

Correspondence

T-cell receptor-mediated cross-reactivity to different allergens is driven by recognition of homologous, phylogenetically conserved epitopes

To the Editor:

I read with interest the exciting article from Westernberg et al,¹ reporting that epitope conservation across allergen species is the major determinant of immunogenicity and the driver of polysensitization in allergic patients. The approach they followed is largely embedded in the present era of “omics.” Here, I would like to bring your attention to a previous “old school” study of ours, which a decade ago produced somehow comparable and complementary results.

We have been long interested in cross-reactivity of the allergen-specific immune response at the T-cell level, on the basis of *in vivo* evidence indicating that allergen-specific T cells are recruited to target organs and expanded with specific and nonspecific mechanisms.^{2,3} At one point, we evaluated the T-cell repertoire of subjects allergic to grass and birch, and studied their proliferation and T-cell receptor fingerprinting by *in vitro* challenging T lymphocytes with either allergen. We were able to identify grass T cells that “cross” proliferated to birch allergens, and among them to profilin (Bet v 2), a highly conserved panallergen.⁴ This drove our attention to the immunodominance of mostly conserved epitopes within this single antigen. We found that CD4 T_H2 cell clones could be derived from subjects allergic to grass plus birch, which promiscuously recognized homologous regions on both Bet v 2 and on grass profilin (Phl p 12). Notably, these regions were those with higher homology among profilins, including those from allergen species different from sensitizing ones. Data presented by Westernberg et al¹ confirm and integrate ours, which pointed to the specific role of panallergens in driving polysensitization. Phl p12 is high scoring across pan-grass and pan-pollen analysis of peptide conservation (Fig 1, panel A in reference 1), and could be among the primary drivers of the T-cell response to homologous allergens from different allergen sources. These could provide new allergenic molecules to a preactivated microenvironment and trigger intermolecular help sustaining the generation of IgE to major (nonpanallergen) proteins.

The observation that sequence conservation is a predictor of immunodominance was anticipated on a theoretical ground by

Landry⁵ in the case of lysozyme and HIV gp120. Landry suggested that this relationship may be a consequence of conformationally labile antigen segments’ exclusion from MHC binding by the proteolytic degradation preceding MHC loading of peptides from the proteasome complex. In evolutionary terms, this selective pattern of recognition may allow the immune system to achieve protection against several different species of invaders by individuals previously exposed to one of them. At the same time, it may also be used by the invader to misdirect the response away from newly occurred variant epitopes.^{6,7} In the context of the allergic response, in the absence of selective pressure, this function would be only detrimental.

In the light of these data, generated with different methodological approaches, immunodominance of homologous, phylogenetically conserved regions of different antigens should be considered the most plausible mechanism underlying epitope spreading in the response to allergens, similarly to immunity against infectious agents.

Samuele E. Burastero, MD

From the Department of Biotechnology, San Raffaele Scientific Institute, Milan, Italy.
E-mail: burastero.samuele@hsr.it.

Disclosure of potential conflict of interest: S. Burastero has consultant arrangements with ALK Abello Italy.

REFERENCES

1. Westernberg L, Schulten V, Greenbaum JA, Natali S, Tripple V, McKinney DM, et al. T-cell epitope conservation across allergen species is a major determinant of immunogenicity. *J Allergy Clin Immunol* 2016;138:571-8.
2. 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.
3. Crimi E, Gaffi D, Frittoli E, Borgonovo B, Burastero SE. Depletion of circulating allergen-specific TH2 T lymphocytes after allergen exposure in asthma. *J Allergy Clin Immunol* 1997;99:788-97.
4. Burastero SE, Paolucci C, Breda D, Longhi R, Silvestri M, Hammer J, et al. T-cell receptor-mediated cross-allergenicity. *Int Arch Allergy Immunol* 2004;135:296-305.
5. Landry SJ. Local protein instability predictive of helper T-cell epitopes. *Immunol Today* 1997;18:527-32.
6. Klenerman P, Zinkernagel RM. Original antigenic sin impairs cytotoxic T lymphocyte responses to viruses bearing variant epitopes. *Nature* 1998;394:482-5.
7. Kundu SK, Dupuis M, Sette A, Celis E, Dörner F, Eibl M, et al. Role of preimmunization virus sequences in cellular immunity in HIV-infected patients during HIV type 1 MN recombinant gp160 immunization. *AIDS Res Hum Retroviruses* 1998;14:1669-78.

<http://dx.doi.org/10.1016/j.jaci.2016.04.055>