Heterogeneity in allergic rhinitis: explained by inducible mechanistic traits?

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Editorial

Heterogeneity in allergic rhinitis: Explained by inducible mechanistic traits?

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Allergic rhinitis is a heterogeneous condition. Phenotyping of rhinitis might be useful in the diagnosis and management of patients by reducing its heterogeneity.

Noninfectious rhinitis comprises 3 main disease entities or phenotypes: allergic rhinitis, local allergic rhinitis, and nonallergic rhinitis.[1] Regarding allergic rhinitis, it is further possible to identify subphenotypes. The well-known phenotypes are based on clinical classifications, such as seasonal allergic rhinitis versus perennial allergic rhinitis driven by pollen and indoor allergy. The Allergic Rhinitis and Its Impact on Asthma classification discerns intermittent versus persistent and mild versus moderate-to-severe rhinitis.[1] The frequency of symptoms over the course of weeks and months and the impact of rhinitis on daily life determine the level of severity. A classification based on the severity of symptoms is essential, as the burden of the disease will decide the management and treatment of the patient. In addition, moderate-to-severe rhinitis, together with polysensitization to allergens, is correlated with the presence of asthma.[2] Patients with allergy are often characterized by multimorbidity. For that reason, the rhinitis-asthma multimorbidity and the rhinitis-asthma-eczema multimorbidity are considered to be specific phenotypes.[1] However, multimorbidity patterns are variable. To overcome this heterogeneity, hypothesis-generating approaches, such as cluster analysis and latent class analysis grouping distinct patterns of symptoms and diseases, have been applied in longitudinal cohorts. For instance, analysis of the unselected whole-population birth cohort population of the Isle of Wight identified 4 clusters of rhinitis among adolescents. This analysis showed that mild adolescence-onset rhinitis in females had the lowest prevalence of comorbid atopy, asthma, and eczema, whereas severe earliest-onset rhinitis with asthma had the youngest age of rhinitis onset plus the highest prevalence of comorbid asthma (of simultaneous onset).[3] The various methods of phenotyping have advantages and shortcomings (Fig 1).

In the study by Smith et al[4] published in this issue of the *Journal of Allergy and Clinical Immunology*, the authors opted for a third, more mechanistic approach to disentangle heterogeneity, similar to the endotype classifications of asthma, to understand different clinical representations. They established inducible mechanistic traits by house dust mite challenge of patients with allergic rhinitis on 4 consecutive days in an allergen challenge chamber. Repeated allergen exposure elicited 3 distinct patterns: a limited rise in symptoms during all challenges (resilient type), a decline in symptoms on days 3 and 4 (adaptive type), and a clear rise that was persistent at all challenges (maladaptive type). These 3 outcome patterns, coined as "mild," "moderate," and "severe" rhinitis, were characterized by increasing loss of epithelial integrity and a rise of inflammation across the phenotypes. The maladaptive type appeared to share clinical and mechanistic features with allergic asthma. Importantly, total symptom score (TSS) at the run-in challenge did not sufficiently distinguish between patients who were later categorized as resilient, adaptive, or maladaptive, although the resilient patients were overrepresented among the group with only mild symptoms. Other clinical characteristics were sparsely presented by the authors, making it difficult to judge whether these groups could have been established at the start of the study.

The authors did an extensive peripheral blood immunophenotyping (flow cytometry and transcriptomics) before and after repeated challenge with the aim to identify baseline and/or inducible mechanistic traits that explain the response patterns in patients with resilient, adaptive, and maladaptive allergic rhinitis. Clear baseline correlates were found for higher specific IgE levels, increased circulated CD8 T-cell count, eosinophil count, and higher TSS. Following challenge, the numbers of eosinophils, CD8 T cells, and natural killer (NK) cells expressing the cytotoxicity receptors CD158 or CD159 were (further) increased in the maladaptive group. Furthermore, several inflammatory characteristics that mirror immune cell features described in asthma pathogenesis were found. For example, increased gene expression of asthma signature genes described by Altman et al[5] as representing "NK/asthma" was correlated with gene signatures for NK cells and effector CD8 ($CD8^{EM}$) T cells. Indeed, pathogenic CD8 T cells have been described in severe asthma, as CD8 T cells are more insensitive to corticosteroids than are CD4 T cells and they can also produce type 2 cytokines such as IL-5 and IL-13.[6] Increased levels of NK cells were reported in individuals with asthma, and expression of the activating receptor NKGD2 and IL-4 production were associated with asthma pathogenesis, as well as with a reduced capacity to induce eosinophil apoptosis.[7] To allow comparisons with other studies in asthma, future studies should investigate allergen-specific cytokine responses and functional capacities in CD8 T cells and NK(-like) cells in patients with allergic rhinitis with moderate-to-severe complaints. Furthermore, in the maladaptive group, expression of genes important in antiviral defense (the Toll-like

