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EDITORIAL

IL-33 MEDIATES ALLERGY THROUGH MAST CELL ACTIVATION: POTENTIAL INHIBITORY EFFECT OF CERTAIN CYTOKINES

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Mast cells (MCs) are hematopoietic immune cells commonly found in adjacent to blood vessels in the lamina propria of airway mucosa. They are important in allergic reactions since the cross-linking of their surface high affinity receptor FcεRI induces activation of these cells, and provokes the synthesis, degranulation and release of inflammatory mediators including arachidonic acid-derived eicosanoids (de novo synthesized), stored enzyme mediators, and inflammatory TH1 and TH2 cytokines, and chemokines. Interleukin (IL)-33 participates in innate and adaptive immunity and inflammation and, acting on CD34+ cells, causes MC differentiation and maturation. IL-33 is generated by activated immune cells, and activates MCs which degranulate and release pro-inflammatory mediators. IL-33 is very important in mediating allergic inflammation and can be induced by IL-1 beta. It is also called "alarmin" and is an inflammatory cytokine IL-1 family member, expressed from mocytes and MCs, which binds its receptor ST2, provoking its release after cell damage. MC-derived allergic compounds in response to IL-33 is critical to innate type 2 immunity. IL-37 is expressed by immune and non-immune cells after pro-inflammatory stimulus. IL-37, an anti-inflammatory cytokine, binds IL-18Rα and suppresses pro-inflammatory IL-1 beta released by activated immune cells such as macrophages. Here, we hypothesize that pro-inflammatory IL-1 family member cytokines released by activated MCs, mediating inflammatory allergic phenomenon, can be suppressed by IL-37.

Cytokines are proteins produced by different cells which mediate the communication of immune cells and inflammatory responses, including allergy. Interleukin (IL)-33 (formerly IL-1F11) is one of the latest IL-1 subfamily members, mainly expressed by immune cells including innate lymphoid cell 2

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(ILC2), and Th2 cells, and its involved in innate and adaptive immunity and inflammation (1).

IL-33 is a 30 kDa cytokine which binds its specific receptor ST2 derived from TLR/IL-1R super family. ST2 receptor forms heterodimer with IL-1 receptor accessory protein (IL-1RAcP) which both bind IL-33. IL-33 is the ligand for the former orphan receptor ST2, also called IL-1R4, and is mainly associated with the TH2 immune response. The immature precursor of IL-33 is cleaved from caspase-1 that produces mature and active IL-33 released after cell damage (2). Therefore, after cell injury or necrosis, NF-kB, p38 and JNK are activated with released IL-33 which is called "alarmin".

IL-33 induces M2 macrophage polarization and favors the production of cytokines/chemokines in these and other cells. It is also a driver of type 2 immune cells in several inflammatory disorders. IL-33 activates dendritic cells and also induces polarization of Th2 cells, playing a role in type 2 diseases. In addition, it regulates innate immune cells through the activation of monocytes and tissue mast cells (MCs) (3).

IL-33 acts on $CD34^+$ cells participating in MC differentiation and maturation. This cytokine is stored in the nucleus and is mainly produced by mononuclear cells, but also several other cells can generate it, including MCs (Table I). In inflammatory diseases, such as asthma and allergy, IL-33 drives nucleus secretion, TH2 polarization, eosinophil recruitment and provokes hyperplasia (4).

Moreover, IL-33 is involved in many different pathological conditions, such as cardiovascular diseases, arthritis, infections, sepsis, atherosclerosis, neurological diseases, cancer and allergy. MC-released IL-33 plays a protective role versus parasites, bacteria and virus infections. However, for unclear reason, IL-1 release suppresses IL-33 (5).

Therefore, MCs express IL-33 ST2 receptor and generate this cytokine which can activate MCs to generate several cytokines such as IL-1, IL-2, IL-4, IL-5, IL-6, and TNF, and also chemokines including CXCL8, CCL1, CCL2, and CCL17, and probably more (6). On the other hand, MCs are involved in the maturation of IL-33 from the immature form. It is interesting that chymase, an MC stored enzyme, can degrade IL-33 into inactive form, as if it were a defensive response to the inflammatory insult.

Parasite infections mediate by MCs strongly induces IL-33 mRNA expression in epithelial cells, demonstrating a significant correlation between MCs and IL-33. The main cells that IL-33 can activate are: MCs, macrophages, NK cells, granulocytes and TH2 cells (7).

