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EDITORIAL

MAST CELLS AND ARACHIDONIC ACID CASCADE IN INFLAMMATION

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Prostaglandin D2 PGD2 is a major cyclooxygenase metabolite of arachidonic acid produced by mast cells and it is released following allergen challenge in diseases, such as allergic diseases. PGD2 may act as a neuromodulator and as an allergic and inflammatory mediator. In allergic diseases, activated mast cell synthesizes prostaglandin D2 (first cyclo-oxygenate mediator) which has bronchoconstrictive and vasodilating effects and attracts several leukocytes. It has been found that activated mast cells, challenged with physiological and non- physiological secretagogues, release elevated histamine and tryptase and chymase, leukotrienes B4, C4 and D4, 5-hydroxyeicosatetraenoic acid, PGD2, Platelet Activating Factor (PAF), heparin, and high-molecular-weight neutrophil chemotactic factor and cytokines/chemokines. PGD2 exerts its biological activity through the DP and CRTH2 receptors and their cDNA cloning which were characterized 15 years ago. In this report, we revisited the biological effects of arachidonic acid compounds released by activated mast cells in allergic and inflammatory states.

In 1878, Sangster described *urticaria pigmentosa* for the first time, and in 1887 Unna noted the presence of mast cells in the skin lesion. Mast cells are characterized by metachromatism as demonstrated by the use of basic dyes, such as Giemsa's reagent and toluidine blue (1-2). Electron microscopy studies of mast cells in allergic tissue show irregularly shaped cells with long and interdigitating cytoplasmatic villi. In airways, mast cells lie adjacent to nerves, blood vessels and lymphatics, which highlight their pivotal importance in regulating allergic inflammatory processes (3-4).

Key words: mast cells, arachidonic acid, inflammation, lipoxygenase, cyclooxygenase

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In asthma, mast cells are predominantly activated by IgE receptor cross linking (5).

TC mast cells, containing tryptase and chymase, present predominance of grating/lattice structures in the granules compared with T mast cells containing tryptase only (6-8). Prostaglandins and leukotrienes are proinflammatory mediators resulting from metabolic degradation of the arachidonic acid originating from membrane phospholipids. Mast cells release substances such as histamine, leukotrienes B4, C4 and D4, 5-hydroxyeicosatetraenoic acid, Prostaglandin D2 (PGD2), Platelet Activating Factor (PAF), heparin and contain tryptase and chymase (9-13). The most important products of enzyme cyclooxygenation of arachidonic acid are prostaglandins D2, E2, F2a, tromboxane A2 and prostacyclin (14-15). Thromboxane A2 plays a certain role in the development of bronchial hyperreactivity and late asthmatic response. Prostaglandin E has suppressive effects on interferon gamma production by Th1 helper cells and increases production of interleukin 4 by the Th2 cells (16-19). Therefore, inhalation of prostaglandin E prevents asthmatic attacks caused by allergens (20).

PGD2 is the major cyclooxygenase metabolite of arachidonic acid released after stimulation of mast cells (21-22). However, whether PGD2 regulates allergic process has remained unknown. Prostaglandins express their tissue effects via the five basic receptor types (23-25). PGD2 exerts its actions by binding to two types of specific cell surface receptors. One is DP, which is better characterized (the PGD receptor) and the other is chemoattractant receptor-homologous molecule expressed on Th2 (CRTH2) (26-28). Pharmacological blockade or genetic ablation of DP e/or CRTH2 is associated with a reduction in tissue inflammation (29-33).

Activation of PGD2 receptor (DP receptor) results in stimulation of adenylyl cyclase, resulting in inhibition of platelet aggregation and smooth muscle relaxation (34-35). A second PGD2 receptor has recently been identified and designated as the DP2 receptor, or chemoattractant receptor-homologous molecule expressed on Th2 cells (36-39). PGD2 acts through the DP2 receptor to induce eosinophil chemotaxis, actin polymerization, calcium mobilization, and adhesion molecule expression (40).

The biological effects of PGD2 include vasodilatation, inhibition of platelet aggregation, bronchoconstriction, and recruitment of inflammatory cells. PGD synthase (H-PGDS) is a cytosolic enzyme that isomerizes PGH2, a common precursor for all PGs and thromboxanes, to PGD2 in a glutathione-dependent manner. H-PGDS is many cells such as mast cells, antigen-presenting cells, and Th2 cells, and is the only mammalian member of the Sigma class of cytosolic glutathione S-transferases (41-43).

