Possible role of mast cells and IL-37 in the pathogenesis of psoriasis

Pio Conti[1]
Alessandro Caraffa[2]
Enrico Spinas[3]
Gianfranco Lessiani[4]
Spiros K. Kritas[5]
Gianpaolo Ronconi[6]
Theoharis C. Theoharides[7]

[1] Immunology Division, Postgraduate Medical School, University of Chieti-Pescara, Chieti, Italy
[2] Department of Pharmacy, University of Perugia, Perugia, Italy
[3] Department of Surgery and Odontostomatological Sciences, University of Cagliari, Cagliari, Italy
[4] Villa Serena Hospital, Città Sant'Angelo (PE), Italy
[5] Department of Microbiology, University of Thessaloniki, Greece
[6] Clinica dei Pazienti del Territorio, Policlinico Gemelli, Roma, Italy
[7] Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, Boston, MA, USA

Address for correspondence:
Pio Conti
Immunology Division, Postgraduate Medical School, University of Chieti-Pescara
V.le Unità d'Italia 73
66013 Chieti, Italy
E-mail: pconti@unich.it

Summary

Psoriasis (PsA) is an autoimmune skin disease characterized by an excessive keratinocyte proliferation, abnormal differentiation, angiogenesis, over-expression of several cytokines/chemokines and elevated mast cell (MC) number. MCs in PsA mediate the chronic inflammation of the skin, contributing to the disease pathogenesis. MCs are usually associated to immediate hypersensitivity and allergic disorders and play an important role in innate and acquired immunity. They respond to many different stimuli including cytokines [interleukin (IL)-1 and IL-33], and microbes and their products (LPS) which bind TLR-4, leading to and causing the generation of MC pro-inflammatory cytokines.
In the inflammatory site, keratinocytes and MCs cross-talk and cooperate, amplifying inflammatory disorders including PsA. In fact, macrophages generate IL-1 and IL-33 which induce NF-kB and MAPK and activate MCs to release TNF, IL-6 and other pro-inflammatory cytokines/chemokines. In this paper, we report an important inhibitory effect of IL-37 on MC pro-inflammatory cytokine generation. IL-37 strongly suppresses pro-inflammatory cytokines, including IL-33 and TNF, in MCs activated by IL-1 in psoriatic plaques. This effect describes the importance of IL-37 in the pathogenesis of PsA, mediated by MCs and highlights new therapeutic strategies.

KEY WORDS: psoriasis; IL-37; mast cells; cytokines; inflammation; immunity.

Introduction

In 1986 we reported that IL-1 is a key mediator of host response to various infectious, inflammatory, neoplastic, and immunologic challenges (1). In the same year, Camp et al. (2) suggested that interleukin 1 plays an important role in the pathogenesis of psoriasis (PsA) (3). In 1989, Dinarello's group found that IL-1 activity is present in a keratinocyte cell line supernatant, and that UVB therapy induces circulating IL-1 which may originate from both keratinocyte and non-keratinocyte sources (4).
The IL-1 family is a growing group of cytokines with both pro- and anti-inflammatory properties involved in immune disorders and inflammation, including PsA (4, 5).
PsA is a common immune-mediated chronic inflammatory skin disease, characterized by skin inflammation, that occurs in 2 to 3% of the worldwide population (6, 7). Approximately 30% of PsA patients is affected by psoriatic arthritis (8). PsA is a chronic relapsing autoimmune disorder which presents excessive keratinocyte proliferation, abnormal differentiation, elevated mast cell (MC) number, enhanced type I IFN, angiogenesis and over-expression of several chemokines and cytokines which contribute to the disease pathogenesis (9). PsA is an inflammatory cutaneous, immune-mediated, and multi-factorial skin disorder, characterized by psoriatic plaques (10). Moreover, PsA is associated with increased risk of depression, cardiovascular disease and arthritis (11).
In PsA, cytokines and chemokines generated by MCs and other immune cells, including keratinocytes, cause the recruitment of leukocytes mediating inflammation (12). The disease is mediated by cross-talk

between keratinocytes and immune cells, such as Th1, Th17, Th22, B cells, macrophages and MCs (13). Activated T-cell subsets, localized in the skin, initiate a local inflammatory process leading to development of a psoriatic plaque (14). Predominantly, Th17-driven process links to the pathways of angiogenesis, excessive and aberrant proliferation of epidermal keratinocytes, and inflammation (15). The balance of Th17/Treg and IL-23/Th17 pathway is determinant for the inflammatory process (16, 17).