MAST CELLS

MCs are immune cells originating from human cord blood $CD34^+$ cells which differentiate and grow into MCs in the presence of stem cell factor (SCF) and IL-6 (8). MCs are ubiquitous in the body and represent one of the most important defensive

Table I. *IL-33 expression.*

a) **Cells that express IL-33 mRNA***:* macrophages, mast cells, epithelial cells, dendritic cells

b) **Cells that express IL-33 protein:** hematopoietic cells, macrophages, dendritic cells, fibroblasts, adipocytes, smooth muscle cells, endothelial cells, bronchial cells, osteoblasts, epithelial cells, hepatocytes

c) **IL-33 organ expression:** stomach, skin, brain, lung, colon, liver, synovial tissue

systems of our organism, in response to numerous different antigens (9). MCs participate in innate and adaptive immunity, and after activation they release pro-inflammatory compounds including chemical mediators, cytokines/chemokines and arachidonic acid products (10). They can clearly respond to allergens and therefore are involved in allergic reaction and inflammation.

MCs express on their surface *c-kit* receptor, and the high affinity receptor ($K_{d=}$ 10^{-10} M) FcεRI for immunoglobulin E (IgE). The stimulation of FcεRI receptor leads to cascade activation of a mitogen-activated protein (MAP) kinase cascade and a phophatidylinositol-specific phospholipase C (PI-PLCγ) (11). The stimulation of mitogen-activated protein (MAP) kinase family members, ERK, JNK and p38, activates many transcription factors including NF-kB, leading MCs to generate and release inflammatory cytokines and chemokines, PGD2, and leukotrienes LTC4, D4 and E4.

Allergy is characterized by the presence of inflammation due to immune cells, where MCs react with TH2 cells and are important elements to the allergenic response (12). Therefore, inflammation in allergic reaction is mediated by both innate and acquired immune cells. Hence, IL-33 induces MCs to secrete Th2 type-cytokines such as IL-4 which promotes TH2 differentiation.

At the intra-cellular level, IL-33 induces MyD88 which plays a critical role in TLR signaling and its deficiency completely abolishes NF-kB and MAP kinase bacterial activation. In addition, MyD88-deficient mice are totally defective in IL-1 and IL-18 cytokine production. Moreover, TLR4-mediated response to LPS involves also MyD88 pathways activating MAP kinases and NF-kB and, consequently, inflammatory cytokine release (Fig. 1).

Toll interleukin-1 receptor (TIR) domain starts with the MyD88 signal, IL-1 receptor-activated kinases (IRAKs), and NFκB (13). When MyD88 becomes phosphorylated, along with IRAKs, it generates a pro-inflammatory signal to the nucleus.

