Eosinophil recruitment and activation: the role of lipid mediators

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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 surviving factors. Even though the majority of studies focused on role of protein mediators like IL5 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 and receptors involved in the regulation of eosinophil migration to 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 display from pro- to anti-inflammatory, pro-resolution, and metabolic activities, mostly controlled by bioactive mediators such as chemokines, cytokines, and eicosanoids, including leukotrienes, prostaglandins, and prostacyclins.

Eosinophils such as asthma, infection, and cancer. This review will first explore the role of some of the most well-studied lipid mediators on eosinophil migration. Then, it will summarize the impact of a varied of these mediators on eosinophil activation, focusing on eosinophil secretory function of leukotriene C4 (LTC4) synthesis/release.

HOW DO LIPID MEDIATORS IMPACT EOSINOPHIL MIGRATION?

Eosinophils 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. Eosinophil 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 eosinophilotactic 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).

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protein-coupled receptors (GPCRs), receptor 1 (BL T1) and receptor 2 (BL T2) (O'Driscoll et al., 1984; Wardlaw et al., 1989; Murray et al., 2003b; Tozawa et al., 2002). Additionally, G protein-coupled receptors (GPCRs) such as BL T1 and BL T2 (Shindo et al., 1993) have provided evidence of expression of active BL T1 on human eosinophils. For instance, it has been shown a BL T1-driven LTB4 secretion that is a key event for recruitment of eosinophils (Figure 1, left panel; Fregonese et al., 2002; Spada et al., 1997; Huang et al., 2013). LTB4 serves as a potent chemoattractant through ligation of BL T1 on target cells. Expression and function of LTB4 receptors on eosinophils remained for long time controversial, in part because LTB4-driven activity seemed to have some selectivity toward neutrophils. However, while strong demonstration of BL T1 expression in human eosinophils is still pending, functional assays using LTB4 as agonist and specific BL T1 antagonists, in vitro and in vivo studies using BL T1-deficient mice have confirmed that ligation of BL T1 by LTB4 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 LTB4, human eosinophils are not LTB4 producers, representing major cellular sources of cysteinyl LTs (Weller et al., 1983). Based on the prominent eosinophil feature of recurrently depend on autocrine/paracrine stimulation to regulate their own functions, it seems 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. LEUKOTRIENE B4

Leukotriene B4 (LTB4) 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 LTB4 have been reported in various allergic diseases and these levels have been related to disease activity and eosinophilia (O’Driscoll et al., 1984; Warren et al., 1989; Shindo et al., 1993). LTB4 can bind to two highly conserved G protein-coupled receptors (GPCRs), BL T1 receptor 1 (BL T1) and the considered low-affinity BL T2 (Toda et al., 2002; Ishikawa, 2011). LTB4 serves as a potent chemoattractant through ligation of BL T1 on target cells. Expression and function of LTB4 receptors on eosinophils remained for long time controversial, in part because LTB4-driven activity seemed to have some selectivity toward neutrophils. However, while strong demonstration of BL T1 expression in human eosinophils is still pending, functional assays using LTB4 as agonist and specific BL T1 antagonists, have provided evidences of expression of active BL T1 on human eosinophils. For instance, it has been shown a BL T1-driven LTB4 ability to trigger calcium influx in human eosinophils (Murray et al., 2003a). On the other hand, murine (m)BL T1 was cloned while searching for novel chemoattractant receptors in murine eosinophils and demonstrated that it encodes a functional receptor for LTB4 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 BL T1 antagonists, in vitro studies using BL T1-deficient mice have confirmed that ligation of BL T1 by LTB4 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 LTB4, human eosinophils are not LTB4 producers, representing major cellular sources of cysteinyl LTs (Weller et al., 1983). Based on the prominent eosinophil feature of recurrently depend on autocrine/paracrine stimulation to regulate their own functions, it seems 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.
Eosinophils, since: (i) cysLT1 receptor CysLT1 appears to play a role in eosinophilopoiesis, inasmuch as CysLT1 antagonism in vivo limits IL-5-responsive eosinophil differentiation and maturation (Saito et al., 2004); (ii) cysLT1 ERs are able to significantly up-regulate adhesion molecules, such as Mac-1 expression (Freginanzo et al., 2002; Saito et al., 2004); (iii) direct administration of LTC4 induce a rapid and significant reduction in leukocyte rolling velocity, further increasing cell adherence odds (Kanwar et al., 1995); (iv) cysLT1 ERs induce RANTES production from isolated lung cells, which in turn might cause RANTES-driven migration of eosinophils into airways (Kawano et al., 2003).