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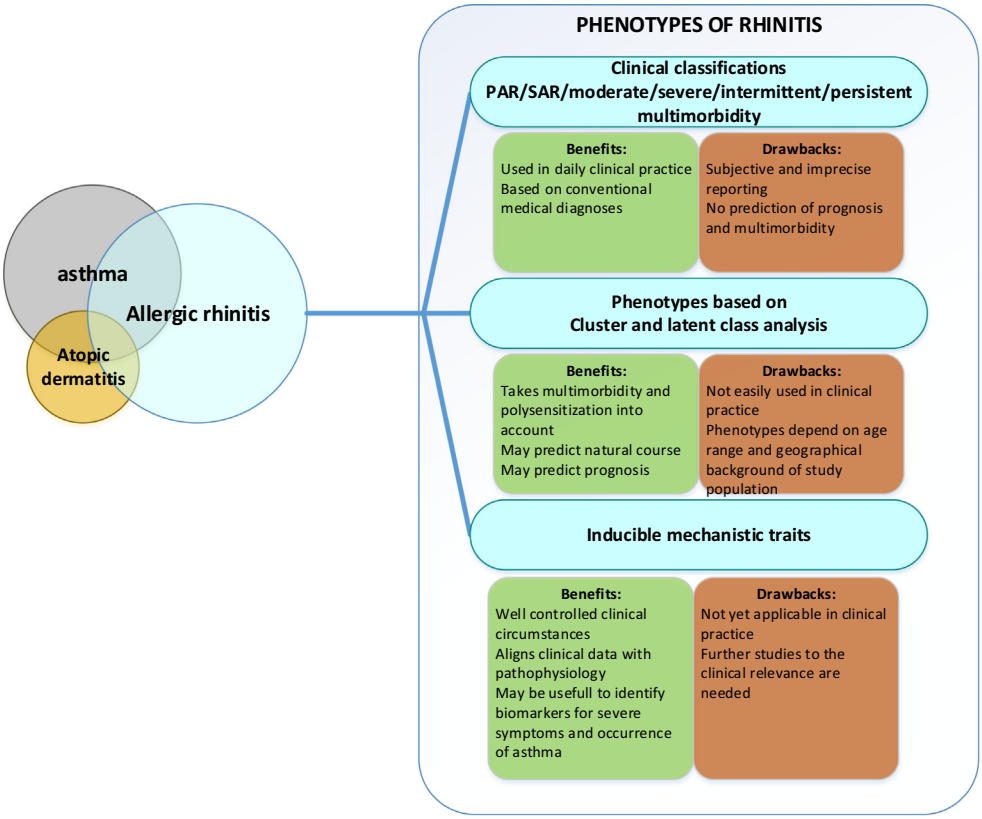

FIG 1. Various methods for phenotyping allergic rhinitis. Benefits and drawbacks are shown for conventional phenotyping based on medical classifications, data-driven analyses to disentangle heterogeneity, and phenotypes based on mechanistic inducible traits as proposed by Smith et al. *PAR*, Perennial allergic rhinitis; *SAR*, seasonal allergic rhinitis.

receptor–interferon regulatory factor–interferon pathway) was lower, as described not only for bronchial epithelial cells but also for myeloid cells in patients with asthma.[8]

Full classification of the 3 groups required the linking of immunophenotyping in peripheral blood to nasal transcriptome data before and after challenge (Fig 2). Here differentially expressed genes in nasal epithelial cells between patients with high or low CD8 and/or eosinophil counts were linked to TSS, identifying genes representative for epithelial barrier integrity or inflammatory processes. Whereas both the adaptive and maladaptive groups had increased inflammatory gene expression (classified as "gain of function"), the adaptive group showed a higher epithelial barrier gene expression similar to that of the resilient group, whereas these genes seemed downregulated in the maladaptive group. This suggests that prolonged inflammation at mucosal surfaces influences epithelial function, inducing an "allergic memory phenotype" with lower barrier function and integrity (classified as "loss of function"), as suggested before by Ordovas-Montanes et al.[9] The question remains as to whether specific treatment can be developed to prevent the imprinting of epithelial cells and a weaker barrier integrity, thereby averting further deterioration and the development of asthma.

