JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 33, no. 3, 669-673 (2019)

EDITORIAL

IMPACT OF MAST CELLS IN SYSTEMIC LUPUS ERYTHEMATOSUS: CAN INFLAMMATION BE INHIBITED?

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Received February 23, 2019 – Accepted April 17, 2019

Systemic lupus erythematosus (SLE), is a complex chronic inflammatory autoimmune disease, with rheumatological manifestations, which afflicts mainly women (1). SLE presents various heterogeneous clinical aspects and different pathogeneses and involves the production of anti-DNA autoantibodies which are deposited as immune complexes in various organs and tissues, provoking inflammation (2). These diseases cause multiple tissue and organ damage in arthritis, skin lesions, hematologic changes, renal and neurologic disorders, and others (Table I). In SLE, serum contains anti-nucleus antibodies and anti-DNA antibodies that can be important biomarkers for patients suffering from this disease (3).

Cytokines mediate inflammatory and immune reactions, they communicate between cells of the immune system and contribute to the pathogenesis of autoimmune diseases, including SLE (4). There is increasing evidence that cytokine IL-1 plays an important role in the development and pathogenesis of chronic autoimmune diseases, such as rheumatoid arthritis and SLE. IL-1 can activate TLR with release of other pro-inflammatory cytokines, therby mediating the pathogenesis of SLE which is the second most common disease after rheumatoid arthritis where TLR plays a key role. TLRs range from 1 to 13, most of which are expressed on the cell membrane; whereas TLR3, TLR7, TLR8, TLR9, TLR11, TLR12 and TLR13 are expressed intracellularly in endoplasmic reticulum, endosomes, endolysosomes, phagosomes, and lysosomes (5). It is important to note that TLR expression is enhanced in immune cells after exposure to pro-inflammatory cytokines. In addition, it must be pointed out that TLR7 is crucial, while the function of TLR9 is controversial. Therefore, IL-1 secretion, involved in inflammation, is due to TLR activation and subsequently to inflammasome which is a cytosolic protein complex important for the maturation of inflammatory caspase-1. In fact, caspase-1 cleaves the inactive pro-IL-1 into its mature form ready to be secreted (5).

Among the various immune cells that mediate inflammation in SLE, we also find the mast cells (MCs) which play a decisive role in this disease (6). It is well known that MCs and their histamine receptors can regulate both TH1 and TH2 cells. In

Key words: mast cell; systemic lupus erythematosus; IL-37; cytokines;inflammation

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0393-974X (2019)

DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

Table I. *Diagnostic rules.*

Manifestations in
Skin: Facial erythema, Photosensitivity, oral ulcers, alopecia.
Joints: Pain, tenderness, swelling, arthritis, swelling, stiffness
Serous sites: Pleuritis, pericarditis, pericardial pain
Renal diseases: Proteinuria, red blood cell casts, cellular cast, renal disorders
Hematologic diseases: Hemolytic anemia, leukopenia, thrombocytopenia, lymphopenia
Immunologic disorders: LE cells, antiphospholipid antibody, low complement C3, C4, hemolytic anemia

SLE skin lesions, immune cells including MCs and T lymphocytes occur, infiltrate into the dermis and release pro-inflammatory cytokines, including IL-1 and TNF (7). Some studies have revealed that in SLE skin lesions, the number of MCs is increased, contributing to the inflammatory phenomenon and representing important cells in the pathophysiology of the disease, since they can also show a protective role (7). In SLE there are high levels of IgE that bind to MCs and basophilic granulocytes, and activate them to produce pro-inflammatory cytokines and to migrate in various tissues.

