

Pumping mast cells out of allergic inflammation— are proton pump inhibitors taking center stage?

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Key words: Mast cell activation, PPI, omeprazole, IgE

Mast cells are myeloid-lineage immune cells that originate from pluripotent progenitor cells of the bone marrow. The committed mast cell progenitors are released into the blood and recruited to the tissues. Under the influence of mainly stem cell factor and IL-3 in the tissues, they undergo differentiation to mature mast cells. Although mature mast cells are present in most tissues, they are most abundant in tissues that act as environmental barriers, such as the skin and mucosal surfaces. Their junctional location between the internal and the external environment and the ease by which they become activated in response to diffuse stimuli (temperature, physical forces, conserved molecular patterns in pathogens, and allergens) allow them to serve as one of the first defense mechanisms against external insults. Although the antigen, IgE, and high-affinity IgE receptor (FcεRI) crosslinking axis is the most recognized mast cell activation pathway, mast cells can be activated in response to pleiotropic stimuli, including cellular, viral, and bacterial triggers, through immunoglobulin (eg, IgG) receptors and pathogen recognition receptors (eg, Toll-like receptors), alarmins, lipids, and complement.¹

Mast cells promote inflammation in various diseases, most notably IgE-dependent anaphylaxis and food allergies,¹ and evidence is accumulating supporting their role in IgE-independent diseases, such as eosinophilic esophagitis (EoE), a chronic food-induced inflammatory disease of the esophagus. In fact, recent studies have shown that mast cell levels correlate with disease symptoms (eg, dysphagia) even more than eosinophil levels. Mast cells likely contribute to the inflammation and tissue remodeling by secreting proinflammatory cytokines and chemokines,

such as transforming growth factor β, which leads to fibrosis and tissue dysfunction.²

A main characteristic of mast cells is their high content of secretory granules that are filled with preformed mediators, including proteases, cytokines, and histamine. In addition, mast cells rapidly generate *de novo* inflammatory mediators, such as eicosanoids. Mast cell granules are commonly described as lysosome-like due to their acid content. Deficiencies in granule homeostasis elicit changes in mast cell morphology and defects in the integrity and activity of the granule constituents.³ Thus, maintaining the acidic environment in the mast cell granule is crucial for mast cell effector functions.

Proton pump inhibitors (PPIs) are a class of drugs that covalently bind and inactivate H⁺/K⁺-ATPase, thereby inhibiting acid secretion from the parietal gastric cells. Historically, PPIs have been widely used for the treatment of acid-related diseases, mainly gastroesophageal reflux disease and peptic ulcer disease. However, in addition to their antisecretory effects, PPIs have antioxidant and anti-inflammatory function likely due to their ability to target multiple cell types, including lung and esophageal epithelium, and endothelial and immune cells, perhaps augmenting their usage in patients with systemic mastocytosis, where their action has been attributed to regulating gastric acid production.^{4,5} For example, PPIs efficiently block eotaxin 3 (CCL26) secretion from epithelial cells by inhibiting signal transducer and activator of transcription 6 phosphorylation and its binding to the eotaxin 3 promoter.⁶ This effect is likely important given the evolving clinical relevance of PPIs in the treatment of EoE.⁷ A number of epidemiologic studies have linked early-life exposure to PPIs as substantial risk factors for the development of atopic disease, including food allergies and EoE, although the operational mechanisms are unclear.⁸

Although PPIs are highly similar in their chemical and pharmacologic properties, their signaling and metabolic pathways differ depending on the variations in their chemical structure. For example, omeprazole and esomeprazole signal through aryl hydrocarbon receptor (AhR), a ubiquitous nuclear receptor involved in integrating multiple environmental signals. Subsequently, activation of AhR leads to induction of the family of CYP450 enzymes that in turn metabolize PPIs. In contrast, the PPI rabeprazole is not a ligand for AhR nor a primary target of CYP450 enzymes.⁹ In addition, it has been suggested that PPIs block nongastric proton pumps, thereby changing intracellular pH. This activity may be critical for cellular responses that require acidic pH for proper functioning (eg, mast cell granules). Indeed, treatment of mast cells with bafilomycin, an acid-neutralizing H⁺-ATPase inhibitor, decreases the protein composition of mast cell granules.³ Taken together, these findings suggest that PPIs can directly target mast cells through several mechanisms involving inhibition of proton pumps and AhR signaling.

