Mechanisms of Mast Cell Activation in Severe Asthma
Beyond IgE

Mast cells (MCs) are present in all heathy human tissues and exhibit marked heterogeneity with respect to their development, mediator content, ultrastructure, and function (1). They secrete a vast arsenal of biological substances including the classical autacoid mediators (histamine, prostaglandin D$_2$, and leukotriene C$_4$), proteases, and cytokines. They respond rapidly to a multitude of perceived tissue insults with the initiation of a coordinated program of inflammation and repair. Potentially beneficial MC roles include protection against infection (2), kidney injury (3), envenomation (4), and in some circumstances, cancer progression (5). However, when a tissue insult is repeated or continuous, the effects of MC mediators are potentially deleterious, and it is not surprising that MCs are implicated in the pathophysiology of many diverse diseases including asthma (1) and idiopathic pulmonary fibrosis (6).

MCs release their mediators in response to all stimuli considered important for the development of asthma, day-to-day symptoms, and exacerbations (reviewed in Reference 1). The biological activity of their mediators can account for all of the physiological and pathological abnormalities present in asthmatic airways. Importantly, there is unequivocal evidence of the ongoing release of MC mediators in the airways of people with both mild and severe asthma, and in both T2-high and T2-low severe asthma (1, 7). MCs are unique among leukocytes in that they infiltrate the airway submucosal glands and airway smooth muscle bundles in asthmatic airways, and infiltrate the airway epithelium, placing activated MCs within these dysfunctional airway elements (1).

For decades the investigation of MC signaling focused on allergen-driven IgE-dependent activation via the high-affinity IgE receptor FcεRI. However, human MCs respond to a wide variety of stimuli including cytokines/growth factors, lipids, nucleotides, complement, proteases, products of infection (human MCs express all Toll-like receptors), pollutants, physical stimuli, occupational agents, drugs, and cell–cell signals (1) (Figure 1). The historic work of Okumura using human adult peripheral blood progenitor–derived MCs showed that although there are core changes in MC gene expression after activation via FcεRI, LPS, and IFN-γ, there are also many stimulus-specific changes, and these are modified with combined stimulation (8). It is likely that many stimuli contribute to MC activation within the airways of an individual over time, but to date, there has been little information on the activity of IgE-independent pathways in asthmatic airways.

In this issue of the Journal, Tiitu and colleagues (pp. 397–411) have used gene set variation analysis to interrogate MC activation signatures in the sputum of the U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes) asthma and healthy volunteer cohort, cross-validated with the ADEPT (Airways Disease Endotyping for Personalized Therapeutics) cohort (with which there was moderate agreement) (9). They looked at the relationship of these activation signatures with asthma severity and sputum inflammation and also mapped them to three molecular clusters of severe asthma they had identified previously, described as transcriptome-associated clusters (TACs) 1–3 (10). The gene sets used were obtained from previous studies using cultured human blood progenitor–derived MCs that were unstimulated, FcεRI-activated (single and multiple activation rounds), LPS-activated, IFN-γ–activated, or IL-33–activated. There was also a signature from MCs identified in mild asthma bronchial biopsies by single-cell sequencing. In severe asthma, the FcεRI-activated, single-cell sequencing signature from mild asthma, LPS−, and IL-33–dependent signatures were enriched compared with heathy controls. These signatures were also enriched in the subset of patients with severe asthma who were eosinophilic, but the LPS− and IL-33–dependent signatures were enriched further in people deemed neutrophilic or mixed granulocytic defined by sputum percentage cell counts. FcεRI-related signatures were enriched predominantly in people expressing the T-help cell type 2 eosinophilic TAC1 molecular phenotype, whereas LPS− and IL-33–dependent signatures were enriched in the TAC2 neutrophil inflammasome–associated phenotype. These same MC signatures were similarly enriched in individuals with asthma with airflow obstruction compared with those without. The MC activation signatures correlated poorly with tissue MC numbers, supporting previous work indicating that MC activation and their tissue localization is more important than absolute numbers.

This is a comprehensive data analysis and the first study in severe asthma to examine MC gene expression signatures generated by different stimuli. The authors have uncovered several interesting associations between stimulus-specific MC gene signatures, clinical features of asthma, and molecular phenotypes, and this represents an important advance in our understanding of IgE-independent factors that may be driving MCs in severe asthma. The study also provides further evidence that MCs are activated across clinical and molecular severe asthma phenotypes.

There are some limitations to the study. Gene set variation analysis has problems because not all genes expressed are necessarily specific for one cell type, although the authors took steps to exclude genes that overlap with other leukocytes. The gene
The study is cross-sectional, which is a strength in that it demonstrates significant MC activation in "steady-state" severe asthma but also a limitation as it is apparent that the TAC sputum molecular asthma phenotypes are unstable over time (11). In addition, true T2-low severe noneosinophilic asthma appears rare, with T2 biomarkers emerging as corticosteroid treatment is reduced (12). It would therefore be interesting to study MC expression signatures longitudinally and...
with corticosteroid reduction and to explore whether airway immunosuppression due to high-dose inhaled corticosteroids promotes IL-33-dependent MC activation.

