Alterations of mitochondrial bioenergetics in human hearts with ischemic and dilated cardiomyopathy

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Background: Heart failure (HF) is a complex multifactorial syndrome characterized by mechanical dysfunction of the myocardium and the inability of the heart to provide adequate blood supply to meet the body's metabolic needs. Defects in mechanisms such as bioenergetics are important pathogenic factors in myocardial dysfunction, since the heart needs a continuous energy supply, which is fulfilled by ATP synthesis through mitochondrial oxidative phosphorylation, a process that takes place in the inner membrane of the mitochondria, whose structure is also affected during the development of HF.

Purpose: The aim of this study was to analyze the alterations in the expression level of mRNAs and proteins involved in mitochondrial function, focusing on bioenergetics and formation of cristae formation in patients with ischemic and dilated cardiomyopathy.

Methods: Transcriptome-level differences between HF and controls (CNT) were investigated in 36 heart samples with RNA-sequencing technology (mRNA-seq; ICM, n=13; DCM, n=13; CNT, n=10). In addition, ATP5I and ATPIF1 protein levels were determined in 30 heart samples (ICM, n=24; CNT, n=6) by Western Blot assay. The miRNAs implicated in the mRNA posttranscriptional regulation were studied through non-coding RNA-seq (ICM, n=22; DCM, n=20; CNT, n=8).

Results: 11 mitochondria genes were detected as altered in bioenergetics and mitochondrial cristae formation in HF. Specifically, we found an overexpression of ATP5I (ICM, FC=2.04, p<0.001) and ATPIF1 (ICM, FC=1.81, p<0.01) mRNA levels that correlated with both diastolic (r=-0.577 and r=-0.562, respectively; p<0.01) and systolic diameter (r=-0.574 and r=-0.563, respectively; p<0.01) and with ejection fraction (r=0.442 and r=0.410, respectively; p<0.05). The analysis of ATP5I and ATPIF1 protein expression showed that only ATPIF1 presented differences in expression when comparing patients with ischemic HF with the control group (FC=1.75, p<0.01). Furthermore, we observed alterations in ATP5I target miRNA, miR-483-3p (FC=1.37, p<0.01), which can induce dysregulation in its protein level.

Conclusions: The alterations of mitochondrial bioenergetics and cristae formation related molecules could reflect damage of the cardiac mitochondria function in HF, interfering in the critical activities of the cardiomyocyte and showing a significant relationship with the ventricular function.