In this issue of the *Journal*, Kanagaratham et al¹⁰ report that omeprazole inhibits mast cell activation and mast cell-dependent

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Disclosure of potential conflict of interest: M. E. Rothenberg is a consultant for Pulm One, Spoon Guru, ClostraBio, Serpin Pharm, Celgene, Astra Zeneca, Allakos, Arena Pharmaceuticals, Guidepoint, and Suvretta Capital Management and has an equity interest in the first 4 listed; receives royalties from reslizumab (Teva Pharmaceuticals), PEESSv2 (Mapi Research Trust), and UpToDate; is an inventor of patents owned by Cincinnati Children's Hospital; and has received recent funds from the National Institutes of Health, CURED Foundation, Dave and Denise Bunning Family Foundation, End-Allergy-Together (EAT), US-Israel Binational Fund, Adare Pharmaceuticals, and Astra Zeneca. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication April 13, 2020; revised May 14, 2020; accepted for publication May 15, 2020.

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J Allergy Clin Immunol 2020;■■■:■■■-■■■.

0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2020.05.036>

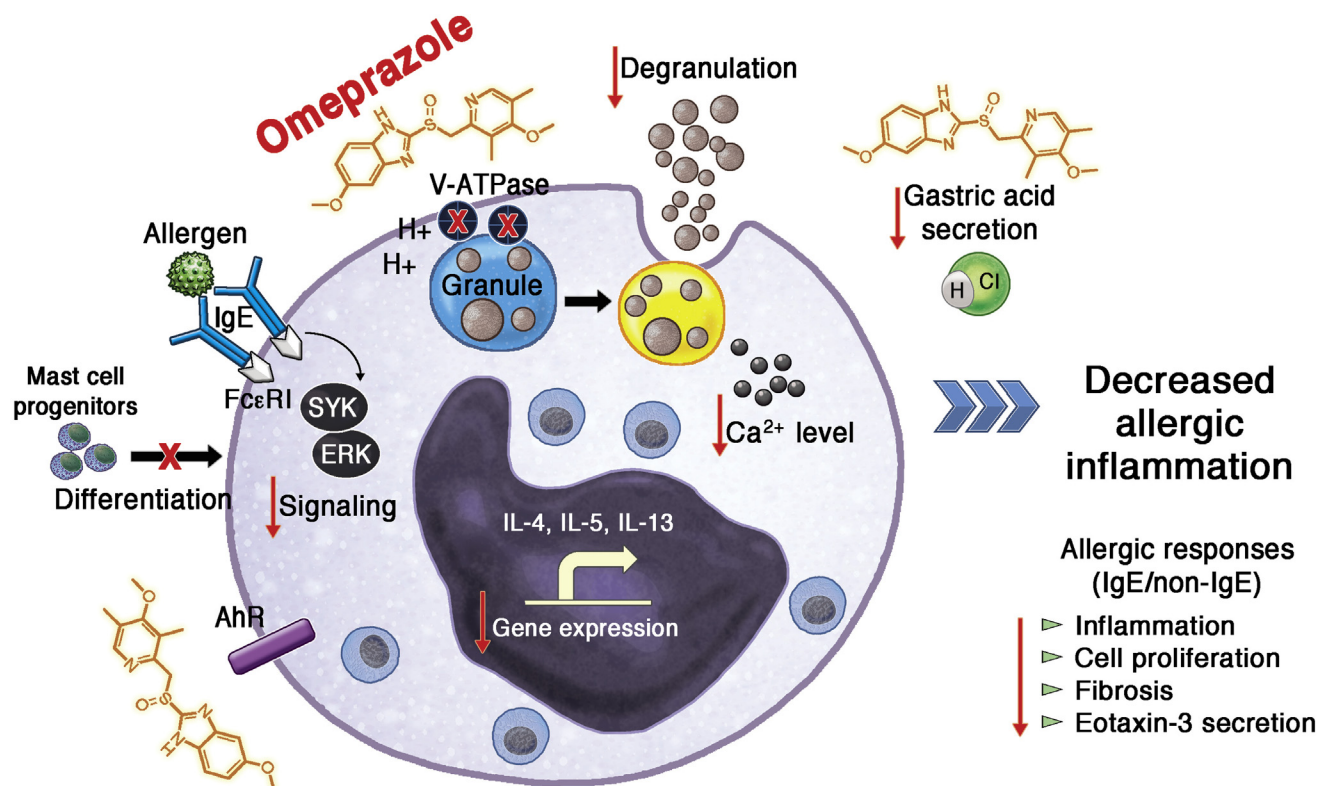


FIG 1. Suggested role of PPIs in the treatment of allergic inflammation. PPIs, such as omeprazole, attenuate mast cell-dependent allergic responses by inhibiting mast cell differentiation and presumably by blocking vacuolar-ATPase (V-ATPase), thus dysregulating the granule and cytosolic pH (indicated by a change in the color of the granule from blue to yellow), attenuating the IgE-mediated signaling and transcriptional response, and decreasing the Ca^{2+} level required for efficient mast cell degranulation. It is conceivable that PPIs can directly signal via the mast cell AhR, as has been demonstrated for other cell types. PPIs are beneficial in the treatment of IgE- and non-IgE-mediated responses, such as EoE, by decreasing secretion of proinflammatory cytokines and the eosinophilic chemoattractant eotaxin-3 and exhibiting antiproliferative and antifibrotic activity either directly or indirectly (by affecting other cells). In addition to blocking cellular proinflammatory mediators, PPIs decrease the gastric acid secretion that contributes to inflammation. Collectively, PPIs are emerging as an effective treatment for allergic inflammatory disorders.

pathology. The authors demonstrate that in presensitized mast cells, omeprazole blocks mast cell degranulation and thereby the release of preformed mediators and proinflammatory cytokines, including IL-4, IL-13, and TNF- α . Mechanistically, following exposure to omeprazole, IgE-sensitized mast cells exhibit reduced phosphorylation levels of spleen tyrosine kinase and extracellular signal regulated kinase proteins, key kinases in the antigen, IgE, and Fc ϵ RI signaling cascade, and decreased cytosolic Ca^{2+} , which is crucial for the granule exocytosis process. In addition, the investigators demonstrate that omeprazole dysregulates the pH of mast cell granules and mast cell cellular morphology. The latter change resembled the effect of bafilomycin, suggesting a common mechanism of action. Finally, Kanagaratham et al¹⁰ demonstrate that omeprazole blocks mast cell maturation *in vitro* and *in vivo*, dampens passive IgE-mediated anaphylaxis, and attenuates mast cell-dependent allergic inflammation in a murine model of food allergy.