In fact, inflammatory skin conditions such as PsA are associated with immune dysregulation, including the imbalance of the Th1 and Th2 pathways, pro-inflammatory cytokine generation and breaking of the epidermal barrier (18, 19). These are all signals mediated by MCs in this immune disease (20).

Mononuclear phagocytes are important immune-cells in PsA, involved in the orchestration and expression of innate immunity and adaptive immune responses (21). Th1/Th2 macrophages undergo two different polarization states: M1 and M2 phenotype. Activated M1 macrophages can be induced by LPS or some inflammatory cytokines (IL-1, TNF); while M2 macrophages, which are poor at antigen presentation, are activated by the cytokine inhibitors IL-4 and IL-13 (22). In the inflammatory sites, M1 macrophages, activated via toll-like receptors (TLRs), release high levels of pro-inflammatory cytokines including IL-1 and IL-33 which activate MCs (23) (Figure 1). The cross-talk between macrophages, keratinocytes and MCs, which in turn cooperate, exacerbate the inflammatory response (24).

Therefore, MCs play a crucial role in PsA, since they represent “sensors” of environmental and emotional stress and participate in the relapse and exacerbation of the disease (25). IL-1 cytokine, which activates MCs, mediates inflammation when released after cell damage or negative regulation of NFκB gene transcription. IL-1 binds MC heterodimeric complex IL-1R protein and induces NF-kB and MAPK activation (26). Up regulation of type I IFN and the activation of TLR-9 in psoriatic dermis also contribute to increased cellular proliferation (27). While great steps forward have been made in targeted treatments for PsA, there is a need to further improve therapies for this proliferative and inflammatory disorder (28).

Mast cells

In allergic and inflammatory reactions, MCs are found in large numbers in the skin around the blood vessels and close to peripheral nerves, where they may have important functions in environmental and emotional stress (29). MCs play a key role in innate or acquired immunity, respond to many different stimuli and are usually associated to immediate hypersensitivity and allergic disorders, as well as in certain protective immune responses to microbes including their products such as LPS, which binds TLR-4, leading to the generation of pro-inflammatory cytokines that are important for the innate immune response against pathogens (30, 31). MCs can be triggered by IL-1, IL-33, IL-9, tryptase, and certain neuropeptides, including substance P (SP) which is released in stress conditions and stimulates keratinocytes to selectively release several cytokines/chemokines without degranulation (32). After activation, MCs are also capable of releasing, in seconds, chemical pro-inflammatory mediators (33).

MCs are activated by IL-1 in skin inflammation which plays a crucial role and has been implicated in the pathogenesis of PsA (34).

The cross-linking between FcεRI, expressed on MCs, and IgE leads to cell activation, and therefore the process provokes the secretion of different mediators, such as extracellular release of preformed mediators including TNF, stored in cytoplasmic granules of the cells, and late the *de novo* synthesis of pro-inflammatory arachidonic acid products and cytokines/chemokines (35). IgE binds FcεRI at about 1×10^{10} M^{-1} (very high affinity) initiating the activation of tyrosine phosphorylation, an event that starts with the activation of Fyn, Blk, and Lyn. In fact, cross-linking of bound IgE by antigen activates Src, Syk, and Tec protein tyrosine kinases which is a process that causes mitogen activation protein (MAP) kinase cascade and phosphatidylinositol phospholipase C (PI-PLCγ). IP3 provokes the activation of intracellular Ca^{2+} and DAG which activate PKC phosphorylating the substrate and generating the release of cytokines and chemokines. In addition, at this stage, Ca^{2+} also activates phospholipase A2 (PLA2), causing the production of arachidonic acid products such as leukotriene C4 (LTC4) and prostaglandin D2 (PGD2) (36, 37) (Figure 1).

MC preformed mediators include histamine, heparin, proteases (tryptase, chimase), hydrolases, cathepsin, carboxypeptidases, peroxidase and TNF; while the *de novo* synthesis are prostaglandins, leukotrienes and cytokines/chemokines. Furthermore, HDC is an important basophilic cell biochemical and functional marker, responsible for the production of histamine from histidine, an indicator of MC presence and activation (37). We previously showed that IL-33 (and its receptor IL-1RL1), another member of the IL-1 family also implicated in inflammatory arthritis, is increased along with histidine decarboxylase HDC in psoriatic skin, demonstrating the involvement and importance of MCs in this skin disease (3).

It is interesting that HDC is increased in psoriatic skin and can be stimulated by LPS and certain cytokines including IL-1. Therefore, significant interest regarding the role of MCs in the pathogenesis of this disease is evident (38).

