



New insight into systemic mastocytosis mediated by cytokines IL-1 β and IL-33: Potential inhibitory effect of IL-37

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ARTICLE INFO

Keywords:

Mastocytosis

IL-1

IL-33

IL-37

Inflammation

Mast cells

ABSTRACT

Systemic mastocytosis in various forms is characterized by mast cell (MC) infiltration of the bone marrow and other internal organs. The most common form is the indolent one with life expectancy similar to the normal population, while the systemic aggressive myeloproliferative type presents serious damage to various organs and is associated with mature and immature atypical mast cells. In systemic mastocytosis patients, MCs could be activated with consequent severe anaphylactic reactions, along with other symptoms. MCs, which are reactive to a variety of external factors such as allergens or other inflammatory or physical stimuli, derive from pluripotent cellular progenitor CD34⁺ which leaves the bone marrow as CD34⁺/CD17⁺ for implantation in the tissues where they reach maturation. MCs participate in the innate and adaptive immune system where they play a role in host defense. Activation of MCs occurs through the binding of IgE to Fc ϵ RI receptor, and initiates the phosphorylation and activation of the p38 tyrosine MAP kinase. After various reactions there is a subsequent translation and generation of pro-inflammatory cytokines which are strongly linked to allergic inflammation and mastocytosis. Human cytokine interleukin-37 (IL-37), a unique IL-1 β family member, has strong protective and anti-inflammatory properties, influencing cellular metabolism. We investigated the effect of IL-37 on inflammation in mastocytosis and report that the hematopoietic expression of IL-37 can reduce the inflammatory state in this disease. IL-37 limits excessive inflammation, which suggests that IL-37 may be beneficial to the metabolic and inflammatory process and is a candidate as a potential new therapeutic agent.

1. Introduction

1. Mastocytosis, described for the first time about two centuries ago (by Nettleship and Tay), includes several disorders characterized by an excessive generation of clonal expansion mast cells (MCs), which occur in tissues such as bone marrow, liver, skin, spleen (Austen, 1992). Mastocytosis presents a mutation of the KIT gene that encodes the tyrosine kinase receptor protein CD117, resulting in abnormal differentiation and survival of MCs. The disease includes various forms of MC disorders, with myeloproliferative activity and sometimes with skin lesions with a severe clinical course (Theoharides et al., 2015). Mastocytosis can have varying degrees of aggression ranging from mild to severe (Metcalfe, 1991). The pathological severity of this disease is

revealed by the presence of serum levels of tryptase and alkaline phosphatase and can especially affect the liver and spleen accompanied by fibrosis (Metcalfe, 1991). In systemic mastocytosis (SM), which mostly occurs in adults, MCs, as well as other cells, such as B lymphocytes, dendritic cells, epithelial cells and natural killer cells, affect micro-vessels containing nucleic acids and a large number of exosomes influencing the immune responses and the physiological state of the affected tissues contributing to the pathological state. In mastocytosis there are many clinical manifestations affecting several organs due to inflammatory mediators, including cytokines released by MCs, which mediate the disease (Deb and Tefferi, 2003).

Furthermore, it has been seen that these phenomena influence the formation of cancer cells with severe pathological consequences

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<https://doi.org/10.1016/j.ejphar.2019.172473>

Received 15 February 2019; Received in revised form 18 June 2019; Accepted 18 June 2019

Available online 19 June 2019

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(Volertas et al., 2018). Inflammation can influence both the formation of cancer cells and their behavior, even if at the moment the real reasons that can influence the formation of cancer cells still remain obscure.

The accumulation of neoplastic MCs is more frequent in the bone marrow, while the skin is less involved (Volertas et al., 2018). The understanding of this disease has evolved with the study of stem cell factor which binds to the KIT receptor and it is critical for human MC development and survival (Gotlib et al., 2016). Therefore, KIT receptor is an important target in mastocytosis, where there is a somatic mutation of this gene, even in the absence of its SCF ligand.