Mast cells

MCs derive from the hematopoietic precursor cells located in the bone marrow ($CD34^+/CD117^+/CD13^+$), and mature and reside in virtually all vascularized tissue (8). MCs are located perivascularly where they produce inflammatory mediators (including histamine), and pro-inflammatory cytokines (Table II) which participate in neuropsychiatric diseases and host response (8). In the brain, MCs are located near vessels, meninges, nerves, and thalamus and hypothalamus, and modulate the innate and adaptive immune response. They can migrate from the brain to the lymphoid organs and *vice versa*, and are good communicators with neurons and glial cells (9). MCs are capable of producing biologically active substances, including chemokines which recruit other cells and mediate inflammation. In addition, chemokines participate in inflammatory responses and CCL2 chemokines can be induced in MCs by IL-1, whose receptor is expressed by a variety of central nervous system (CNS) cells and tissues (10).

MCs of peripheral tissues generate immune mediators and communicate with spinal and encephalic dura mater, giving sensitivity to tissues. MCs are in communication with sensory nerves, and cross-talk with the cells of the microglia of the brain and spinal cord. One of the MC dysfunctions can affect the inflammatory pathway (11). MCs actively participate in neurodegenerative diseases including SLE. Clarifying the mechanism of MC activation and inhibition in SLE can help improve the therapeutic treatment of this autoimmune inflammatory disease (12).

IL-1 generated by several immune cells, such as macrophages, lymphocytes and MCs, has the ability to induce itself and it is involved in the release of other pro-inflammatory cytokines, which are very important effector molecules implicated in autoimmune disorders. IL-1 plays a key role in the induction and development of pathphysiology (13). IL-1, along with TNF, can induce the production of IFN-γ, an effect demonstrated in some inflammatory diseases. IFN-γ is a potential biomarker for SLE and its decrease is associated with severity and poor prognosis in patients with lupus.

Macrophages and MCs, together with other cells, express IL-1 receptors (IL-1R) and mediate primary immunity by responding to IL-1. This pro-inflammatory cytokine can act through TH1 cells, and can also amplify the response to TH2. The alteration of the TH1/TH2 equilibrium can lead to a greater susceptibility to SLE (5). In this disease,

