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Role of interleukin-18 in the pathophysiology of allergic diseases

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ABSTRACT

Interleukin (IL)-18 is an IL-1 family cytokine expressed by macrophages, dendritic cells, epithelial cells, and keratinocytes and is implicated in various aspects of both the innate and adaptive immune systems. IL-18 signals similar to IL-1β intracellularly to activate gene transcription. Since its discovery, IL-18 has been demonstrated to play a key role in pathogen defense from helminths and some bacteria. Recently however, evidence has accumulated that IL-18 expression is increased in many presentations of allergic disease. A pathologic role for IL-18 includes stimulating mast cell and basophil degranulation, recruiting granulocytes to sites of inflammation, increasing cytotoxic activity of natural killer (NK) and NK-T cells, inducing Immunoglobulin (Ig)E production and isotype switching, and affecting a broad range of T cells to promote a type II helper T cell (Th2) response. Evidence and importance of these effects are presented, including novel results from our lab implicating IL-18 in the direct expansion of mast cells, basophils, and other myeloid-lineage cells from bone-marrow precursors. The development of urticaria, asthma, dermatitis, rhinitis, and eosinophilic disorders all have demonstrated correlations to increased IL-18 levels either in the tissue or systemically. IL-18 represents a novel site of immune regulation in not only allergic conditions, but also autoimmune diseases and other instances of aberrant immune functioning. Diagrammatic summarized abstract for readers convinance is presented in Fig. 1.

1. Introduction

Interleukin (IL)-18, discovered only 20 years ago, was first known as interferon (IFN)-γ inducing factor due to its ability to induce Type 1 helper T (Th1) cells to release IFN-γ [1]. Since then, this novel cytokine has been found to be expressed by macrophages, dendritic cells (DCs), epithelial cells, and keratinocytes and to activate a wide variety of lymphoid- and myeloid-derived cell types [2–4]. Induced IL-18 is now identified in a number of disorders, like autoimmunity, atopic and allergen-induced allergic responses, and defense against pathogens, most notably helminths. IL-18 is also known to be an IL-1 family cytokine implicated in various aspects of the innate and adaptive immune system, with some analogy to IL-1β. Like IL-1β, IL-18 is produced in an inactive precursor form and requires processing from IL-1β converting enzyme (ICE), or caspase-1, before activation and secretion [5]. Caspase-1 is induced by inflammasomes, multimeric complexes in the cytosol that are in turn activated by mediators such as the nucleotide binding and oligomerization domain-like receptor (NLR) sensor molecules [6,7]. The inflammasomes generally consist of a pattern recognition receptor (PRR) and an apoptosis-associated speck-like protein (ASC) [8]. Characterization of inflammasomes has demonstrated similarities to the apoptosome and has shown the ability to induce pyroptosis, a novel type of cell death distinct from apoptosis [9]. Additional pathways mediated by inflammatory cells lead to the production of active IL-18. Chymase, a secreted enzymatic product of mast cells, can process pro-IL-18 into an active IL-18 fragment extracellularly that is

Abbreviations: 5-LO, 5-lipooxygenase; APC, antigen-presenting cell; ASC, apoptosis-associated speck-like protein; CTMC, connective-tissue mast cell; DC, dendritic cell; ECP, eosinophil cationic protein; EoE, eosinophilic esophagitis; FcεRI, high affinity Immunoglobulin E receptor; GM-CSF, granulocyte/macrophage colony stimulating factor; ICE, IL-1β converting enzyme; IFN-γ, interferon-γ; Ig, immunoglobulin; IL, interleukin; IL-18Ra, interleukin-18 receptor-α; iNKT, invariant natural killer T cell; IRAK, interleukin-1 receptor-associated kinase; MMC, mucosal mast cell; mMCP, mouse mast cell protease; MyD88, myeloid differentiation 88; MZB, marginal zone B cell; NF-κB, nuclear factor-kappa B; NK, natural killer cell; NKT, natural killer T cell; PAR, perennial allergic rhinitis; PRR, pattern recognition receptor; PR3, neutrophil proteinase-3; SAR, seasonal allergic rhinitis; SCF, stem cell factor; SNP, single nucleotide polymorphism; STAT6, signal transducer and activator of transcription 6; TCR, T cell receptor; Th1, type I helper T cell; Th2, type II helper T cell; Th17, T helper 17; Treg, regulatory T cell; TSLP, thymic stromal lymphopoetin.

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unique from caspase-1-derived IL-18 [10]. Additionally, IL-18 is also reported to be secreted by epithelial cells in vitro in response to neutrophil proteinase-3 (PR3) independent of caspase-1 [11]. Similar to the receptor for IL-1 molecules, the IL-18 receptor is a complex of a primary IL-18Rα protein that binds IL-18 with low affinity, and an accessory protein IL-18RB that imparts high affinity binding [12,13]. The downstream signaling process is analogous to IL-1β signaling, including recruitment of myeloid differentiation 88 (MyD88) and IL-1R-associated kinase (IRAK) and eventual translocation of nuclear factor-kappa B (NF-κB) [14–16] (Fig. 1).

