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GUT MICROBIOTA DEPLETION PRESERVES HEART FUNCTION, SUPPRESSES CARDIAC FIBROSIS AND HYPERTROPHY IN A NON-ISCHEMIC HEART FAILURE MOUSE MODEL

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The gut is a major reservoir of T cells and diverse resident microbes, microbiota, which can influence immune responses in sites distant from the mucosal surfaces. Complete sterilization of the gut has proven to be beneficial in some experimental models of T cell mediated diseases, whereas partial recolonization post sterilization leads to microbial perturbations, a process called dysbiosis, and, worsens the outcome. Gut dysbiosis is thus recently becoming associated with the pathogenesis of several diseases, in part, by mechanisms in which certain bacteria promote T cell activation and enhance disease progression in a vicious cycle. The complex syndrome of heart failure (HF), a leading cause of morbidity and mortality affecting more than 24 million people worldwide, is recently becoming associated with gut dysbiosis and T cell mediated systemic inflammation in patients, but the mechanisms regulating this emerging gut-heart axis, and whether T cell activation and heart infiltration play a role remains unclear. We have previously reported that T cells infiltrate the heart in patients with non-ischemic HF, and using the transverse aortic constriction (TAC) mouse model of HF, demonstrated that T cells are critical regulators of adverse cardiac remodeling and HF. We hypothesized that sterilization of the gut by microbiota depletion prevents adverse cardiac remodeling and HF in a T cell dependent manner. C57/BL6 mice were orally treated with a well-established cocktail of antibiotics and antifungal (ABX) and subjected to TAC or Sham surgery. ABX treatment started 1 week before TAC surgery and was terminated 4 weeks after TAC. *In vivo* transthoracic echocardiography and hemodynamics showed a preserved ejection fraction and fractional shortening in mice treated with ABX as compared to untreated mice. Furthermore, gut microbiota depletion with ABX resulted in decreased left ventricular interstitial and perivascular fibrosis, and decreased cardiac hypertrophy in response to TAC, as compared to non-ABX treated TAC mice. These changes correlated with significant reduction of CD4 T cell activation in the mediastinal lymph nodes (mLNs) draining the heart, determined by FACS, as well as in the number of CD4 T cells infiltrated in the heart in ABX treated mice. Our findings indicate that ABX treatment results in distal effects in T cell activation occurring during TAC and protects from adverse cardiac remodeling, supporting the potential importance of gut microbiota in pressure overload induced HF. Future studies will determine whether dysbiosis post ABX treatment contributes to pathological cardiac remodeling and the mechanisms regulating the gut-heart axis in non-ischemic HF.

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