One caveat in the study by Smith et al[4] is that total RNA sequencing analysis has been applied as opposed to single-cell transcriptomics. Most of the genes related to barrier integrity (clustered in "community 2") are linked to basal cells and fibroblasts; however, whether this is the result of shifts in gene expression or the result of differences in cell type composition and/or differentiation is unclear. In addition, the nasal epithelial cells analyzed were first cultured by using a conditional reprogramming method with fibroblast feeder cells and a ROCK inhibitor as opposed to 3-dimensional organoid cultures or unmanipulated *ex vivo* analysis.[10] What the influence of the less defined culture conditions with feeder cells and FCS might be is unclear, as is the question of whether this has affected the composition of the epithelial cell layer and/or their gene expression and therefore the outcome of the study. Future studies using single-cell RNA sequencing directly on nasal scrapes from larger numbers of patients should evaluate whether these results can be confirmed.

This study represents a shift from clinically based to mechanism-based phenotyping of rhinitis. The question is what is better. In general, there is a weak correlation between symptoms elicited by challenges and naturally occurring symptoms. The experiments reported by Smith et al[4] are not an exception, as occurring symptoms during the days preceding the challenges and the symptoms following exposure were not correlated. Cosensitization to other allergens did not influence the patterns, which is at variance with the outcome of other studies showing that concomitant allergies may enhance nasal responsiveness due to nasal priming.

There is, however, an increasing awareness that the management of allergic rhinitis requires a more personalized approach. Clinical questions need to be addressed. Which patients need early intervention? Who will deteriorate? Which patients will benefit

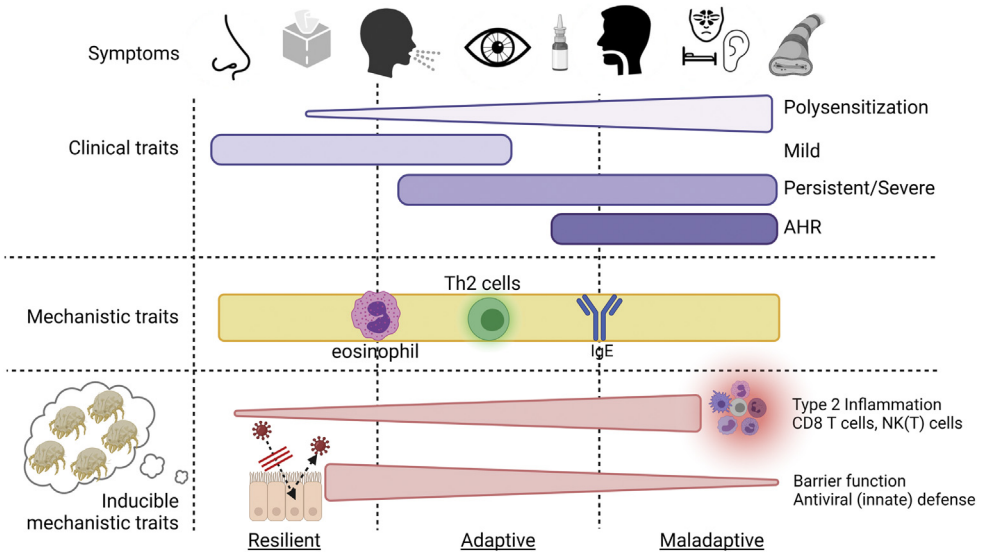

FIG 2. Inducible mechanistic traits may explain the heterogeneity of allergic rhinitis. Patients with allergic rhinitis display a heterogeneity from the standpoint of clinical traits, which includes a wide range of monosenstization to polysensitization for various allergens combined with mild-to-persistent and/or moderate typical rhinitis complaints, including comorbidities characteristic for asthma, such as airway hyperresponsiveness (AHR). The heterogeneity cannot be explained on the basis of mechanistic traits in which type 2 inflammation (eg, eosinophils, T_H2 cells, innate lymphoid cells, and specific IgE) is dominant in all conditions. However, Smith et al[4] propose a model of inducible mechanistic traits in response to repeated allergen challenge, showing a dichotomy in induced inflammatory signals (with a predominant appearance of CD8 T cells and NK(T)-like cells and gene signatures) in peripheral blood versus the loss of barrier function and integrity combined with fewer gene transcripts important for antiviral defense mechanisms in the nasal epithelium. Combining inducible mechanistic signals in 2 compartments allows division into the categories resilient, adaptive, and maladaptive.

from treatments such as allergen immunotherapy? Classical clinically based phenotyping does not provide us with such an approach. The concept of inducible mechanistic traits links basic biologic mechanisms with well-controlled clinical conditions. This model offers a better understanding of the pathophysiology of allergic rhinitis and the rhinitis-asthma axis at least for patients belonging to the maladaptive type. Mechanistic differences between the resilient and adaptive types were less clear and mostly related to differences in inflammation. However, this may not be essential, as it is mostly maladaptive patients who will deteriorate and become treatment resistant. Those patients would benefit from early recognition, personalized treatment approaches, and the use of alternatives such as biologics.

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