Autoimmunity and inflammation in heart failure

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The aim of our group is to investigate the pathogenic importance of autoimmune mechanisms in the development of idiopathic dilated cardiomyopathy (DCM). We and others have previously demonstrated the existence of autoantibodies against β1-adrenergic and M2 muscarinic receptors in patients with DCM. However, a number of questions remained to be answered: Do these anti-receptor autoantibodies cause disease? Why and how is autoimmunity initiated? Do cytokines play an important role? How do interactions between autoimmunity and cytokines happen? How do they cause cardiac remodelling and, later on, heart failure? How can autoimmune heart failure be prevented?

[Diagram of the relationship between viral infection, genetic defect, smoking, hypertension, diabetes, aging, etc., autoimmunity, cytokines, ang II, aldosterone, catecholamine, remodeling (global & cellular), stiffness, heterogeneity, diastolic dysfunction, systolic dysfunction, and progression of HF.]
Autoantibodies against β1-adrenergic and M2 muscarinic receptors cause disease

We have successfully shown that anti-myocardial antibodies to β-adrenergic receptors and muscarinic receptors are pathogenetic factors in the development of cardiomyopathy and arrhythmias. For example, cardiomyopathy can be induced either by active immunization of rabbits, rats and mice with antigenic β-adrenergic receptor peptide, or by passive transfer of peripheral blood lymphocytes from patients with dilated cardiomyopathy to mice with severe combined immunodeficiency. Placebo-controlled and randomized studies in rabbits have shown that specific immunoabsorption of β-adrenergic receptor autoantibodies in autoimmune cardiomyopathy improves both cardiac structure and function.

Increased cytokine activation in hypertensive heart failure

Elderly patients with chronic heart failure have increased plasma levels of the cytokine interleukin-6 (IL-6), which is a significant prognostic indicator of one-year mortality. We have shown increased expression of IL-6 and brain natriuretic protein mRNA and decreased expression of β1-adrenergic receptor mRNA in spontaneously hypertensive rats (SHR) displaying diastolic heart failure.

Tumor necrosis factor alpha (TNFα) is one of the best characterized inflammatory mediators in chronic heart failure, but recent clinical trials of TNFα antagonists in chronic heart failure have been disappointing. In our SHR model of heart failure, the TNFα antagonist etanercept was shown to upregulate IL-6 mRNA expression and to exert a positive inotropic effect. Moreover, it seems that etanercept is able to induce eccentric hypertrophy. These findings may explain why chronic treatment with etanercept is not an effective treatment strategy.

Concluding remarks

In summary, we have shown that anti-myocardial autoantibodies to β-adrenergic and muscarinic receptors cause disease. Immunoabsorption of β-adrenergic receptor autoantibodies could be an effective emerging therapy in autoimmune cardiomyopathy.
In addition, we have evidence to suggest that proinflammatory cytokines such as IL-6 might be involved in the development of heart failure.

We are currently investigating the prevalence and prognostic significance of autoimmunity and inflammation in heart failure by comparing a large population of patients with heart failure resulting from different aetiologies with: (1) patients with other cardiovascular diseases but no heart failure; and (2) healthy volunteers. We are also investigating the interplay between autoimmunity, inflammation and remodelling in experimental heart failure, and the mechanisms involved in emerging immune therapies such as immunoabsorption and anti-inflammatory treatment.

References


