NEWS Beyond Our Pages

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Novel roles of basal epithelial progenitor cells in patients with chronic nasal inflammation

Basal cell hyperplasia is a fundamental feature of severe allergic inflammatory diseases, including chronic rhinosinusitis, and occurs secondary to enhanced accumulation of epithelial progenitor cells. To clarify the interactions and roles of this enigmatic cellular population in the context of allergic inflammation, Ordovas-Montanes et al (Nature 2018;560:649-54; https://doi.org/10.1038/s41586-018-0449-8) generated genome-wide transcriptional profiles of more than 50,000 individual cells through unbiased single-cell RNA sequencing of nasal surgical and scraping samples from patients with chronic rhinosinusitis. Striking differences in composition and transcription were observed in patients with rhinosinusitis with polyps, including enriched basal cells, decreased numbers of glandular cells, and alterations in the antimicrobial gene expression of secretory cells compared with those without polyps. Furthermore, epigenetic alterations were observed in basal cells from patients with polyps, potentially inhibiting their terminal differentiation toward mature functional cells. These changes led unstimulated basal cells derived from polyps to express increased levels of several IL-4– and IL-13–responsive genes after a month of ex vivo culture, indicating a memory of immune events. Finally, the authors demonstrated that blocking IL-4 and IL-13 in vivo was able to partially erase this memory in 1 patient, suggesting a basis for potential future interventions. Collectively, these results demonstrate that type 2 cytokine–induced functional changes in epithelial progenitor cells promote the chronicity of sinonasal inflammation and suggest a need to address both immune and parenchymal cells. Image attribution: Figure By Thomas Shafee [CC BY 4.0 https://creativecommons.org/licenses/by/4.0)], from Wikimedia Commons.

Type 2 cytokine–induced functional changes in epithelial progenitor cells promote the chronicity of sinonasal inflammation

Nora Barrett and Alex Shalek

We asked co-senior authors Nora A. Barrett, MD, of Brigham and Women's Hospital and Alex K. Shalek, PhD, of the Massachusetts Institute of Technology, Boston, Mass, to comment on the study. Dr Shalek writes, "We used Seq-Well—massively parallel single-cell RNA sequencing tailored for clinical use—to characterize cell types in nasal tissues from human patients with chronic rhinosinusitis, producing the first single-cell atlas of a human barrier tissue. Our study revealed that epithelial stem cells in polyp tissue contain type 2 cytokine–driven transcriptional and epigenetic changes that might lock them into a 'stuck' state, explaining the characteristic basal cell hyperplasia associated with polyposis, and also highlights the importance of holistically examining the cellular etiology of complex inflammatory diseases." Dr Barrett added, "Our work demonstrates the remarkable degree of epithelial cell specialization in the respiratory mucosa and the extent of airway remodeling that can occur in disease states. Additionally, findings from our study support the idea that epithelial cell gene expression finely reflects the surrounding inflammatory milieu, with pathobiologic and therapeutic implications."

Baloxavir is efficacious in treating infection with influenza virus

Pharmacologic treatment of influenza virus infection can include neuraminidase inhibitors, such as oseltamivir. In response to widespread resistance the M2 ion-channel inhibitors, they are not currently recommended. Resistance to oseltamivir has also emerged, so that alternative treatment strategies need to be developed. Hayden et al (N Engl J Med 2018;379:913-23; https://doi.org/10.1056/NEJMoa1716197) recently performed phase 2 and phase 3 randomized controlled trials investigating baloxavir marboxil, a selective inhibitor of influenza endonuclease that limits viral messenger RNA transcription in the treatment of acute influenza in healthy adolescent and adult subjects. In the phase 2 trial a range of doses of baloxavir decreased the median time to resolution of symptoms after influenza infection by 23.4 to 28.2 hours compared to placebo ($P < .05$). In the phase 3 double-blind trial 1064 influenza-infected patients were randomized to receive single doses of 40 or 80 mg of baloxavir (based on weight), 5 days of 75 mg of oseltamivir twice daily, or corresponding placebos. Baloxavir reduced viral load after 1 day of treatment to a greater extent than either placebo or oseltamivir. Baloxavir also decreased the median time to resolution of symptoms

Baloxavir treatment promotes resolution of influenza viral infection in otherwise healthy individuals

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compared with placebo (53.7 vs 80.2 hours, P < .001); however, no statistically significant differences were observed between the baloxavir and oseltamivir treatment groups. Notably, amino acid substitutions in the influenza polymerase acidic protein conferring reduced susceptibility were detected in a small number of baloxavir-treated patients during both trials. These results show that baloxavir treatment promotes resolution of influenza viral infection in healthy individuals and could represent a useful alternative pharmacologic treatment strategy against influenza infection.

