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EDITORIAL

STIMULATED MAST CELLS RELEASE INFLAMMATORY CYTOKINES: POTENTIAL SUPPRESSION AND THERAPEUTICAL ASPECTS

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Mast cells (MCs) are derived from bone marrow precursors and are immune cells involved in acute and chronic inflammation. MCs are ubiquitous and play a crucial role in innate and acquired immunity. They are activated through cross-linking of their surface high affinity receptors (FcεRI), leading to immediate secretion of stored inflammatory mediators, and late production and release of pro-inflammatory cytokines/chemokines without degranulation. Therefore, MCs are important in inflammatory responses. Members of the interleukin (IL)-1 cytokine family, such as IL-1 and IL-33, and various antigens markedly increase IL-1 and tumor necrosis factor (TNF) expression and secretion from MCs. One of the latest cytokines is IL-33, an IL-1 family member acting via its ST2/IL-1R4, which has been shown to regulate MCs. IL-1 and IL-33 are cytokines found to be implicated in many inflammatory disorders including rheumatoid arthritis, atherosclerosis and psoriasis. In general, IL-1 family member cytokines play a pro-inflammatory role and increase the pathological state. IL-37 is a member of the IL-1 family with anti-inflammatory activity through inhibition of pro-inflammatory cytokines. IL-37 particularly suppresses IL-1-mediated innate inflammatory response, but also acts on the acquired immune response. IL-37 is activated by pro-inflammatory agents and cytokines, playing a protective role against inflammation. This cytokine is a natural regulator of immunity and is a therapeutic promise against inflammatory diseases. Since IL-1 is produced by and activates MCs to release IL-33 and TNF, here we hypothesize that MCs can be inhibited by IL-37 and therefore reduce their pro-inflammatory activity. However, the maturation, transport and secretion of IL-37 remain to be clarified.

Mast cells

In 1878, Paul Ehlich for the first time, identified the presence of mast cells (MCs) on aniline-based preparations. MCs derive from the hematopoietic cells, migrate and mature into various tissues including nerves, blood vessels, skin, gastrointestinal

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tract and brain (1). They can be stimulated by various compounds, including antigens, and IgE, neuropeptides, cytokines, drugs and toxins, but the classic activation occurs with the aggregation of the FcεRI receptor with the consequent release of inflammatory mediators including cytokines and chemokines (2). Furthermore, MCs can respond to pharmacological stimuli and compounds derived from the environment, mediating immunological and inflammatory phenomena (3). MC-mediators can be distinguished in preformed stored compounds in the cytoplasmic granules, and *de novo* synthesized mediators (Table I) (4).

The interaction of anti-IgE to the high-affinity receptor FcεRI on MC surface initiates important cascade biochemical events leading to degranulation (1).

Table I. *Biological mediators released by mast cells.*

Stored and secreted biological mediators from cytoplasmatic granules.
- Tryptase
- Histamine
- Phospholipases
- Heparin
- Chymase
- Carboxypeptidase A
- Hydrolases
- Peroxidases
- Kinogenases
- TNF
De novo synthesized
- Arachidonic acid products: LTB4, LTC4, PGD2, PGE2.
- Cytokines:IL-1,2,3,4,5,6,9,10,13,31,33
-Chemokines: RANTES, CXCL8, CCL2, MCP-3, MCP-4
- Growth factors: Vascular permeability factor (VPF) fibroblast growth factor (FGF-2), vascular endothelial growth factor (VEGF)
- Peptides: Substance P (SP), Pro-neurotensin, Corticotropin-Releasing Hormone (CRH), Vasoactive Intestinal Peptide (VIP).

The MC receptor FcεRI is formed by one α-subunit, four β, and two γ (1). The alpha subunit binds the IgE antibody which subsequently binds the antigen and thus the MC is stimulated, initiating the phosphorylation, with the activation of the tyrosine kinase. Subsequently, the phospholipase C (PKC) is activated, with calcium release and formation of IP3 and diacillglycerol (DAG) and activation of the mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK) and p38 (5). The cascade ends with the generation of cytokines and phospholipases A2 (6).

