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Emerging Role of Mast Cells as Biological Markers in the Pathogenesis of Infectious Diseases and their Projection in Health Emergencies

Rol Emergente de los Mastocitos como Marcadores Biológicos en la Patogenia de Enfermedades Infecciosas y su Proyección en Emergencias Sanitarias

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SUMMARY: Mast cells (MC) are cells of the immune system that regulate cell and tissue homeostasis, are found in low numbers, have an intact plasma membrane, and a cytoplasm with a wide variety of inflammatory chemical mediators. The activation or degranulation of mast cells implies the release of these chemical mediators (interleukins, cytokines, and more), causing tissue actions ranging from the activation of metalloproteinases to the development of anaphylactic hypersensitivity of different degrees, alterations in vascular permeability, and loss of cell homeostasis. This behavior would allow them to act as sentinels responding to pathophysiological processes. During the COVID-19 pandemic, in positive human patients, the available literature reports the presence and degranulation of mast cells in a generalized manner, especially in the respiratory tract. This study aimed to analyze the emerging role of MCs in the pathogenesis of diseases and their projection as biological markers in the treatment of diseases or pandemics. The analysis of human biopsies showed that MCs are observed as cells with diameters between 8 to 20 µm, and in inflamed tissues, degranulation of MCs is observed. The action of MCs degranulation was related to different inflammatory processes of autoimmune diseases. It is concluded that the potential of MC as therapeutic targets and biomarkers could raise new pharmacological targets, as supportive therapy, and possibly of great help in the treatment of future emerging pandemics such as the current monkeypox.

KEY WORDS: Mast cells; COVID-19; Histology; Health Emergency; Therapy.

INTRODUCTION

Mast cells (MC) are immune system elements widely distributed throughout all tissues and express various cell surface receptors. Their origin is related to the bone marrow (regulated by stem cell factor), where they travel to the connective tissue according to signaling by specific chemical mediators (Lam *et al*., 2021). MC activation (or degranulation) is characterized by the release of preformed mediators that re-synthesize a broad spectrum of inflammatory and immunomodulatory mediators, allowing them to act as sentinels in response to pathophysiological processes. Noto *et al*. (2021) determine that regulating mast cell activities in different inflammatory processes and tumor microenvironments may be critical for uncovering potential therapeutic targets in treating autoimmune diseases and cancer and biomarkers in disease severity and treatment outcome.

MCs are multifunctional immune cells widely distributed throughout the body but preferentially present in the pulmonary system (Kilinç & Kilinç, 2020; Rodríguez *et al*., 2020). There are two main types of mast cells: connective tissue type (CTMC) and mucosal type (MMC). CTMCs typically reside in the skin and peritoneal cavity, whereas MMCs are predominantly in the mucosal layer of the lung (epithelium and chorion) and the intestine (Nakamura *et al*., 2017).

MC distribution and activation are associated with the circadian rhythm through two main pathways: IgE/FceRI-mediated signaling and the IL-33/ST2 pathway. The pineal gland participates in this regulation through melatonin and histamine. The interaction of melatonin, histamine, and

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mast cells could be a potential therapeutic tool mediated by the circadian rhythm in inflammatory diseases. The quantity and activity of mast cells would be controlled by the circadian rhythmic variation and environmental factors, such as light intensity and nutritional intake (Elieh Ali Komi *et al*. 2020; Pham *et al*., 2021).

The study's objective is to analyze the emerging role of MCs in the pathogenesis of diseases and their projection in confronting pandemic health emergencies such as COVID-19 or other pandemics through their potential as therapeutic targets or biomarkers to improve the results of the treatments.

MATERIAL AND METHOD

Anonymized biopsies available from the repository of the Faculty of Medicine of Universidad de Chile were fixed in 10% formalin and buffered in saline phosphate solution at pH 7.2. Subsequently, they were processed for specific histological techniques of mast cell recognition with 1% Toluidine blue. Finally, 5um sections were mounted in Canada balsam (Eukit). The observation, recognition, and analysis of mast cells were performed under a light microscope (Olympus CX43-BINO100XKIT, USA).

