Genetic regulation of myocardial fibrosis in hypertrophic cardiomyopathy

V. Patel[1], P. Syrris[2], C. Coats[1], J. Lucena[3], E. Lara-Pezzi[4], P. Garcia-Pavia[4], P.M. Elliott[1]

[1]University College of London, London, United Kingdom;

[2]University College of London, Centre for Heart Muscle Disease, Institute of Cardiovascular Science, London, United Kingdom;

[3]Institute of Legal Medicine and Forensic Sciences of Seville, Seville, Spain;

[4]University Hospital Puerta de Hierro Majadahonda, Madrid, Spain

Background: Myocardial fibrosis is a common feature of hypertrophic cardiomyopathy (HCM) but its pathophysiology has yet to be elucidated.

Purpose: In this study, we used a multiplex approach to examine the genetic regulation of pathways associated with fibrosis in patients undergoing septal myectomy.

Methods: Myocardial tissue was collected at time of surgical intervention. Control biopsy samples were obtained from the left ventricular free wall from structurally normal hearts during autopsy following non-cardiac related death. Tissue was either snap frozen in liquid nitrogen and subsequently stored at −80 degrees or collected in RNA later™ and frozen 24 hours later at −80 degrees. Total RNA was extracted from HCM tissue samples using the Qiagen RNeasy fibrous tissues mini kit and from control samples using mirVana isolation kit (Ambion), according to the manufacturer's protocol. Quantitative PCR (qPCR) was performed on the extracted RNA using a RT. Profiler™ Human finrosis PCR Array.

Results: The study cohort comprised 22 HCM samples and 5 controls. The relative regulation of genes involved in myocardial fibrosis in patients with HCM compared to controls is shown in figure 1.

In patients with HCM, there was increased expression of genes involved in collagen synthesis. A significant two-fold upregulation in type III procollagen mRNA was observed relative to controls ($p=0.013$) with a similar trend identified for type I procollagen (1.5 fold up-regulation, $p=0.081$). The gene expression of MMP3 (−1.5 fold, $p=0.029$) and MMP8 (−1.8, $p=0.002$) which are involved in collaged degradation were downregulated in the HCM group.

The gene expression of pro-fibrotic mediators TGF-β2 (4.8 fold, $p=0.008$) and CCN2 (2.9 fold, $p=0.021$) was also significantly elevated. Within the HCM group, there was a correlation between the fold regulation of TGF-β1 ($r=0.570$, $p=0.006$; $r=0.528$, $p=0.012$), TGF-β2 ($r=0.569$, $p=0.006$; $r=0.514$, $p=0.014$) and TGF-β3 ($r=0.738$, $p<0.001$; $r=0.496$, $p=0.019$) to gene regulation of type I and III procollagens respectively.

The expression of BMP-7 which has been shown to reduce myocardial fibrosis by antagonising TGF-β mediated endothelial – mesothelial transformation of fibroblasts was also down-regulated in HCM (−3.8, $p=0.015$).

Conclusions: Genetic expression of procollagen is significantly upregulated in patients with HCM relative to controls. TGF-β and CCN2 mediated signalling appear to be key mediators in promoting collagen expression.

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Figure 1. Gene expression in HCM.