of LTB$_4$, LTC$_4$, PAF, or PGD$_2$-induced eosinophil chemotaxis and LTC$_4$ synthesis. Left eosinophil scheme displays the ability of the four lipid mediators to trigger eosinophil chemotaxis by activating receptor-mediated distinct intracellular signaling. In contrast, the right eosinophil scheme shows that only PGD$_2$ and PAF are capable of activating LTC$_4$ synthesizing machinery, yet again by eliciting distinct signaling, but both by a lipid body-dependent mechanism. The right scheme also illustrates that both leukotrienes LT$_{B4}$ and LT$_{C4}$, even thought activate their specific receptors in eosinophils (see left panel), failed to trigger lipid body biogenesis or LTC$_4$ synthesis. In vivo studies using BLT1-deficient mice have confirmed that ligation of BLT1 by LT$_{4\alpha}$ is a key event for recruitment of eosinophils (Tager et al., 2000). However, it is noteworthy that while mouse eosinophils may generate only negligible amounts of LT$_{4\alpha}$, human eosinophils are not LT$_{4\alpha}$ producers, representing major cellular sources of cysteinyl LTs (Wellner et al., 1983). Based on the prominent eosinophil feature of recurrently depend on autocrine/paracrine stimulation to regulate their own functions, it seemed to be potentially more important the role of cysteinyl LTs in inducing eosinophilic responses, including autocrine/paracrine roles in induction of eosinophil chemotaxis and activation.
PLATELET ACTIVATING FACTOR

One major chemotactant for eosinophils is the ether-linked phospholipid, PAF. PAF (1-O-alkyl)-2-acetyl-sn-glycero-3-phosphocholine is another potent lipid mediator synthesized by a range of cell types, including monocytes/macrophages, mast cells, platelets, neutrophils, endothelial cells as well as eosinophils. PAF is capable of eliciting both chemokinetic and chemotactic activity in vitro and triggering eosinophil influx and accumulation in vivo (Wardlaw et al., 1986; Kuma et al., 1988; Martins et al., 1989; Kato et al., 2004). Acting via a single class of identified receptor – named PAFR – a seven-trans-membrane G protein-coupled receptor, PAF evokes not only migration-related activities but also a variety of eosinophilic functional responses (Grigg, 2012). Of note, while it became more and more clear that human and mouse eosinophils shared profound dissimilarities (Lee et al., 2012), both express functional active PAFR which mediates eosinophilic activity of PAF in human and mouse cells by a pertussis toxin (PTX)-sensitive manner. Several studies have collectively unveiled that PAF-induced eosinophil chemotaxis, and although still controversial, it is now recognized that eosinophilic responses triggered by PAF depend on activation of mitogen-activated protein (MAP) kinases, while upstream signaling events are regulated by activation of phosphoinositide 3-kinase (PI3K; Xue et al., 2007). Eosinophils co-express both the classic PI3K (Monneret et al., 2001). Whilst DP1 is coupled to Gαs protein and signals through elevation of intracellular levels of cyclic adenosine monophosphate (cAMP), DP2 is coupled to Gαi and its activation leads to elevation of intracellular calcium, reduction in cAMP (Sawyer et al., 2002) and downstream activation of PKC (Xue et al., 2007). Eosinophils co-express both the classical DP1 receptors coupled to adenyl cyclase, as well as, PTX-sensitive DP2 (Monneret et al., 2001).

PROSTAGLANDIN D2

Prostaglandin D2 has emerged as a key mediator of allergic diseases such as asthma (Matsuoka et al., 2008), in part due to its now well-characterized ability to promote eosinophil chemotaxis and activation (Powell, 2003). PGD2-driven cellular functions are all mediated by high-affinity interaction with two receptors, namely D prostaglandin receptor 1 (DP1) and chemotactractant receptor-homologous molecule expressed on T helper type 2 cell (TH2) cells (CRTh2, also known as DP1). Whilst DP1 is coupled to Gαs protein and signals through elevation of intracellular levels of cyclic adenosine monophosphate (CAMP), DP2 is coupled to Gαi and its activation leads to elevation of intracellular calcium, reduction in cAMP (Sawyer et al., 2002) and downstream activation of PKC (Xue et al., 2007). Eosinophils co-express both the classical DP1 receptors coupled to adenyl cyclase, as well as, PTX-sensitive DP2 (Monneret et al., 2001).

