Molecular background of impairments in skeletal muscle of heart failure patients

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Background: Heart failure (HF) is characterised by systematic inflammation and chronic metabolic dysregulation. HF enhances the release of pro-inflammatory cytokines, induces activation of the complement system, production of autoantibodies, and over-expression of the major histocompatibility (MHC) complex class II molecules. It is known that skeletal muscles are exposed to the immunologic injury in disease; and muscle tissue appeared to be affected by HF leading to the muscle weakness and exercise intolerance development. However, molecular abnormalities occurring in HF patients' muscles and the mechanisms underlying its development are not clarified.

Purpose: To understand the molecular mechanisms underlying skeletal muscle immune and non-immune impairments in HF.

Methods: 8 health donors and 5 HF patients with reduced ejection fraction (NYHA Class II and III) were enrolled in this study in accordance with the principles under the Declaration of Helsinki (1989). mRNA of skeletal muscle biopsies of gastrocnemius lateralis were sequenced on Illumina HiSeq. RNA-seq analysis was performed using STAR with reference genome GRCh38 and featureCounts program; differentially expressed genes (DEGs) were assessed using R package DESeq2 with FDR=0.01 and log2 fold change (l2fc) $>$1.5 filter; pathway analysis was performed using clusterProfiler in R (FDR=0.01).

Results: 1404 differentially expressed genes distinguish muscles of HF patients and controls. Among upregulated genes there are different classical MHC molecules and specific one HLA-G (l2fc=2) that has been previously shown appeared in muscles under autoimmune myopathies, and potentially protect them. Unregulated DEGs were responsible for the activation of many molecular immunological pathways: type I interferon signaling pathway (16 DEGs out of total 89), regulation of T cell proliferation (14/153), neutrophil degranulation (31/485), granulocyte differentiation (7/32), negative regulation of viral process (11/53), that indicates about specific inflammatory response in HF muscles. Response to hypoxia (22/314) and gluconeogenesis pathways (12/87) were also activated. Downregulated genes include SLC5A1 (l2fc=−4) sodium glucose cotransporter; NRP3 (l2fc=−4) that plays a role in modulating intravascular volume and vascular tone; MMP1 (l2fc=−13) involved in the breakdown of extracellular matrix; the expression of many genes responsible for DNA-repair (44/534) and cilium assembly (34/366) was also suppressed.

Conclusion: Transcriptome analysis shows immunological and non-immunological alterations in HF skeletal muscles and provides the information about molecular mechanisms of its development.