The Underestimated Role of Mast Cells in the Pathogenesis of Rhinopathies

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Abstract

Mast cells (MCs) are involved in several biological processes, such as defense against pathogens, immunomodulation, tissue repair after injury, and angiogenesis. MCs have been shown to change from protective immune cells to potent pro-inflammatory cells, influencing the progression of many pathological conditions, including autoimmune diseases and cancers. The role of MCs in the pathogenesis of rhinopathies has often been underestimated, since previous studies have focused their attention on eosinophils and neutrophils, while MCs were considered involved exclusively in allergic rhinitis. However, recent nasal cytology findings have shown the involvement of MCs in several rhinopathies, such as NARMA, NARESMA, and CRSwNP. These recent evidences highlight the crucial role that MCs play in orchestrating the inflammation of the nasal mucosa, through complex biological mechanisms, not yet fully understood. In this context, a better understanding of these mechanisms is fundamental for practicing Precision Medicine, which requires careful population selection and stratification into subgroups based on the phenotype/endotype of the patients, in order to guarantee the patient a tailored therapy. Based on this background, further studies are needed to understand the pathophysiological mechanisms involving MCs and, consequent-

ly, to develop targeted therapies aimed to obtain a selective inhibition of tissue remodeling and preventing MC-mediated immune suppression.

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Introduction

Mast cells (MCs) were first described by Paul Ehrlich in his doctoral thesis [1]. Their original function is to be found in parasite and bacterial defense of the host and as a general inducer of inflammation. This early type of cell has differentiated toward a more complex cellular entity involved in different regulatory processes, such as immunomodulation, tissue repair and remodeling after injury, angiogenesis, and other biological functions [2]. MCs are localized at the junction point of the host and external environment at places of entry of antigens (gastrointestinal tract, skin, and respiratory epithelium). In humans, MCs reach densities of up to 500–4,000 per mm³ in the lungs, 7,000–12,000 per mm³ in the skin, and 20,000 per mm³ in the gastrointestinal tract. The selective placement of MCs near the vasculature may ensure that the release of MC-derived pro-inflammatory products has instantaneous effects on the endothelium [3].

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MCs change from protective immune cells to potent pro-inflammatory cells, influencing the progression of many pathological conditions, including autoimmune diseases and tumors. The role of MCs in tumor biology is controversial due to the variety of processes they are involved in enacting both pro- and anti-tumorigenic effects depending on the context [4].

MCs release in the surrounding microenvironment a broad array of preformed mediators and signaling molecules affecting different resident tissue cells, like fibroblasts, smooth muscle cells, endothelial cells, and epithelial cells. In addition, they synthesize and release both serine and metalloproteases, which cause extracellular matrix degradation and tissue remodeling [5]. These functional properties put MCs in a central, strategic position to maintain tissue homeostasis [6].

Mast Cells in the Respiratory Tract

In the respiratory system, the greatest concentration of MCs is found in the trachea and large bronchi, just underneath the epithelium, but some MCs are present also within the bronchial epithelium. The lungs do not have many MC progenitors in a normal physiological state. Upon antigen-induced inflammation of the respiratory endothelium, MC progenitors are recruited [7]. Human MCs from different lung compartments contain granules with distinct protease content, which can be classified as MCs containing either tryptase only (MC_T), chymase only, or both tryptase and chymase (MC_{TC}) in their granules [8, 9]. The MC_T subtype predominates in the lung parenchyma, bronchial lamina propria, and bronchial epithelium, while the MC_{TC} subtype surrounds pulmonary blood vessels with close proximity to the vascular endothelial cells [10, 11].

Apart from their well-established presence in the conducting airways, MCs in the human respiratory system are also abundant in the alveolar parenchyma or respiratory lymphoid tissue [10]. In the respiratory tract, the immune response to MC activation results in airway constriction, increased mucous production, and cough.

Mucosal MCs in the nasal epithelium are activated by antigens that diffuse across the mucosa after being inhaled. MC degranulation, in turn, increases vascular permeability and local edema, which can obstruct nasal airways and lead to congestion [12].