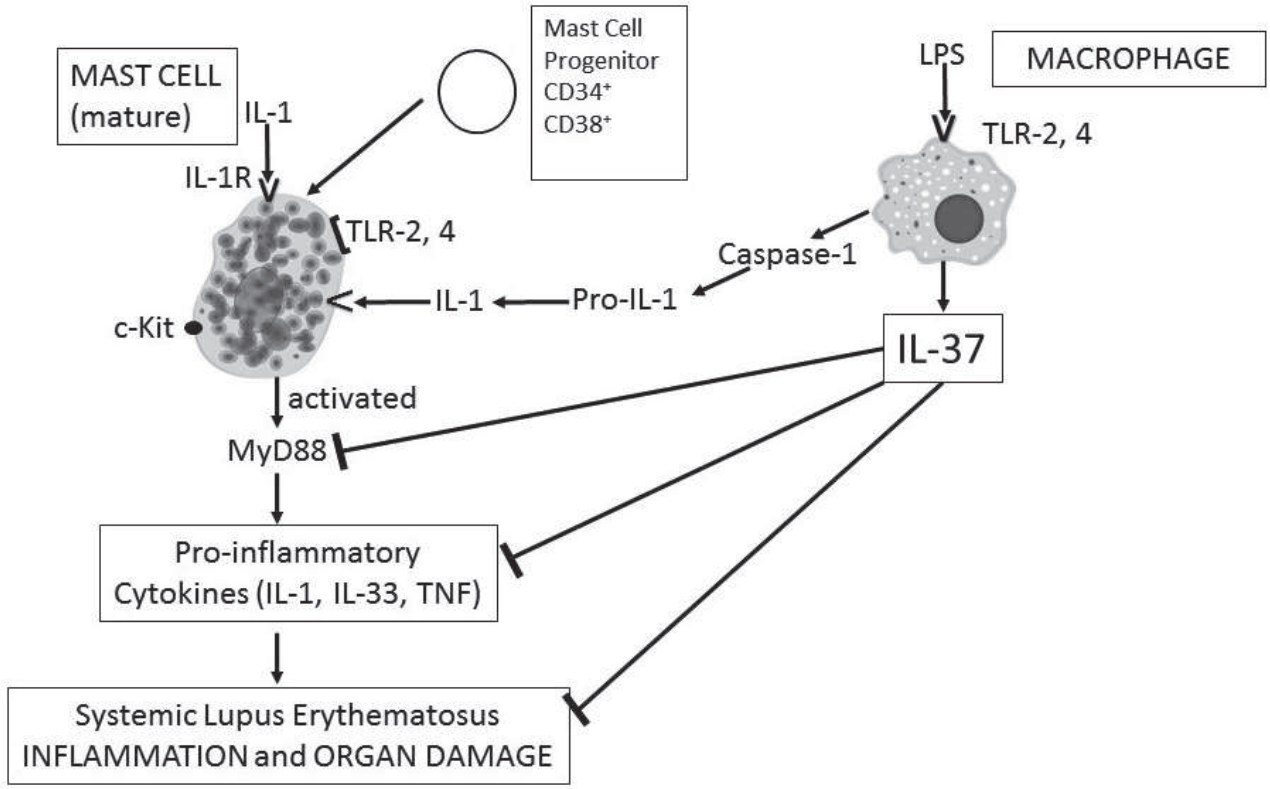

Fig. 1. *In systemic lupus erythematosus mature mast cells can be activated by IL-1, provoking the release of proinflammatory cytokines and causing inflammation and multi-organ damage, an effect that can be inhibited by IL-37 from activated macrophages.*

Table II. *Inhibitory effect of IL-37 in diseases.*

Diabetes, intestinal inflammation, multiple sclerosis, inflammatory arthritis, allograft rejection, fibromyalgia, arthritis, atherosclerosis, fibrosis, endotoxemia, asthma, migraine, depression, autoimmunity, allergy, mold inducing inflammation, ischemia, hepatitis, neuroinflammation, cancer Inflammation.

the TH1/TH17 ratio is dysregulated, and a balance in favor of TH17 cells is increased and the cells are more responsive in SLE. Thus, IL-1 plays a potential role in the pathogenesis of SLE.

In addition, in SLE, the neurological manifestation is involved in which also MCs participate and mediate the phenomena of vasculitis and hemorrhagic inflammation, contributing to the pathogenesis of this disease (14). MCs are recalled by the release of MCP-1/CCL2 which is abundant in SLE and can be an important marker.

However, often the SLE diagnosis is not always easy and it would take more experiments on mice to clarify the true role of MC activation, in particular with IL-1.

To date, important studies on SLE therapy have missed the goal, even though some progress has been made. The classical therapy adopted for this disease is often based on the administration of cortisone and other immune suppressors (15). We believe

that understanding the imbalance of the IL-1 family members is fundamental for future therapeutic approaches. In this editorial, we propose a new therapeutic strategy based on MC-IL-1 inhibition with a natural cytokine inhibitor IL-37 (16).

IL-37

IL-F7 (most commonly called IL-37) is a member of the IL-1 family which binds IL-18 receptor alpha (IL-18Rα) chain and suppresses innate and acquired immunity (17). IL-37, is involved in the pathogenesis of the inflammatory autoimmune diseases including psoriasis, rheumatoid arthritis, fibromyalgia, Crohn's disease, SLE, and others (Table II).

It has been reported that IL-37 protects against inflammatory insults and blocks pro-inflammatory cytokines including IL-1, IL-33. IL-37 may also inhibit TNF with an indirect effect, since this highly pro-inflammatory cytokine can be induced by IL-1 (17).

This new IL-1 family member acts through the down-regulation on MyD88 in the nuclear biochemical cascade, which is necessary for the generation of pro-inflammatory cytokines, including IL-1 (18). In SLE, where there is strong local and systemic inflammation mediated by IL-1, the blocking of this cytokine could certainly reduce both inflammation and tissue damage, and bring relief to patients suffering from this autoimmune disease (19-20) (Fig. 1). However, treatments with this cytokine could also have side effects on the immune system as the precise doses of administration in humans and its exact functioning are not yet known.

