Prevalently carried HLA allele associates with inflammation and poor prognosis in HF patients via co-stimulatory, adhesion and MHC-II enhanceosome regulation

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Background: Heart failure with reduced ejection fraction (HFrEF) is associated with impaired inflammation resolution, adverse remodeling, restricted function, and poor prognosis. Furthermore, immune cells play crucial roles in pathological remodeling in cardiovascular diseases. Thus identifying subsets of patients with unique inflammatory profiles may aid in better risk stratification and precision therapies for chronic HFrEF patients with altered immune profiles.

Methods and Results: A pilot study using scRNA-seq of circulating immune cells (n=16) showed strong T cell activation in HFrEF patients, which was validated via flow cytometry in HFrEF patients and healthy controls (n=180 patients) with a shift into the memory/effector phenotype (p<0.0001). Thus, HFrEF patients may have unique MHC signatures promoting aberrant T cell activation, leading to chronic inflammation and pathology. We investigated antigen-presenting cells (APCs) that activate CD4+ T cells via MHC-II and costimulatory molecules. Indeed, we found MHC-II and costimulatory molecule signatures associated with HFrEF and T cell activation, such as HLA-DRB5 (DRB5) and ICAM-1, indicating both T cell activation potential and a pro-inflammatory status.

To study whether HLA-DRB5 selectively promotes immune dysregulation, circulating monocytes from healthy DRB5 carriers and non-carriers were investigated using scRNA-seq showing enhanced antigen presentation, co-stimulatory and inflammatory molecule expression (e.g. HLA-DRA, ICAM-2, JAK2). ScRNA-seq confirmed HLA-DRBS regulation of MHC-II, inflammatory and adhesion (e.g. ITGAM and ITGB1) properties by silencing HLA-DRB5 in THP1 cells. In silico analysis of monocyte epigenome data predicted unique transcription factors (e.g. ERG) controlling of HLA-DRB5 via regulatory elements suggesting a role in selective MHC-II molecule activation.

To gain insights as to whether HLA carrier status might associate with prognosis, we performed HLA sequencing on age and gender matched HFrEF patients (n=93). During follow up of this cohort we identified HLA-DRB5*0101, which belongs to the DR2-supertype, as a predictor for death (p<0.05). We hypothesized whether HLA-DRB5 expression could impact T cell infiltration into the heart. Thus, we stimulated naïve T cells with pre-treated THP1-derived DCs (stress v. no stress cardiac organoid medium) and found HLA-DRB5 silencing reduced the infiltration of T cells into unstressed cardiac organoids compared to control group.

Conclusions: This is the first study to provide mechanistic insights for how HLA-DRB5 regulates innate and adaptive immunity in the context of heart failure, while also showing corresponding changes in T cell activation, infiltration capacity and prognosis in HFrEF patients. These data provide novel insights for risk stratification of heart failure patients and novel immunological interventions which may improve prognosis in HFrEF patients.