2. Mast cell and mastocytosis

Mastocytosis can be classified according to various parameters (according to D.D. Metcalfe, 1991) (Metcalfe, 1991) some of which include blood data, molecular markers (such as CD), tryptase assays, and KIT study. The illness can present in more aggressive and less aggressive forms, and the prognosis can differ among the various forms (Azaña et al., 2016). In mastocytosis, MCs express CD2 and CD25 receptors related to lymphomas and not expressed in normal MCs (Brockow and Metcalfe, 2010).

There are two forms of MC leukemia (MCL), a less frequent one presenting more than 10% of MCs compared to the total white blood cells, and a non-leukaemic (MLC) with less than 10% (Brockow and Metcalfe, 2010). MLC is also divided into acute and chronic, where the acute is more severe and involves the organs, while the chronic is less aggressive and does not affect the organs (Metcalfe, 1991). The less severe forms can have a good prognosis and the subjects can have an almost normal life, while the more serious forms can lead to death.

Many clinical experimental therapies have been carried out and are being studied in mastocytosis. One of these is based on progenitor stem cells and oncogene KIT, considered a crucial therapeutic target, and this can open new ways of treatment (El-Agamy, 2012). Moreover, a number of molecular and biochemical pathways are studied focusing on KIT-dependent oncogenesis, and on the analysis of tyrosine-protein kinase and STAT, but the results are not yet defined. In fact, this disorder is a pathological phenomenon which still has many dark sides.

3. Mast cells

MCs are granular immunocytes generated by a pluripotent cellular progenitor CD34⁺ which leaves the bone marrow as CD34⁺/CD117⁺ for implantation in the tissues where they reach maturation (Wilcock et al., 2018; Galli et al., 2005). Both immature and mature cells have many receptors including those of cytokines and chemokines (Galli et al., 2005). MCs are specialized secretory cells of the innate immune system that play an important role in host defense (Conti et al., 2007). MCs mature and reside in vascularized tissues and serous cavities, where they interact with the environment (Theoharides et al., 2004). They are strongly linked to the pathology of allergic diseases, which can also lead to anaphylaxis and they can also participate in host defense as components of T helper cell type 2 immune responses (Tettamanti et al., 2018a,b).

It is well known that MCs play a role as critical effector cells in inflammatory reactions and acute IgE-mediated allergic diseases, but also other molecules can activate MC receptors, such as c-KIT, Toll-like receptors (TLRs), interleukin (IL)-33, IL-1, neurotransmitters such as substance p and CRH, etc. (Theoharides et al., 2004). IL-1, associated with innate immunity, and TLR families share similar functions.

MCs can be activated through various receptors when they are exposed to the corresponding ligands. Activation occurs when antibody IgE bound to surface FcεRI receptors and cross-linking multivalent antigens, or when immune complexes bind to Fcγ receptors (Theoharides et al., 2007).

The classic activation of MCs *in vitro* occurs when the IgE binds to its

FcεRI receptor at a very high affinity ($1 \times 10^{10} \text{ M}^{-1}$). This receptor is expressed on MCs and it is formed by one alpha, four beta, and two gamma subunits (Galli et al., 2005). The gamma sub-units initiate the reaction that is amplified by the beta sub-units. Stimulation of MC occurs through binding of the antibody to the antigen, such as the allergen, with the initiation of phosphorylation and activation of Src, Syk, and Tec family protein tyrosine kinases. Through phosphorylation, many molecules are recruited with the activation of phospholipase Cγ (PLCγ) and protein kinase C (PKC) (Galli et al., 2005). PLCγ regulates the release of intracellular Ca⁺⁺, while PKC hydrolyses membrane phospholipids with inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) formation. Subsequently, there is the formation of mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 MAPK, which are involved in transcription, and the biochemical pathway that includes MAPK leads to the transcription and generation of cytokines. In addition, the activation of PLA2 leads to the formation of arachidonic acid metabolites: prostaglandins, and leukotrienes (Galli et al., 2005).

MCs play an important role in many inflammatory diseases including allergies, asthma, atherosclerosis, and psoriasis. (Valent et al., 2017).