Frederick G. Hayden

We asked first author Frederick G. Hayden, MD, of the University of Virginia School of Medicine, Charlottesville, Virginia, to comment on the study. He writes, "The results of a recently presented phase 3 study in higher risk outpatients, including those with asthma and COPD, confirmed the clinical and virologic efficacy of baloxavir treatment compared to placebo. Baloxavir is also being studied in children and, in combination with standard of care antiviral treatment, in seriously ill hospitalized patients. Studies of its prophylactic activity are also planned."

Age-specific differences in the cellular driver of IL-13–mediated airway hyperresponsiveness

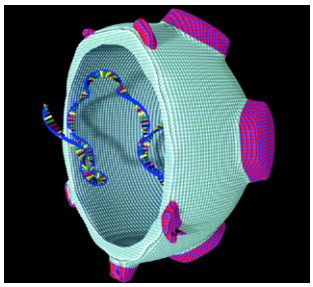
IL-13 is a critical driver of airway hyperresponsiveness (AHR) in asthma, with important sources in the lungs being $CD4^+$ T cells and group 2 innate lymphoid cells (ILC2s). Saglani et al (Sci Immunol 2018;3; https://doi.org/10.1126/sciimmunol.aan4128) investigated the relative contributions of T cells and ILC2s to AHR in neonatal and adult mice. Intranasal administration of the proallergic cytokine IL-33 predominantly induced AHR in both neonatal and adult mice with different lymphoid sources of IL-13. IL-13–producing ILC2s were predominantly induced in adult mice, whereas neonatal mice exhibited similar increases in both IL-13–producing $CD4^+$ T cells and ILC2s. Depletion of IL-13–producing $CD4^+$ T cells through either genetic means or coadministration with the Acinetobacter lwoffii bacterial isolate protected neonatal mice from AHR despite maintaining increased amounts of IL-33 and IL-13–producing ILC2s. In total, the authors have identified differential age-dependent contributions of ILC2s and T cells to allergic responses because IL-13–producing $CD4^+$ T cells, rather than ILC2s, appear to be critical for inception of AHR in neonates.

Sejal Saglani and Clare M. Lloyd

We asked authors Clare M. Lloyd, PhD, FRSB, and Sejal Saglani, MB-ChB MRCPCH MD, both of Imperial College London, London, United Kingdom, to comment on the study. They write, "The predominant cellular source of IL-13, a mediator central to the development of AHR, is distinct in early life and adulthood, highlighting the need to investigate mechanisms of asthma inception in age-appropriate experimental models if we are to find targets for disease prevention that can be translated to children."

Eosinophils modulate antiviral immune responses in patients with mild asthma

Eosinophil depletion through neutralization of IL-5 by mepolizumab is an effective treatment strategy in patients with severe asthma but not in those with mild asthma, suggesting a potential nonpathologic role of eosinophils in patients with mild asthma. Eosinophils can modulate both innate and adaptive immune responses to viral infections, which are a major cause of asthma exacerbation and morbidity. Therefore Sabogal Piñeros et al (Am J Respir Crit Care Med 2018; https://doi.org/10.1164/rccm.201803-0461OC) examined the effect of mepolizumab on the immune response to influenza infection in the context of mild asthma. Patients with mild steroid-naive asthma initially received a single injection of 750 mg of intravenous mepolizumab or placebo and then were challenged 2 weeks later with rhinovirus 16. At baseline, treatment with mepolizumab enhanced peripheral natural killer cell counts and decreased blood eosinophil counts and activation status, although it did not prevent activation of the remaining eosinophils. After infection with rhinovirus 16, mepolizumab altered the humoral and cellular immune response. Mepolizumab potentiated key elements of antiviral immunity, including enhancing secretory IgA production and preventing decreases in numbers of B cells and macrophages in the airways. Despite these changes, the net effect of mepolizumab treatment was proinfective because it increased viral load in nasal swabs at postinfection day 7 compared with placebo. Additionally, mepolizumab decreased neutrophil levels and activation. The authors conclude that mepolizumab does not completely prevent eosinophil activation and alters antiviral immune responses in patients with mild asthma and propose that this might underlie the lack of efficacy of mepolizumab in treating mild asthma. However, the effect of long-term treatment with mepolizumab should be investigated.



Mepolizumab does not completely prevent eosinophil activation and alters antiviral immune responses in patients with mild asthma

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

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