

Central Role of Mast Cells in Mastocytosis, Hereditary α -Tryptasemia, Mast Cell Activation Syndrome, Urticaria, and Angioedema

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Abstract

Mast cells are the central cells in the pathogenesis of many conditions that are associated with mediator release. New information is emerging about the role of mast cells in a number of conditions. This review summarises current knowledge on the topic.

Some conditions such as mastocytosis have a confirmed genetic background; however, the genetic background of hereditary α -tryptasemia has only recently been described, and routine testing is yet to be set up in genetic laboratories. It is still unknown whether there is a genetic predisposition leading to the development of mast cell activation syndrome as well as urticaria and angioedema, and research is under way in this direction.

The best known mediator contained in mast cells is histamine 2-(4-imidazolyl)-ethylamine, but it is not the only one. The effects of other mediators are significant in mast cell-mediated conditions, and can be future therapeutic targets. Diamine oxidase deficiency is responsible for digestive issues in some people, and although not directly linked with mast cell pathology, it falls under this umbrella due to symptoms related to the effects of externally consumed histamine.

Mast cell-mediated diseases are usually defined through the detection of an elevation of mast cell mediators, response to antihistamines, mast cell stabilisers, and, in some cases, anti-IgE treatment when indicated. They comprise of mastocytosis, hereditary α -tryptasemia, mast cell activation syndrome, urticaria, and angioedema.

Key Points

1. The understanding of the role of mast cells in different conditions is evolving, which may contribute to an improved patient quality of life.

2. Mast cell activation syndromes are prevalent and heterogeneous, with an unclear aetiology at present.

3. Mast cells are essential in several antiparasitic responses, although they can also contribute to hypersensitivity reactions.

INTRODUCTION

Mast cells are at the centre of many conditions, leading to symptoms associated with mediator release,¹⁻⁶ and have been implicated in many diseases beyond allergy.⁷ Mastocytosis-associated hereditary tryptasemia has a defined genetic background. Other mast cell related conditions are deemed to have external activation of the mast cells through the mechanisms of auto allergy and autoimmunity.⁸

The quality of life (QoL) of patients with a range of mast cell mediated diseases is significantly compromised, and the evaluation of QoL is not regularly performed in clinics. However, it is very important to assess the patients' QoL in light of a steady increase in the prevalence of mastocytosis, chronic spontaneous urticaria (CSU) and angioedema, atopic and contact dermatitis, and hereditary angioedema.⁹

Mast cells are classified as granulocytic immune cells that are positioned in barrier organs and carry out proinflammatory and anti-inflammatory activities, utilising their ability to release a variety of mediators.¹⁰ The important task of mast cells is the recognition of tissue injury, as they are closely associated with the epithelium and play an active role in the initial inflammatory response. Mast cells rely on receptors to detect tissue damage, leading to the release of mediators kept in granules, as well as the *de novo* production of these mediators. The activation of mast cells can happen via IgE receptors or via toll-like receptors, complement receptors, and IgG receptors. Mast cells have a unique role of repairing damaged tissue. Over time, mast cells reach the tolerance state, where the response to self-antigens and auto-immune antibodies levels to baseline.¹¹

The progenitors of mast cells are haematopoietic stem cells. Mature, highly granulated mast cells have a *KIT* gene and receptor which are present in almost all tissues. *KIT* receptors undergo stem cell factor binding, and are not found in the blood stream.

In increasing numbers of patients, aberrant mast cell activation has led to a range of symptoms in the absence of systemic mastocytosis or antigen-specific mast cell disease. Systemic mastocytosis, in the World Health Organization (WHO) reclassification,¹² represents a rare genetic disease, characterised by the activation of mast cells with aberrant proliferation, leading to multiorgan symptoms and, in some patients, severely debilitating symptom burden.¹³

Mast cell activation syndrome is a more prevalent, heterogeneous condition with an unclear aetiology, but has clinically similar symptoms¹⁴ associated with an impaired tolerance of mast cells.¹⁵ The ethology and mechanisms of chronic mast cell dysregulation are not well understood, with many clinical studies emphasising the role of the epithelium or the presence of acute inflammation, which leads to mast cell activation.¹⁶ The proposed mast cell activation syndrome diagnostic criteria are based on detecting the increased levels of mast cell mediators, as well as the treatment response with mast cell stabilising medications or therapies directed at interaction between released mast cell mediators and receptors.¹⁷