The stimuli of the MCs are many and can also be of different nature, as shown in Table II.

Table II. *Triggers of mast cells.*

Cytokines: 1, 33, TNF, SCF, TGF- β1
Neuropeptides: Substance P, NGF, CRH, Neurotensin
Biochemical toxins: LPS, Borrelia, mold
Drugs: Polymyxin B, and others

There are many cytokines involved in the activity of MCs, here we will limit ourselves to study only some of them, especially those pro- and anti-inflammatory of IL-1 family members (7).

IL-1

Interleukin (IL)-1 is a classical pro-inflammatory cytokine of innate immunity of which there are different types (IL-1α, IL-1β, IL-18, IL-33, IL-36 α, β, and γ, IL-37, and IL-38) and receptors (8). IL-1 has multiple biological effects including the induction of cyclooxygenase type 2, increased cell expression of adhesion molecules, nitric oxide synthesis and cytokine/chemokine production (9). The IL-1 family is involved in a broad spectrum of both immunological and inflammatory diseases including arthritis, atherosclerosis, Alzheimer's (the most common cause of dementia), and skin diseases such as psoriasis (10). IL-1 is produced by many types of cells, but mostly by monocytic cells (11). IL-1 (distinct in IL-α and IL-1-β) is a soluble mediator of inflammation with extracellular biological activity (8). In this study we will refer to IL-1-β, which is the most present in man in extracellular form.

IL-1 is found in the cytosol in immature form (35-kDa) and is transformed into a mature form (17-kDa) from the caspase IL-1-converting enzyme (ICE) in the active form IL-1-β. The release of IL-1-β is induced by extracellular macrophage ATP (8).

In vitro, MCs stimulated with IgE through the receptor FcεRI, produce various cytokines including TNF, IL-6, IL-31, IL-33 and IL-1, suggesting that there are links between the mediated IgE allergic phenomena and the stimulation of inflammatory cytokines (12). IL-1 stimulates human MCs to secrete IL-6 without tryptase.

In allergic diseases, MCs interact with IL-33 that can be induced by IL-1 which is recognized by different types of cells (13). Therefore, the blockade of IL-1 can certainly produce relief in allergic diseases.

TNF

Tumor necrosis factor (TNF) was first described in activated macrophages, and there is evidence that resident mouse peritoneal MCs constitutively contain large amounts of TNF (14). It was recently reported that substance P plus IL-33 produces massive amounts of TNF (12). Therefore, MCs produce a broad panel of multifunctional cytokines including TNF, a multifunctional cytokine that influences physiological and pathological mechanisms (15).

In addition to the newly synthesized TNF secretion (in several hours), MCs are the only immune cells that store and rapidly secrete (in about 10 minutes after IgE stimulation) preformed TNF. Therefore, MCs activated with IgE *in vitro* produce extracellular TNF and exhibit higher levels of TNF messenger RNA. Thus MCs have a preformed TNF and an immunologically inducible TNF (16).

TNF is a cytokine which has been implicated in inflammatory processes and TNF gene is expressed in cultured human LAD2 and primary MCs derived from umbilical cord blood (12).

It has been noted that some tissues exposed to substance P (or other neurotransmitters) and other stimulators, produce TNF, both preformed and inducible, which can play the role of recalling other inflammatory cells such as neutrophils and macrophage granulocytes, and it can also activate the T cell receptor (17). In addition, TNF induces adhesion molecules such as ICAM-1 and ELAM-1 involved in the recruitment of inflammatory immune cells. TNF-derived MCs stimulates fibroblasts in the production of collagen, playing an important role in allergic reactions (17). Moreover, the production of TNF by MCs also has an anti-tumor role since the number of cytokines produced by MCs is higher in cancer. Therefore, IL-33 can also play a protective immune role, as it stimulates TH2 cells to produce cytokines and increases the type 2 lymphoid cells (17).

