

00407 Cardiac Tissue Factor Regulates Inflammation and Hypertrophy in Mouse Model of Type 1 Diabetes Mellitus

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Aims: Diabetes mellitus (DM) is on the rise and cardiovascular diseases cause highest mortality in DM. Patients with DM have 2-5-fold increased risk of heart failure(HF). Diabetes has higher prevalence in HF with preserved ejection fraction (HFpEF). The role of DM in HF is less established and current treatment of HF is not effective in HFpEF. Aim- to understand mechanisms of HF in mouse-model of Type1DM; hypothesis-cardiac Tissue Factor(TF) signaling regulates inflammation and hypertrophic-remodeling.

Methodology: Diabetes was induced in wildtype(WT) C57BL/6 mice using STZ. We also used TF knockout(KO) transgenic and TF hetero(Het) mice as diabetics and controls. Hyperglycemia(HG), body-weight(BW) and cardiac function was measured. Heart-tissues were harvested for molecular studies at 18-weeks diabetes.

Result: 1)Significant upregulation of cardiacTF (mRNA and protein) in WT diabetic hearts vs. nondiabetic control indicated increased TF may play a role in downstream cardiac changes. 2)Increased inflammation in hearts of WT and TF-Het diabetic mice vs. control, but inflammation was significantly reduced in TF-KO. 3)Cardiac hypertrophy was evident in WT diabetic mice than control; less clear in TF-Het; and absolutely no hypertrophy in TF-KO. 4)Increased activation (in WT and TF-Het) of pro-survival (anti-apoptosis) pathway, which was significantly downregulated in TF-KO hearts. 5)Cardiac-function- All diabetic mice had preserved EF with some evidence of diastolic dysfunction (in WT) (HFpEF). 6)Presence of HF was confirmed with natriuretic peptides, the levels being higher in failing-diabetic heart than control. 7)In vitro studies in H9C2-cells, using HG and TFsiRNA supported TF role in inflammation and hypertrophy.

Conclusion: Tissue factor regulated inflammation and cardiac-remodeling (hypertrophy) leads to HF with likely pEF in T1DM. Novel finding in DM showing TF-signaling in anti-apoptosis. Present understanding of TF role in DM in thrombosis is now extended to its new roles in cardiac cells. Further studies in T2DM model may aid in development of effective treatment for HF in diabetes.