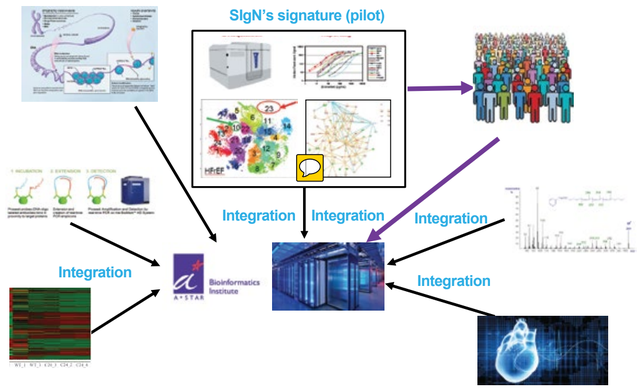
Role of Chronic Inflammation in Driving Progression of Heart Failure

Hui Xian Chin[1], Joni Chong[1], Sandra Hubert[1], Vipin Narang[1], Josephine Lum[1],Crystal Tan[1], Tan Ru San[2], David Sim[2], Loh Seet Yoong[4], Fazlur Jaufeerally[5], Sheldon Lee[6], Dinna Soon[2], Carolyn Lam Su Ping[2], Arthur Mark Richards[3], Brian Abel[1], Anis Larbi[1]

[1]Singapore Immunology Network, Agency for Science Technology and Research, Singapore, [2]National Heart Centre, Singapore, [3]Cardiovascular Research Institute, National University of Singapore, Singapore, [4]Tan Tock Seng Hospital, Singapore, [5]Singapore General Hospital, Singapore, [6]Changi General Hospital, Singapore

Introduction

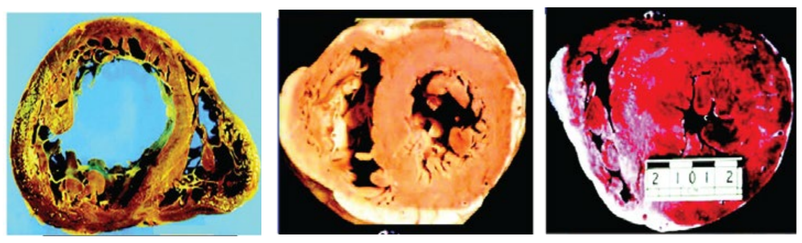
Heart failure (HF) is now recognized in international guidelines as a staged disease in which risk factors progress to asymptomatic cardiac changes and finally to the overt clinical manifestation - either HF with preserved Ejection Fraction (HFpEF) or HF with reduced Ejection Fraction (HFrEF). Despite new therapies, HF remains a leading cause of mortality and morbidity, particularly for HFpEF for which there are currently no proven therapies. Recently, chronic inflammation, specifically mediated by T cells, has been implicated as a key factor driving the progression of HF. T cells are central players in the regulation of chronic inflammation, and may influence innate cell development, such as monocyte differentiation into macrophages and dendritic cells (DCs), thus affecting tissue homeostasis, remodelling and repair. In this study, we aim to deepen our understanding of the role played by the immune system in driving HF progression towards differing disease outcomes by characterizing the immune cell phenotype and cellular distribution, as well as evaluating their associations with the circulating inflammatory milieu. Gaining insight into the inflammatory burden associated with HF might lead to rational interventional strategies to reverse the adverse effects of HF or prevent disease progression.



Aim

To characterize the role mediated by the immune system in developing HF and driving disease progression towards differing HF phenotypes.

Clinical Images: Left Ventricle (LV) Autopsies



HFrEF | Normal | HFpEF

Characteristic	HFrEF	HFpEF
Left Ventricle Ejection Fraction	< 50%	> 50%
LV pattern of remodelling	Eccentric	Concentric
End-diastolic volume	Increased	Near Normal
Wall thickness (and mass)	Slightly increased	Increased
Ratio of mass to volume	Decreased	High

Circulation. 2006;113:296-304.