MCs produce a number of cytokines that contribute to inflammation (Theoharides et al., 2004). Cytokines act through their cellular receptors and begin the kinase signal transduction inside the cell, an effect that mediates a wide range of diseases (Sismanopoulos et al., 2013).

The accumulation of MCs in mastocytosis, in particular in the skin, lymph nodes and bone marrow, play a pathological role, including inflammation, and their proliferation is due to the mutation of the oncogene c-KIT responsible for the encoding of the SCF receptor (Theoharides and Conti, 2004). Both pro- and anti-inflammatory cytokines and chemokines participate in these reactions (Petra et al., 2014). However, the mechanism(s) in these cells are still unclear, since the results obtained to date are not coming from the direct study on MCs.

The scientific literature is a little scarce in articles concerning the cytokines/chemokines released in mastocytosis because there are not direct study of MCs (Nowicki, 2014). In particular in mastocytosis, HMC-1 migrate under the action of different compounds including complement factors C3a, C5a, C1q, histamine, leukotrienes, and TNF cytokine, TGF-β1, VEGF, PGDF, SCF, IL-3, IL-4, IL-6, IL-15, IL-16 and IL-18 mediating inflammation (Nedoszytko et al., 2015).

Some authors have based their work on *in vitro* cell lines such as HMC-1 which are leukaemic MCs, where it has been seen that they can generate both chemokines and cytokines, including their receptors, thus fueling the inflammatory process. The reason that these authors use HMC-1 is because they assume that the responses of this cell line may reflect those of human MCs, even though it is not really correct (Min et al., 2007).

MC-release and secretion products contribute in many pathological processes, but there are no clinical studies evaluating the therapeutic effect in the treatment of MC-mediated diseases. Therefore, the specific inhibition of the powerful inflammatory cytokines would be of great help for a targeted therapeutic action. In this paper we studied the pro-inflammatory cytokines IL-1 family members and their eventual inhibition, proposing IL-37 as a therapeutic immune cytokine to be added to the classic mastocytosis treatments (Fig. 1).

4. Activated MCs release IL-33 and IL-1

4.1. Interleukin-33

MC IL-1 activation and production *in vitro*, can exert both autocrine and paracrine actions and its signals take place in many clinical inflammatory diseases including skin allergies, asthma and mastocytosis, where other immune cells participate, exacerbating the pathological state (Mendonça et al., 2017). The activation of pattern recognition

