IDENTIFICATION OF A NOVEL COMPLEMENT-INDUCED SIGNALING PATHWAY IN ENDOTHELIAL CELLS THAT IS IMPLICATED IN THE DEVELOPMENT OF CORONARY GRAFT VASCULOPATHY

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The efficacy of cardiac transplant is limited by coronary allograft vasculopathy (CAV), a prevalent and irreversible process of diffuse coronary stenosis. Chronic antibody mediated rejection (CAMR), characterized by donor specific antibody and complement binding to graft endothelial cells (EC) is a risk factor for CAV, however the mechanism(s) linking CAMR to CAV is unknown.

To model CAMR, we used ‘high panel reactive antibody (PRA)’ sera taken from highly-sensitized listed patients to deposit alloantibody and sub-lytic complement on EC (Fig 1a). We assessed EC gene expression by microarray analysis and measured the ability of PRA sera-treated EC to activate and recruit alloimmune CD4+ T cells in vitro using two cell-based assays and in vivo in a humanized mouse model of CAV.

EC treated with PRA sera initiated an inflammatory gene program (1b) that increased the capacity of EC to recruit (1c) and activate (1d) alloreactive CD4+ T cells. PRA sera-treated coronaries also developed worsened CAV in vivo (e). Unexpectedly, these processes were driven by complement-induced activation of non-canonical nuclear factor kappa B (NF-kB) signaling in EC. We identified a pathologic role for non-canonical NF-kB signaling and found evidence of pathway activation in vivo in a humanized mouse model and in biopsies of patients with CAMR (1f).

Our studies identify a novel complement-mediated pathway involving non-canonical NF-kB signaling in EC that mechanistically links CAMR with development of CAV.