By releasing these compounds, these cells are the most important cells of the early phase or immediate reactions and cause inflammation. However, other cells might also be involved in this immediate response such as macrophages, eosinophils, and platelets; while late-phase reactions appear to be a consequence of infiltration with neutrophils, eosinophils, and macrophages. These cells are recruited and activated either by mast cell-associated chemotactic non-specific factors such as LTB4, PAF, the eosinophil chemotactic factor of anaphylaxis (ECF-A), and chemotactic specific factors: chemokines (44-46). These compounds also participate in the late phase reactions six hours subsequent to the exposure to the allergen (47).

Chemokines mediate inflammation in asthma by acting on endothelial cells, alveolar cells, neutrophils, eosinophils, basophils, mast cells, monocytes, and lymphocytes, which are inhibited by corticosteroids. Mast cells, in response to activation, release preformed mediators that are stored bound to proteoglycans, for example, TNF-alpha, IL-4, IL-13, histamine, tryptase and chymase. New synthesis of arachidonic acid metabolites [leukotriene C4 (LTC4), leukotriene B4 (LTB4) and prostaglandin D2 (PGD2)] and further cytokines are stimulated (48-52).

The mononuclear cell interactions are under the control of regulatory T cells (suppressor T cells) and it is speculated that the availability of these subsets may determine the magnitude of the late-phase response (53-54). However, histamine and LTC4, but not PGD2, are found during the late phase. This phase is generally considered as a direct consequence of the effects of mediators released from mast cells activated during the early reaction. Inflammatory and allergic diseases are mainly

orchestrated by antigen-specific CD4+ T cells, eosinophils and mast cells (55). Prostanoids are one of the arachidonic metabolites, which are produced by a variety of inflammatory cells upon stimulation and are thought to be involved in the pathogenesis of diseases as well as the regulation of homeostasis. It has been described that among Th2-associated chemokine receptors, CCR3, CCR4 and CCR8 play a central role in allergic inflammation (56-57). However, CCR3 is mainly expressed on basophils, eosinophils and mast cells, and it is poorly expressed by Th2 cells; while CCR4 is also expressed by Th subsets but different from Th2 cells.

Allergen challenge in the airways induces marked vasodilatation lasting for about 60-90 min in the circulation. Histamine stimulates smooth muscle cell contraction, vasodilatation and increased vascular permeability and further mucus secretion. LTC4, LTB4 and PGD2 affect vascular permeability and can regulate the activation of immune cells. Histamine seems to be important in the early phase (0-20 min) of these responses in the airways, while cyclooxygenase products (possibly PGD2) may be responsible for the long-lasting component. A cyclo-oxygenase product is presumably also released from the lung into the circulation after bronchial allergen challenge and thereby induces a delayed, long-lasting vasodilatation. Histamine may be the main vasoconstrictor agent released in the immediate allergic reaction (58).

Some cytokines selectively activate neutrophils, eosinophils and monocytes. For instance, TNFα produced by macrophages amplifies the inflammatory response by its capacity to enhance the cytotoxicity of some inflammatory cells.

Cytokines such as IL-1, TNF alpha, and IL-4 are also be secreted. In addition, mast cell activation leads to the release of granulocyte-macrophage colony-stimulating factor and other interleukins. TNF-alpha induces adhesion molecules on endothelial cells and subsequent transmigration of inflammatory leucocytes (59).

Cytokines that interact with mast cells to cause cell activation and secretion of mediators are called Histamine Releasing Factors (HRF). Histamine release is the best characterized and this potent inflammatory compound is the principal mediator of the immediate allergic reaction. However, other inflammatory mediators, as well as neuropeptides (substance P), 48/80 compound, calcium ionophore A23187, C3a, LPS and others substances, also contribute to the mast cell degranulation. Neuropeptide stimulation of mast cells induces a rapid release of histamine with minimal generation of PGD2 and LTC4 and the time course and calcium dependency of release by substance P differ from anti-IgE. The ability of neuropeptides to stimulate skin mast cell histamine release suggests a mechanism whereby their release from dermal nerve endings is coupled to changes in microvasculature. Therapeutic treatment includes the use of H1 and H2 antihistamines, oral disodium chromoglycate, psoralens plus ultraviolet A photochemotherapy, and potent corticosteroid preparations (60).

