Circulating sphingosine-1-phosphate as a non-invasive biomarker of heart transplant rejection

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Topic(s):
Heart Transplantation

Citation:

Funding Acknowledgements:
National Institute of Health [PI16/01627, PI17/01925, PI17/01232], Consorcio Centro de Investigación Biomédica en Red, M.P. [CB16/11/00261], and FEDER

Background: Nowadays the detection of heart transplant rejection by non-invasive methods represents a challenge. Changes in sarcoplasmic reticulum calcium ATPase 2a (SERCA2a) serum levels occur in cardiac allograft rejection, demonstrating a good potential for detection. Although many SERCA2a-related genes and proteins involved in the regulation of myocardial Ca2+ fluxes have been explored, its related metabolites remain poorly studied.

Purpose: Our objective was to identify circulating SERCA2a-related metabolites altered in cardiac allograft rejection and to determine whether these could serve as non-invasive biomarkers.

Methods: Sixty plasma samples from adult heart transplant recipients (15 without allograft rejection and 45 with diagnosis of biopsy allograft rejection: 15 Grade 1R, 15 Grade 2R, 15 Grade 3R) were included in a metabolomic analysis.

Results: We identified thirteen differential metabolites and focused on sphingosine-1- phosphate (S1P), metabolite closely related with SERCA. S1P plasma levels were increased in patients with cardiac rejection (p<0.0001). A receiver-operating characteristic analysis showed that S1P strongly discriminated between patients with and without rejection: non-rejection grafts vs. all rejecting grafts (AUC=0.911, p<0.0001), non-rejection grafts vs. Grade 1R (AUC=0.819, p<0.01), non-rejection grafts vs. Grade 2R (AUC=0.911, p<0.0001), non-rejection grafts vs. Grade 3R (AUC=0.996, p<0.0001).

Conclusions: This metabolomic study reveals that circulating S1P determination could be a novel approach to detect cardiac rejection, even at lower grades, showing a robust capability for detection that improve gradually with the severity of rejection. The alteration of this SERCA-related metabolite demonstrates once again the implication of calcium regulation on the pathophysiology of transplant rejection.