Collectively, Kanagaratham et al¹⁰ provide interesting new insight into the emerging role of PPIs in treating allergic inflammation. Although the study is primarily focused on IgE-mediated responses, the findings may apply to non-IgE-mediated, mast cell-associated diseases, such as EoE and sinusitis with nasal

polyposis, in which PPI therapy has been shown to have beneficial effects, likely unrelated to simply neutralizing gastric acid.^{6,7} The ability of omeprazole and likely other PPIs to block mast cell differentiation and cytokine secretion complements their previously described anti-inflammatory and antifibrotic effects (Fig 1). A better understanding of the cellular responses to PPIs, including the acid-independent effects through AhR signaling, will likely advance their use as emerging antiallergy drugs.

REFERENCES

- Krystal-Whitemore M, Dileepan KN, Wood JG. Mast cell: a multi-functional master cell. *Front Immunol* 2015;6:620.
- Martin LJ, Franciosi JP, Collins MH, Abonia JP, Lee JJ, Hommel KA, et al. Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS v2.0) identify histologic and molecular correlates of the key clinical features of disease. *J Allergy Clin Immunol* 2015;135:1519-28.e8.
- Pejler G, Hu Frisk JM, Sjostrom D, Paivandy A, Ohrvik H. Acidic pH is essential for maintaining mast cell secretory granule homeostasis. *Cell Death Dis* 2017;8:e2785.
- Kedika RR, Souza RF, Spechler SJ. Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implications. *Dig Dis Sci* 2009;54:2312-7.
- Pardnani A. Systemic mastocytosis in adults: 2015 update on diagnosis, risk stratification, and management. *Am J Hematol* 2015;90:250-62.

6. Min JY, Ocampo CJ, Stevens WW, Price CPE, Thompson CF, Homma T, et al. Proton pump inhibitors decrease cotaxin-3/CCL26 expression in patients with chronic rhinosinusitis with nasal polyps: possible role of the nongastric H,K-ATPase. *J Allergy Clin Immunol* 2017;139:130-41.e11.
7. Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SS, Rothenberg ME. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. *J Allergy Clin Immunol* 2015;135:187-97.
8. Jensen ET, Dellon ES. Environmental and infectious factors in eosinophilic esophagitis. *Best Pract Res Clin Gastroenterol* 2015;29:721-9.
9. Pace F, Pallotta S, Casalini S, Porro GB. A review of rabeprazole in the treatment of acid-related diseases. *Ther Clin Risk Manag* 2007;3:363-79.
10. Kanagaratham C, El Ansari YS, Sallis BF, Hollister BA, Lewis OL, Minnicozzi SC, et al. Omeprazole inhibits IgE-mediated mast cell activation and allergic inflammation induced by ingested allergen in mice. *J Allergy Clin Immunol* 2020;146:XXX-XXX.