The central role of FAP dysregulation and cardiac fibroblast activation in heart failure patients

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**Funding Acknowledgements:** Type of funding sources: Public grant(s) – National budget only. Main funding source(s): National Institute of Health “Fondo de Investigaciones Sanitarias del Instituto de Salud Carlos III” co-funded by European Union

**Background:** Excessive cardiac fibrosis is an important factor in the progression of heart failure (HF). Fibroblast activation protein (FAP) is a type-II transmembrane serine protease expressed almost exclusively to pathological conditions, being robustly expressed by activated fibroblasts of scarring tissue. Previously different studies have reported alterations of fibrillar and non-fibrillar collagen expression in heart failure linked to fibrosis. However, despite its relevance, the role of FAP in cardiac fibrosis is not fully elucidated.

**Purpose:** We hypothesized that FAP expression level was altered in heart tissue of heart failure (HF) patients. Furthermore, given the central role of FAP in fibroblast activation, we also studied the expression levels of profibrotic genes and microRNAs associated with fibrosis process, and the relationships between FAP and these altered molecules.

**Methods:** We analysed transcriptome-level differences in genes involved in fibrosis between HF (n=26) and controls (n=10) in human hearts by RNA-sequencing, and a total of 50 samples were also analysed (HF, n=42; and controls, n=8) by ncRNA sequencing to study the expressions of microRNAs.

**Results:** We found an overexpression of FAP gene (FC=1.98, \(p<0.05\)), and observed that the expression of other molecules, whose activity is also relevant in the activation of fibroblasts, were overexpressed, such as POSTN (FC=3.05, \(p<0.05\)), THY1 (FC=4.33, \(p<0.001\)) and VIM (FC=1.33, \(p<0.05\)). On the other hand, we found several fibrosis-associated genes whose expression was also altered in HF patients. Specifically, THBS4 (FC=3.03, \(p<0.001\)), AEBP1 (FC=1.9, \(p<0.01\)), ELN (FC=2.1, \(p<0.01\)), COL1A1 (FC=1.72, \(p<0.01\)), COL1A2 (FC=1.97, \(p<0.01\)), COL3A1 (FC=2.1, \(p<0.01\)), and MFAP5 (FC=2.34, \(p<0.001\)). Interestingly, most of these overexpressed genes showed a correlation (\(p<0.05\)) with FAP mRNA expression. We highlight the positive correlations between COL1A2 (\(r=0.643, \ p<0.001\)) and COL3A1 (\(r=0.651, \ p<0.001\)) with FAP expression. Furthermore, we observed dysregulation in several microRNAs related with an antifibrotic or profibrotic function. Specifically, we showed underexpression of a microRNA with antifibrotic function, miR-29c-3p (FC=−1.2, \(p<0.01\)), which has COL1A1, COL1A2, COL3A1 as target genes.

**Conclusions:** In this study, we showed significant alterations in FAP and other specific genes involved in fibroblast activation in HF. We also identified correlations between FAP and key fibrosis markers, giving FAP a central role in cardiac fibrosis process. Fibroblast activation molecules could serve as a potential therapeutic target for the prevention of cardiac fibrosis and cardiac diseases.