MCs are involved in the pathophysiology of PsA which is triggered and/or exacerbated by acute stress (39). They are important in PsA, where there is excessive angiogenesis and they are increased in lesional psoriatic skin where they appear to be in association with the sensory nerves (in fact, emotional stress worsens PsA) (40).

Substance P

MCs can also be activated by neurotransmitters such as SP, which is an inflammatory peptide (11-amino

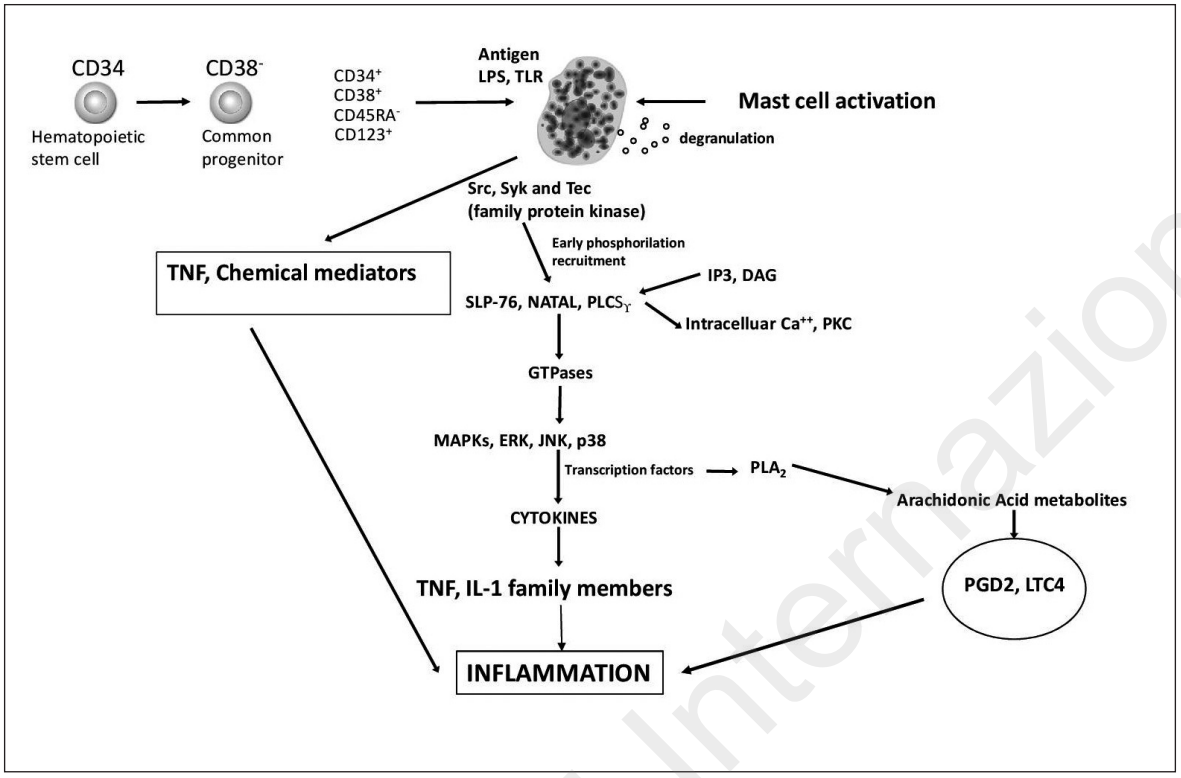

Figure 1 - Activation of mast cell by antigen participates in TNF and IL-1 family member cytokines, mediating inflammation.

acid) elevated in emotional stress, where it plays an important role as a trigger for MC skin PsA (39). SP-positive nerve fibers are more dense in psoriatic lesions and have an increased number of MC contacts compared with normal skin (39). Therefore, MCs activated by SP mediate the pathogenesis of inflammatory skin disorders, including PsA.