**Platelet activating factor**

One major chemoattractant for eosinophils is the ether-linked phospholipid, PAF. PAF [1-O-alkyl-2-acetylt-6-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 in vitro and triggering eosinophil influx and accumulation in vivo (Warclaw et al., 1986; Kimani et al., 1998; Martins et al., 1989; Kato et al., 2004). Acting via a single class of identified receptor – named PAFR – a seven-transmembrane 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 eosinophilicotropic activity of PAF in human and mouse cells by a pertussis toxin (PTX)-sensitive manner. Several studies have tried to characterize the signaling pathways involved in PAF-induced eosinophil chemotaxis, and although still controversial, it is now recognized that eosinophilicotropic 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; Figure 1; left panel; Dent et al., 2000; Mükke et al., 2008). Indeed, these findings are in agreement with the demonstration that PI3K inhibitors suppress PAF-mediated tissue eosinophilia in diseases such as asthma (Mühra et al., 2005).

**Prostaglandin D2**

Prostaglandin D2 has emerged as a key mediator of allergic diseases such as asthma (Matsuoka et al., 2000), in part due to its now well-characterized ability to promote potent eosinophil chemotaxis and activation (Powell, 2003). PGD2-driven cellular functions are all mediated by high-affinity interaction with two receptors, namely D prostaglandon receptor 1 (DP1) and chemotactic receptor homologous molecule expressed on T helper type 2 cell (TH2) cells (CRTh2, also known as DP2). Whilst DP1 is coupled to Gα 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 PKA (Xue et al., 2007). Eosinophils co-express both the classic 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 DP2 receptor expressed on eosinophil surface (Monneret et al., 2003). Several pharmacological studies show the involvement of DP2 in the establishment of eosinophilia in models of allergic inflammation. For instance, intratracheal injection of PGE2 or selective DP2 agonist induced eosinophilia in rats, whereas the use of selective DP1 agonist failed to trigger eosinophil accumulation (Emery et al., 1989). Likewise, intratracheal administration of DP2 agonist or PGD2 induced specific airway eosinophilia in mice previously exposed to the allergen or IL-5 (Shiraishi et al., 2003). DP2 antagonist abrogated the PGD2-induced mobilization of eosinophils from the bone marrow of the guinea-pig confirming a crucial role of DP2 in this response (Royer et al., 2008). A specific DP2 agonist not only increased eosinophil recruitment at inflammatory sites but also the pathology in two in vivo models of allergic inflammation: atopic dermatitis and allergic asthma (Spik et al., 2005). Concurring, selective DP2, but not DP1 antagonists were capable to inhibit eosinophil accumulation in a model of PGD2-induced eosinophilic pleurisy (Musquita-Santos et al., 2011). In vitro, PGD2 is able to promote additional migration-related activities, such as increased expression of cell adhesion molecules CD11b and L-selectin, calcium mobilization, actin polymerization, chemokinesis and a rapid change in eosinophil morphology (Gervais et al., 2001; Monneret et al., 2001). Of note and as illustrated in Figure 1 (left panel), these and other in vitro 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, intra-cellular effects (Monneret et al., 2003; Ulven and Kostenis, 2006; Sandig et al., 2007). However, further studies appears 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 DP2 activation in eosinophils (Musquita-Santos et al., 2011). A process that although may not play roles in eosinophil migration, it appears to be critical to PGD2-induced eosinophil activation (see below).

**Do lipid mediators activate eosinophil effector functions?**

At the sites of eosinophilic accumulation, through their ability to secrete a range of cytokines, basic proteins, reactive oxygen species as well as lipid mediators, eosinophils contribute to the physiopathology of a growing list of conditions including classical eosinophil-related diseases such as bronchial asthma, novel and quite surprising pathologies such as cancer, multiple sclerosis, Duchenne muscular dystrophy as well as physiological process such as mammary development (Jacobsen et al., 2012). While the regulation of eosinophil migration to the inflammatory focus is a critical stage in eosinophilic pathologies, understanding the mechanisms by which eosinophil activation is stimulated and its consequences appear to be even more important in defining potential targets for therapeutic interventions, since the specific stimulatory molecules, its receptors and signaling pathways involved in

