Cardiac rejection diagnosis using serum mRNA encoding proteins related to fibrotic process

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Background: Finding a standardized, non-invasive method of diagnosis of rejection is still a challenge in the field of heart transplantation. A novel alternative for allograft rejection diagnosis is the detection of biomarkers present in serum. Cardiac fibrosis appears to be present in patients who are experiencing cardiac allograft rejection. Thus, the process of fibrosis could offer a wide range of candidate molecules to explore as possible biomarkers.

Purpose: This study aimed to determine the expression of fibrosis-related coding mRNAs in serum of patient with cardiac rejection and evaluate the diagnostic capacity as potential biomarkers for the non-invasive detection of mild (grade 1R) and moderate/severe (grade ≥2R) cellular rejection.

Methods: We included consecutive serum samples from transplant recipients undergoing routine endomyocardial biopsies. Non-coding RNA sequencing analysis (Illumina HiSeq 2500) was performed on 40 samples, 28 diagnosed with acute cellular rejection (Grade 1R, n=16; and Grade ≥2R, n=12) and 12 samples without cardiac rejection.

Results: We detected 228 mRNA related to fibrosis in serum, which 38 presented differential expression in patients with cardiac rejection of Grade ≥2R. We obtained 16 molecules that showed excellent diagnostic ability in moderate-severe rejection (AUC > 0.800). We highlight RELB that was able to detect mild rejection (AUC=0.734, p<0.05). We stand out TNS1 (AUC=0.972), COL4A2 (AUC=0.958) and JAK1 (AUC=0.944), p<0.0001, for its relevant diagnostic capacity of acute cellular rejection.

Conclusions: We propose serum mRNA levels of genes encoding fibrosis related proteins as potential biomarkers of cardiac rejection. We highlight the role of RELB due to its excellent diagnostic capacity for acute cellular rejection correlating with the severity of the episode.