IL-33

IL-33 is a member of the family of IL-1 ST2/IL-1R4 receptor involved in a number of diseases and is considered a cytokine "alarmin", as a recognized signaling mediator of inflammation not due to infections, but to trauma and stress (sterile inflammation) (18). The immature form of IL-33 is cleaved by a caspase-1 which makes cytokines active. To date, it is known that from the proteases of MCs some mature forms of IL-33 derive that activate lymphoid cells which also participate in the inflammatory process (17).

IL-33 is a pro-inflammatory cytokine and is found to augment mainly allergic diseases, as well as being involved in rheumatoid arthritis, atherosclerosis, psoriasis, inflammatory bowel disease, neurological disorders, etc. However, the nuclear suppression of IL-33 proves a systemic inflammation that can also be lethal, demonstrating that this cytokine also plays an anti-inflammatory role (18).

We and other authors have already reported that IL-33 is a cytokine which acts through the ST2 receptor that belongs to the toll like receptor (TLR)/IL1R super family. IL-33 is primarily expressed by different types of structural cells including dendritic cells, macrophages, endothelial cells, intestinal epithelial cells, fibroblasts, adipocytes, smooth muscle cells, bronchial and osteoblast (18).

MCs also produce many cytokines (including IL-33) and chemokines, as reported in Table I, and may also promote the maturation of $CD34^+$ cell, which is an MC progenitor. In fact, IL-33 plays a role in the maturation of MCs which, in turn, can produce mediators for the maturation of IL-33 from the immature form (17).

IL-33 increases the production of IL-31 released by MCs without allergic stimulation (17). IL-31, which is involved in tissue remodeling, induces pro-inflammatory cytokines, regulates cell proliferation, and is very pruritogenic. IL-31 and IL-33 work

together and their expression is involved in disease severity. In fact, IL-33 activates MCs without degranulation and therefore, without the release of stored chemical mediators. Moreover, this cytokine is capable of increasing non-allergic stimuli such as the neurotransmitter substance P, intervening in non-allergic inflammatory diseases (19) In addition, IL-33 increases the effect of IgE on MCs and TNF gene expression, favoring allergic reactions.

We recently reported that IL-33 has been implicated in the pathogenesis of psoriasis via keratinocyte and MC activation (14).

IL-18

IL-18 possesses an IL-18Rα receptor inducible (which binds IL-18) and IL-18Rβ which is expressed constitutively and mediates signal transduction (20). Members of IL-1R family with TIR domain are shared with TLRs. Cytoplasmic TIR domains cooperate with the MyD88 factor which activates the nuclear factor NF-κB and generate cytokines (20)

IL-18 is involved in many immune and inflammatory mechanisms. It is expressed essentially by macrophages, dendritic cells, epithelial cells, keratinocytes and other cells, participating in the innate and adaptive immune responses. IL-18 is important in the defense of the human body against bacteria and parasites, but also participates in allergic diseases, where MCs play a crucial role (17). In fact, IL-18 contributes to the activation and degranulation of MCs and its level is high in allergic phenomena. IL-18 was originally called IFN-γ-inducing factor (IGIF) and it was reported that it may also be activated in an inflammasome-independent manner by proteases, such as proteinase 3 and chymase. This cytokine can also play a chemotactic role, causing inflammatory cell recruitment, including macrophages, neutrophils and basophils (17).

It is known that IL-18 promotes the response of TH2 cells involved in both sensitization and later response to allergens, autoimmune diseases and cancer. However, IL-18 does not directly stimulate TH2 cells, which mediate allergic responses induced by antigens and produce many effects on inflammatory cells. Therefore, activated APC cells, release IL-18, provoking TH2 cell and granulocyte recruitment (20). In addition IL-18 causes cell proliferation, cytotoxic and B cell activity in hypersensitive state