Vascular endothelial growth factor (VEGF)

Stimulated MCs, endothelial cells, hematopoietic stem cells, monocytes, neurons, macrophages, platelets and keratinocytes, secrete VEGF, which is one of the most important pro-angiogenic growth factors regulating the neovascularization involved in psoriatic plaques and other inflammatory disorders (41, 42). VEGF is generated in response to soluble mediators, such as cytokines, and its major receptor kinase-insert-domain-containing receptor (KDR) which has a selective mitogenic effect on endothelial cells (43).
It has been found that the epidermal over-expression of VEGF in transgenic mice, stimulated by inflammatory cytokines, leads to a phenotype nearly identical to that of PsA (44). VEGF stimulation with cytokines is therefore involved in PsA pathogenesis and several different VEGF polymorphisms are associated with an increased risk of developing PsA. VEGF and VEGF mRNA expression can also be induced by substance P in human MCs along with IL-1, an effect increased by IL-33, one of the newest inflammatory members of the IL-1 cytokine family (3). VEGF inhibitors have a dramatic impact on the clinical course of inflammatory disorders and neovascular diseases (3) (Figure 2).
Interleukin-33 (IL-33) is expressed and secreted by endothelial cells, TH2 cells and SP-activated MCs where it acts as a chemoattractant and trigger, and also induces release of IL-6 (another pro-inflammatory cytokine) from cultured MCs (3). IL-33 is a potent MC activator and is increased in affected psoriatic skin (3). In murine MCs, IL-33 induces the release of IL-6, and the induction takes place in the absence of degranulation and therefore histamine and protease release. IL-33 may also provoke infiltrating lymphocytes, proliferating keratinocytes, and endothelial cells from new vessels, contributing to inflammation, including PsA (3). IL-33 is inhibited by IL-37 binding to the α chain of the IL-18 receptor, down-regulating inflammatory disorders including PsA (45).
IL-1 and IL-17 ($CD4^+$ and $CD8^+$ T cells in PsA lesions produce IL-17A and IL-17F) have a critical role in initiating the inflammatory psoriatic state (46), followed by a TH1 reaction that can be inhibited with therapeutic intervention, for example the blocking of IL-1 and IL-33 with IL-37.
IL-1 or other stimuli may trigger the activation of MCs, leading to an excessive inflammatory process. Current treatment options for PsA do not always allow to reach the therapeutic objectives (47).
Recent advancement in the knowledge of the immunopathogenesis of PsA has allowed to develop novel drugs including IL-1 blocker and its precursors.

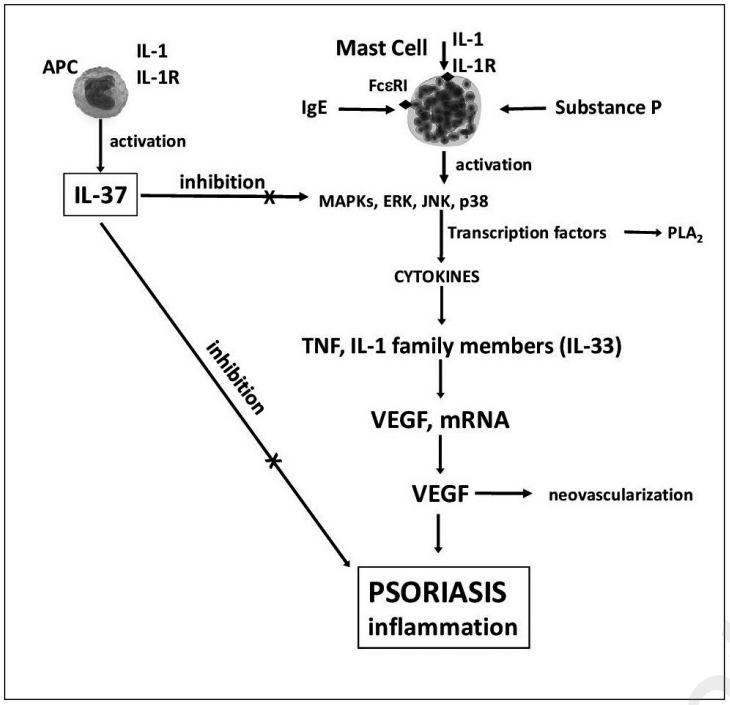

Figure 2 - Mast cell activation by IL-1 generates IL-1 family member cytokines and VEGF, mediating inflammatory psoriasis inhibited by IL-37.

Various drugs have been studied and developed for the inhibition of IL-1, since this process could be particularly advantageous for treating skin conditions where MCs are heavily involved (39).

Inhibition of intracellular IL-1 (caspase-1) during inflammation blocks the extracellular release and proinflammatory effects.

These observations may provide a starting point for the development of novel drugs based on the inhibition of IL-1, aimed at preventing release of caspase-1 substrates and the IL-1 pro- inflammatory family members (48).

Interleukin-37 (IL-37) (formerly IL-1F7) cytokine is a natural suppressor of innate inflammation and acquired immunity and is an inhibitor of IL-1 inflammatory family members (49). Five variants exist of IL-7, ranging from (a) to (e) and IL-37b is the largest cytokine member, and the most studied. IL-37b precursor can be processed by caspase-1 into the mature form, and translocate actively into the nucleus of the cell (49).

