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INVITED COMMENTARY

The complexity of the humoral immune response against HLA antigens

Stefan Schaub, Gideon Hönger and Patrizia Amico

Transplantation Immunology and Nephrology, University Hospital Basel, Basel, Switzerland

Correspondence
Stefan Schaub, Transplantation Immunology and Nephrology, University Hospital Basel, 4031 Basel, Switzerland.
Tel.: +41 61 265 45 33;
fax: +41 61 265 24 10;
e-mail: stefan.schaub@usb.ch

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In the past years, our ability to detect HLA antibodies has significantly improved allowing for a better assessment of the humoral immune response. The presence of donor-specific HLA antibodies [DSA] both pretransplant and *de novo* post-transplant is associated with the occurrence of antibody-mediated rejection [AMR] and inferior allograft survival [1,2]. However, patients with DSA demonstrate variable clinical courses. Therefore, it is of major interest to better define the 'pathogenicity' of individual DSA, which could help to guide diagnostic and therapeutic interventions. One possible approach is to explore the humoral immune response in more detail by measuring the IgG subclasses and the IgA/IgM fractions of HLA antibodies.

It is well known that after the initial class switch from IgM to IgG, the IgG fraction first comprises the IgG3 and IgG1 subclasses, which are both strong complement-fixing antibodies. A further expansion to weak or noncomplement-fixing IgG2, IgG4 and IgA is possible, as well as a complete switch to these noncomplement-fixing antibodies. As a consequence, three patterns of antibody profiles are theoretically possible: (i) isolated complement-fixing [CF] antibodies (ii) isolated weak or noncomplement-fixing [NCF] antibodies and (iii) a mixture of both. As complement activation is a potent effector mechanism of the humoral immune response, it seems to be obvious that assessing the complement-fixing capability of HLA antibodies might provide important hints to define their clinical relevance.

In this issue of the journal, Arnold *et al.* [3] investigated in a cross-sectional study of 274 patients the antibody pattern of *de novo* DSA occurring 8 years post-transplant. Ninety-four of 274 patients (34%) developed *de novo* DSA. The antibody pattern of DSA was as follows: 81% had isolated CF-DSA, 18% had a mixture of CF-DSA and NCF-DSA (=expansion to NCF-DSA), and 1% had isolated NCF-DSA. During a follow-up of 3.5 years, 46 allograft biopsies were obtained in these 94 patients with *de novo* DSA and 36/94 allograft (38%) failed. Histological features of AMR were observed more often in patients with an expansion to NCF-DSA compared to isolated CF-DSA (78% vs 35%). However, allograft survival was similar between the two groups.

The expansion to NCF-DSA can be interpreted in different ways. On one hand, the expansion to NCF-DSA might

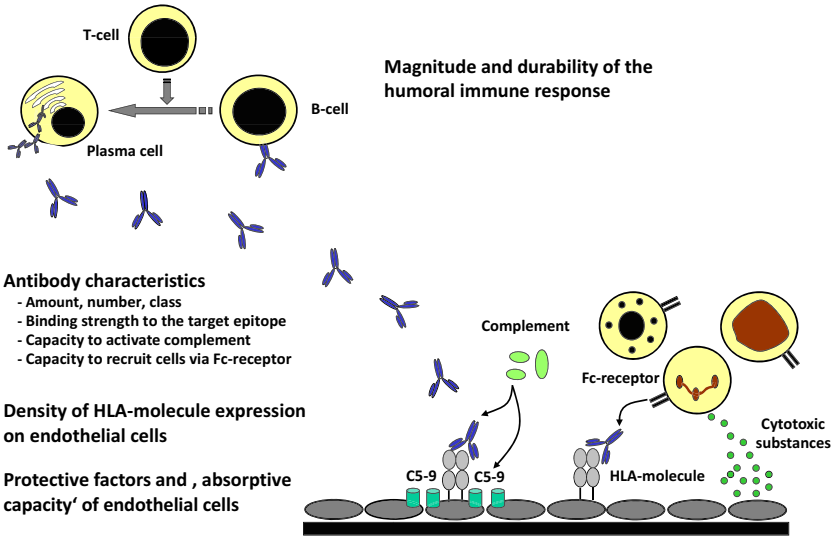

Figure 1 Factors that might influence the clinical impact of donor-specific HLA antibodies.

indicate a broader immune response – as each class switch is T cell dependent – and thus define patients at heightened risk. On the other hand, the expansion to NCF-DSA might be beneficial because NCF-DSA could compete for HLA-molecule binding sites and thus 'block' binding of CF-DSA, which are considered to be more harmful. The data in this study rather point towards the first interpretation because patients with an expansion to NCF-DSA had a higher frequency of AMR than patients with isolated CF-DSA.

A complete switch to NCF-DSA without detection of CF-DSA anymore might be associated with a favourable outcome, but this DSA composition seems to be rare (1% in this study; 5% in the study by Hönger *et al.* [4]; <1% in the study by Lowe *et al.* [5]). As discussed above, a quantitative dominance of NCF-DSA compared to CF-DSA could be beneficial due to 'blocking' of the presumably more harmful CF-DSA. Testing this hypothesis would require a reliable quantification of IgG subclasses, not only a binary assignment as 'positive' or 'negative' based on a defined cut-off. A previous study investigating 71 patients with pretransplant DSA found that the NCF fraction of IgG (i.e. IgG2 and IgG4) accounts on average for less than 10% of total IgG [4]. However, such a quantitative assessment has not yet been performed for post-transplant DSA. It is important to mention that quantification of IgG subclasses of DSA is not trivial – as is the quantification of DSA *per se* – and that a validated assay has not been developed so far [4,5].

In conclusion, (sub)classes of DSA seem not to be a major determinant for the pathogenicity of the humoral immune response, likely because CF antibodies dominate in terms of frequency and relative amount. We have to keep in mind that several factors with variable contributions shape the clinical presentation of the humoral immune response against HLA antigens (Fig. 1). The complexity of this process is enormous, and the search to define the most relevant influencing factors has to go on.

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