Prostaglandin D2-mediated eosinophilic effect is due to direct activation of the DP1 receptor expressed on eosinophil surface (Monneret et al., 2003). Several pharmacological studies have collectively unveiled that PGD2-driven eosinophil chemotaxis may be determined by a balance between opposing downstream signaling pathways: cAMP-dependent inhibitory DP1 versus prevailing stimulatory DP2 intracellular effects (Monneret et al., 2003; Ulven and Kostenis, 2006; Sandig et al., 2007). However, further studies appear to be still needed to fully explain PGD2 mechanisms of actions, since recently it has been shown that DP1 and DP2 may form heteromers representing a distinct functional signaling unit on eosinophil membrane with non-changed ligand-binding features (Sedej et al., 2012). In fact, these are not the first findings showing the ability of DP2 receptors to amplify the biological response to DP1 activation in eosinophils (Mesquita-Santos et al., 2011). However, further studies appear to be still needed to fully explain PGD2 mechanisms of actions, since recently it has been shown that DP1 and DP2 may form heteromers representing a distinct functional signaling unit on eosinophil membrane with non-changed ligand-binding features (Sedej et al., 2012).
Eosinophil activation and subsequent mediator secretion may each be susceptible to inhibition. Indeed among different parameters of eosinophil activation, eosinophil secretory activity may represent the most attractive target to development of therapeutical maneuvers. Upon activation, eosinophil may engage both in secretion of pre-formed granule-stored contents, including eosinophil specific toxic proteins, enzymes, cytokines, chemokines, and other bioactive mediators, as well as de novo synthesized/released molecules including oxygen free radicals but prominently lipidic AA-derived mediators. The unique eosinophil pattern of oxidative metabolism of AA generates a specific array of eicosanoids.

Eosinophils can synthesize lipoxin A4 (LXA4) and the aptly named LTB4, cysteinyl LTS, PAF and the recently identified PGD2. However, when properly stimulated, eosinophils prominently synthesise cysteinyl LTS. Of note, eosinophils are a major cellular source of cysteinyl LTS and have been identified as the principal LTc4 synthesize expressing cells in bronchial mucosal biopsies of asthmatic subjects (Bandeira-Melo and Weller, 2003). Hence, much interest in understanding the regulation of eicosanoids formation in eosinophils has focused on the mechanisms that regulate eosinophil cysteinyl LTS formation and release. Briefly, free AA can be metabolized within eosinophils by 5-LO, which is the limiting enzyme of leukotriene synthesis. 5-LO catalyses a two-step reaction. First, 5-LO targets free AA in concert with the 5-LO activating protein (FLAP) to insert one oxygen molecule into the 5 position of AA to form 5S-hydroperoxycicosatetraenoic acid (HPETE). Then transforms 5S-HPETE into an unstable allylic epoxide, named LTα. The subsequent metabolism of LTα also differs between leukocytes. In neutrophils, for instance, LTα hydrolyse enzymatically hydrolyses 5-LO metabolite LTα to LTβ. In contrast within human eosinophils, which do not express LTα hydrolyse and therefore are incapable of LTc4 synthesis, a specific glutathione S-transferase, named LTc4 synthase (LTc4S), catalyzes the addition of reduced glutathione (a tripeptide composed by glutamic acid, glycine, and cysteine) to LTα to form LTc4. After energy-dependent export, LTc4 is converted to LTd4 and LTε4 through sequential enzymatic removal of the glutamic acid by γ-glutamyl transpeptidases and then the glycine by dipeptidases. Therefore, because these LTs share a cysteine, LTc4 and its extracellular derivatives LTd4 and LTε4 are collectively called cysteinyl LTs.

Similar to how we presented the roles of lipid mediators in inducing eosinophil migration, here we will also summarize some activating roles of LTβs, cysteinyl LTs, PAF and PGD2, but we will give special emphasis to a prototype parameter of eosinophil activation: eosinophil activity to activate LTc4 synthesizing machinery. 

**LEUKOTRIENE LTβ**

Even though LTβ receptors have been indirectly and directly found to be expressed on human and murine eosinophils, respectively, there are not many successful studies reporting LTβ-driven eosinophil activation. Mainly using as cell model guinea-pig eosinophils, it has been shown that LTβ was capable of stimulating eosinophil recruitment, release of AA, homotypic eosinophil aggregation, as well as, rapid and transient activation of the NADPH oxidase (Faccioti et al., 1991; Lindsay and Gienappczy, 1997; Teixeira et al., 1999). Of note, the intracellular mechanisms that mediate LTβ-driven NADPH oxidase activation involve mediation by lyn kinase, PKC, and PLA2, but occurs essentially independently of changes in the intracellular calcium, phospholipase D, PI3K, and ERK1/2 (Perkins et al., 1995; Lindsay et al., 1998a; Lynch et al., 1999) Specifically regarding induction of LTc4 synthesizing function, stimulation of human eosinophils with LTβ failed to mount a LTc4 synthesizing response (Figure 1, right panel). In addition, eosinophil stimulation with LTβ was also unable to trigger synthesis of other eicosanoids such as PGD2 or even the biogenesis of lipid bodies – organelles, which compartmentalize AA metabolism within eosinophils and other cell types, and that are promptly assembled under stimulation that leads to eicosanoid synthesis (Bozza et al., 1997b).

