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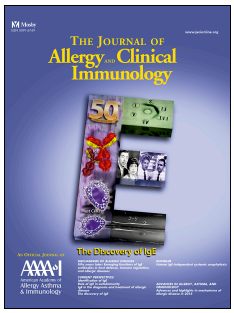

It's a lot of work to be non-allergic

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It's a lot of work to be non-allergic

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Edward Jenner developed the first successful vaccine on the basis of the observation that people exposed to the poxvirus pathogens, who did not succumb to the disease, became protected from further encounters[1]. In more recent trials much has been learned about correlates of health and protection from controlled challenges in infectious diseases as diverse as influenza and malaria, where the study of exposed individuals who mount an appropriate immune response may hold the key to development of treatment and vaccination alike.

The paper by Ahuja et al. in this issue of the Journal[2] underlines that this maybe the case for allergic diseases as well, namely that important lessons are to be learned not only by studying people that are suffering from allergic disease, but also investigating the molecular mechanism associated with immune responses in non-allergic people that are exposed and do not develop IgE sensitization and/or clinical symptoms.

The study shows that there is an immune response to HDM allergen challenge, in both allergic and non-allergic subjects. This means the non-allergic status is not a based on lack of recognition and response to the allergen, but is associated with a distinct and protective response. Similar conclusions have recently been reached in a study of T cell recognition of seasonal pollen exposure[3]. This seems to indicate that individuals, who are exposed and non-allergic, do have an immune response to an allergen, and the response may actually be protective.

The investigators studied the effect of Nasal Allergen Challenge (NAC) in individuals allergic (M+) and non-allergic (M-) to house dust mites (HDM), performing immunological characterization and using the power of mRNA profiling to determine changes in transcriptional patterns associated with the challenge. After NAC, non-allergic (M-) individuals manifested an adaptive “healthy” response with increased expression of genes related to the epidermal/epithelial barrier and reduced expression of

genes involved in inflammation, as compared with the responses of HDM-allergic (M+) individuals.

A rich set of data was collected, including time-of-flight mass cytometry (CyTOF) to perform immune-phenotyping of PBMCs, and both cross-sectional and longitudinal analysis of transcriptional profiles in M+ and M– participants. The authors further performed a modular framework analysis framework[4] to interpret the changes in transcriptional patterns observed. In peripheral blood, markers of CD4+ and CD8+ T-cell activation were downregulated in M- but increased in M+ individuals. In M-, genes that promoted epidermal/epithelial barrier function such as filaggrin were upregulated, while chemokines and innate immunity genes (interferon) were downregulated.

An important aspect of the study was that the challenge of M- individuals was safe. During HDM challenge, only M+ persons developed AR symptoms, and at least during the follow up period reported, no adverse reactions were noted. This suggests that such an approach may be employed more generally to perform similar studies in this and other allergen systems. Follow up studies could utilize similar strategies to recruit study participants from populations with previous exposures, indicating that allergen exposure in these individuals would be unlikely to result in development of allergic disease.

In the study by Ahuja et al., functionality of HDM-specific T cells were not monitored (although CD69/HLA DR positive cells as a marker of activation were measured). Discordance between M− and M+ subjects was observed in Th1 (IFNγ+/CXCR3+) vs. Th2 (IL-4+/CCR4+) memory cells and regulatory T cells ($CD25^{hi}$CD127-CCR4+). The authors point out that it is possible that, in M+ Th2 responses to HDMs and/or lack of a Treg- response may contributes to the differences observed in epithelial transcriptional profiles. However, it is also possible that, in M− subjects, the response toward preservation of the epidermal/epithelial barrier may be

sufficient to prevent the inflammatory response.

The fact that non-allergic individuals do harbor allergen-specific T cells has been known for quite some time. A study by Hinz et al. noted that seasonal exposure to timothy grass (TG) allergens had opposite effects on TG specific T cells in allergic and non allergic donors[3]. TG specific T cell responses were enhanced by the seasonal allergen exposure in TG allergic donors. Conversely TG-specific T cells were detectable out-of-season, but were specifically down-modulated in pollen season in non-allergic donors. Thus, it seems allergen exposure of non-allergic individuals results in both enactment of a barrier specific program and modulation of antigen-specific T cell responses.