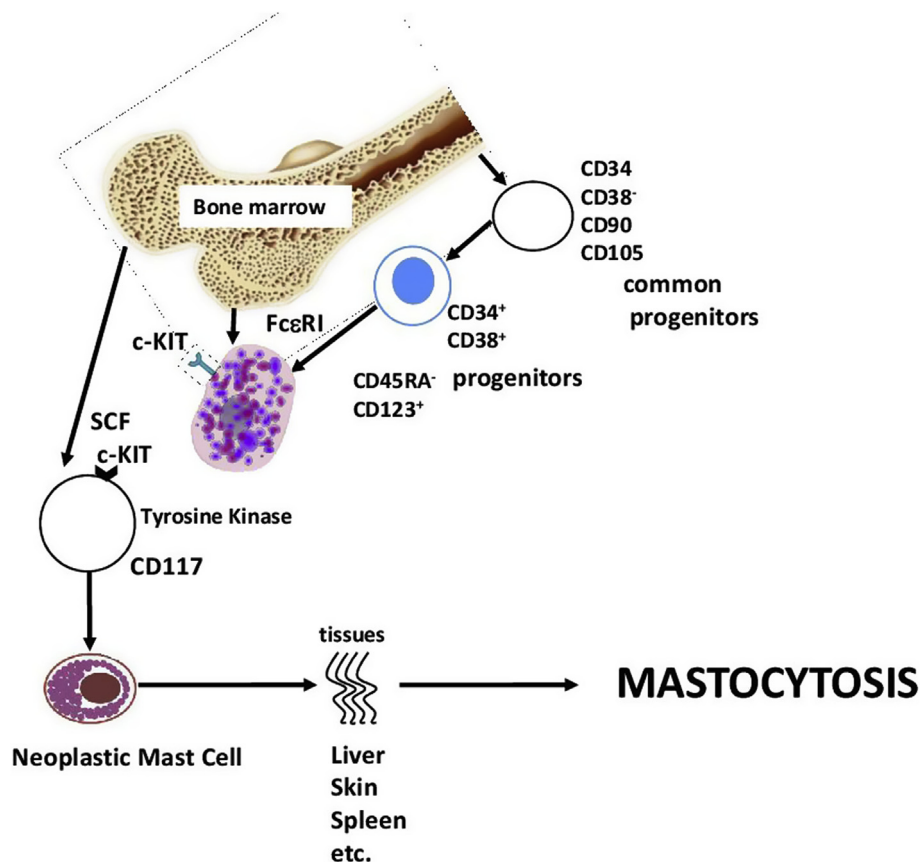


Fig. 1. Neoplastic mast cell proliferation participating in mastocytosis.

receptors (PRRs) increases the expression of pro-IL-1 β that will be transformed into mature and active forms of IL-1 β by the inflammatory named NOD-like receptor family pyrin domain-containing-3 (NLRP3) (Jin and Flavell, 2010). As previously stated, IL-1 β is a good inducer of MC and increases the gene expression and protein release of IL-33 *in vitro* (Taracanova et al., 2018).

The cytokine IL-33 genes and those of its ST2 receptor (IL-1R4) have recently been identified as susceptibility genes in studies of allergic diseases (Tettamanti et al., 2018a,b). The binding of IL-33 to its ST2 receptor leads to activation of the MyD88 and IRAK-4 metabolic pathway with an increase in Th2 cytokines and, therefore, of the allergic reaction where an increase and degranulation of MCs are involved (Shik et al., 2017).

Recently it was reported that MyD88 may be inhibited by IL-37, a cytokine member of the IL-1 family, with potential therapeutic effect on inflammatory disorders (Zhan et al., 2017). Thus clinically blocking IL-1 would have a significant curative effect on inflammation (Conti et al., 2018a,b,c; Varvara et al., 2018).

4.2. Interleukin-1

IL-1 β is elevated in inflammatory diseases and is very important for the development of acute and chronic inflammation including autoimmune disease, where MCs play a role (Dinarello, 2009). In addition, the proinflammatory cytokine IL-1 regulates gene expression of other inflammatory mediators (Gallenga et al., 2019). Therefore, in experimental studies, IL-1 β has a stimulatory effect on MCs, leading to the generation of proinflammatory cytokines (Kandere-Grzybowska et al., 2003). In fact, *in vitro* this interleukin stimulates and activates MCs to secrete IL-6 without degranulation.

Stimulation of MCs with a specific Ag with IgE bound to its high-affinity receptor, FcεRI causes the release of the granule-associated MC

protease, tryptase, and other pro-inflammatory mediators, and an increase in intracellular levels of calcium ions; while IL-1 β stimulates MCs without any effect on intracellular calcium (Metcalf, 1991; Georgilis et al., 1987). The pro-inflammatory cytokines of the IL-1 family injected experimentally into the skin trigger a series of inflammatory reactions (Schlapbach and Simon, 2014). Moreover, since IL-1 β induces the expression of its own genes, which serves as a positive-feedback loop that amplifies the IL-1 response in an autocrine or paracrine manner (Ghezzi and Dinarello, 1988), and also stimulates other pro-inflammatory cytokines, such as TNF in macrophages and mast cells, it is likely that IL-37, besides having an inhibitory action on IL-1 β , is also capable of inhibiting other pro-inflammatory cytokines that mediate mastocytosis. In mastocytosis there is involvement of MCs producing cytokines and increased levels of tryptase (Pardananani, 2015). Experimental inflammatory infiltrative diseases of the skin, similar to mastocytosis, present urticarial skin rash with recurrent fever, elevated CRP and leukocytosis, and are mediated by IL-1 β , an effect that is inhibited by IL-1Ra (Nasti and Timares, 2012). In addition, in skin inflammation, keratinocytes produce IL-1 β and IL-18 which activate the inflammatory process, Th2 and IgE-mediated responses (Corsini and Galli, 1998). On the other hand, agonists that activate Toll-like Receptor (TLR) on dendritic cells promote Th0 and Th1 responses, which are sources of pro-inflammatory cytokines. Even in these cases, blocking IL-1 β could have a notable therapeutic effect against skin diseases including mastocytosis (Caraffa et al., 2018).

