

A027 Cardiac Pressure Overload Induces Gut Dysbiosis That Promotes T Cell Activation and Maladaptive Remodeling Downregulating the Aryl Hydrocarbon Receptor Expression

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Introduction: Heart failure (HF) patients present gut dysbiosis (alterations in gut microbial populations), and systemic inflammation. Activated T-cells that infiltrate the heart drive maladaptive remodeling in experimental models of HF. The gut, a major reservoir of T-cells, contains microbiota that can modulate T-cell activation locally and in distal organ inflammation through metabolites and other molecules. The aryl hydrocarbon receptor (AhR) is one of such receptors involved in immunomodulation that recognize ligands that include gut derived tryptophan metabolites. We hypothesized that gut dysbiosis induced by cardiac pressure overload modulate adverse cardiac remodeling and function in a T-cell-dependent manner through AhR signaling in the heart and in the gut. **Methods:** Gut dysbiosis and associated bacterial metabolism were analyzed by 16S rRNA sequencing in fecal samples from WT or T-cell deficient (*Tcra*^{-/-}) mice subjected to Sham or transverse aortic constriction (TAC) surgeries. For gut microbiota depletion, water was supplemented with an antibiotic (ABX) cocktail. Systolic function was evaluated by echocardiography. Heart was collected for maladaptive remodeling examination, and gut and lymph nodes (LNs) for T-cell activation analysis by flow cytometry. Gene expression of several markers was quantified by qPCR. **Results:** TAC induced enrichment of phylum Bacteroidetes, and decreased abundance of genus *Lactobacillus*, a tryptophan producer, as compared to Sham. Gut dysbiosis was not detected in *Tcra*^{-/-} TAC mice, which were protected from maladaptive remodeling and showed a closer gut microbiota profile to WT Sham than to WT TAC mice. These changes did not result in T cell activation in the gut or gut barrier disruption. Outstandingly, microbiota depletion in WT mice resulted in reduced heart T cell infiltration, less cardiac fibrosis and protection from systolic dysfunction in response to TAC. Spontaneous reconstitution of the microbiota moderately reversed these effects. We observed decreased cardiac expression of *AhR* and enzymes associated with tryptophan metabolism in WT mice, but not in *Tcra*^{-/-} mice, or in mice depleted of the microbiota, that did not develop systolic dysfunction. **Conclusion:** We show that cardiac pressure overload induced gut dysbiosis and T cell immune responses contribute to maladaptive remodeling, and identify the importance of the tryptophan/AhR axis in protecting from adverse cardiac remodeling and systolic dysfunction in HF.