Abstract: P145

Distinct alterations between transcriptomic profiles of fibrotic porcine hearts induced by cardiac remodeling, hypertrophy, or cardiotoxicity

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Topic(s):
Basic Science - Cardiac Diseases: Fibrosis

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Background: Myocardial fibrosis is characterized by a profound qualitative and quantitative alteration of the interstitial collagen network in the heart and facilitates the development of cardiac dysfunctions. Fibrosis can be caused by a variety of diseases or cardiac insults, resulting in similar symptoms of systolic and/or diastolic heart failure.

Purpose: We hypothesized that, despite similar clinical phenotypes, various causes of fibrosis would result in different alterations in the transcriptome of affected porcine hearts. We investigated fibrotic porcine myocardial samples from the remodeled remote zone of myocardial infarction (FIBRO), of animals treated with cardiotoxic drugs (doxorubicin /DOX/ and liposomal doxorubicin /MYO/), and of hypertrophic hearts (HYPI; developed by experimental artificial aortic stenosis). Subtle differences in molecular fibrotic mechanisms may significantly affect severity and reversibility of myocardial fibrosis, and delineation may be essential for developing individual disease-specific treatment strategies.

Methods: The transcriptomes of these samples were analyzed by next generation sequencing (NGS). For RNA-sequencing, strand specific libraries of 500 ng total RNA for paired end sequencing were prepared and mapped to the Sus scrofa genome. We analysed the data using moderated statistics, principal component analyses (PCA), and signaling pathway impact analyses (SPIA), and constructed heat maps for result presentation.

Results: Myocardial infarction, hypertrophy and cardiotoxicity resulted in predominantly systolic, diastolic and combined systolic/diastolic heart failure, respectively. PCA indicated several common similarities of myocardial fibrosis on the molecular level that are independent of the trigger, highlighting shared mechanisms. However, cardiac remodelling after AMI and cardiac hypertrophy were characterized by greater overlaps, while the transcriptome of hearts treated with the cardiotoxic agents DOX and MYO differed more strongly (Figure 1). These data indicate a varying mechanism and/or a distinct stage of fibrosis. In particular, the p53 and MAPK pathways, as well as genes involved in DNA damage and oxidative stress were more strongly induced in FIBRO and HYPI compared to DOX and MYO. Collagens and collagen processing enzymes were moderately upregulated in all groups.

Conclusions: Transcriptomic analyses revealed different mechanisms of myocardial fibrosis upon cardiotoxic drug treatment compared to cardiac remodeling after AMI or hypertrophy. The results highlighted common characteristics of fibrosis, and might facilitate precision medicine for treatment of cardiac fibrosis associated with a distinct mechanism.
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