Targeting mast cell tryptase to treating asthma?

Maun et al (Cell 2019;179:417-31.e19. doi: https://doi.org/10.1016/j.cell.2019.09.009) discovered that mast cell–derived tryptase levels correlate with asthma severity independent of the degree of type 2 inflammation present. Furthermore, genetic alleles that increase the activity of tryptase decrease response to treatment with the IgE-neutralizing antibody omalizumab. In response to these findings, the authors generated a noncompetitive allosteric inhibitor of tryptase, which potently inhibited airway tryptase activity and reduced anaphylaxis in experimental animal models. Thus, allosteric inhibition of tryptase represents a promising potential therapeutic strategy for the treatment of severe asthma irrespective of the presence of type 2 inflammation. 

Figure attribution: Public Domain at Wikimedia Commons by user Nevit Dilmen [CC BY-SA 3.0 (http://creativecommons.org/licenses/by-sa/3.0/)]. Author photo credit: Neko Ota. The authors are pictured with statues of Genentech founders Bob Swanson and Herb Boyer.

Characterization of chromatin changes after mast cell activation

Despite their important roles in health and disease, the regulation of mast cell activity remains incompletely understood. To address this gap in knowledge, Cildir et al (Immunity 2019;51:949-65. e6. doi: https://doi.org/10.1016/j.immuni.2019.09.021) meticulously characterized the epigenetic and transcriptional changes induced in mast cells after activation by diverse stimuli. In particular, intracellular calcium levels regulated changes in chromatin accessibility and gene transcription after cross-linking of the high-affinity IgE receptor FceRI. Finally, single nucleotide polymorphisms associated with diverse disease pathologies were mapped onto identified regulatory regions in mast cells. In total, the authors have generated rich datasets that will serve as an important resource for further study of mast cells.

We asked senior author Vinay Tergaonkar, PhD, of the National University of Singapore, to comment on the article. He writes, “Our findings may provide insights into the mechanisms that govern onset and resolution of allergic inflammation.”

Allergens activate clusters of neurons and mast cells to regulate allergic skin inflammation

Activation of sensory neurons, which is involved in the development of pruritus, is an important pathological feature of allergic skin diseases, although the underlying molecular mechanisms remain poorly understood. Serhan et al (Nat Immunol 2019; 20:1435-43. doi: https://doi.org/10.1038/s41590-019-0493-z) identified an important role for direct interactions between
common domestic allergens and sensory neurons. Specifically, cysteine protease-containing allergens from house dust mites directly activated nociceptive sensory neurons (ie, nociceptors). This led to degranulation of mast cells in close proximity to such nociceptors, through release of Substance P and activation of the newly described receptor, MrgrpB2. The authors thus have identified a novel neuro-immune crosstalk that regulates the development of pathogenic type 2 immunity and atopic dermatitis-like disease in the mouse.

We asked senior authors Stephen J. Galli, MD, and Nicolas Gaudenzio, PhD, of Stanford University in Stanford, California, and Université de Toulouse, in Toulouse, France, to comment on the article. They write, “In our mouse study, we found that interactions between TRPV1+ nociceptors and MrgrpB2+ mast cells are required to trigger the development of pathogenic type 2 immune responses and subsequent allergic skin inflammation in response to house dust mite allergens. Interfering with such neuro-immune cross-talk might potentially represent a new therapeutic opportunity in the prevention and/or treatment of atopic dermatitis in humans.”

Post-hoc analysis identifies COPD patients who may respond to anti-eosinophil treatment

Because treatment with the anti-eosinophil antibody benralizumab did not reduce the annual exacerbation rate in patients with both chronic obstructive pulmonary disease (COPD) and elevated peripheral blood eosinophil counts in the GALATHEA and TERRANOVA trials, Criner et al (Lancet Respir Med 2019 Sep 27. doi: https://doi.org/10.1016/S2213-2600(19)30338-8) performed a hypothesis-generating post-hoc analysis to identify subgroups with enhanced clinical response. Indeed, a positive response to benralizumab was identified in subjects with peripheral eosinophilia (≥ 220 cells per µL) with ≥ 3 exacerbations within the previous year and low baseline lung function and response to bronchodilator. Although further investigation is required, this post-hoc analysis suggests that a subpopulation of COPD patients would benefit from benralizumab treatment.

Supplementation with CMF for at least the first 3 days of life increased the development of allergic reactions to cow’s milk

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We asked first author Mitsuyoshi Urashima, MD, MPH, PhD, of Jukei University School of Medicine in Tokyo, Japan, to comment on the article. He writes, “Our observations suggest that food allergies, even anaphylaxis, can be primarily prevented using simple methods, ie, avoiding exposure to cow’s milk formula or changing to amino acid-based elemental formula for at least the first 3 days of life in addition to breastfeeding. These methods can be easily and immediately applied in clinical settings around the world.”

Avoiding allergy by avoiding cow’s milk at birth

Urashima et al (JAMA Pediatr 2019 Oct 21. doi: https://doi.org/10.1001/jamapediatrics.2019.3544) examined whether exposure to cow’s milk formula (CMF) very early in life affects the development of food allergy through a randomized controlled trial in infants at increased risk of atopy. Supplementation with CMF for at least the first 3 days of life increased the development of allergic reactions to cow’s milk, including immediate reactions and anaphylaxis. Interestingly, a prespecified subgroup analysis revealed that this effect only occurred with patients in the middle tertile of vitamin D blood levels (21-36 ng/mL). While further study is needed, these collective results demonstrate that avoiding cow’s milk very early in life may decrease the development of food allergy.

News items were written by medical writer Jared Travers, MD, PhD.