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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. Eosinophil can synthesize lipoxin A4 (LXA4) and the aptly named after eosinophil, eosin C4 (EXC4), besides the prostanoids thromboxane B2 (TXB2), PGD2 and the recently identified PGE2. However, when properly stimulated, eosinophils prominently synthesize cysteinyl LTs. Of note, eosinophils are a major cellular source of cysteinyl LTs and have been identified as the principal LTC4 synthase expressing cells in bronchial mucosal biopsies of asthmatic subjects (Bandeira-Melo and Weller, 2003). Hence, much interest in understanding the regulation of eicosanoid 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 catalyzes 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-hydroperoxyeicosatetraenoic acid (HPETE), then transforms 5S-HPETE into an unstable allylic epoxide, named LTE4. The subsequent metabolism of LTE4 also differs between leukocytes. In neutrophils, for instance, LTE4 hydrolyzes enzymatically hydrolyses 5-LO metabolite LTE4 to LTE5. In contrast within human eosinophils, which do not express LTE4 hydrolyase and therefore are incapable of LTE4 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 LTE4 to form LTC4. After energy-dependent export, LTC4 is converted to LTD4 and LTE4 through sequential enzymatic removal of the glutamatic acid by γ-glutamyl transpeptidases and then the glycine by dipeptidases. Therefore, because these LTs share a cysteine, LTC4 and its extracellular derivates LTD4 and LTE4 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 LTs on pulmonary eosinophils, respectively, but we will give special emphasis to a prototype parameter of eosinophil activation: eosinophil ability to activate LTC4 synthesizing machinery.

**LEUKOTRIENES B4**

Even though LTE4 receptors have been indirectly and directly found to be expressed on human and murine eosinophils, respectively, there are not many successful studies reporting LTE4-driven eosinophil activation. Mainly using as cell model guinea-pig eosinophils, it has been shown that LTE4 was capable of stimulating eosinophil recruitment, release of AA, homotypic eosinophil aggregation, as well as, rapid and transient activation of the NADPH oxidase (Faccidori et al., 1991; Lindsay and Gienybcz, 1997; Teixeira et al., 1999). Of note, the intracellular mechanisms that mediate LTE4-induced 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 LTD4 failed to mount a LTC4 synthesizing response (Figure 1, right panel). In addition, eosinophil stimulation with LTD4 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 as adhesion and expression of cell surface molecules, as well as, secretory functions, including supernoxide production and release of cationic granule proteins and stored cytokines (Wardlaw et al., 1986; Krögel et al., 1989; Zoratti et al., 1991; Takazawa 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 chemoncotic 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 cysteLT 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, cysteLT (Panettieri et al., 1998; Ravasi et al., 2000; Melot et al., 2002).

Inasmuch as eosinophils express functional receptors for cysteinyl 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,
cysteiny L Ts 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 eosinophils derived in vitro from human cord blood progenitors (Bandeira-Melo et al., 2002a). Although some controversy exists (Murray et al., 2003b), cysteiny L Ts 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, eosinocyan L Ts are now also recognized to display autocrine effects. Indeed, eosinophil-derived cysteiny L Ts 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, cysteiny L Ts-responsive receptors have been identified on the membranes of intracellular eosinophil granule organelles and appear to function mediating cysteiny L Ts-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, none endogenous or exogenous cysteiny L Ts 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 eosinophil cytotoxic 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 DP2 a role in modulating, not only eosinophil migration, but also activation (Gervais et al., 2001). We have also shown that, in addition to its eosinophilactotic activity, PGD2 controls allergic-relevant eosinophil activation parameter: the increased LTC4-synthesizing capacity of these cells (Mesquita-Santos et al., 2006). Indeed, other eosinophilactotic mediators, including eotaxin, RANTES, and PAF are capable of triggering LTC4 synthesis within eosinophils through activation of their cognate Gα-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 DP1 receptor-activated lipid bodies and concurrent DP2 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 cysteiny L Ts 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 potentials 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 eosinophilactotic activity and has emerged as a potent mediator of eosinophil activation. Among a number of data on eotaxin/AA metabolite interdependency, 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 intracrine 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 oSLDL-driven MCP1, for instance,
and vasoactive intestinal peptide VIP (El-Shazly et al., 2013). Moreover, RANTES, IL-16 and MIF are also protein mediators capable of activating eicosanoid synthesizing machinery within eosinophils culminating with the generation of LTC4 and PGD2, that in turn intracrinically or autocrinically mediate eosinophil secretory functions (Bandeira-Melo et al., 2002b; Vieira-de-Abreu et al., 2011).
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