Donor-specific IgE can amplify allospecific responses through its low affinity receptor CD23

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Introduction: The presence of IgE antibodies targeting donor MHC has been observed in murine transplant models and highly sensitized transplant recipients. While IgE is well-known for its role in allergies and other TH2-associated conditions, its involvement in transplant rejection remains poorly understood. Beyond mediating immediate hypersensitivity via its high-affinity receptor FcεRI, IgE also enhances allergen-specific T cell activation and antibody production through the low-affinity receptor FcεRII/CD23, a mechanism known as 'facilitated antigen presentation' (FAP).

Objectives: This study explores whether MHC-specific IgE can amplify adaptive alloresponses through a CD23-dependent pathway.

Methods: *In vitro*, serum from C57BL/6 mice that had rejected a BALB/c cardiac allograft was incubated with fluorophore-labelled donor MHC tetramers and naïve B cells. B cell-bound MHC was measured via flow cytometry and compared to serum controls without IgE or CD23-blocked B cells. *In vivo*, a footpad immunization model was used to assess the IgE/CD23-dependent impact on alloresponse. First, we co-injected serum with MHC monomers into the footpads of naïve or anti-CD23-treated (clone B3B4) mice. After 7 days alloimmune responses in the draining lymph nodes (dLN) were analysed. In a second approach, fluorophore-labelled MHC tetramers were injected into pre-sensitized mice with or without anti-CD23 treatment to evaluate their transfer into the dLN.

Results: *In vitro*, donor-specific IgE facilitated donor MHC tetramer binding to B cells via CD23. *In vivo* the presence of IgE led to enhanced T cell activation and proliferation, resulting in elevated levels of donor-reactive and germinal center (GC) B cells in dLNs in a CD23-dependent manner. Of note, blocking of CD23 reduced the transport of the donor MHC tetramers to the dLN in sensitized mice.

Conclusions: These findings demonstrate that donor-specific IgE amplifies alloresponses by promoting the activation and proliferation of donor-reactive lymphocytes through CD23-mediated mechanisms, suggesting a potential role for IgE in transplant rejection.