The overactivity of mast cells and subsequent parthenogenesis can affect the connective tissue. This can lead to the development of rare inherited diseases, such as Ehlers-Danlos syndrome.¹⁸

Histamine intolerance is often attributed to mast cells but, in fact, is not directly linked with any abnormalities of mast cells. This condition is associated with disorders of the digestive tract due to the reduction in activity of the diamine oxidase (DAO) enzyme, which is responsible for degradation of histamine within the gastrointestinal system.¹⁹

HISTAMINE AND DIAMINE OXIDASE

Histamine was discovered over 100 years ago. Also known as 2-(4-imidazolyl)-ethylamine, it is produced as a result of the decarboxylation of histidine, and is the most well-known biological mediator that has been attributed to mast cells.¹⁹

This biogenic amine is released from intracellular storage vesicles of basophils and mast cells after stimulation, leading to nitric oxide synthesis.²⁰ Histamine can affect the gastrointestinal, cardiovascular, and respiratory systems, as well as the skin, as a result of the activation of histamine receptors 1 and 2 on smooth muscle cells, endothelium of blood vessels, and the bronchial tree.^{21,22} This leads to vasodilation, vascular hyperpermeability, angioedema, and hypotension,²³⁻²⁶ which correlates with histamine concentrations.²⁷ Elevated histamine levels, when mean histamine concentrations can rise to 140 ng/mL,²² were shown to increase vascular permeability, lead to airway constriction due to effects on smooth muscle cells, and promote chemotaxis of white blood cells, thus playing a leading role in various forms of anaphylaxis or life-threatening angioedema.²⁸ Mast cell tryptase is a useful factor in confirming the diagnosis of anaphylaxis, and should be taken in all acute settings as soon as it is practical and upon recovery.²⁹

An enzyme that degrades histamine, E.C. 1.4.3.6 human DAO (hDAO), is encoded by the *AOC1* gene.^{30,31} As a homodimer copper-containing amine oxidase, hDAO is produced in the intestinal³² and proximal tubular kidney epithelial cells,³³ and extra villous trophoblasts.³⁴ After secretion, hDAO binds in the lamina propria to the basolateral membranes. Serum hDAO degrades histamine at a mean concentration of 125 ng/mL, with a half-life of 3.4 min.³⁵

MAST CELLS

Mast cells are found in all vascularised tissues, and are granulated effector immune cells with multiple functions.³⁶ They were discovered by Nobel Prize-winning physician Paul Ehrlich over 140 years ago as a part of the innate immune system maintaining the first line of immune defence.¹ Mast cells take part in many physiological and pathological processes. In addition to known proinflammatory roles in allergic reactions, they are important in angiogenesis and tissue repair.² Mast cell maturation can be influenced by location, leading to functional and phenotypical heterogeneity. They are important in host defence, homeostasis, innate and acquired immune functions, and immunoregulation. They also play a key role in IgE mediated antiparasitic response and atopy,³⁷ response to infections, systemic disorders, development of tumours, and disorders of cardiovascular system.³⁸

Mast cells display tyrosine-protein kinase KIT (cluster of differentiation 117), the receptor for stem cell factor Fc ε receptor 1 (FcεRI), which is a high-affinity receptor for IgE and G protein-coupled receptors on the cell surface, including the Mas-related G protein receptor X2, which has been linked to CSU, atopic dermatitis, asthma, and other mast cell-related diseases.³⁶ The granules of mast cells contain vascular endothelial growth factor and fibroblast growth factor 2 angiogenic cytokines, which contribute to the regeneration of nerve fibres and wound healing.³⁹

Mast cells can be usually activated by FcεRI, a high-affinity receptor that is connected to a specific IgE to define antigens through mechanisms not involving FcεRI. These mechanisms involve binding the cells to different ligands. In general anaesthetics, positively charged hydrophobic molecules of morphine and vancomycin, quinolone antibiotics, muscle relaxant atracurium, and rocuronium, all lead to a release of mediators.⁴⁰

Subpopulations of mast cells M1 and M2 are being studied, and current data suggest that, in various pathological conditions, the two major subtypes could have different or even opposite functions.⁴¹ Pro- and anti-inflammatory mediators³⁷ (biogenic amines such as histamine

and serotonin; lysosomal enzymes; proteoglycans such as heparin and chondroitin sulphates)³⁷ and proteases such as tryptase, carboxypeptidase, cathepsin G, serine S1, granzyme, chymase, and TNF- α ⁴² that are released by mast cells have important immunomodulatory functions in the barrier organs (the skin, lungs, and gastrointestinal tract).⁴³ Inflammatory mediators, released by mast cells, promote growth and differentiation of endothelial cells and fibroblasts. Mast cell granules are present within a lipid membrane, which fuses with the plasma membrane.⁴⁴ The activation of mast cells can lead to the secretion of extracellular vesicles, such as microvesicles; exosomes with a variety of biological properties, and can influence other cells, located either closely or at distance, and modulate the inflammatory response, allergic inflammation, tumour development,⁴⁵ physiologic processes, and the maintenance of tissue homeostasis.⁴⁶

