TRANSPLANTATION
PROGNOSTIC VALUE OF C3D-BINDING DSA

The identification of patients who are at risk of allograft loss following a diagnosis of antibody-mediated rejection (AMR) is important for therapeutic decision making, but is limited by a lack of accurate prognostic assays. Now, new findings show that the presence of C3d-binding donor-specific anti-HLA antibodies (DSAs) at the time of AMR strongly predicts kidney allograft loss and may enable accurate risk stratification of these patients.

AMR is a major cause of kidney allograft loss but the outcomes associated with AMR are highly heterogeneous. "It is difficult to predict the individual fate of a given patient using the currently available tools," explains researcher Olivier Thaunat. Previous studies had shown that DSAs can cause graft destruction through activation of the classical complement pathway. "We hypothesized that complement activation by DSAs could accelerate the development of lesions, thereby enabling the identification of patients at high risk of graft failure."

The researchers used two different approaches to evaluate the ability of DSAs to activate complement at the time of AMR diagnosis in 69 kidney transplant recipients. First, they used indirect immunofluorescence to detect C4d deposits in kidney biopsy samples. Second, they used recently developed assays to test for the presence of C3d-binding DSAs in serum samples. C4d deposition in graft biopsy samples was not associated with risk of graft loss. By contrast, the presence of C3d-binding DSAs was associated with risk of graft loss. The prognostic value of the C3d-binding assay was further confirmed in an independent cohort of 39 patients with AMR. "Finally, when a multivariate analysis was conducted, the presence of circulating C3d-binding DSAs was, apart from estimated glomerular filtration rate <30 ml/min/1.73 m^2, the only independent predictor of allograft loss at AMR diagnosis," notes Thaunat.

The researchers say that in addition to identifying patients at risk of allograft failure, their findings provide a basis for future clinical trials to test the efficiency of complement inhibitors in patients at risk of allograft loss.

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Original article Sicard, A. *et al*. Detection of C3d-binding donor-specific anti-HLA antibodies at diagnosis of humoral rejection predicts renal graft loss. *J. Am. Soc. Nephrol.* doi:10.1681/ASN.2013101144