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TRANSPLANTATION

ROLE OF AECAS IN GRAFT REJECTION

Evidence from clinical studies has implicated non-HLA anti-endothelial cell antibodies (AECAs) in transplant rejection. However, the pathogenic mechanisms by which these antibodies might contribute to renal allograft dysfunction are not well understood. Now, new data from Annette Jackson, Tara Sigdel, Minnie Sarwal and colleagues suggest that AECAs activate the vascular endothelium, resulting in inflammation and microvascular injury.

To investigate their role in allograft rejection, the researchers first isolated AECAs from the sera of 10 renal transplant recipients with antibody-mediated rejection (ABMR) in the absence of donor-specific HLA antibodies (HLA-DSAs). Using a proteomics approach, they identified four novel antigenic targets for these AECAs that are known to be expressed on endothelial cells: endoglin, Flt3 ligand, EDIL3 and ICAM4.

ELISA analysis of pre-transplant serum samples from a validation cohort of 150 renal transplant recipients detected ≥1 AECA in 37% and all four AECAs in 24% of patients. Moreover, the presence of these antibodies prior to transplantation was associated with the identification of HLA-DSAs after transplantation, ABMR and early transplant glomerulopathy. After exclusion of patients with high levels of HLA-DSAs, histopathology scores for microvascular injury in post-transplant biopsy samples were higher in recipients who tested highly positive for AECAs on ELISA than in those who tested negative.

"Finally we showed that *in vitro* incubation of endothelial cell cultures with AECAs resulted in endothelial cell activation and production of the inflammatory cytokines RANTES, PDGF, and resistin," says Jackson. "Correlations between these *in vitro* experiments and our *in vivo* histopathology data suggest that AECAs activate the vascular endothelium, amplify the alloimmune response and increase microvascular damage."

The researchers hope that their findings will lead to routine clinical testing for AECAs. "A risk score for vascular rejection secondary to AECAs could enable improved induction therapy and avoidance or reversal of rejection, with downstream benefits of improved graft survival and function," explains Sarwal.

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Original article Jackson, A. M. *et al*. Endothelial cell antibodies associated with novel targets and increased rejection. *J. Am. Soc. Nephrol*. doi:10.1681/ASN.2013121277