Role of Chronic Inflammation in Driving Progression of Heart Failure

Hui Xian Chui1, Joni Chong1, Sandra Hubert1, Vipin Narang1, Josephine Lum1, Crystal Tan1, Tan Ru San1, David Sim1, Loh Seet Yoong1, Faizur Jaufeerally1, Sheldon Lee1, Dinna Soor1, Carolyn Lam Su Ping2, Arthur Mark Richards3, Brian Abel4, Anis Lari1

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

**HFpEF vs. Controls vs. HFrEF**

- **HFrEF Normal HFpEF**
  - Characteristic
    - Left Ventricular Ejection Fraction: <50% vs. >50%
    - LV pattern of remodelling
      - Eccentric vs. Concentric
    - Wall thickness (and mass)
      - Slightly increased vs. Increased
    - Ratio of mass to volume
      - Decreased vs. High

Methods

A. Subject Recruitment

- Healthy controls
- HFpEF
- HFrEF

B. Diverse Immunomonitoring Assays Conducted on Subject Samples

- Flow Cytometry
- PBMCs (Peripheral Blood Mononuclear Cells)
- Plasma
- Transcriptomics
- Inflammatory Milieu

C. Analytic Tools

- R package - ANOVA
- EdgeR

Preliminary Cellular Immunophenotyping

**Senescent Subsets**

- **KLRG1+ CD57-**
- **KLRG1+ CD57+**

**c-Met Subset**

- Cardiomyocytes
- Cardiocytes
- C-met+ cardiotropic cells

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+CD4+ T cells, and an increased expression of c-Met+ T cell recruitment to the heart during cardiac inflammation may lead to increased damage during HF.

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 cardiotoxic c-Met+CD4+ T cells in HF patients.

Preliminary Transcripomic Analysis by RNAseq

- Inflammatory and immune pathways are upregulated in HF patients
- 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

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 immunoprofile 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.