HLA-DRB1 polymorphism, anti-citrullinated protein antibodies, and rheumatoid arthritis

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Jean Roudier[‡§¶1], **Nathalie Balandraud**[‡§¶], **and Isabelle Auger**[‡§]

From [‡]*INSERM UMRs1097, Marseille-Luminy 13009, France,* [§]*Aix Marseille Université, Marseille 13007, France, and* [¶]*Department of Rheumatology, Institut du Mouvement et de l'appareil Locomoteur, Assistance Publique Hôpitaux de Marseille, Marseille 13005, France*

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IgG autoantibodies to citrullinated proteins (ACPA) precede the development of rheumatoid arthritis (RA). HLA-DR alleles with a 5-amino acid stretch called "shared epitope (SE)" in their P4 pocket are associated with ACPA and RA. The recent article by Ting *et al.* (1) suggests that the basis for this association is preferential binding of citrullinated peptides by SE-positive HLA-DR molecules. It shows binding of 13 selected peptides (3 from vimentin and 2 from fibrinogen) and their 18 citrullinated variants to 3 SE-positive alleles and presents 8 crystal structures of 3 SE-positive HLA-DR alleles complexed with a citrullinated peptide.

Our binding data on 96 overlapping peptides from fibrinogen and their 71 citrullinated variants (2) and Sette's data on 200 peptides from vimentin and collagen (3) do not show preferential binding of citrullinated peptides to SE-positive HLA-DR alleles. Solving the RA/ACPA/HLA-DR association will require the identification of T cells that help the production of ACPA. In normal mice, PAD (peptidyl arginyl deiminase, the citrullinating enzyme) immunization triggers anti-citrullinated fibrinogen antibodies by a hapten carrier mechanism (4).

The "shared epitope binds citrullinated peptide" hypothesis requires many T helper cells specific for many citrullinated peptides. We suggest the "shared epitope binds PAD peptides" alternative, which may open the field of PAD vaccination to prevent RA.

The authors declare that they have no conflicts of interest with the contents of this article.

[1] To whom correspondence should be addressed. E-mail: jean.roudier@inserm.fr.

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