Blocking IL-1 β with IL-37 could induce an important and new clinical response (Kritas et al., 2018).

5. Interleukin-37

IL-37 (also called IL-1F7) is a human cytokine, member of the IL-1 family, with anti-inflammatory properties (Cavalli and Dinarello,

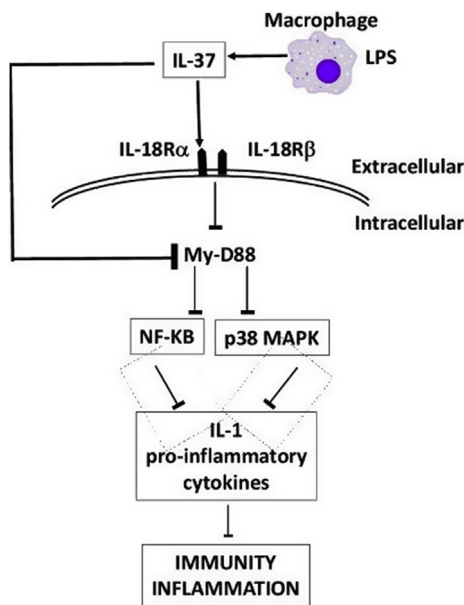


Fig. 2. IL-37 is released by activated TLR 2, 4 macrophages, both IL-37 precursor and mature bind IL-18R α . A pro-IL-37 is cleaved by caspase-1 into mature IL-37, some of which enters the nucleus and the rest is released along with pro-IL-37 outside the cell. Extra cellular protease can then process pro-IL-37 into a much more biologically active form which inhibits cytokine genes expression and innate inflammation.

2018). There are 5 types of IL-37 ranging from “a” to “e”, of which IL-37b is the most effective and studied *in vitro* and in mice, so in this article we discuss only IL-37b (Dinarello et al., 2016). IL-37, which is not expressed in mouse but only in human, is generated in peripheral blood mononuclear cells (PBMC) and in other different tissues, with an inhibitory activity on innate and acquired immunity (Garlanda et al., 2013). However, a specific receptor for IL-37 has not yet been identified (Ballak et al., 2018). IL-37 is stimulated *in vitro* by bacteria and their

products, such as lipopolysaccharide (LPS), and is elevated in experimental and clinical inflammatory diseases, with an action opposed to pro-inflammatory IL-1 family cytokines (Conti et al., 2018a,b,c). IL-37 is made as a precursor (pro-IL-37) cleaved by caspase-1 into mature IL-37, of which some enter the nucleus and the rest is released along with the pro-IL-37 outside the cells (Cavalli and Dinarello, 2018). However, the precise inhibitor mechanism(s) of action of IL-37 is presently unknown (Conti et al., 2019).

Activation of IL-37 leads to anti-inflammatory pathways with an increase of several compounds including STAT3 and 6, FoxO transcription factors, AMPK gene and protein expression; and a reduction of NF- κ B pathways, AP-1 family members, c-Jun, p38 MAPK, and pERK (Mastrangelo et al., 2018). In addition, IL-37 promotes tolerogenic dendritic cells, an increase of Treg CD4⁺ cells, and IL-10 production (Cavalli and Dinarello, 2018) (Fig. 2).

IL-37 has the ability to act on the metabolism of immune cells and to reduce the production of cytokines induced by TLR4 activation and IL-1 (Dinarello et al., 2016). It has been reported that IL-37 exerts a remarkable anti-inflammatory action in many experimental and clinical diseases including those mediated by MCs, such as allergy, atherosclerosis, asthma, allograft rejection, migraine, obesity, fibrosis, endotoxemia, ischemic liver disease, acute lung injury, experimental colitis, myocardial infarction, spinal cord injury, cancer and type 2 diabetes (Hoeke et al., 2017; Sakai et al., 2012; Conti et al., 2018a,b,c; Coll-Miró et al., 2016). Moreover, the transgenic expression of IL-37 and the administration of exogenous IL-37, protect from inflammatory disorders (Coll-Miró et al., 2016).