Methods

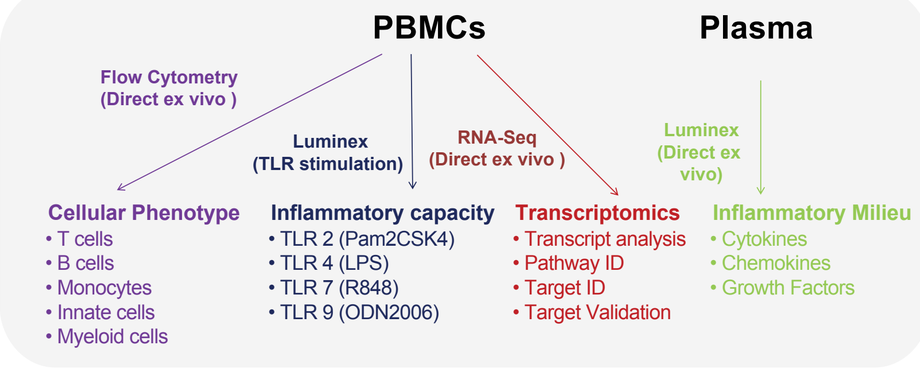
A. Subject Recruitment

- Healthy controls
- HFrEF
- HFpEF

C. Analytic Tools

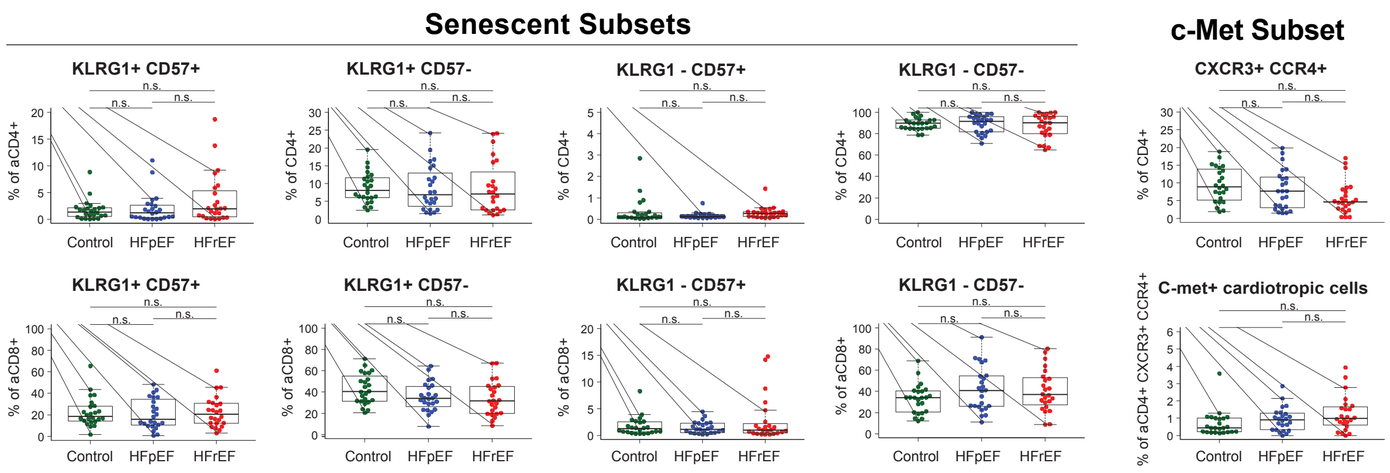
- R package - ANOVA
- EdgeR

B. Diverse Immunomonitoring Assays Conducted on Subject Samples



- Peripheral Blood Mononuclear Cells (PBMCs) isolated by Ficoll Gradient

Preliminary Cellular Immunophenotyping

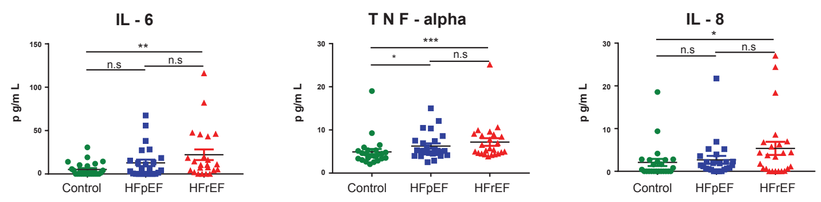


No significant difference in the frequency of either CD4 or CD8 T senescent subsets in controls vs HF patients, which indicates that the aging of the immune system is not a cause of HF.

