HFWM: The missing link between the immune system and endothelial dysfunction in HFpEF

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Heart failure with preserved ejection fraction (HFpEF) is a major public health concern, characterized by normal heart ejection fraction but with inability of the myocardium to relax normally. It lacks effective therapies, and is worsened by obesity, diabetes and hypertension epidemics in an ageing population.

Recent advances in HFpEF pathophysiology were possible due to the development of the ZSF1 obese rat model, which display HFpEF phenotype, including preserved systolic function and diastolic dysfunction. Mounting evidence suggest that these associated comorbidities prime a systemic pro-inflammatory milieu and microvascular endothelial activation which trigger subsequent myocardial dysfunction.

Targeting the immune response has been proposed as an effective strategy to prevent cardiovascular dysfunction in HFpEF. However, a comprehensive analysis on immune alterations and the subsequent implications to endothelial and organ dysfunction are yet to be reported. This work aimed to characterize systemic immune cell populations in a HFpEF animal model, and their crosstalk with endothelial cells.

Flow cytometry characterization of immune cell populations in blood, spleen and lymph nodes of ZSF1 obese rats showed a variation in their proportions, when comparing with lean animals, namely an increase in CD11b/c⁺ myeloid cells accompanied by a decrease in T and B cells. These data indicate that systemic immune alterations occur in HFpEF and suggest a higher involvement of innate immunity in the disease. We also detected higher expression levels of the senescence marker p21 in peripheral blood mononuclear cells which is a scenario compatible with chronic inflammation.

Although we observe that endothelial activation correlates with augmented inflammatory infiltration in ZSF1 obese animals, their association is yet to be defined. Based on this, we studied the interaction between immune cells, namely bone marrow-derived macrophages, with microvascular endothelial cells (MVEC), stimulating MVEC with extracellular vesicles isolated from cultures of macrophages from obese and lean ZSF1 rats. Preliminary results suggest an involvement of macrophage secretome in MVEC activation status. In conclusion, our findings suggest that in HFpEF alterations in the immune system precede endothelial dysfunction. However, further studies are required to advance current understanding on the role of the immune system in disease pathophysiology, and to translate this knowledge in the identification of effective therapeutic targets.