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Research Update (Minireview)

Mast Cells and Lipid Mediators

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Human mast cells are potent effector cells in host defense mechanisms of innate and acquired immunity, including inflammatory diseases such as asthma and atherosclerosis. Mast cells originate from pluripotent hematopoietic progenitors in the bone marrow. Activation of mast cells by different stimuli triggers the release of a large range of mediators, including de novo synthesized eicosanoids which are highly biologically active lipid mediators. For the generation of lipid mediators, cytoplasmic lipid droplets have been shown to function as a major intracellular pool of arachidonic acid, the precursor for eicosanoids biosynthesis. The article summarizes current knowledge on mast cell biosynthesis of lipid mediator and the role in inflammation.

Key Words: Mast cell, Lipid droplet, Eicosanoids, Inflammation

INTRODUCTION

Inflammation is a fundamental protective response in higher eukaryotes to a variety of external stimuli such as environmental toxins, pathogens, or allergens. These stimuli are encountered by immune cells such as mast cells, which mediate the initial defense reaction against external "invaders" (1). Mast cells reside throughout vascularized tissues and are especially prominent near body surfaces defining the border between the external and internal environments. Mast cells are considered the main "effector" cells in allergic disorders and tissue remodeling (2). However, more recent evidence suggests that mast cells are also involved in inflammatory reactions associated with obesity, atherosclerosis, autoimmune disorders, and cancer (3). For the mast cells to act as disease-causing or disease-modifying effector cells, they need to be activated. Upon activation by immunological or nonimmunological stimuli, mast cells immediately exocytose a fraction of their preformed mediators. A main aspect of this review is the lipid mediators from mast cells regarding the biosynthesis and roles in inflammation.

1. Origin, development, and morphology of human mast cells

Mast cells are members of the innate immune system that develop from hematopoietic precursor cells in the bone marrow. They are released as progenitor cells that circulate in the blood and finally mature from mast cell-committed progenitors when entering tissues (4). Committed mast cell progenitors express specific surface markers including CD34, CD13, and CD117, but lack the expression of the high

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affinity IgE receptor (FcεRI). Tissue-homing of mast cells mediated by different molecules including KIT ligand (also termed stem cell factor (SCF)) (5), eotaxin, and integrins (6). The phenotypes of mature mast cells is determined by growth factors and cytokines of the tissue microenvironment in a strictly regulated process (7). Among all mast cells maturation factors, the most essential molecule for their differentiation is the KIT ligand. KIT ligand is secreted by various tissue cells, such as fibroblasts and endothelial cells and binds to the mast cell surface receptor CD117 (c-kit) (8). Once mature, mast cells reside in various body tissues. They typically located at sites where the host tissue can encounter external antigens, allergens, toxins and microbes, e.g., the upper dermal skin, respiratory tract and bowel mucosa (3). Especially, mast cells are well positioned to participate in cutaneous immune responses, as skin mast cells are located predominately in the dermis near blood and lymphatic vessels and nerves (9). Generally, mature human mast cells contain a single, large nucleus and harbor in their cytoplasm membrane-bound secretory granules that are filled with pre- formed, highly active biological molecules (10).

2. Mast cell lipid droplet (LDs)

Cytosolic LDs are highly dynamic organelles, which depending on the metabolic state of the organism, can be found in almost any type of cell. Currently, the role of LDs in the pathophysiology of obesity dependent metabolic diseases involving insulin resistance is studied intensively (11). LDs are also present in various types of inflammatory cells, where they are usually called lipid bodies and participate in cell signaling and in the generation of biologically active lipid mediators evoked by inflammatory and infectious conditions (12~14). Particularly, the mast cells produce and secrete powerful lipid mediators. Mast cells have exceptional capability to store pre-formed biologically active mediators within secretory granules and to trigger their release upon cellular activation (15). There is growing evidence that LDs represent a dynamic compartment with lipid regulatory functions in mast cells.

In eukaryotic organisms, LDs form from the endoplasmic reticulum (ER). Although direct visualization and knowledge for the initial stages of the formation process are lacking, many lines of evidence support a model whereby LDs are derived from the ER. For example, most of the enzymes involved in triacylglycerol or sterol ester synthesis are localized to the ER (in the absence of LDs). Moreover, electron microscopy data reveal close apposition between LDs and the ER (16). LDs consist of a neutral lipid core that is surrounded by a monolayer of amphipathic lipids (phospholipids and unesterified cholesterol) and by proteins involved in the formation and trafficking of the LDs and in the turnover of their lipids. The most well-known LDs proteins are the members of perilipin (PLIN) family. Among five perilipins (PLIN1, PLIN2, PLIN3, PLIN4, and PLIN5) from the protein family, PLIN2 and PLIN3 were expressed in the developing and mature human mast cells, the former member being localized to the surface of LDs, and the latter being distributed throughout the cytoplasm in a punctate pattern (17).