Several drugs targeting IL-1 have been developed, and methods aimed at preventing IL-1 secretion could prove particularly advantageous for treating skin conditions such as PsA (50). IL-37 inhibits IL-1β, one of the most important cytokines, which plays a crucial role in PsA, and can be stimulated by cytosolic DNA via inflammasome activation (51).

It has been reported that IL-37 is an inhibitor of innate immunity, and reduces the secretion of inflammatory cytokines in innate immune cells and can be released after immune cell stimulation by TLR ligands (52).

Recombinant IL-37 emerges as an important suppressor of systemic inflammation in rheumatoid arthritis and other disorders mediated by IL-1 (53). In addition, we previously reported that IL-37 has an inhibitory effect on human asthma pathogenesis mediated by cytokines/chemokines generated by MCs and other innate immune cells (54).

MCs challenged with 48/80, LPS or neuropeptides such as substance P, generate the pro-inflammatory cytokines IL-1, TNF, IL-6 and IL-33, which increase p38, MAPK and JNK phosphorylation, effects that can be inhibited by IL-37 (55).

Pro-inflammatory cytokine IL-1 induces differential release of IL-6 from human mast cells without concomitant release of the preformed mediator tryptase (32). In addition, IL-33 also induces release of IL-6 from cultured MCs (56).

MC-activated IL-1, inhibited by IL-37 leads to a reduction of the production of TNF and IL-6, including other inflammatory cytokines/chemokines generated by the MCs (49). Furthermore, the inhibition of IL-1-induced MCs by IL-37 can also be extended to the generation of chemical mediators of inflammation, for example proteases and histamine (55). We believe that the ratio of IL-1 to IL-37 is a contributing or determining factor in inflammatory psoriatic disease.

The development of IL-37 inhibitor of IL-1-induced generation of IL-6 from MCs, could provide novel therapeutic options for the treatment of inflammatory conditions including PsA. Despite the availability of several therapies, many patients remain untreated, and do not have an adequate response in this skin disorder. Therefore, the development and introduction of new therapies for PsA is exceptionally important.

We also strongly believe that it is intriguing that IL-37 treatment is effective in reducing the signs and symp-

toms of PsA, suggesting that IL-37 receptor plays a central role in the disease by directly driving downstream signaling in keratinocytes. Therefore, the inhibition of IL-1-inducing MC activation reduces the inflammatory process in PsA through the down-regulation of other pro-inflammatory cytokines such as TNF, IL-6, IL-33 and chemical mediators including histamine and proteases.

In addition, it has been reported that IL-37 is capable of inhibiting some chemokines including CXCL8 generation, ameliorating the inflammatory process in PsA by suppressing inflammation (18).

Since MCs are sensitive to the power of attraction of certain chemokines (38), as reported in our previous studies, the inhibition of these proteins by IL-37 could also improve the inflammatory state.

Therefore, for therapeutic intervention on PsA, there is a need for more effective and safer drugs, and the current availability of the inflammatory cytokine blocking agents, such as IL-37, can change the management of PsA.

IL-37 emerges as an important suppressor of systemic inflammation in PsA mediated by MCs and could represent an anti-psoriatic drug. We strongly confirm a link between MC inflammation, IL-1 and the inhibitory effect of IL-37.

The inhibitory effects of IL-37 in the pathogenesis of inflammatory skin diseases, including PsA, mediated by MCs, have not been demonstrated previously.

Here, we describe, for the first time, that IL-37 is a potent anti-inflammatory agonist protein and can be active in the inhibition of IL-1 activating MCs and mediating inflammation in psoriasis.

Our studies support the idea that IL-37 inhibits the inflammatory process in PsA mediated by MCs by the down-regulation of pro-inflammatory cytokine production, such as IL-1, IL-6, TNF, and IL-33, highlighting new therapeutic strategies. Furthermore, an additional role of mast cells in the pathogenesis of psoriasis could be via the release of pro-chemerin which attract specifically plasmocytoid dendrititic cells (57).

However, future research using animal models will help to better understand the exact role of IL-37 in the context of PsA, and further studies on IL-37 need to clarify its potential use and the safety and tolerability as a novel therapeutic agent.

These studies may provide a benefit with regard to IL-37 therapy in PsA. More research into the role of IL-37 in the pathogenesis this disease is ongoing in our laboratory.

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