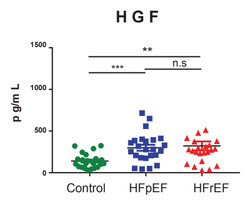
Engagement of the Hepatocyte Growth Factor (HGF) receptor, c-Met on T cells by cardiac-produced HGF during priming in the lymph nodes instructs T cell cardiotropism and recirculation, which has been associated with a specialized cardiac homing "signature", namely, c-Met+CCR4+CXCR3+ T cells. In our pilot study, we report a decreased frequency of CXCR3+CCR4+ CD4 T cells, but an increased CXCR3+CCR4+c-Met+ subset in HFrEF vs. controls, suggesting that c-Met+ T cell recruitment to the heart during cardiac inflammation may lead to increased damage during HF.

Immunity, 2015 Jun 16;42(6):1087-99

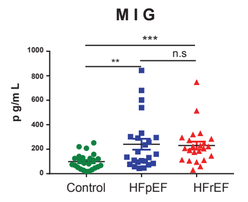
Preliminary Cytokine Profiling by Luminex



Serum level of pro-inflammatory cytokines is elevated in patients with HF

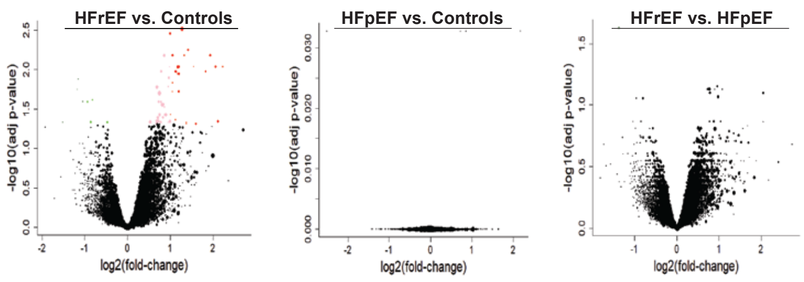


c-Met ligand, HGF is elevated in the serum of HF patients correlating with an increased expression of cardiotropic c-Met+CD4+ T cells in HF patients.



Serum CXCL-9 (MIG) is elevated in patients with HF suggesting that CXCL-9 might play a role in the recruitment of T cells into the heart.

Preliminary Transcripomic Analysis by RNAseq



62 DEGs (29 > 2-fold differential) | Zero DEGs | 1 DEG (CENPK)

Multiple testing correction, using FDR < 0.05 to define DEGs

Chronic inflammation contributes to cardiac fibrosis, a crucial factor in HF.

Increase in glucose uptake and its subsequent diversion into the oxidative pentose phosphate pathway (oxPPP) is an important contributor to cardiac oxidative stress in HF.

Inflammasome and pentose phosphate pathway are upregulated in HF patient

Conclusions and next steps

Preliminary findings from the pilot study suggest that aging of the immune system is not a cause of HF. Inflammation and recruitment of cardiotropic T cells may be important contributors to HF disease, and further investigation may provide insight into the role of the immune system in HF.

Samples from porcine models of HF will be characterized immunologically to reproduce & mechanistically dissect earlier findings from patient cohorts (Joni Chong et al., poster).

Data integration and deeper immunoprofiling will lead to the identification of biomarker candidates, which will be validated in larger cohorts.

Gaining insight into inflammatory burden associated with HF might lead to rational interventional strategies to reverse the adverse effects or to prevent HF development.