Correspondence

Reply

To the Editor:

We thank Burastero for his comments[1] on our article.[2] We agree with his conclusion that phylogenetic conservation of antigens drives their immunodominance. His commentary adds several references of pioneering work that support this conclusion beyond the recent studies we referenced.

Interestingly, we observe T-cell cross-reactivity in allergen protein families other than the profilins Burastero mentions, such as Phl p1, Phl p3, Phl p5, Phl p13, and several novel Phl ps[3] (Figs 3 and 4). This suggests that even if an entire protein is not sufficiently conserved to belong to a pan-pollen protein family, some T-cell epitopes within it may be conserved enough to elicit cross-reactive responses.

Furthermore, we want to clarify some points of confusion or disagreement. Burastero references Landry's work[4] to state that peptide cleavage by the proteasome contributes to the immunodominance of conserved sequences in the context of CD4 responses. However, the proteasome plays a role only in MHC class I processing. In fact, Landry suggests that T-cell epitopes are found close to labile regions in proteins more susceptible to proteolysis by lysosomal and endosomal proteases, not the proteasome.[4] Also, Landry indicates that the proteolytic cleavage is not sequence specific. Instead, he suggests that local structural stability of the antigen is responsible for selective presentation and immunodominance. If proteolytic cleavage is based on structure, not sequence, we do not see an obvious link between protein stability, sequence conservation, and epitope immunogenicity.

In addition, we would not refer to cross-reactive epitopes becoming immunodominant as "epitope spreading." *Epitope spreading* is a process by which peptides not originally recognized by T cells become recognized in an ongoing immune response[5] due to an increasingly inflammatory environment, resulting in a lower threshold for immunogenicity, allowing the response to "spread" to new epitopes. Instead of epitope spreading, we hypothesize that increased frequency of exposure to conserved epitopes makes them more dominant (Fig 5).

We agree that in allergy we observe a mechanism that has evolved in the context of infectious diseases. In viral infections, it is advantageous to respond to conserved epitopes and thereby develop memory to multiple related viruses after being exposed to only one. For influenza, we and others have shown that the dominant epitopes in the 2009 flu pandemic were recognized by preexisting T cells, recognizing conserved epitopes and associated with protection.[6] In the context of dengue, repeated exposure to different serotypes results in expansion of T cells recognizing conserved epitopes, likely contributing to pan-dengue protection after infection with 2 serotypes.[7] In the context of tuberculosis, epitopes shared by mycobacterium tuberculosis and other mycobacteria have enhanced immunogenicity.[8] In contrast, epitopes similar to sequences encountered in the host microbiome were less immunogenic, presumably as the immune system has learned to coexist with them.[9] This underlines that the rules of immunogenicity are subtler than those imagined on the basis of a simple "one-off" encounter between a host and a potential immunogen. Our immune system is constantly exposed to a "cloud" of proteins that often bear similarities to other proteins shaping immunologic memory.

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