LDs contain eicosanoid-forming enzymes and this would allow for the focal formation of eicosanoids within LDs and the utilization of the substantial amounts of arachidonic acid (AA) in the triglyceride pool of the LDs (18). The putative enzymes involved in AA liberation from triglycerides included hormone sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) (19).

3. Mast cell activation and lipid mediators

Mature tissue mast cells are long lived highly granulated cells whose activation and subsequent degranulation can be triggered by immunological (e.g., FcεRI cross-linking) and non-immunological (e.g., pathogens and peptides) stimuli, thus leading to granule-mediated modification of the microenvironment of the activated cells. The secretory granules of mast cells are filled with various preformed mediator molecules, the best known of which are histamine, serotonin, heparin, the proteases tryptase, chymase and cathepsin G, as well as various cytokines, including IL-8. Besides the secretion of preformed mediators during degranulation, mast cell activation also triggers the release of acutely *de novo* synthesized lipid mediators. Among the known lipid mediators of mast cells, eicosanoids play the most prominent role. The

common precursor molecule for eicosanoids is AA. Three major pathways of eicosanoid biosynthesis are established, in which free AA is oxidized either by (i) cyclooxygenases 1 and/or 2 (COX-1 and/or COX-2) to form prostaglandins (PGs), (ii) lipoxygenases to generate hydroperoxyeicosatetraenoic acids and subsequently leukotrienes (LTs), or (iii) cytochrome P450 epoxygenase and ω-hydroxylase to produce epoxyeicosatrienoic acids and hydroxyeicosatetraenoic acids, respectively. Upon activation, mast cells rapidly generate three major eicosanoid molecules from AA: prostaglandin D_2 (PGD_2) and the leukotrienes B_4 (LTB_4) and C_4 (LTC_4), all of them contributing to the pathophysiology of allergic and inflammatory diseases (18). Although other cells also produce PGD_2, mast cells may be a predominant source of PGD_2 and its metabolites in peripheral tissues affected by allergic pathologies such as nasal polyposis (20), eosinophilic chronic rhinosinusitis with nasal polyps (21) and eosinophilic esophagitis (22). Indeed, PGD_2 has been proposed as a selective indicator of mast cell activation in some diseases such as bronchial asthma and mastocytosis (23). The transcription of enzymes involved in PGD_2 synthesis in mast cells is enhanced by inflammatory and environmental signals, and this can augment the PGD_2 response to antigen stimulation (24).

PGD_2 produced mostly by mast cells during the early phase of an allergic reaction has been considered an essential link between the early and late-phase of inflammation by promoting the recruitment of inflammatory cells. Prostaglandin D_2 receptors 1 (DP_1 receptors) are expressed in dendritic cells and T_H1 cells, but not in significantly in T_H2 cells while prostaglandin D_2 receptors 2 (DP_2 receptors) receptor is viewed as a specific marker for human T_H2 cells (25). Both DP_1 and DP_2 receptors may support a T_H2-type inflammatory profile. Whereas DP_2 is the major PGD_2 receptor contributing to the recruitment of T_H2 cells, eosinophils and basophils and promoting T_H2 cytokine production (26), DP_1 supports T_H2 polarization by suppressing the production of T_H1-driving cytokines such IL-12 in dendritic cells. In addition to immune cell recruitment, infusion of PGD_2 in human causes nasal stuffiness, hypotension, and flushing, suggesting an overall participation for PGD_2 in immediate hypersensitivity processes (25). The higher expression of prostaglandin D synthase (PGDS), DP_1 and DP_2 receptors in the nasal mucosa of patients with allergic rhinitis is also consistent with a role for PGD_2 in nasal congestion and inflammatory cell infiltration (20). Indeed, a reduction in rhinitis symptoms has been observed after treatment of perennial rhinitis with ramatroban, an effect that has been attributed to its antagonistic effects on DP_2 receptors (27). Asthma severity also was found to associate with PGD_2 in BAL fluid as well as increased hematopoietic isoform of PGDS (H-PGDS) mostly from mast cells and DP_2 expression levels (28). The use of DP_2 antagonists has shown relatively modest but significant results in recent clinical trials in some asthmatic populations (29).

LTs exert pro-inflammatory actions on arterial endothelial cells and smooth muscle cells. LT production by arterial mast cells may contribute to their pro-inflammatory and pro-atherogenic activities in the arterial wall (30).

CLOSING REMARKS

In this review, I emphasize that mast cells are the major producers of eicosanoids, thus contributing to the development of several inflammatory conditions, including asthma, rheumatoid arthritis and atherosclerosis. While mast cell-derived lipid mediators and the reciprocal receptors provide attractive therapeutic targets for treating allergic inflammation, the pleiotropic functions and complex biology associated with these molecules pose a significant challenge to find a way modulating broad spectrum of disease. Also, the strict regulation of lipid droplet may reflect one of the underlying mechanisms sustaining immune tolerance in steady state considering the tissue distribution of mast cells such as intestine or skin.

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