**PLATELET ACTIVATING FACTOR**

Human eosinophils are prominent among cell populations that respond to PAF stimulation displaying, besides chemotaxis, numerous PAF-driven functions, including migration-related activities such adhesion and expression of cell surface molecules, as well as, secretory functions, including supernoxide production and release of cationic granule proteins and stored cytokines (Warlaw et al., 1986; Kroegel et al., 1989; Zoratti et al., 1991; Takizawa et al., 2002; Dyer et al., 2010). Equally important is the notion that although only one PAFR has been identified, PAF-driven signaling has emerged as a complex phenomenon, displaying differences between eosinophil chemoattractive versus secretory functions and therefore suggesting the existence of yet non-characterized receptors (Kato et al., 2004).

It is noteworthy that PAF was the first stimulus to have its lipid body-dependent mechanism of eliciting LTc4 synthesis characterized. PAF acting via its G-protein-linked receptor induces lipid body formation via a downstream signaling involving PKC and phospholipase C ( PLC) activation (Figure 1, right panel, Bozza et al., 1996, 1997a, 1998). Even more relevant to PAF ability of inducing LTc4 synthesis, it was the demonstration that the major enzymes involved in the enzymatic conversion of AA into LTc4, 5-LO, and LTc4 synthase, were found compartmentalized within PAF-induced newly assembled eosinophil lipid bodies (Bozza et al., 1997a, 1998) and that these enzymes were functional and producing LTc4 within these organelles (Bandeira-Melo et al., 2001).

**CYSTEINYL LEUKOTRIENES**

Cysteinyl leukotrienes exert their actions by engaging specific receptors. At least two cysteyl receptors (cysLTs) have been cloned and characterized, the CysLT1 and CysLT2 receptors (Lynch et al., 1999; Sarau et al., 1999; Hesse et al., 2000; Nothacker et al., 2000). These receptors can be distinguished with pharmacologic inhibitors and by their differing ligand-binding affinities. In addition, various findings suggest the existence of other, not yet cloned, cysteiny receptors (Panettieri et al., 1998; Ravasi et al., 2000; Mellor et al., 2002).

Inasmuch as eosinophils express functional receptors for cysteiny LTs, it has been investigated their potential role as stimuli of eosinophil activation. Indeed, a series of reports showed cysteinyl LTs ability to affect various eosinophil responses. For instance,
cysteinyl LTs promote CysLT1-dependent calcium influx on HL-60 (Thivierge et al., 2000; Murray et al., 2003b). We have also shown that LTC4, LTD4, and LTE4 induced a dose- and time-dependent, vesicular transport-mediated release of pre-formed IL-4 from human eosinophils derived in vitro from human cord blood progenitors (Bandeira-Melo et al., 2002a). Although some controversy exist (Murray et al., 2003b), cysteinyl LTs also appear to be able to induce an in vitro survival of human eosinophils by activation of CysLT2 receptors (Lee et al., 2000; Becker et al., 2002).

It is noteworthy that in addition to their recognized activities as paracrine mediators, eicosanoids like cysteinyl LTs are now also recognized to display autocrine effects. Indeed, eosinophil-derived cysteinyl LTs exert autocrine effects to enhance eosinophil survival triggered by GM-CSF, as well as, mast cell- and lymphocyte-derived molecules (Lee et al., 2000). Moreover, the capacity of eotaxin to stimulate the vesicular transport-mediated release of pre-formed IL-4 from human eosinophil granules is dependent of an endogenous LTC4, formed at eosinophil lipid bodies, that acting as an intracrine signaling molecule regulates this CCR3-elicited IL-4 release (Bandeira-Melo et al., 2002c). Thus, LTC4 may act intracellularly as intracrine signal transducing mediators. Indeed, cysteinyl LTs-responsive receptors have been identified on the membranes of intracellular eosinophil granule organelles and appear to function mediating cysteinyl LTs-stimulated secretion from within eosinophil granules, including those granules found extracellularly (Neves et al., 2010). On the other hand ans as illustrated in Figure 1 (right panel), specifically regarding the ability of activating LTC4 synthesis, not endogenous or exogenous cysteinyl LTs displayed the ability to trigger lipid body biogenesis or to elicit their own synthesis (Bandeira-Melo et al., 2002c).

