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Th17 signature, autoimmunity and differentially expressed genes in cardiomyopathy and heart failure

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Topic(s):
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National Heart Lung and Blood Institute, Bethesda, MD, USA

Background: Cardiomyopathy may occur due to viral infections or drug induced heart damage. Cardiac myosin released from damaged heart has been shown to be a damage associated molecular pattern which binds to TLR2 or TLR8 and can act as an adjuvant to induce a strong autoimmune response against the heart. The result is autoimmunity against the heart which can lead to apoptosis, fibrosis and heart failure.

Purpose: Immune biomarkers of the early stages of heart failure are needed to identify individuals who develop progressive heart failure, do not recover their ejection fraction and may be candidates for immunotherapies.

Methods: Forty-one patients with myocarditis and heart failure <6 months after onset were followed for 12 months and compared to age matched controls. Peripheral blood mononuclear cells were analyzed by FACS analysis and serum analyzed by ELISA for autoantibodies and cytokines. Statistical analysis was determined by Mann Whitney test. Peripheral blood of 10 patients with dilated cardiomyopathy (DCM) vs 19 healthy controls were analyzed for gene expression by RNA sequencing and pathway analysis using Reactome.

Results: Autoantibodies against human cardiac myosin and the beta-adrenergic receptor were significantly elevated in our cohort and functionally acted on cardiomyocytes to activate protein kinase A. Concomitantly, a Th17+ immunophenotype was significantly elevated in blood as well as in cardiac biopsies. CD4+IL17+ T cells (p=0.0008) and Th17-promoting cytokines TGF beta (p<0.0001), IL-6 (p<0.0001), IL-23 (p=0.0001), GMCSF (p=0.0336) and GMCSF-secreting CD4+ T cells (p=0.0006) were significantly elevated in blood. A Th17 immunophenotype was significantly associated with heart failure primarily in males (p=0.029). Persistent heart failure (NYHA class III and IV) and non-recovery of left ventricular function were associated with significantly higher percentages of IL17A-producing T cells at baseline, 6 and 12 months after onset, and IL-17A (p=0.019) and elevated Th17-promoting cytokines IL-6 (p=0.0001) and TGF-beta (p=0.0076). Decreased T regulatory immunosuppressive cells were significantly (p=0.0006) decreased and correlated with elevated Th17 cytokines in heart failure. Overrepresentation analysis of differentially expressed genes (adj p<0.05) in blood of patients with DCM >1year were identified using Reactome which revealed significant (FDR = 1.52E-13) enrichment of neutrophil degranulation (48 genes).

Conclusion: Our study illustrates a strong Th17 signature in more severe heart failure early in disease with elevated anti-cardiac myosin autoantibodies in non-recovery of left ventricular function. We observed a strong correlation with Th17-related neutrophil degranulation pathways in later disease, which may be biomarkers of fibrosis progression and disease severity in patients with heart failure. Cardiomyopathy with a Th17 signature might be treated with preventive immunomodulatory therapies such as anti-IL17A.
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