There is no data on mast cell deficiency, leading to the conclusion that the functions of the mast cells are vital for life. Therefore, the use of the results from ongoing research into anti-c-Kit monoclonal antibody treatments should be approached with extreme caution.⁴⁷

DISORDERS ASSOCIATED WITH MAST CELLS

Mast cell-activated diseases cover a very heterogeneous range of mast cell-mediated conditions, including urticaria, angioedema, systemic mastocytosis, mast cell leukaemia, and mast cell activation syndrome.⁴⁸ Clinical distinction between systemic mastocytosis, hereditary α -tryptasemia, and mast cell activation syndrome is difficult due to overlapping symptoms and pathophysiology.⁴⁹

Mastocytosis

The WHO classification of mastocytosis has placed it into two groups: cutaneous mastocytosis and systemic mastocytosis.¹²

Cutaneous mastocytosis is responsible for 80% of mastocytosis cases. They mainly affect the skin during childhood, and improve or resolve completely by adolescence.⁵⁰ Cutaneous mastocytosis is considered a benign, self-limited condition, with a generally favourable prognosis and spontaneous

regression of symptoms at puberty. It is the most common mast cell disease in children, presenting as urticaria pigmentosa.⁵¹

Systemic mastocytosis is diagnosed in over 95% of the cases, and usually persists for a longer time due to a gain-of-function mutation in the *KIT* gene, resulting in abnormal proliferation of clonal mast cells in various organs.⁵² The mutation is found in the gene coding *KIT* D816V tyrosine receptor kinase (cluster of differentiation 117),⁵³ and can lead to increased and prolonged activation of the mutated mast cells as a result of abnormal apoptosis and proliferation.⁴

The prevalence of systemic mastocytosis in Europe is 0.3–13.0:100,000,⁵⁴ affecting males and females equally with unknown incidence.⁵⁵ It can be more challenging to diagnose in adults as it can lead to multiple organ dysfunction, with a very heterogeneous clinical presentation when there is no skin involvement. A maculopapular monomorphic fixed exanthema (urticaria pigmentosa, the typical presentation of cutaneous mastocytosis in adults, can precede other clinical symptoms for many years) presents in over 90% of the cases and is associated with systemic involvement.¹⁰ Brown-red maculopapular skin lesions, 0.5 cm in diameter with local redness, can be noted. Pruritus (Darier's sign) and urticarial swelling is associated with mast cell mediator release, which can be provoked by physical factors and co-factors.⁵⁶ Less favourable outcomes are predicted for advanced systemic mastocytosis, while almost normal life expectancy and excellent prognosis can be predicted for the most common forms of indolent systemic mastocytosis,⁵⁷ with a moderate mast cell accumulation in the bone marrow and other organs.⁵⁸

In all types of systemic mastocytosis, gastrointestinal symptoms can occur. Patients present with flushing, hypotension, tachycardia, sudden attacks of diarrhoea, nausea, and vomiting.^{14,59} When genetic trait hereditary α -tryptasemia (H α T) is present, there is a higher incidence of severe, life-threatening anaphylaxis in patients with systemic mastocytosis, especially in patients with IgE-mediated allergy, including a food, venom, or drug allergy.⁶⁰

Based on the WHO diagnostic criteria for systemic mastocytosis, an essential test for this condition includes a bone marrow biopsy.⁵⁸

Hereditary α -Tryptasemia

In 2016, Lyons et al.⁶¹ described H α T as a new genetic condition that is associated with slightly elevated basal tryptase levels,⁶² and characterised by extra copies of the α -tryptase encoding gene *TPSAB1*. The genetic diagnosis requires the analysis of the duplication of the *TPSAB1* gene, which can have a total number of five or more copies; however, the total number of copies for *TPSAB1* and *TPSAB2* in individuals who are not affected is four.⁶³ Unfortunately, such genetic testing is not yet routinely available in many genetic laboratories. The routine availability of a genetic test will help to identify a cohort of patients with this condition and study risks for severe anaphylaxis or development of systemic mastocytosis.⁶⁴ Patients with H α T display multiorgan symptoms of mast cell activation, which is common for mast cell activation syndrome and systemic mastocytosis; however, some can be completely asymptomatic.⁶⁵