**PROSTAGLANDIN D2**

Besides migration-related cell functions, it is now well-characterized that PGD2 is a potent inducer of eosinophil activation, being capable of promoting eosinophytic secretory activity. For instance, PGD2 is capable of triggering eosinophil degranulation, which appears to be induced by the selective DP2 agonist but not by selective DP1 agonist, suggesting for DP2s a role in modulating, not only eosinophil migration, but also activation (Gervais et al., 2001). We have also shown that, in addition to its eosinophilitactic activity, PGD2 controls allergic-relevant eosinophil activation parameter: the increased LTC4-synthesizing capacity of these cells (Mesquita-Santos et al., 2006). Indeed, other eosinophilitactic mediators, including eotaxin, RANTES, and PAF are capable of triggering LTC4 synthesis within eosinophils through activation of their cognate G protein-coupled chemotactic receptors (e.g., CCR3; Bozza et al., 1996; Bandeira-Melo et al., 2001). However, PGD2-induced LTC4 synthesis, surprisingly and distinctly from other parameters of eosinophil activation evoked by PGD2, was not mediated by the stimulatory activation of DP2 receptors while being counter-balanced by a parallel inhibitory cAMP-dependent DP1 receptor activation. On contrary, it does depend on a novel kind of interaction between the PGD2 receptor types expressed on eosinophils (Figure 1, right panel). Eosinophil LTC4 synthesis triggered by PGD2 is controlled by complementary stimulatory events between DP2 receptor-activated lipid bodies and concurrent DP1 receptor signaling (Mesquita-Santos et al., 2011). While PGD2 emerges as a potent inflammatory mediator of allergic disorders and as an interesting therapeutic target, because of the mandatory dual activation of DP1 and DP2 receptors for increasing eosinophil LTC4 synthesis, either DP1 or DP2 receptor antagonists might be highly effective candidates as anti-allergic tools to control cysteinyl LTs production regulated by the activation of eosinophils at sites of allergic reactions. On the top of that, we had recently also found out that upon proper stimulation, both human and mouse eosinophils can produce significant amounts of biologically relevant PGD2 (Luna-Gomes et al., 2011). PGD2 intracellular synthesis within eosinophils led to PGD2 receptor-mediated paracrine/autocrine functions, contributing to eosinophil activation. Indeed, eosinophil-derived PGD2 appears to be capable of regulating both eosinophil motility, as well as, lipid body-driven LTC4 synthesis within eosinophils stimulated with eotaxin, for instance.

**FINAL REMARKS**

It is clear that several relevant aspects of lipid mediator impact on eosinophil biology need to be further characterized, however knowledge on this subject had evolved dramatically in the last decades. Among the most significant advances on eosinophil/lipid mediator axis are: (i) the recognition that eosinophils express the multitude of lipid mediator receptors on their surface, even those receptor pairs with apparently opposing functional outcomes under activation; (ii) the appreciation that not only eosinophil migration is elicited by lipid mediators, but maybe even more therapeutically relevant, activation of eosinophil secretory functions; and (iii) the acknowledgment of a wide-ranging induced signaling and consequently functional potentiality for lipid mediator-stimulated eosinophils that have still unpredicted impact to surrounding eosinophilic immuno-pathologies.

Still of special interest for eosinophil biology with roles in maximizing eosinophil functional potentialities is the rising observations unraveling intricate interactions between lipid mediators (such as LTC4 and PGD2) and eosinophil-relevant chemokines and other proteic stimuli. Possibly the most illustrative example of such cross-talking is eosinophil stimulation by eotaxin, a key mediator in the development of allergic eosinophilia that is known by its potent eosinophilitactic activity and has emerged as a potent mediator of eosinophil activation. Among a number of data on eotaxin/AA metabolites interdependence, some hallmarks are the sequential events: (i) eotaxin particular ability to acutely enhance PGD2 synthesis by eosinophils by stimulating CCR3 receptors (Mesquita-Santos et al., 2006; Luna-Gomes et al., 2011); (ii) the subsequent autocrine/paracrine induction of lipid body biogenesis and lipid body-located LTC4 synthesis by eosinophil-derived PGD2 (Luna-Gomes et al., 2011); followed by (iii) LTC4-driven intracellular induction of piecemeal degranulation of granule-stored IL-4 by eotaxin-stimulated eosinophils (Bandeira-Melo et al., 2002c). Nevertheless, eotaxin is not the only example of such lipid/protein cooperation. It is still noteworthy that cell types other than eosinophils also undergo such lipid mediator/protein mediator cross-talking in regulating cell activation. Either infection-elicited or oxLDL-driven MCP1, for instance,
and vasoactive intestinal peptide VIP (El-Shazly et al., 2013). Moreover, RANTES, IL-16 and MIF are also proteic mediators capable of activating eosinocytic synthesizing machinery within eosinophils culminating with the generation of LTC4 and PGD2, that in turn intracrinally or autocrinally mediate eosinophil secretory functions (Bandeira-Melo et al., 2002b, Vieira-de-Abreu et al., 2011).


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