2. Role of IL-18 in allergic disease

An allergic disease is a hypersensitive state mediated by specific immunologic mechanisms. Classical allergic diseases are mediated by immunoglobulin (Ig)E, although other cell-mediated processes can occur as well [17]. Although a classic allergic response is mediated by IgE, a vast array of leukocyte types are involved in both the sensitization and later response to allergens.

2.1. IL-18 stimulates the differentiation and activation of mast cells and basophils

The classical definition of allergy describes diseases driven primarily by Immunoglobulin E (IgE)–dependent mechanisms [18]. Basophils and mast cells, myeloid-derived leukocytes that contain granules of vasoactive and pro-inflammatory molecules, degranulate in response to Immunoglobulin E cross-linking with the high affinity IgE receptor (FcεRI) and are well-established as the primary mediators of allergic responses [19,20]. In addition, evidence shows that basophils and mast cells can be stimulated and degranulate in response to different immunoglobulins such as IgG and IgM as well as non-immunoglobulin signals [21,22]. Basophils and mast cells, while serving similar roles, are different in more than just primary location (mature basophils in the blood and mature mast cells resident in tissue). Traditional IgE-mediated anaphylaxis, the most severe presentation of allergy, appears to be primarily dependent on mast cells, with little contribution from basophils [23]. However, IgG-mediated anaphylaxis-like reactions appear to be primarily basophil-driven [23,24]. Mast cells and basophils, as the primary effectors of allergic processes, release a wide variety of vasoactive and inflammatory molecules. Studies support the ability of both mast cells and basophils to selectively release some of these molecules in a process of "activation" without full degranulation [25–28]. Histamine and leukotrienes, two main targets of most commercial anti-allergy treatments, are some of the many molecules released by both mast cells and basophils. Histamine and leukotrienes have immediate effects like increasing vascular permeability and bronchoconstriction [29,30] and long-term effects mediated by regulation of other inflammatory cells, including eosinophil recruitment and adhesion and Th2 promoting DCs [31,32]. The ability of basophils to independently recruit eosinophils and neutrophils in chronic allergic inflammation was demonstrated in a mouse model, and the low abundance (<2%) of basophils in the infiltrates suggested that basophils initiate rather than effect chronic inflammation [33]. In addition, mast cells have the ability to secrete serotonin, enzymes like chymase and tryptase, peptides, growth factors, cytokines, and chemokines, which act as powerful chemoattractants, regulate migration of mast cells, and activate platelets, among many other effects [34–37]. Important cytokines produced by both mast cells and basophils include thymic stromal lymphopoetin (TSLP), IL-4, IL-5, IL-13, IL-25, and granulocyte/macrophage colony stimulating factor (GM-CSF) [38–42]. Additionally, mast cells produce IL-3 and IL-31 [43,44].

Recent research now supports the direct effects of IL-18 on mast cells and basophils. Mature basophils and to a lesser extent mast cells have been shown to express the IL-18Rα chain, but primary

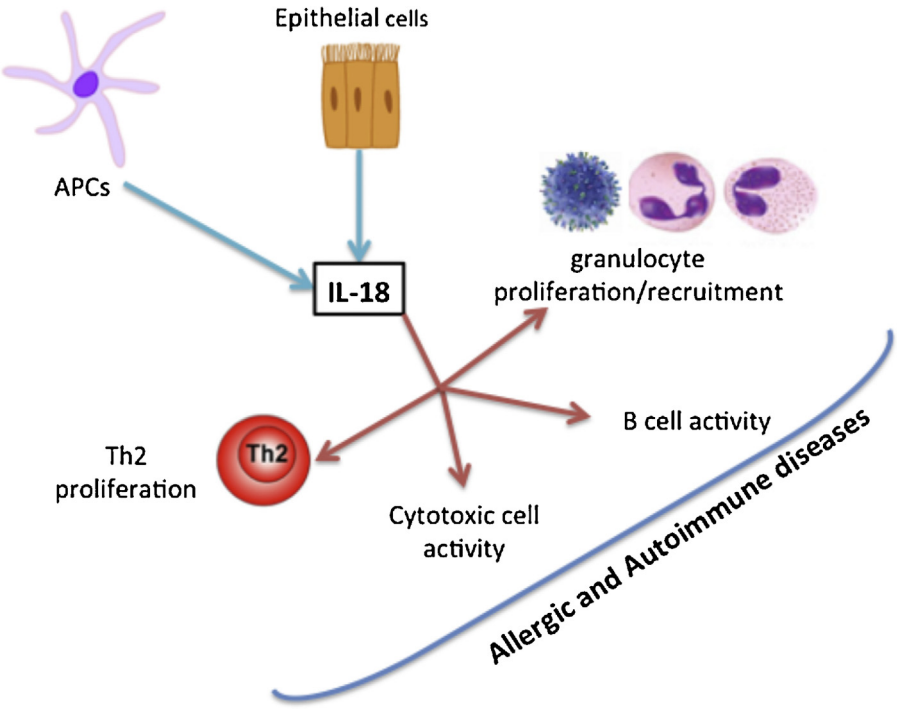

Fig. 1. Abstract Summary. Diagrammatic presentation of review summary on IL-18 secretion by the epithelial and antigen presenting cells and its role in promoting allergic and autoimmune diseases by activating inflammatory cells.