Title: Endothelial Cell STING Contributes to Capillary Rarefaction and Systolic Dysfunction Induced by Cardiac Pressure Overload

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Introduction: Capillary rarefaction and cardiomyocyte (CM) hypertrophy are hallmarks of heart failure (HF). Endothelial cells (EC) and CM communicate in cardiac remodeling and new signals continue to emerge. Stimulator of Interferon Genes (STING) is highly expressed in EC and contributes to vascular inflammation, yet its role in HF is unknown. We hypothesize that EC STING to CM crosstalk modulates CM hypertrophy and systolic dysfunction in HF.

Methods: Inducible EC STING$^{-/-}$ or EC STING$^{+/+}$ littermate controls (*Cad5*$^{ERTCre2+/-}$ *Sting*$^{fl/fl}$ treated with Tamoxifen or oil, respectively), wildtype (WT), and global deficient (STING$^{-/-}$) mice were subject to transverse aortic constriction (TAC) or Sham surgery. Cardiac function was analyzed by echocardiography after 2-8 weeks and left ventricular (LV) sections were stained with wheat germ agglutinin and isolectin to analyze CM hypertrophy and capillary density. Gene expression was analyzed by qPCR. Bulk RNA Sequencing was performed on CD45- CD31+ heart EC (MHEC) from EC STING$^{+/+}$ and EC STING$^{-/-}$ mice 4 weeks after TAC.

Results: In contrast to WT mice, global and EC STING$^{-/-}$ mice were protected from declined fractional shortening, capillary rarefaction and LV hypertrophy in response to TAC. RNASeq revealed reduced levels of pro-hypertrophic IL6 and increased anti-hypertrophic and pro-angiogenic Neuregulin1 (Nrg1) in TAC STING$^{-/-}$ MHEC compared to WT. Similarly, IL6 gene expression was reduced in EC STING$^{-/-}$ TAC hearts compared to EC STING$^{+/+}$, as Nrg1 was increased.

Conclusions: Our data demonstrate that EC STING modulates both EC and cardiac expression of IL6 and Nrg1, suggesting a mechanism of EC-CM communication that contributes to CM hypertrophy, capillary rarefaction and systolic dysfunction in response to pressure overload.