Mast Cell Activation Syndrome

Clinically, mast cell activation syndrome is an extremely heterogeneous disease, with aetiology and pathology that is still not fully understood, making the diagnostic process more difficult.⁶⁶ Current evidence suggests that mast cell activation syndrome is associated with a number of mutations in signal transduction proteins that pathologically stimulate activated mast cells, kinases, and receptors in different organ systems.⁶⁷ *KIT* D816V point mutation is typical in systemic mastocytosis, but is not present in mast cell activation syndrome.⁶⁸

Mast cell activation syndrome is characterised by aberrant inappropriate release of mast cell mediators.⁴⁸ The suspected mechanisms lead to pruritus, pain, abdominal cramping, vomiting, nausea, and flushing include increased mast cell proliferation, accumulation of altered or mutated mast cells, and decreased apoptosis.⁶⁸ The symptoms, depending on the organ system involved, can mimic systemic mastocytosis.⁶⁷ Mast cell related symptoms may include wheezing and upper respiratory inflammation, sneezing, rhinorrhoea, hypotensive syncope, tachycardia, flushing, pruritus, urticaria and angioedema, dizziness, vomiting, abdominal cramps, gastritis, nausea, diarrhoea, fatigue, and impaired concentration.⁶⁹

Patients with long-COVID often report other unspecific symptoms in addition to classical mast cell mediator-induced symptoms, including fatigue, unexplained weight loss, organ enlargement, musculoskeletal symptoms, depression, and reflux.⁷⁰

Diagnosis of mast cell activation syndrome is difficult as it has an extremely heterogeneous symptomatology. It involves different organ systems, is based on clinical and immunohistochemical findings in biopsies, and laboratory parameters within the diagnostic criteria. Mast cell activation syndrome reoccurs episodically, with subsequent remissions and symptom-free intervals; however, these intervals often become shorter as the disease progresses.⁶⁷

The most common type of EDS is hypermobile EDS, uniting disorders, which results in chronic constitutive tissue defects. Reactive mast cell activation was introduced to the scope of mast cell disorders,⁶⁶ however mast cells are not affected in all patients with hypermobile EDS.

Urticaria and Angioedema

Chronic urticaria and angioedema represents a significant burden in the healthcare system and society in general, as well as patients and their families.⁷¹

Although the pathogenesis of CSU and angioedema is not yet fully understood, they occur due to the release and effects of mast cell mediators following mast cell activation in the skin.⁷² Recently, the causes of CSU and angioedema were defined as autoimmunity Type I (autoallergic CSU, with IgE autoantibodies to self-antigens) and autoimmunity Type IIb (with mast cell-directed activating autoantibodies), with the remaining cases due to unknown causes. At the present time, unknown mechanisms are relevant for the degranulation of skin mast cells.⁷³

DISCUSSION

Mast cell pathology ranges from non-specific to specific activation of mast cells and degranulation. An immediate hypersensitivity reaction to IgE is the most well-known (Type I). It represents antiparasitic immune responses, as

well as hypersensitivity reactions when specific IgE produced against harmless antigens land on high-affinity FcεRI, which are expressed on mast cells. Crosslinking of two IgE receptors occupied with specific IgE to the same antigen leads to mast cell degranulation.

The release of mast cell mediators can lead to a wide range of effects, resulting in rhinitis, bronchospasm, urticaria and angioedema, and, in the most severe cases, anaphylaxis.

The treatment of mast cell disorders begins with medications affecting mast cells and their mediators. Antihistamines block the interaction of histamine receptors with histamine. Cromolyn sodium is a stabiliser of mast cells and can act on signalling proteins in the cell membrane and

chloride channels, resulting in reduction of degranulation. Anti-IgE treatment is the centre of treatment for uncontrolled urticaria and angioedema.

Mast cells are very important as they maintain antiparasitic responses, play a role in tissue repair, and maintain homeostasis of connective tissues; however, they also trigger hypersensitivity reactions and a range symptoms due to mediator release.

Due to high-speed developments in the field of mast cells, it is important to follow the WHO classification of mast cell diseases; diagnostic criteria, which includes evidence of mast cell mediator release; and clinical benefits of treatments.

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