Over the last few years, studies concerning nasal cytology and sinonasal histology have highlighted the presence of MCs in several rhinopathies. Although their

pathophysiological role in allergic forms is well known, in non-IgE-mediated rhinopathies, these aspects are still largely unknown.

The Role of Mast Cells in Rhinitis

Rhinitis is a heterogeneous group of inflammatory disorders of the nasal mucosa, characterized by the presence of several symptoms, including rhinorrhea, sneezing, nasal obstruction, and itching, variously associated [13]. Based on the etiology, rhinitis can be mainly subdivided into infectious, inflammatory, vasomotor, medicamentous, hormonal, occupational, and atrophic [14]. Among vasomotor rhinitis, characterized by nasal hyper-reactivity, 2 big groups can be distinguished: allergic rhinitis (AR) and non-allergic rhinitis (NAR).

In particular, non-allergic forms, once defined as “non-specific,” have gained a nosological dignity over the time thanks to nasal cytology and are nowadays classified according to the predominant cell types into NARNE (NAR with neutrophils – Fig. 1a), NARES (NAR with eosinophils – Fig. 1b), NARMA (NAR with MCs – Fig. 1c), and NARESMA (NAR with eosinophils and MCs – Fig. 1d). Nasal cytology, in fact, is a useful diagnostic tool that allows to evaluate the characteristics of the cellular infiltrate and, thus, of the nasal immunoflogosis [15]. In this context, the evaluation of rhinitis from a cytological point of view has highlighted the crucial role that MCs play in the pathogenesis of these diseases, too often underestimated.

Mast Cells and Angiogenesis in Rhinitis

MCs release several proangiogenic factors, including fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), tumor necrosis factor alpha, transforming growth factor beta, angiopoietins, and nerve growth factor. Moreover, MCs migrate in vivo and in vitro in response to VEGF and placental growth factor-1 [16]. Tryptase, stored in MC preformed granules, stimulates the proliferation of endothelial cells, promotes vascular tube formation in vitro, and activates proteases, which in turn degrades the extracellular matrix, releasing VEGF or FGF-2 [17].

A cross-link between the majority of these angiogenic factors and allergic symptoms has been clearly established in rhinitis. The ability of MCs to secrete angiogenic factors is enhanced by the cross-linking of IgE attached to the high-affinity IgE receptor FcεRI with the bivalent antigen [18]. IL-8 induces inflammatory migration and the

Fig. 1. **a** Non-allergic rhinitis with neutrophils (NARNE). **b** Non-allergic rhinitis with eosinophils (NARES). **c** Non-allergic rhinitis with mast cells (NARMA). **d** Non-allergic rhinitis with eosinophils and mast cells (NARESMA). Neutrophil (N), eosinophil (E), mast cell (MC), degranulation (D). May Grunwald-Giemsa (MGG) staining; magnification, $\times 1,000$.

production of chemical mediators such as leukotriene and histamine from MCs, which are responsible for the induction of AR clinical symptoms [19]. VEGF and FGF-2 increase vasodilation and vascular permeability, involved in swelling of the nasal mucosa, increase in watery rhinorrhea, and infiltration of inflammatory cells in the nasal walls [20]. Tumor necrosis factor α is involved in AR through the enhancement of Th2-type cytokine secretion and the infiltration of Th2-type T cells into the site of allergic inflammation [21].

