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# IL-1 ACTIVATES MAST CELLS IN RHEUMATIC INFLAMMATORY DISEASE: POSSIBLE INHIBITORY EFFECT OF IL-37

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**ABSTRACT**

Rheumatoid arthritis (RA) is a chronic inflammatory disease which can be mediated by mast cell (MC) products. Activated MCs secrete pro-inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor (TNF) and several chemokines including CC5, CCL2, MCP-1 and CXCL8. The activation of MCs in the synovium of RA contributes to inflammation and tissue destruction. In addition, this chronic disease can affect the central nervous system (CNS), causing neuropsychiatric disorders such as depression and anxiety. However, more studies are needed to clarify the complex mechanism/s involved.

**KEYWORDS:** *Rheumatoid arthritis, IL-1, IL-37, mast cells, inflammation, immune, central nervous system*

## INTRODUCTION

IL-1 is a pleiotropic cytokine that functions at very low concentrations on both in vitro cells and brain tissue. IL-1 was discovered over 35 years ago and the pro-inflammatory cytokines of the IL-1 family orchestrate acute and chronic inflammatory diseases, including autoimmune disorders, with a broad-spectrum of action (1). IL-1 is a pro-inflammatory cytokine that stimulates genes for chronic inflammatory diseases. It activates inflammatory molecules such as cyclooxygenase type 2 (COX-2) (an inducible molecule), type 2 phospholipase A, and nitric oxide synthase (iNOS) (2). IL-18 also belongs to the IL-1 family, which is involved in autoimmune diseases and can increase the levels of adhesion molecules such as ICAM-1 and vascular VCAM-1 (3). Rheumatoid arthritis (RA) is a debilitating inflammatory autoimmune disease where IL-1 plays a crucial role (4-6). In experimental models of RA, when the serum of RA mice containing IL-1 is transferred to healthy animals it can cause them to develop joint inflammation (7). RA is often associated with type 2 diabetes (8) and cardiovascular events (9) mediated by IL-1. IL-1 orchestrates leukocyte communication and stimulates the generation of other pro-inflammatory cytokines. Therefore, the inhibition of this cytokine certainly leads to an improvement in the pathological state of the disease. In addition, several lines of evidence support the importance of IL-1 in RA (10), but less is known about the populations of innate immune cells that contribute

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to the production of IL-1 in this disorder. Certainly, the cells of innate immunity such as macrophages and mast cells (MCs) intervene in a decisive manner. MCs emerge as important elements of innate immunity against invading pathogens, producing stored products such as histamine and tryptase, but also pro-inflammatory cytokines such as IL-1 (11). In RA, MCs contribute to acute arthritis especially in the early stages. It has been reported that tyrosine kinase inhibitors have shown therapeutic benefits in RA experimental models and in human *in vivo* (12).

Inflammation is mediated by inflammatory cytokines, particularly by IL-1 and tumor necrosis factor (TNF), and other MC products. In addition, other pro-inflammatory elements can intervene, such as complement, intracellular molecules including protein kinases (PK) and NF-kB. In both innate and adaptive immunity and in rheumatic inflammation, different types of immune cells are present, producing pathophysiological substances such as cytokines and chemokines. In models of rheumatic inflammation, the production of anti-inflammatory cytokines such as IL-10 produced by MCs, and IL-37 generated by macrophages, can reduce many features of inflammation in the affected sites (13,14).

Monocytes /macrophages express high levels of the FcγR activation receptor, can respond to various stimuli and play an important role in rheumatic inflammation, even though the compounds generated by these cells still play an unclear role.

*Mast cells (MCs)*

MCs are produced from bone marrow, mature in tissues, and are classic cells of allergic inflammation, but they also help to defend the organism against bacterial and helminthic infection. MCs can also be activated in many inflammatory disorders such as atopic dermatitis, asthma, psoriasis, multiple sclerosis, anaphylaxis, asthma, and inflammatory arthritis. The proliferation, differentiation, and activation of MCs is regulated by the stem cell factor (SCF) which binds receptor kit and also by IL-3, but other cytokines intervene to a lesser extent (15). MCs are stimulated by IgE but can also be activated by neuropeptides, bacterial products, chemical agents, and cytokines (16). The classic role of MCs is performed in IgE-dependent allergies and in anaphylaxis, where the MCs express a high number of high-affinity receptors for IgE immunoglobulins. The molecular mechanism of IgE has been extensively revised.