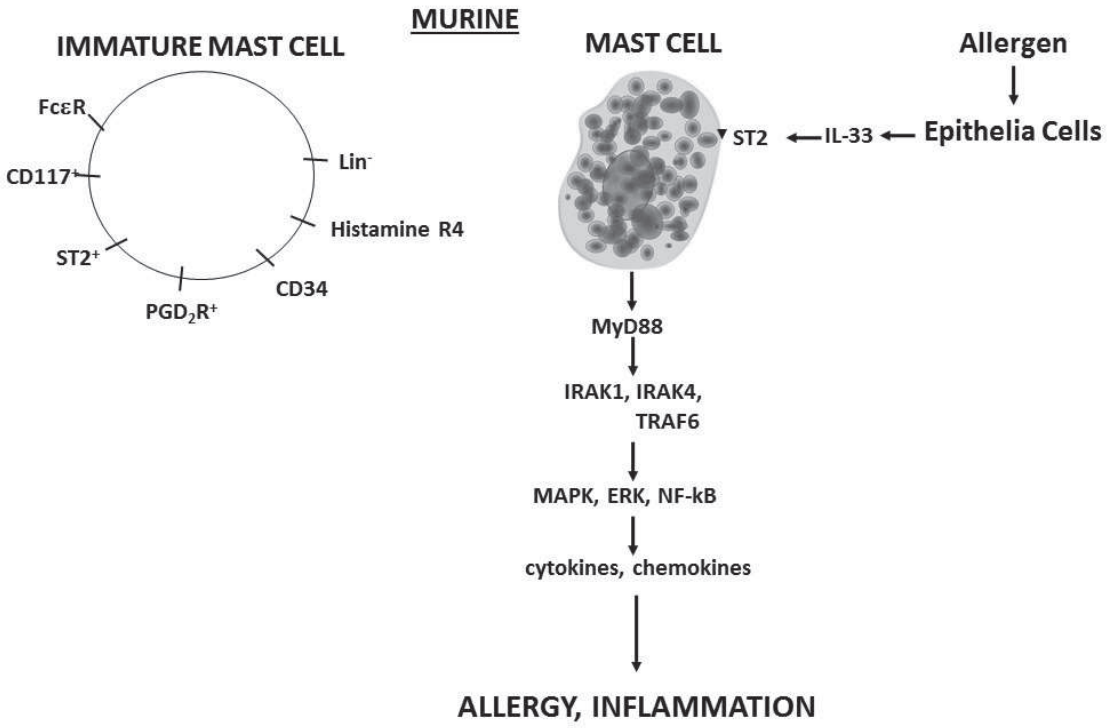

Fig. 1. *Murine mast cells derived from immature mast cells can be activated by ST_2 receptor through IL-33 generated by epithelial cells stimulated by allergen. This effect leads to the production of MyD88 and the release of cytokines/chemokine mediating allergic inflammation. MyD88 can be inhibited by IL-37 released from activated macrophages.*

Hence, MyD88 binds to the TIR domain and begins the cascade of kinases leading to the activation of NFkB and inflammatory cytokine production.

Stimulation of MCs with IL-33 induces also cytokines IL-13 and IL-5, while activating cells with anti-IgE results in a hyperproduction of IL-13. Furthermore, there is a drastic up-regulation of the chemokine CCR7 mRNA receptors after stimulation of MCs with IL-33 or anti-IgE.

MCs express and produce IL-33 which drives allergic diseases, causes inflammation and induces gamma IFN in viral infections. Moreover, IL-33 plays a role in skin inflammation and atopic dermatitis (14). In this disease, the allergens stimulate the epidermis that releases IL-33 which activates both the MCs and the 2 innate lymphoid cells (ILC2) which respectively produce IL-2 with activation of Treg cells, and production of IL-5 and IL-13 which stimulate allergic eosinophils. On this occasion, the Treg lymphocytes go into clonal duplication and produce IL-10 which inhibits the production of IL-5 and IL-13 (15).

IL-33 knock-out mice fail to express allergic inflammatory reaction, showing that this cytokine is decisive for the expression of atopic dermatitis (1).

After cell injury or necrosis there is the activation of NF-kB, p38 and JNK with release of IL-33 which exacerbates inflammation. Therefore, cytokine IL-33 plays an important role in several inflammatory diseases including allergy, asthma, autoimmune diseases, rheumatoid arthritis, sepsis and atherosclerosis (1).

IL-37

Previously, other cytokines, such as IL-10 and TGF-β, were found to be anti-inflammatory. In addition, IL-1 receptor antagonist (IL-1RA), acting on IL-1 receptor down-regulates inflammation (16).

IL-37 is an important new inhibitor of innate immunity and inflammatory IL-1 family members, including IL-1β, IL-18 and IL-33. IL-37 is also decisive in acquired immunity since it has an effect on T cells (17). IL-37 level increases in inflammatory conditions, and is expressed and mainly generated by immune cells, including circulating monocytes, tissue macrophages, dendritic cells, tonsillar B cells, and plasma cells (18).

Caspase-1 is a fundamental intracellular processing enzyme responsible for the maturation of IL-1β, IL-18 and IL-37 (19). Caspase-1 inhibitors partially down-regulate IL-1, demonstrating that it is not the only one responsible for the processing of IL-37. IL-37 inhibits allergic inflammation induced by TLR and its *in vivo* suppression leads to an increase in inflammatory cytokines such as IL-1 (20). Mice *in vivo* treatments with IL-37 effectively reduce the infiltration of immune cells and inflammation induced by IL-1, IL-6, and TNF (17, 21).

Allergic reactions are mediated by several cytokines including IL-1, TNF and MC-released IL-33. In these inflammatory reactions IL-37 has an important potential inhibitory effect (22).

Dinarello et al. report that transgenic mice (IL-37tg) expressing the human gene of IL-37 are less likely to encounter inflammatory diseases (17). Therefore, as the allergy mediated by cytokines is an inflammatory disease, it is possible that IL-37 plays a therapeutic inhibitory role (23).

However, more studies are needed to understand the specific effect of IL-37 and its likely side effects.

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