REFERENCES

1. Tsokos GC Systemic lupus erythematosus. N Engl J Med 2011; 365(22):2110-21.
2. Jung JY, Bae CB, Suh CH. Promising biomarkers for systemic lupus erythematosus. Expert Opin Med Diagn 2013; 7(6):601-13.
3. Tsokos GC, Lo MS, Costa Reis P, Sullivan KE. New insights into the immunopathogenesis of systemic lupus erythematosus. Nat Rev Rheumatol 2016; 12(12):716-30.
4. Gottschalk TA, Tsantikos E, Hibbs ML. Pathogenic inflammation and its therapeutic targeting in systemic lupus erythematosus. Front Immunol 2015; 6:550.
5. Joosten LA, Abdollahi-Roodsaz S, Dinarello CA, O'Neill L, Netea MG. Toll-like receptors and chronic inflammation in rheumatic diseases: new developments. Nat Rev Rheumatol. 2016 Jun;12(6):344-57.
6. Kolkhir P, Pogorelov D, Olisova O, Maurer M. Comorbidity and pathogenic links of chronic spontaneous urticaria and systemic lupus erythematosus--a systematic review. Clin Exp Allergy 2016; 46(2):275-87.
7. Liew FY, Girard JP, Turnquist HR. Interleukin-33 in health and disease. Nat Rev Immunol 2016; 16(11):676-689.
8. Galli SJ, Kalesnikoff J, Grimbaldeston MA, Piliponsky AM, Williams CM, Tsai M. Mast cells as "tunable" effector and immunoregulatory cells: recent advances. Annu Rev Immunol 2005; 23:749-86.
9. Petra AI, Panagiotidou S, Stewart JM, Conti P, Theoharides TC. Spectrum of mast cell activation disorders. Expert Rev Clin Immunol 2014; 10(6):729-39.
10. Conti P, D'Ovidio C, Conti C, et al. Progression in migraine: Role of mast cells and pro-inflammatory and anti-inflammatory cytokines. Eur J Pharmacol 2019; 844:87-94.
11. Theoharides TC. Neuroendocrinology of mast cells: Challenges and controversies. Exp Dermatol 2017; 26(9):751-59.
12. Siiskonen H, Smorodchenko A, Krause K, Maurer M. Ultraviolet radiation and skin mast cells: Effects, mechanisms and relevance for skin diseases. Exp Dermatol 2018; 27(1):3-8.
13. Theoharides TC, Petra AI, Taracanova A, Panagiotidou S, Conti P. Targeting IL-33 in autoimmunity and inflammation. J Pharmacol Exp Ther 2015; 354(1):24-31.
14. Barile-Fabris L, Hernández-Cabrera MF, Barragan-Garfias JA. Vasculitis in systemic lupus erythematosus. Curr Rheumatol Rep 2014; 16(9):440.
15. Shih A, Jackson KC 2nd. Role of corticosteroids in palliative care. J Pain Palliat Care Pharmacother 2007; 21(4):69-76.
16. Gallenga CE, Pandolfi F, Caraffa A, Kritas SK, Ronconi G, Toniato E, Martinotti S, Conti P.

Interleukin-1 family cytokines and mast cells: activation and inhibition. J Biol Regul Homeost Agents 2019; 33(1):1-6.
17. Cavalli G, Dinarello CA. Suppression of inflammation and acquired immunity by IL-37. Immunol Rev 2018; 281(1):179-90.
18. Conti P, Caraffa A, Mastrangelo F, et al. Critical role of inflammatory mast cell in fibrosis: Potential therapeutic effect of IL-37. Cell Prolif 2018; 51(5):e12475.
19. Conti P, Caraffa A, Ronconi G, et al. Mast cells participate in allograft rejection: can IL-37 play an inhibitory role? Inflamm Res 2018; 67(9):747-55.
20. Conti P, Caraffa A, Ronconi G, et al. Impact of mast cells in depression disorder: inhibitory effect of IL-37 (new frontiers). Immunol Res 2018; 66(3):323-31.