NAC has been used for many years for a variety of investigational purposes. One particular application is of great potential significance in the development of Allergen-specific Immunotherapies (AIT), where NAC has been utilized to objectively measure clinical responses to the same extract administered as immunotherapeutic[5]. In the study of Ahuja et al., the immune responses activation markers were measured after 3 hours. Several studies of NAC in the context of immunotherapy suggest that allergen-specific T cell responses are initially increased a few hours after challenge, but decrease afterword, possibly reflective of migration in the nasal tissues and/or lymphoid sites[5-7]. It will be of interest to examine the kinetics of immune responses both in allergic and non-allergic individuals, to determine if additional molecular events are associated with the non-allergic T cell responses, such as lack of response downmodulation/tissue migration of the allergen specific T cells in the non-allergic as compared to allergic individuals.

The study describes a “healthy“ response to allergen exposure. Successful AIT is also associated with a modulation of the immunological response to allergen encounters, both in the course of the controlled administration, and in terms of subsequent natural exposure. It will be interesting to investigate whether the NAC response of individuals

that benefitted from AIT in terms of clinical symptoms resembles the one observed in the M- donors.

The study by Ahuja et al. brings to the forefront the importance of the mucosal barrier and nasal epithelium in allergen sensitization. In addition, many studies report that defects in the skin barrier are early, critical events in the pathogenesis of atopic dermatitis, and development of other diseases such as food allergy, asthma, allergic rhinoconjunctivitis (AR), and eosinophilic esophagitis[8-10]. This in turn implies that strategies to safeguard and repair defects in the epidermal/epithelial barrier function could be of significant therapeutic value. Finally, the authors point out that their study has potential implications for biomarker discovery. Research aiming at studying phenotypes or transcriptional profiles associated with different disease severity or therapeutic responses should consider allergen exposure as a relevant variable.

In conclusion the concept that is arising is that non-allergic individuals mount "healthy " responses to allergen exposure. These responses involve both a "resilient" epidermis/epithelium barrier function and regulation of reactivity at the T cell level, orchestrating specific transcriptional profiles. A more in depth understanding of these responses may sharpen our understanding of different phenotypes associated with disease, and have important implications for biomarker development, evaluation of AIT efficacy, and development of new therapeutic interventions.

References

1. Lakhani S. Early clinical pathologists: Edward Jenner (1749-1823). J Clin Pathol 1992; 45:756-8.

2. Ahuja SK, Manoharan MS, Harper NL, Jimenez F, Hobson BD, Martinez H, et al. Preservation of epithelial cell barrier function and muted inflammation in

resistance to allergic rhinoconjunctivitis from house dust mite challenge. J Allergy Clin Immunol 2016.

3. Hinz D, Seumois G, Gholami AM, Greenbaum JA, Lane J, White B, et al. Lack of allergy to timothy grass pollen is not a passive phenomenon but associated with the allergen-specific modulation of immune reactivity. Clin Exp Allergy 2016; 46:705-19.

4. Chaussabel D, Baldwin N. Democratizing systems immunology with modular transcriptional repertoire analyses. Nat Rev Immunol 2014; 14:271-80.

5. Scadding GW, Eifan AO, Lao-Araya M, Penagos M, Poon SY, Steveling E, et al. Effect of grass pollen immunotherapy on clinical and local immune response to nasal allergen challenge. Allergy 2015; 70:689-96.

6. Borgonovo B, Casorati G, Frittoli E, Gaffi D, Crimi E, Burastero SE. Recruitment of circulating allergen-specific T lymphocytes to the lung on allergen challenge in asthma. J Allergy Clin Immunol 1997; 100:669-78.

7. Shamji MH, Bellido V, Scadding GW, Layhadi JA, Cheung DK, Calderon MA, et al. Effector cell signature in peripheral blood following nasal allergen challenge in grass pollen allergic individuals. Allergy 2015; 70:171-9.

8. Platts-Mills TA. The allergy epidemics: 1870-2010. J Allergy Clin Immunol 2015; 136:3-13.

9. Leung DY, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. J Allergy Clin Immunol 2014; 134:769-79.

10. Brough HA, Liu AH, Sicherer S, Makinson K, Douiri A, Brown SJ, et al. Atopic dermatitis increases the effect of exposure to peanut antigen in dust on peanut sensitization and likely peanut allergy. J Allergy Clin Immunol 2015; 135:164-70.