Cardiac ion channels in dilated cardiomyopathy: A transcriptomic analysis using RNA-Seq

Author: Block Miguel Rivera, Ana Ortega, Estefania Tarazon, Micaela Molina, Carolina Gil Cayuela, Hosp La Fe, Valencia, Spain; Juan Carlos Triviño, Sistemas Genomicos, Paterna, Spain; Maria Garcia Manzanarres, Esther Rosello, Alba Martinez, Luis Martinez Dolz, Ignacio Sanchez Lazaro, Hosp La Fe, Valencia, Spain; Francisca Lago, Hosp Clinico, Santiago, Spain; Ivan Moreno, Alfredo Perello, Hosp La Fe, Valencia, Spain; Pedro Morillas, Hosp San Juan, Alicante, Spain; Luis Almenar, Hosp La Fe, Valencia, Spain; Vicente Bertomeu, Hosp San Juan, Alicante, Spain; Pablo Garcia Pavia, Hospita Puerta de Hierro, Madrid, Spain; Jose Ramon Gonzalez Juanatey, Hosp Clinico, Santiago, Spain; Jose Montero, Antonio Salvador, Manuel Poratoles, Hosp La Fe, Valencia, Spain

Abstract:
Introduction: Dilated cardiomyopathy (DCM) is characterized by chamber enlargement and ventricular dysfunction. Disruptions in cardiac ion channels have shown to influence cardiac contraction.

Methods: We performed RNA sequencing (RNA-Seq) analysis to elucidate the transcriptomic changes of 13 DCM patients compared to a control (CNT, n = 9) group.

Results: We analysed the differential gene expression of the cardiac ion channel category, and we found a total of 34 altered genes in this pathology highly involved in the contraction-relaxation process of the cardiomyocyte, and hence in the disease progression. Moreover, we found an inverse relationship between CACNG8 with LV ejection fraction (r = -0.776, P = 0.003) and fractional shortening (r = -0.774, P = 0.003).

Conclusion: A broad set of deregulated genes have been directly implicated in setting the action potential of cardiac cells in DCM patients. These altered genes regulate the specific mechanisms intimately involved in the onset and maintenance of LV dysfunction in this cardiomyopathy. Furthermore, CACNG8, responsible for inactivating the main calcium channel, is closely associated with LV function. Our data offer new insight on the relationships between cardiac ion channels and DCM development and thus may provide the basis for further investigating new therapeutic options.
Differential Gene Expression of C-Type Natriuretic Peptide and its Related Molecules in Ischemic and Dilated Cardiomyopathy: A New Option in the Management of Heart Failure

Author Block Miguel Rivera, Estefania Tarazon, Ana Ortega, Carolina Gil Cayuela, Hosp La Fe, Valencia, Spain; Juan Carlos Triviño, Sistemas Genomicos, Paterna, Spain; Esther Rosello, Maria Garcia Manzanares, Micaela Molina, Alba Martinez, Ignacio Sanchez Lazaro, Luis Martinez Dolz, Hosp La Fe, Valencia, Spain; Francisca Lago, Hosp Clinico, Valencia, Spain; Ivan Moreno, Alfredo Perello, Hosp La Fe, Valencia, Spain; Vicente Bertomeu, Hosp San Juan, Alicante, Spain; Jose Ramon Gonzalez Juanatey, Hosp Clinico, Santiago, Spain; Jose Montero, Antonio Salvador, Manuel Portoles, Hosp La Fe, Valencia, Spain

Abstract:
Introduction: There have been few studies on C-type natriuretic peptide (CNP) in heart failure (HF). Our objective was to evaluate the potential role of the CNP gene (NPPC) and its related molecules in HF using RNA sequencing (RNA-Seq). We also studied other natriuretic peptides (NP) -related molecules in the left ventricular (LV) tissue of HF patients.

Methods: RNA-Seq analysis was performed in 32 human LV tissue samples obtained from 8 control donors (CNT) and patients with dilated (DCM, n=12) and ischemic cardiomyopathy (ICM, n=12) undergoing cardiac transplantation.

Results: Compared with CNT, we found that NPPC mRNA levels (2.28-fold) and its enzyme FURIN (-1.37-fold) were altered only in the ICM group, while its clearance receptor NPR3 was altered in DCM (1.55-fold) and ICM (1.58-fold). In contrast, we noted that NPPB (BNP gene) was upregulated and its enzyme CORIN was downregulated in both groups, while its receptor NPR1 was downregulated only in the DCM group. We validated these results using Real-Time quantitative PCR, increasing the total number of LV samples to 50. Furthermore, NPPC mRNA levels were inversely related to LV function in ICM (r=-0.641, p<0.05).

Conclusion: This study shows a differential change in the CNP gene expression in heart tissue of patients with DCM and ICM. NPPC and its endoprotease FURIN change their expression only in the ischemic LV tissue. NPPC is significantly related to decreased LV function in ICM. These results could provide new etiology-specific diagnostic and therapeutic options in HF.
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Functional Networks of Nucleocytoplasmic Transport-Related Genes are Different Depending on the Heart Failure Ischemic or Dilated Etiology: A New Diagnostic and Therapeutic Opportunity

Author Block Miguel Rivera, Micaela Molina, Ana Ortega, Estefania Tarazon, Hosp La Fe, Valencia, Spain; Juan Carlos Triviño, Sistemas Genomicos, Paterna, Spain; Carolina Gil Cayuela, Maria Garcia Manzanares, Luis Martinez Dolz, Hosp La Fe, Valencia, Spain; Francisca Lago, Hosp La Fe, Santiago, Spain; Jose Ramon Gonzalez Juanatey, Hosp Clinico, Santiago, Spain; Antonio Salvador, Manuel Portoles, Hosp La Fe, Valencia, Spain

Abstract:
Introduction: Heart failure provokes alterations in the expression of nucleocytoplasmic transport-related genes. To elucidate the nucleocytoplasmic transport-linked functional network underlying the two major causes of HF, ischemic cardiomyopathy (ICM) and dilated cardiomyopathy (DCM), we examined global transcriptome profiles of the left ventricular (LV) myocardium.

Methods: We analyzed left ventricular myocardium samples from 31 subjects (ICM, n = 10; DCM, n = 13) undergoing heart transplantation and control donors (CNT, n = 8), using RNA-Seq and GeneMANIA.

Results: Comparative profiling of ICM versus control and DCM versus control showed 1081 and 2440 differentially expressed genes, respectively (>1.29-fold; P < 0.05). GeneMANIA revealed differentially regulated functional networks specific to ICM and DCM. In comparison with CNT, differential expression was seen in 8 and 12 nucleocytoplasmic transport-related genes in ICM and DCM groups, respectively. DDX3X, KPNA2, and PTK2B were related to ICM, while SMURF2, NUP153, IP05, RANBP3, NOXA1 and RHOJ were involved in DCM pathogenesis. Furthermore, the two pathologies shared 6 altered genes: XPO1, ARL4, NFKB2, FHL3, RANBP2, and RHOJ showing an identical trend in expression in both ICM and DCM. Notably, the core of the derived functional networks composed of nucleocytoplasmic transport-related genes (XPO1, RANBP2, NUP153, IP05, KPNA2, and RANBP3) branched into several pathways with downregulated genes. Moreover, we identified genes whose expression levels are significantly correlated with left ventricular mass index and ventricular function.

Conclusions: Our study provides a clear distinction between the two pathologies at the transcriptome level and opens up new possibilities to search for appropriate specific therapeutic