The stimulus for mediator cell activation may be either immunologic (IgE-dependent) or non-immunologic (i.e. 48/80 or calcium ionophore A23187). The relationship of HRF to the cytokine/chemokine molecules is very important in understanding the pathogenesis of allergic diseases and inflammation. Within minutes of exposure to allergen, mast cells produce histamine, leukotriene C4, and prostaglandin D2. The release of mediators from mast cells represents the central event in the development of immediate hypersensitivity reactions with release of many secretagogues including cytokines.

The characteristics of the arachidonic acid mediators released at an inflammatory site is dependent not only on the individual cells and inflammatory stimuli present but also on a complex interaction between neighboring cells and their prostanoid compounds. These mediators share overlapping activities, and current research is directed toward determining the critical molecules involved in the pathogenesis of particular inflammatory states. The release of leukotrienes, PAF, and cyclooxygenase products by cells infiltrating allergic inflamed tissue may be involved in the vascular constriction and edema, observed during the late phase response. Most non-steroidal anti-inflammatory drugs inhibit the enzyme cyclooxygenase, and thus also prostaglandin biosynthesis and release.

We hope that in the future, the therapeutic use of specific antagonists of the biosynthetic enzymes of the 5-lipoxygenase pathway and receptor antagonists

of the eicosanoids and PAF holds great promise for the modulation of allergic and inflammatory diseases.

Several reports have shown that some cytokines can influence not only the proliferation but also the functional activity of human inflammatory cell, including mast cells. For instance, IL-3 is capable of enhancing the release of histamine and can also influence the proliferation of basophils *in vitro*. In addition, it has been reported that SCF causes, on human mast cells, a significant mediator release of both preformed histamine and *de novo* synthesis of PGD2.

Mast cells and other inflammatory cells are attracted by chemotactic mediators such as PGD2. In addition to prostaglandin D2, prostaglandin F2a and thromboxane A2 also have bronchoconstrictive actions, while prostacyclin and prostaglandin E have bronchodilating effects. However it is well established that basophils do not release PGD2.

Prostaglandin D2 (PGD2), a major prostanoid produced by activated mast cells, has long been implicated in allergic diseases. PGD synthase catalyzes the isomerization of PGH2, a common precursor of various prostanoids, to produce PGD2 in the presence of sulfhydryl compounds. PGD2 induces sleep, regulates nociception, inhibits platelet aggregation, acts as an allergic mediator, and is further converted to 9 alpha, 11 beta-PGF2 or the J series of prostanoids, such as PGJ2, delta 12-PGJ2, and 15-deoxy-delta 12,14-PGJ2.

Hematopoietic PGD synthase is widely distributed in the peripheral tissues and localized in the antigen-presenting cells, mast cells, and megakaryocytes. The hematopoietic enzyme is the first recognized vertebrate homolog of the sigma class of glutathione S-transferase.

Recent studies have shown that PGD2 exerts its effects through two different G-protein-coupled receptors (GPCRs), the D-prostanoid receptor and the chemoattractant receptor-homologous molecule expressed on T helper-2 cells (61). PGD2 is a major arachidonic acid compound generated in the central nervous system and is involved in the regulation of sleep and pain responses through DP receptors. This powerful inflammatory product is also actively produced by mast cells, basophils, and Th2 cells, acting as an allergic mediator through DP and CRTH2 receptors. PGD2 is further dehydrated to produce PGJ2, delta12-PGJ2, and 15-deoxy-delta(12,14)-PGJ2, the last being a ligand for the nuclear receptor PPARgamma. PGD synthase (PGDS) catalyzes the isomerization of PGH2 to PGD2 in the presence of sulfhydryl compounds. Two distinct types of PGDS have been identified: one is the lipocalin-type PGDS (L-PGDS); and the other, the hematopoietic PGDS (H-PGDS) (62). However, the exact role of the arachidonic acid products in the pathogenesis of inflammation, remain to be determined.

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