RESULTS

Figures 1, 2, and 3 show the histological results. In humans, MCs are histologically observed as intensely metachromatic granules for staining with Toluidine Blue. Figure 1 shows a microphotograph of a section of a human pineal gland showing the presence of a mast cell with an appearance within normal limits. It is observed as a considerable cell between 8 to 20 um in diameter, with a purple nucleus and reddish metachromatic cytoplasm.

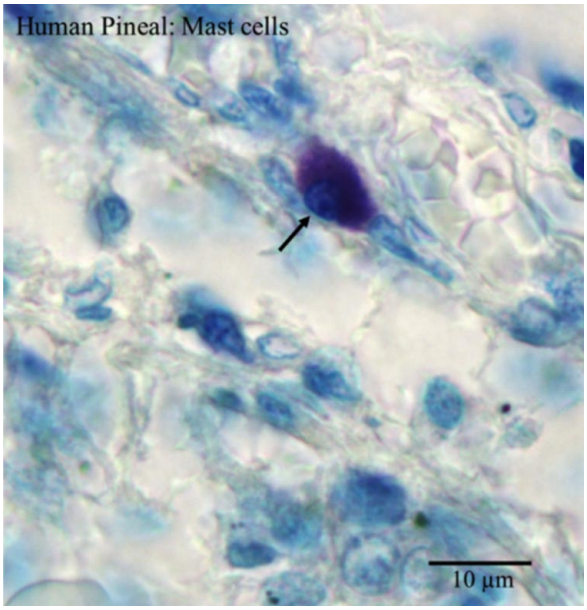

Fig. 1. Photomicrograph of a human pineal gland section. The presence of a non-degranulated mast cell is observed (arrow). Toluidine blue stain. 100x.

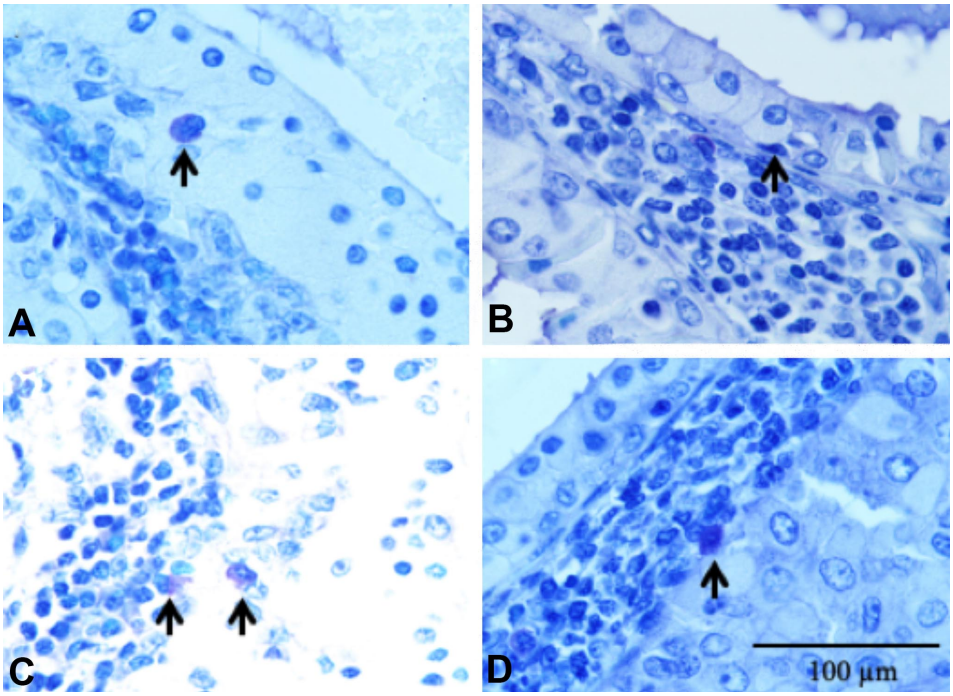

Fig. 2. Human prostate biopsy microphotographs (blue). 40x.

Figure 2 shows a human prostate biopsy with different locations in mast cells' epithelial and connective tissues. The mast cells are observed with a rounded central nucleus and ample cytoplasm filled with blue metachromatic granulations.

Figure 3 shows a photomicrograph of a pineal gland section with an inflammatory process. The arrow indicates the presence of a degranulated mast cell. A considerable cell with many metachromatic granules in the extracellular matrix is observed.