Here we briefly report that the cross-linking of antigen-specific IgE bound to the receptor FcεRI causes receptor aggregation with cellular activation. These reactions are mediated by a series of biochemical events that lead to the production of chemical mediators that are immediately released and to pro-inflammatory proteins such as cytokines and chemokines that are belatedly released. Therefore, there is much evidence showing that MCs are involved in inflammatory rheumatic disorders. Histamine as well as tryptases are stored and released by the MCs granules, contributing to allergic reactions (17). The tryptases secreted constitutively by MCs are derived from α- and β-pro-tryptases and are more stable than histamine (18). They are considered to be potentially important mediators of acute inflammation and promote osteoarthritis-associated pathology, where the levels of tryptase are very high in the synovial fluids (19).

In the innate immune system, MCs are real sentinels of the human body, ready to react immediately with external pathogens that can cause damage. In fact, these cells release IL-33 which is considered an alarm cytokine for the body and called "alarmin". Furthermore, MCs can release other pro-inflammatory cytokines and neuropeptides with appropriate stimuli. Thus, MCs participate in osteoarthritis, a disease characterized by progressive degeneration of joint cartilage and low-grade synovial inflammation due to dysregulated innate immunity which is mainly mediated mainly by IL-1 (20). MCs express interleukin-1 receptor 1 protein (IL-1RL1) which binds the IL-33 expressed in many inflammatory diseases including RA (21).

The chemokines RANTES and MCP-1, and other cytokines, are produced by the rheumatoid synovium and are potent proteins with the power to recruit inflammatory immune cells and thus contribute to the immunopathogenesis of RA (22). Therefore, in synovial inflammation, both the cytokines as well as the chemokines that cause the recruitment of inflammatory cells are produced. Over 20 years ago, we reported that when the chemokines Rantes and MCP-1 were injected under rat skin, they recruited inflammatory MCs and stimulated the levels of histidine decarboxylase (HDC) in vivo in the rat. This effect highlighted the role of chemokines in inflammation with activation of leukocytes and tissue MCs (23)

After activation, MCs release preformed mediators such as histamine and tryptases from their granules but can also produce synthesized cytokines such as IL-6, IL-1, IL-31, IL-33 and TNF (which can be stored also in the granules) and several chemokines such as CC5, CCL2, MCP-1, and CXCL8. MCs produce high amounts of TNF, both intra and extra-cellularly. This cytokine helps the body fight bacterial infections, but it is also a highly inflammatory protein. TNF proteolytically cleaves intracellular caspase-1 and stimulates IL-1 production with a self-inflammatory mechanism (24). Caspase-1 needs a complex intracellular protein called inflammasome to be activated. TNF-induced inflammation inhibitors such as IL-37 can be very effective whereas other compounds such as steroids or anti-TNF may be refractory and unsuccessful. In addition, IL-37 blocking IL-1 can reduce the severity of inflammation, joint damage, and pain in patients with RA (25).

MCs are known to play an important role in the pathogenesis of RA, as these cells are activated in the synovium and contribute to inflammation and tissue destruction. At the inflamed site, there is a high number of MCs, a characteristic phenomenon of autoimmune diseases. The presence of activated MCs leads to the secretion of cytokines that mediate the inflammatory phenomenon. Therefore, MCs not only mediate IgE-dependent immune responses, but may also intervene

in non-IgE-mediated immune diseases. In RA, the cleavage of complement C5a and autoantibodies can activate MCs which participate in the pathogenesis of the disease (26).

It is well known that chronic peripheral inflammation can affect the central nervous system (CNS) (27). Individuals with RA may also have neuropsychiatric disorders including depression, anxiety related to neurodegenerative disease, and age-related problems (28,29). Autoimmune diseases, including RA, present with a dysfunction of the immune system involving the CNS and mediates neurodegenerative and psychiatric diseases. It seems that these relationships are due to genetic problems involving the human leukocyte antigen (HLA) site on chromosome 6 (30). But regarding these last observations more studies are needed to clarify the relationship between RA and the CNS.

*Conflict of interest*

The author declares that they have no conflict of interest.

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