6. Conclusion

In mastocytosis there is an activation of the MCs ((Theoharides et al., 2019)) with production of chemokines and pro-inflammatory cytokines including IL-1 β which is strongly inhibited by IL-37.

In this disorder, activation of the MCs lead to the production of pro-inflammatory IL-1 β , which is inhibited by IL-37 (Fig. 3). IL-37 binds to the IL-18R α receptor, blocks MyD88 and down regulates IL-1 β . Therefore, inhibition of IL-37 on pro-inflammatory cytokines exerts a

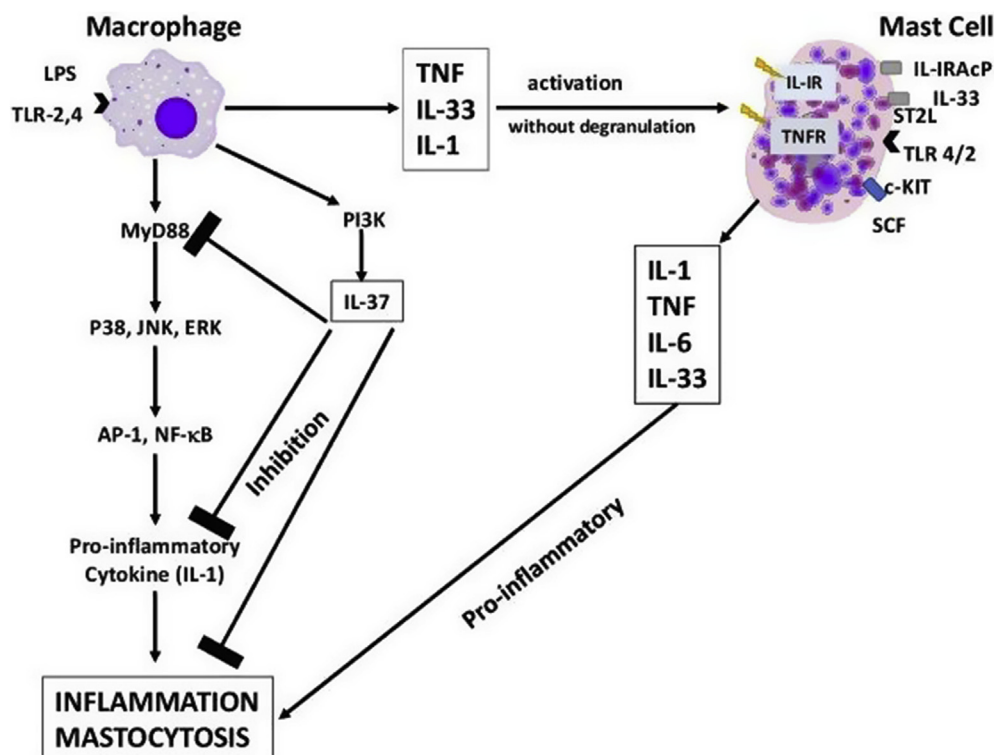


Fig. 3. Activated macrophages by TLR2/4 lead to proinflammatory cytokine mediating inflammation and participating in mastocytosis, an effect inhibited by IL-37. Moreover, macrophage-derived IL-1 induces mast cell activation without degranulation, and therefore provokes the release of proinflammatory cytokines and MCP-1 chemokine.

beneficial action in mastocytosis.

In the present article, we propose for the first time IL-37 as a possible therapeutic cytokine suppressor of inflammation induced by IL-1 β -derived MCs in mastocytosis. However, at the moment we do not know whether IL-37 only reduces inflammation or if it also influences the development and the course of mastocytosis.

Disclosure

All authors report no conflict of interest relevant to this article.

Funding

None. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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