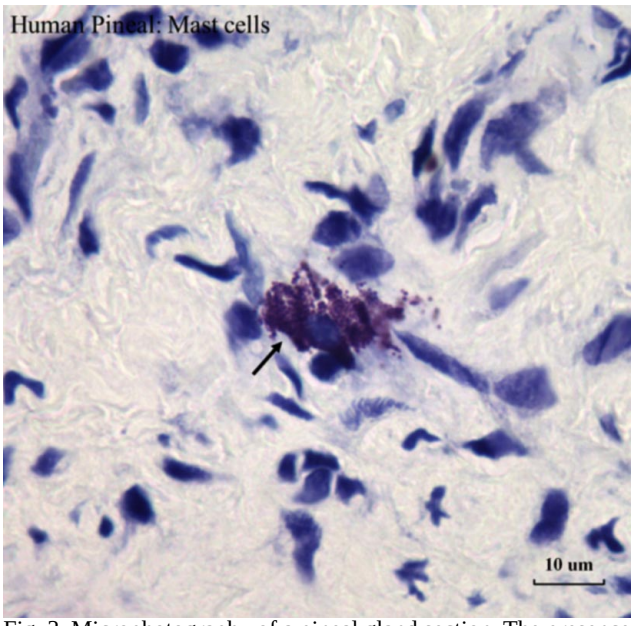

Fig. 3. Microphotography of a pineal gland section. The presence of a degranulated mast cell is highlighted (arrow). Toluidine blue stain. 100x

DISCUSSION

Generally, in states of cellular and tissue homeostasis, mast cells are found in sparse numbers, with an intact plasma membrane and a cytoplasm loaded with granules whose contents are a wide variety of pro-inflammatory, inflammatory, and anti-inflammatory chemical mediators, depending on the stimulus, MCs calibrate their mediator release pattern, modulate the amplification of allergic inflammation and are involved in the resolution of immune responses (Elieh Ali Komi *et al*., 2020; Dahlin *et al*., 2022).

MC immunological effects present in tissues are mainly based on the expression of their multiple pathogen recognition receptors on the cell surface and in the cytoplasm. Mast cells are now described to express FceRI, a high-affinity receptor of the IgE receptor IL-33 (ST2L), associated with mechanisms of tissue damage and inflammation (Olivera *et al*., 2018). Mast cell activation has several ways of generating an acute pathological state. Thus, the levels of metabolic (oxidizing agents) or infectious (viruses, bacteria, fungi, or parasites) stressors activate the MCs, whose response is represented by cytoplasmic degranulation and release of chemical mediators whose tissue actions range from activation of metalloproteinases, development of anaphylactic hypersensitivity, alterations of vascular permeability, and loss of cellular homeostasis (Krystel-Whittemore *et al*., 2016).

The binding of IgE to its receptor activates several mechanisms that stimulate allergic inflammation. Consequently, it generates the release of basophil granules of sulfated proteoglycans (chondroitin sulfate), heparin, histamine, serotonin, and mast cell-specific proteases, paralleling an elevated production of inflammatory mediators that positively or negatively modulate inflammation (Galli & Tsai, 2012).

MCs affect vascular permeability and tone, generating tissue hypoxia. In cardiovascular pathophysiology, it has been evidenced that mast cells are located in the vasculature associated with cardiac hypertrophy, specifically in the right ventricle, due to hypertension (Luitel *et al*., 2017). Xu *et al*. (2018) observed the accumulation of these cells around the pulmonary vasculature in patients with pulmonary hypertension. In Dengue hemorrhagic fever, where there is elevated mast cell activation (mainly by granular enzymes such as chymases), coagulation defects and blood vessel ruptures have been shown (Syenina *et al*., 2015). In adrenocorticotropic hormone (ACTH) activated mast cells, there is an increase in proinflammatory factors, which contribute to various Central Nervous System (CNS) disorders. Likewise, neuroinflammation is critically implicated in the onset and development of neurodegenerative disorders such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease (Zhang *et al*., 2016a).