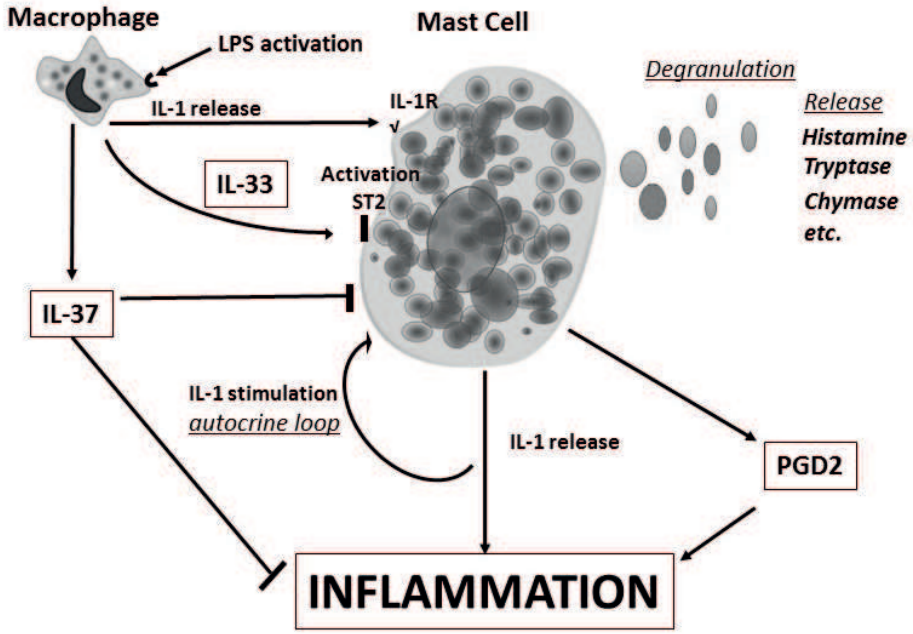

Fig. 1. *This figure depicts that LPS activates macrophages and releases IL-1 and IL-33 which induce mast cell activation mediating inflammation. In addition, macrophage produces also IL-37 which inhibits mast cell IL-1 release and inflammation.*

and other disorders. In allergic reaction, IL-18 increases IL-5, influences eosinophilia, and induces cell differentiation in rodents. Moreover, IL-18 stimulates eosinophilia in asthma and activates CXC and CC chemokine generation. On MCs, IL-18 binds to its IL-18R receptor, provoking the release of IL-4, IL-13 and histamine, similar to the activation of MCs with the allergen that binds FcεRI receptor (17).

Inhibition of the actions of this cytokine would certainly provide relief both to individuals suffering from allergic diseases and to those with acute and chronic inflammatory disorders. IL-18 can be inhibited by both IL-18BP found in nature, and by IL-37, which down-regulates signal transduction and responses caused by IL-18 and, therefore, inhibits inflammation (20).

IL-37

IL-37, previously called IL-1 family member 7 (IL-1F7), is a cytokine of the IL-1 family which includes IL-1α, IL-1β, IL-1RA, IL-18 and IL-33, and can improve inflammatory response (21). IL-37 is a natural suppressor of both innate and acquired immune responses. IL-37 is expressed in a variety of tissues and cells, including monocytes, endothelial cells and epithelial cells. It has been reported that IL-37 inhibits many inflammatory states, suppressing monocytes and macrophages, but may also increase after a pro-inflammatory stimulus caused by LPS (22). IL37 binds IL-18Rα chain, acts with an intracellular mechanism translocating to the nucleus, which inhibits the expression of pro-inflammatory signals cJun, MAP kinase p38, STAT transcription factors and p53.

IL-37 acts by inhibiting the inflammatory signals NF-κB, and transcription factors AP-1, which lead to the production of pro-inflammatory cytokines of the IL-1 family.

Activated MCs produce pro-inflammatory cytokines, including IL-1 and TNF (23-24). IL-37 possesses a pleiotropic anti-inflammatory activity with inhibition of macrophage activation, leukocyte adhesion, metalloproteinase production and IL-1-inducing TNF generation in MCs.

TNF is induced by many pro-inflammatory proteins including IL-1. Furthermore, IL-1 possesses the autocrine property of inducing itself (Fig. 1). Hence, IL-1 induces IL-1 and TNF in macrophages and MCs. Since IL-37 blocks IL-1 and IL-1-induced TNF, these inhibitory effects could be of great benefit in the treatment of inflammatory disorders including those mediated by MCs (25-26). It will be important to develop IL-37 formulation that can deliver it selectively to the cell target including MCs and macrophages.

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