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The clinical significance of epitope mismatch load in kidney transplantation

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Aim: Since the beginning of kidney transplantation a key strategy to maximize graft survival by avoiding allorecognition is to minimize HLA mismatching between donor and recipient.
As HLA antibodies are now recognized as being specific for epitopes and donor-recipient HLA mismatch at the amino acid level can now be determined, epitope-based permissible mismatching could be a new strategy.

Methods: In our multicenter study, we retrospectively collected data on 216 patients who underwent kidney transplantation in 2012 to evaluate graft failure after a 5-year follow-up in function of HLA antigen mismatch and epitope mismatch load.
Two algorithms HLAMatchmaker and PIRCHE-II were used to determine differences between donor and recipient in their epitope load. Each HLA antigen mismatch has a B-cell epitope load that is primarily determined by the recipient's HLA type representing a repertoire of self-epitopes to which no antibodies can be made. HLAMatchmaker (www.epitopes.net) can be used as a quantitative tool to determine the degree of a mismatch, i.e. the number of mismatched epitopes. On the other hand HLA-derived T-helper epitopes can also be used to estimate the risk of graft failure. These T-helper epitopes, designated as PIRCHE-II (Predicted Indirectly ReCognizable HLA Epitopes presented by HLA-DRB1), are involved in the production of HLA specific IgG antibodies, as T-helper epitopes are required for B-cell activation and IgM-to-IgG isotype switching. (www.pirche.org)

Results: Our preliminary data showed that an epitope mismatch load provides a more accurate analysis of HLA relatedness between donor-recipient pairs than conventional HLA antigen mismatch assessment in relation to graft failure. Although, a high epitope load was not always correlated with bad outcome which may be attributed to the immunodominance of epitopes.

Conclusions: We confirm that epitope-based permissible mismatching helps in identifying suitable donors with minimal risks for graft failure.
However, epitope specificity studies with larger sample sizes are required to determine which epitope mismatches are truly immunodominant and if immunodominance is more commonly linked to graft loss.