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Letter to the Editor

ROLE OF IL-4 AND IL-31 IN MASTOCYTOSIS

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INTRODUCTION

Mast cells (MCs) are immune cells that originate in the bone marrow and are present in all tissues, especially around small vessels and nerve endings (1). Mastocytosis is a disease characterized by an abnormal increase in MCs in various tissues or organs (2). Interleukin (IL)-4 and IL-31 are immune mediators which are involved in many diseases including allergic diseases (allergic rhinitis and eczema), autoimmune diseases (systemic lupus erythematosus and rheumatoid arthritis), and infectious diseases.

DISCUSSION

IL-4 is a cytokine that functions primarily as a regulator of IgE-mediated immune reactions, MCs, and eosinophils. After activation by IL-4, Th2 cells subsequently produce IL-4, which is important for activating B cells. The T cell that initially produces IL-4, thus inducing differentiation toward Th2, has not been identified, but recent studies suggest that basophils may be the effector cell.

IL-31 is a cytokine encoded by a gene located on chromosome 12 in humans. IL-31 binds to its specific receptor that is expressed mainly on the cell surface of T helper lymphocytes and, to a lesser extent, on dendritic cells.

The binding of interleukin to its receptor, which is expressed on the surface of some neurons on which the TRPV1 receptor is also expressed, is responsible for some biological effects including the sensation of itching. Both IL-4 and IL-31 are cytokines that play a significant role in the immune response and are associated with the symptoms and pathophysiology of mastocytosis (3).

In mastocytosis, IL-4 is produced primarily by T cells and MCs. It plays a key role in the immune response by promoting the differentiation of naive T cells into Th2 cells, enhancing IgE production by B cells, and suppressing Th1-mediated inflammatory responses. Elevated levels of IL-4 can increase IgE production, which contributes to MC activation and degranulation. IL-4 can exacerbate the allergic symptoms and hypersensitivity reactions commonly seen in patients with mastocytosis. Therefore, IL-4 influences MC behavior and may support their survival, further contributing to disease progression.

IL-31 is a cytokine produced primarily by Th2 cells and MCs. It is a crucial molecule involved in the sensation of itch and the pathology of skin diseases such as atopic dermatitis. In mastocytosis, IL-31 is directly associated with the severe itch that patients with this disease often experience. IL-31 binds to the IL-31 receptor (IL-31R) on sensory neurons to mediate the sensation of itch. High levels of IL-31 contribute to the dermatological manifestations of mastocytosis, such

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as urticaria pigmentosa with itchy, pigmented skin lesions. IL-31 can also increase inflammation, worsening systemic symptoms. In mastocytosis, dysregulated production of IL-4, IL-31, and other cytokines amplifies the severity of the disease by perpetuating a cycle of MC activation, immune response, and symptom manifestation.

Biological therapies targeting IL-4 or IL-31 are being studied to manage symptoms such as pruritus and allergic reactions in mastocytosis and other MC-related diseases. Systemic mastocytosis occurs primarily in adults and is characterized by multifocal lesions of the bone marrow and it often involves other organs, usually the skin, lymph nodes, liver, spleen, and/or gastrointestinal tract (Table I).

Table I. *Classification of systemic mastocytosis.*

- Asymptomatic mastocytosis presents no organ dysfunction and a benign prognosis.
- Mastocytosis associated with other hematologic disorders (eg, myeloproliferative disorders, myelodysplasia, lymphoma).
- Progressive mastocytosis is characterized by impaired organ function.
- Mast cell (MC) leukemia presents with > 20% MCs in bone marrow, multiorgan failure, and a poor prognosis (with no skin lesions).

Blockade of IL-4 receptors can suppress the activity of both IL-4 and IL-13, providing a broad-spectrum immunomodulatory effect (4).

CONCLUSIONS

Studies of IL-4 and IL-31 in mastocytosis are critical for developing new, more targeted therapies and improving symptom management in patients with this disease.

Conflict of interest

The author declares that they have no conflict of interest.

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