The role of MHC-specific IgE in antibody-mediated transplant rejection

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Background
Transplantation is the gold standard for treatment of patients with end-stage organ failure. While the 1-year graft survival rate has increased significantly, long-term allograft survival is still limited due to antibody-mediated rejection (ABMR) caused by either pre-existing or de novo donor specific antibodies (DSA) [1]. Especially the occurrence of DSAs of the IgG isotype is strongly correlated with an increased risk of graft loss [2, 3]. To our knowledge our group was the first to describe DSAs of the IgE isotype in mice and humans upon allograft rejection [4].

Methods
Hearts from fully mismatched BALB/c (H-2b) or Bm12.K1/IE mice, a recipient model for studies on chronic ABMR, are transplanted heterotopic into C57BL/6 (H-2D) mice [8]. The parental strains of this donor model have to be revitalized from frozen embryos by our animal facility. As an additional murine model we will employ C57SK50 recipients as a model for acute ABMR established by the group of Fairchild et al. [9]. For measurements of MHC-specific IgE and IgG1 a custom-made ELISA employing MHC monomers, allowing us to distinguish between MHC class I and class II DSA specificities, is used. IgE effector cells during cardiac allograft rejection are analyzed in peripheral blood and in the graft using flow cytometry. Therapeutic interventions targeting IgE, mast cells or eosinophils are performed using α-IgE, cromoglicat or α-IL5, respectively.

Preliminary Data
Our laboratory recently demonstrated the occurrence of IgE specific for MHC antigens in mice and highly sensitized kidney transplant patients. IgE specific for donor MHC class I or class II antigens was detectable in WT C57BL/6 mice as early as 2 weeks after transplantation of a fully mismatched skin or cardiac allograft until at least 12 months post-transplant. Importantly, IgE-DSAs also developed in two murine models of humoral rejection employing either Bm12.Kd/IE cardiac donors as model for chronic ABMR (Fig. 1) or C57SK0 recipients as model of acute ABMR (Data not shown). Through a rat basophil leukemia cell degranulation assay and a cutaneous type I hypersensitivity reaction we demonstrated in vitro and in vivo that MHC-specific IgE that developed in murine recipients undergoing rejection was functional (Fig. 2).

Hypothesis & Specific Aims
IgG-DSAs mediate graft injury mainly by targeting endothelial cells causing vascular lesions through complement activation, FcyR-mediated antibody-dependent cellular cytotoxicity or target cell activation through cross-linking. In contrast, IgE-DSAs mainly target mast cells, basophils and eosinophils in the graft, thus the hypothesized effector functions would be distinct from IgG-DSAs. Therefore, we hypothesize, that donor-specific IgE antibodies might play a specific and distinct role in mediating immunologic graft injury.

The overall goal of this project is to determine the role of IgE specific for donor MHC antigens in the pathology of ABMR.

Specific Aim 1
To investigate the effect of eliminating IgE on immune-mediated graft injury in a murine heart transplant model of chronic ABMR.

Specific Aim 2
To determine the role of mast cells in an IgE-DSA positive murine heart transplant model of chronic ABMR.

Specific Aim 3
To investigate whether therapeutic interventions targeting IgE, mast cells or eosinophils improve outcome in a murine heart transplant model of chronic ABMR.

References