During the COVID-19 pandemic, the hallmark of pathogenesis was the activation of monocytes/macrophages, dendritic cells, T cells, MCs, and neutrophils, which induced a cytokine storm in the lungs (Kempuraj *et al*., 2020). In murine experimental animals, in non-human primate models (NHP) infected with SARS-CoV-2 and in human patients with COVID-19, Tan *et al*. (2021) described widespread MC degranulation in the airways, they also detected high levels of chymases with alterations of the RAS system. Once the virus binds to the ACE2 receptors of the epithelial cells of the respiratory and digestive tract, it activates the MCs of these mucous membranes (Theoharides, 2020). MCs' rapid degranulation with excessive release of chemical mediators would cause inflammation of the alveolar epithelium and lung injury with different intensity in patients with persistence of inflammatory responses (Xu *et al*., 2018; Huang *et al*., 2020; Wu *et al*., 2021; Batiha *et al*., 2022). Several strategies to achieve plasma membrane stabilization of MCs and thus preventing degranulation would be a breakthrough in future therapies. Zhang *et al*. (2016b) determined that drugs used in MC stabilization processes could be beneficial in treating infectious pathologies; among these stabilizing agents, they highlight sodium cromoglycolate. Borriello *et al*. (2014) propose that further study of surface receptors and signaling pathways involved

in MC activation could provide new pharmacological targets, which may be promising for treating various MC-mediated disorders.

Christ *et al*. (2018) consider that forward-looking medicine should consider the rhythmic nature of MCs and the immune responses generated by their signaling pathways that play a critical role in allergic and inflammatory reactions (Silveira e Souza *et al*., 2011; Galli & Tsai, 2012; Relan *et al*., 2021). Furthermore, Noto *et al*. (2021) suggest that regulating mast cell activities may be critical to treating different inflammatory processes and a possible therapeutic agent and biomarker of disease and treatment outcome. Kilinç & Kilinç (2020) determined the importance of mast cell stabilization as a supportive therapy to alleviate fatal inflammatory responses and pulmonary complications due to COVID-19.

CONCLUSIONS

MCs are multifunctional immune cells widely distributed throughout the body. Mast cell degranulation involves the release of many chemical mediators whose tissue actions alter vascular permeability and loss of cellular homeostasis. These cells play an essential role in humans in the first line of defense against viruses, bacteria, or other pathogens that enter our body. Understanding their mechanism of action could have been very helpful in treating SARS-CoV2 infection to relieve inflammatory and pulmonary responses and reduce deaths from this pandemic. Finally, the potential of MCs as therapeutic targets and biomarkers could pose new pharmacological targets, as a supportive therapy, and possibly be of great help in the treatment of future emerging pandemics such as the current monkey pox.

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RESUMEN: Los mastocitos (MC) son células del sistema inmune que regulan la homeostasis celular y tisular, se encuentran en escasas cantidades, presentan una membrana plasmática íntegra, y un citoplasma con una amplia variedad de mediadores químicos. La activación o degranulación de los mastocitos implica la liberación de estos mediadores químicos (interleuquinas, citoquina y más), provocando acciones tisulares que van desde la activación de metaloproteinasas hasta el desarrollo de hipersensibilidad anafiláctica de distinto grado, provocando la pérdida de la homeostasis celular. Durante la pandemia de la COVID-19, en pacientes humanos positivos, se informa recurrentemente la presencia y degranulación de mastocitos de manera generalizada sobre todo en las vías respiratorias. El análisis de la degranulación de los MCs podría proporcionar información que podría utilizarse en el desarrollo de tratamientos preventivos contra infecciones virales, bacterianas u otros patógenos. Este comportamiento les permitiría actuar como centinelas en respuesta a procesos fisiopatológicos. El objetivo de este trabajo fue analizar el rol emergente de los MCs en la patogenia de enfermedades y su proyección como marcadores biológicos en el tratamiento de enfermedades o pandemias. En análisis de biopsias humanas se muestran que MCs se observan como células con diámetros de entre 8 a 20 μm, en tejidos inflamados se observa degranulación de MCs. Se relacionó el accionar de degranulación de los MCs en diferentes procesos inflamatorios de enfermedades autoinmunes. Se concluye que el potencial de MC como dianas terapéuticas y biomarcadores podrían plantear nuevos objetivos farmacológicos, como terapia de apoyo, y posiblemente de gran ayuda en el tratamiento de futuras pandemias emergentes como la actual viruela del mono.

PALABRAS CLAVE: Mastocitos; COVID-19; Histología; Emergencia Sanitaria; Terapia.

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