Studying sputum in asthma clearly provides important insight into disease pathophysiology, but MCs are rare in sputum compared with other granulocytes. There are also many further potential MC activators at play (Figure 1) with potential interactions between them. It is not known currently to what extent other relevant MC activators might overlap with the LPS and IL-33 signatures and, therefore, how much of the signal described here is due to these molecules exclusively. Thus, understanding the MC molecular response to multiple activators, ideally within human airway tissue stimulated ex vivo, and compared with tissue from various asthma phenotypes, using techniques such as single-cell sequencing and spatial transcriptomics/proteomics/lipidomics, would likely provide more granularity regarding the pathways driving MCs in any individual at the point in time they are studied. However, these may change from day to day, and particularly so during exacerbations, which highlights the challenge of targeting MCs effectively in asthma. A treatment for one set of pathways may be ineffective for another, exemplified by the partial efficacy of omalizumab in severe atopic asthma. Of note, a study targeting Kit signaling with mastinitib to reduce MC survival looks promising in both eosinophilic and noneosinophilic asthma (13).

In summary, Tiotiu and colleagues provide insight into some IgE-independent pathways that are active in the airways of people with severe asthma. These data should be considered the tip of the iceberg in unraveling the multiple factors that might be driving MC activation in an individual. The challenge now is to delve deeper, taking into account the many other potential activators of MCs present in asthmatic airways, and find where there is commonality in the signaling pathways, so that multiple MC activation pathways can be targeted effectively at the same time pharmacologically. ■

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References

1. Bradding P, Arthur G. Mast cells in asthma–state of the art. Clin Exp Allergy 2016;46:194–263.
2. Trivedi NH, Guentzel MN, Rodriguez AR, Yu JJ, Forsthuber TG, Arulanandam BP. Mast cells: multitalented facilitators of protection against bacterial pathogens. Expert Rev Clin Immunol 2013;9:129–138.
3. Madjene LC, Pons M, Danelli L, Claver J, Ali L, Madera-Salcedo IK, et al. Mast cells in renal inflammation and fibrosis: lessons learnt from animal studies. Mol Immunol 2015;63:86–93.
4. Akahoshi M, Song CH, Piliponsky AM, Metz M, Guzzetta A, Abrink M, et al. Mast cell chymase reduces the toxicity of Gila monster venom, scorpion venom, and vasoactive intestinal polypeptide in mice. J Clin Invest 2011;121:4180–4191.
5. Welsh TJ, Green RH, Richardson D, Waller DA, O’Byrne KJ, Bradding P. Macrophage and mast-cell invasion of tumor cell islets confers a marked survival advantage in non-small-cell lung cancer. J Clin Oncol 2005;23:8959–8967.
6. Bradding P, Peijer G. The controversial role of mast cells in fibrosis. Immunol Rev 2018;282:198–231.
7. Hinks TS, Zhou X, Staples KJ, Dimitrov BD, Manta A, Petrossian T, et al. Innate and adaptive T cells in asthmatic patients: relationship to severity and disease mechanisms. J Allergy Clin Immunol 2015;136:323–333.
8. Okumura S, Kashiwakura J, Tomita H, Matsumoto K, Nakajima T, Saito H, et al. Identification of specific gene expression profiles in human mast cells mediated by Toll-like receptor 4 and FcepsilonRI. Blood 2003;102:2547–2554.
9. Tiotiu A, Badi Y, Kermani NZ, Sanak M, Kolmert J, Wheelock CE, et al. Association of differential mast cell activation with granulocytic inflammation in severe asthma. Am J Respir Crit Care Med 2022;205:397–411.
10. Kuo CS, Pavlidis S, Loza M, Baribaud F, Rowe A, Pandis I, et al.; U-BIOPRED Study Group. T-helper cell type 2 (Th2) and non-Th2 molecular phenotypes of asthma using sputum transcriptomics in U-BIOPRED. Eur Respir J 2017;49:1602135.
11. Kermani NZ, Pavlidis S, Xie J, Sun K, Loza M, Baribaud F, et al.; U-BIOPRED study group. Instability of sputum molecular phenotypes in U-BIOPRED severe asthma. Eur Respir J 2021;57:2001836.
12. Heaney LG, Busby J, Hanratty CE, Djukanovic R, Woodcock A, Walker SM, et al.; Investigators for the MRC Refractory Asthma Stratification Programme. Composite type-2 biomarker strategy versus a symptom-risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multicentre, single-blind, parallel group, randomised controlled trial. Lancet Respir Med 2021;9:57–68.
13. Davidescu L, Chanez P, Ursol G, Korzh O, Deshmukh V, Kuryk L, et al. Late breaking abstract - mastinitib in severe asthma: results from a randomized, phase 3 trial. Eur Respir J 2020;56:4612.

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