Small nucleolar RNA SNORD3A: a potential new biomarker and molecular player in heart failure

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Background: Despite optimal therapy, heart failure (HF) remains a relentless and deadly disease. Given the relative inaccessibility of myocardial human tissues, identification of circulating biomarkers mirroring myocardial pathological signaling pathways, especially in peripheral blood mononuclear cells (PBMC) is expected to be extremely relevant. Small Nucleolar RNAs (snoRNAs) have been shown to play important roles in various cellular physiological processes. However, the connection between snoRNAs and pathological dysfunction in the heart or peripheral blood mononuclear cells (PBMC) is still poorly understood.

Purpose: To identify novel circulating PBMC biomarkers linked to myocardial dysfunction and HF.

Methods: Myocardial left ventricle (LV) samples and PBMC were obtained from patients affected by ischemic HF (HF, n=13) undergoing heart transplantation and control donors (CD, n=7) and analyzed by RNA sequencing analysis (RNASeq). SNORD3A expression levels in the different groups were evaluated by quantitative real-time PCR. HF was induced in 8-week-old wild type C57BL/6 mice by transverse aortic constriction (TAC). Sham-operated mice (sham) were used as controls. After twelve-week-TAC (12w) or sham operation, mice were anesthetized, cardiac function was analyzed by echocardiography, and cardiac/PBMC samples were collected after sacrifice. In order to test the role of SNORD3A in cardiomyocyte hypoxia, H9C2 cardiomyoblasts were transfected with SNORD3A-targeted antisense oligonucleotides (ASO) and cell survival was analyzed by cleaved caspase-3 and PARP1 immunoblotting.

Results: RnaSeq analysis identified a small set of genes differentially expressed in the heart and PBMC from HF patients. Among these, SNORD3A was up-regulated in cardiac and PBMC samples from HF patients compared to CD (Figure 1A-B). Similarly, in murine HF induced by 12w TAC, SNORD3A levels were increased by rtPCR, both in the heart and PBMC (Figure 1C-D). SNORD3A expression levels were also significantly increased in H9C2 cells exposed to in vitro hypoxia (Figure 1E). Interestingly, H9C2 transfection with SNORD3A-specific ASO significantly reduced hypoxia-induced SNORD3A upregulation and reduced hypoxia-induced cell death (Figure 1F-G).

Conclusions: In this study, we identify SNORD3A as a novel possible biomarker in human HF, similarly up-regulated in the heart and PBMC, induced by hypoxia in vitro and modulating cell survival.

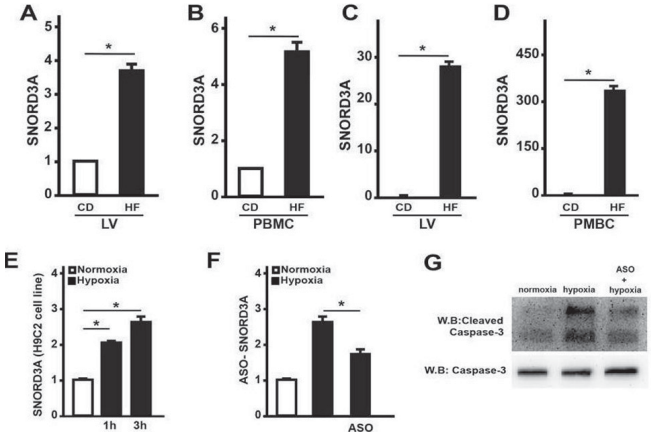

Figure 1

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