Allergic Rhinitis and Mast Cell-Mediated Inflammation

The allergic reaction consists of a so-called early phase, mainly mediated by histamine, and a late phase, due to the influx of inflammatory cells. In AR, this response is always characterized by the presence of inflammatory cells infiltrating the nasal mucosa that release several

chemical mediators, which provoke the main symptoms (itching, nasal congestion, runny nose, and sneezing). When the allergen exposure is of low intensity but persistent in time, as is typical of perennial rhinitis, the rhinocytogram shows a “minimal persistent inflammation,” characterized by a persistent infiltration of neutrophils overall and only minimally by eosinophils, even in the absence of symptoms. MCs and important signs of eosinophilic-MC degranulation are rarely found. As far as seasonal AR is concerned, the rhinocytogram changes depending on whether the patient is examined during or off the pollen season. In the first condition, the patient presents all the clinical signs of the disease: nasal cytology is characterized by neutrophils, lymphocytes, eosinophils, and MCs, largely degranulated (Fig. 2); conversely, if assessed out of season, the patient clearly presents a clinical and cytological “silence.”

MC-mediated inflammation is essential for AR, since the cross-linking between antigen (Ag)-IgE complexes and FcεRI on the surface of sensitized MCs triggers their degranulation, with releasing of inflammatory mediators, chemokines, and cytokines associated with type I hypersensitivity [22]. This leads to increased production of mucus, vasodilation, increased vascular permeability, and plasma extravasation, with consequent nasal congestion and edema responsible for the typical symptoms of AR, represented by nasal obstruction, rhinorrhea, and post-nasal drip. Moreover, MCs express transient receptor potential (TRP) cation channels (e.g., TRPC1–7, TRPV1/2/4/6, TRPM2/4/7/8, and TRPA1), which are implicated in several physiological processes taking place in the upper airways, such as chemosensation, thermosensation, regulation of vascular permeability, release of neuropeptides, ciliary beating, and mucus secretion. Although the role of these receptors in the pathogenesis of rhinitis is not yet fully understood, they probably promote the inflammatory milieu and MC degranulation [23]. Thus, they are involved in the mechanisms underlying nasal hyperreactivity, in both AR and NAR. In fact, in the early phase of the allergic reaction, the degranulation of MCs stimulates the sensory nerves, causing the release of neuropeptides and neurokinins that initiate neural responses characterized by cholinergic reflexes such as lacrimation, sneezing, and cough. Furthermore, TRP channel activation causes the release of substance P (SP), which in turn determinates the onset of several symptoms, including itching and burning sensation.

Non-Allergic Rhinitis with Mast Cells

In patients affected by NAR, the TRPV1/SP pathway has been shown to be upregulated, leading to neurogenic inflammation. Moreover, MC proteases can amplify neurogenic inflammatory responses, probably by the activation of protease-activated receptor 2. Indeed, activated MCs produce a tryptase that interacts with neural protease-activated receptor 2 in the airways, leading to the release of SP and the calcitonin gene-related peptide, which promote neurogenic inflammation. However, tryptase and chymase from the MCs may also degrade excessive neuropeptides, according to a bio-feedback mechanism, which decreases neurogenic inflammation [24]. Among NARs, according to the cellular prevalence at nasal cytology, a mast-cell form (NARMA), characterized by the presence of MCs in the nasal mucosa (MCs $\geq 10\%$ of total cells), partially degranulated, is distinguished [25] (Fig. 1c). The clinical presentation of this disease is usually severe and associated with the presence of asthma

Fig. 2. Acute phase allergic rhinitis. Nasal cytology is characterized by neutrophils (N), lymphocytes (L), eosinophils (E) and mast cells (MCs), largely degranulated. May Grunwald-Giemsa (MGG) staining; magnification, $\times 1,000$.

and/or nasal polyps. Moreover, NARMA is now considered a transitional form, leading to non-allergic rhinitis with eosinophils and mast cells (NARESMA), which has been identified as a cytological entity only in recent years. NARESMA is characterized by the presence of eosinophils and MCs, in variable proportions, with a relevant degranulation (Fig. 1d). The mixed inflammatory infiltrate is responsible for more severe and difficult to treat forms, often associated with nasal polyposis, asthma, and rhinosinusitis [14].

