Abstract: The potential pathological role of cardiac autoantibodies in the development of heart failure

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Background
Inflammation plays an important role in cardiovascular disease. Although the effect of immune cells after a myocardial infarction has become more evident over the past years, the role of the immune response in the progression towards heart failure (HF) is less well understood. Recently, in end-stage HF patients, large deposits of cardiac autoantibodies were observed in the myocardium. However, the exact contribution of these autoantibodies to the development of HF is unclear.

Purpose
We investigated the role of infiltrating immune cell subsets and the presence and targets of cardiac autoantibodies in myocardial tissue and circulation of end-stage HF patients.

Methods
Plasma was obtained from healthy controls and end-stage HF patients with ischemic heart disease (IHD) or dilated cardiomyopathy (DCM). Myocardial tissue was obtained from explanted hearts from end-stage HF patients at heart transplantation or LVAD placement. Cryosections of remote myocardium were used for immunohistochemistry (IHC) and tissue lysates. Both plasma and tissue lysates were used to measure IgG subclasses, IgM, and IgA antibody levels using multiplex immunoassay. In addition, tissue lysates were used for immunoprecipitation of IgG and western blot. Peripheral blood mononuclear cells (PBMC) were freshly isolated to measure cell composition using flow cytometry. Furthermore, an epitope discovery screening array was performed to learn more about the targets of the detected auto-antibodies.

Results
An increased production in vitro of IgG1 and IgG3 was observed from PBMC derived from HF patients compared to healthy controls. IgG1 and IgG3 levels were also increased in the plasma of heart failure patients (IHD: IgG1 p<0.0001; IgG3 p<0.010) and DCM (IgG3 p<0.050)). Furthermore, HF patients showed a shift in B-cell subsets, namely more plasma cells and fewer regulatory B cells (CD24+, CD38+) were found in the circulation. In remote myocardium, we found increased levels of infiltrating T cells, B cells, and macrophages in both IHD and DCM patients compared to healthy controls (p<0.05 - p<0.001). A significant increase of IgG was found in the myocardium of IHD patients (p<0.01) compared to controls. IHC showed the presence of both IgG3 and complement component 3 (C3c), indicative for complement activation in the myocardium upon HF. Based on the epitope discovery screening, epitopes were selected for future screening assays.

Conclusion
Cardiac autoimmune antibodies are present in both the circulation and the myocardium of end-stage HF patients, with the highest level in IHD patients. Concomitantly, there is a progressive increase in the percentage of plasma cells and a decrease in regulatory B cells in these patients. These results support a pathological role of an autoimmune response in the development of HF and currently, selected epitopes are being explored.
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