The role of MCs in the pathogenesis of other forms of rhinitis has been underestimated over the years, since MCs were merely thought to be involved in allergic diseases. Thanks to nasal cytology, which has shown that MCs are actually involved in many rhinitis, there is nowadays increasing emphasis on the pivotal role of these cells in the pathogenesis of sinonasal disorders. As a matter of fact, increasing data suggest that MCs act as innate immune cells against pathogens and initiate defensive responses, being receptive to various noxious and innocuous agents through the expression of their corresponding receptors and strategically localized close to portals of microbial entry, such as the respiratory tract [26, 27]. As a demonstration of this, it has been shown that initial stages of viral rhinitis are characterized by the accumulation of MCs which, together with T and B lymphocytes, triggers the inflammatory cascade in the nasal mucosa.

Therefore, the complexity of MC biology in the context of innate immune responses suggests that these cells could orchestrate much of the inflammatory responses in

the nasal mucosa. Hence, better understanding of their functions is important in order to develop targeted and effective therapeutic strategies.

CRSwNP: Mast Cell Endotype

Chronic rhinosinusitis (CRS) is a common inflammatory disorder of the nose and paranasal sinuses, characterized by persistent symptoms of nasal obstruction, rhinorrhea, facial pain, and hyposmia lasting longer than 8–12 weeks. CRS can be subdivided, according to the phenotype, into 2 groups: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps [28].

Eosinophilic inflammation has been considered to be a cardinal feature of CRSwNP in Caucasians for a long time [29]. On the contrary, the role of MCs in the pathogenesis of CRS has long been underestimated.

Recent studies have shown that MCs are significantly increased in nasal polyps and are primarily accumulated in the epithelium. In particular, based on their tissue microlocalization and their protease expression, 2 major human MC subtypes have been recognized: subepithelial MCs (MC_{TC}), coexpressing tryptase and chymase in conjunction with cathepsin G and carboxypeptidase A3, and mucosal epithelial MCs (MC_T), expressing only tryptase. Type 2 inflammation changes the number, distribution, and phenotype of MCs, and, in particular, severe asthma and CRSwNP are associated with the expansion of intraepithelial MC_T expressing carboxypeptidase A3 and MC_{TC}, which infiltrate the airway smooth muscle and subepithelial glandular tissue [30]. These subtypes produce an abundance of cytokines that activate eosinophils and directly promote tissue remodeling through the degradation of the extracellular matrix [31].

Interestingly, MC levels are higher in nasal polyps of patients with eosinophilic CRS compared to nasal polyps of patients with non-eosinophilic CRS, suggesting the positive correlation between eosinophilia and MC activation in CRS [31, 32]. In particular, flow cytometric analysis had demonstrated increased frequencies of total MCs and IgD1 MCs in eosinophilic but not non-eosinophilic polyps, in comparison with control tissues, which facilitate IgE production and eosinophilic inflammation [33].

In addition, MCs infiltrating nasal polyps have been shown to have increased expression of T-cell/transmembrane immunoglobulin and mucin domain protein 3 (TIM-3), a receptor that promotes MC activation and production of cytokines [34]. Chronic inflammation underlying CRSwNP could be promoted and propagated at the epithelial cell layer and perhaps mediated by errone-

ous initiation of signaling cascades, leading to TIM-3-mediated MC activation and degranulation. Furthermore, although TIM-3 MC expression is higher in the epithelial layer than in the stroma of nasal polyps, the preferential activation in the stroma may contribute to greater severity of the disease. As a matter of fact, the infiltration of MCs into the stromal layer is significantly correlated with the clinical severity of CRSwNP and with refractory to medical and surgical treatments [35].

It is nowadays known that MCs can be activated by local IgE and then secrete substantial quantities of type 2 cytokines, especially IL-5 and IL-13, which facilitate type 2 responses and eosinophilic inflammation in CRSwNP. However, the disease-specific MC-triggering mechanisms apart from IgE are poorly studied in CRSwNP.

The role of an endotoxin-releasing strain of *Staphylococcus aureus* in the activation of MCs is worth mentioning. In particular, the combined effect of staphylococcal enterotoxin B and viable intracellular *S. aureus* stimulates MC degranulation, releasing proinflammatory mediators and cytokines into the extracellular space. Moreover, staphylococcal enterotoxin B causes directly a damage to epithelial cells, leading to epithelial proliferation and remodeling, resulting in a disorganized and defective epithelial barrier. This could lead to localized stromal edema and downstream promotion of the formation and growth of nasal polyps [36]. As a matter of fact, the net impact of MCs on the pathogenesis of CRS may be a result of a balance between detrimental and protective effects, mediated by distinct MC proteases in the main 2 MC phenotypes.

Actually, the dualism between eosinophilic and neutrophilic inflammation underlying CRS should be re-evaluated, since MCs have a crucial role in the pathogenesis of CRSwNP, orchestrating eosinophilic inflammation and causing the most severe forms, usually refractory to traditional treatments. Nasal cytology findings support this hypothesis, since previous studies have shown that the inflammatory cytotypes in nasal polyps are represented prevalently by eosinophils (61.8%) and by eosinophils-MCs (31.9%) (Fig. 3a), while MCs (Fig. 3b) and neutrophils are, respectively, found in 3.5% and 2.8% of the cases [37]. Moreover, eosinophilic-MC inflammation has been shown to cause more severe forms of CRSwNP. In particular, the severity of CRSwNP and, therefore, the Prognostic Index of Relapse (PRI) can be assessed according to Clinical-Cytological Grading (CCG), which is based on both endotype (nasal cytology findings) and phenotype (asthma, allergy, and ASA sensitivity). High-grade CCG is significantly associated with

Fig. 3. CRSwNP. **a** Eosinophils-mast cells endotype. **b** Mast cells endotype. Mast cells (MCs), neutrophil (N), lymphocyte (L), ciliated cells with dystrophic ciliary apparatus (Ci). May Grunwald-Giemsa (MGG) staining; magnification, $\times 1,000$.

more frequent comorbidities, recurrent surgery, and mixed eosinophilic-MC phenotype [38].

Furthermore, recent studies under publication demonstrate the strong correlation between the CCG and the expression of galectin-10, a reliable predictor of recurrence of CRSwNP, which mainly colocalizes with infiltrating eosinophils and MCs. These evidences highlight the involvement of MCs in the pathogenesis of CRS and, in particular, in the spectrum of pathologies underlying type 2 inflammation, such as CRSwNP.

Therapeutic Approaches

A specific diagnosis, based on the pathophysiological mechanisms underlying the nasal inflammation, is essential to guarantee the patient a tailored therapy. Therefore, a careful stratification of patients into subgroups based on their phenotype/endotype is mandatory in order to obtain satisfactory therapeutic results [39]. The management of AR includes the removal of the allergen, pharmacological treatments (local and systemic antihistamines, antileukotriene drugs, and topical corticosteroids), and allergen immunotherapy [40]. On the other hand, NARs respond well to both topical and systemic corticosteroid therapy and antileukotriene drugs, but not to allergen immunotherapy [14]. In this context, identifying overlapped rhinitis is essential to avoid false expectations of a “definitive” recovery after medical treatment, especially if the rhinopathy is characterized by a mixed eosinophil-MC phenotype [41]. Moreover, all forms of rhinitis require a

regular clinical and cytological assessment, to evaluate the evolution of the disease over time, both to avoid over-treatment and to ascertain the possible evolution to CRSwNP. Regarding the latter rhinopathy, medical treatment is tailored to the degree of severity of the disease, according to CCG, and includes topical and local corticosteroid treatment, antileukotrienes, and antihistamines [42]. Furthermore, the recent approval of biological agents for the treatment of CRSwNP could pave the way for new tailored therapeutic strategies for most severe forms [43].

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Gelardi M. conceived and designed the study, made a bibliographic analysis, and revised the manuscript. Giancaspro R. and Ribatti D. made a bibliographic analysis and wrote the manuscript. Cassano M. made a bibliographic analysis and revised the study. All authors approved the final manuscript.

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