Effect of Donor Simvastatin Treatment on Gene Expression Profiles in Human Cardiac Allografts During Ischemia-Reperfusion Injury

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Purpose

Numerous studies have shown that statin therapy initiated early after heart transplantation has beneficial effects on the development of cardiac allograft vasculopathy. Recently, we were able to show in a randomized clinical trial that simvastatin treatment of brain-dead donors conditions the heart transplant to withstand ischemia-reperfusion injury and to reduce the need for rejection treatments early after transplantation. In this study, we analyzed myocardial gene expression profiles in cardiac allografts after donor simvastatin treatment.

Methods

84 heart transplant donors received 80 mg of simvastatin via nasogastric tube (n=42), or no treatment (n=42) in a prospective, double-blinded randomized controlled trial. Transmural Tru-Cut biopsies were taken from the apex of left ventricle of the donor heart immediately before reperfusion and 1 hour after reperfusion. 20 heart biopsies from donors without treatment and 20 heart biopsies from donors with simvastatin treatment will be analyzed with RNA sequencing.

Results

The preliminary analysis of RNA sequencing data from myocardial biopsies revealed altogether 137 significantly differentially expressed genes in all pairwise comparisons. The overall biological functions of these genes were related to gene ontology terms such as response to toxic substance, leukocyte migration, neutrophil mediated immunity, response to lipopolysaccharide, and response to oxidative stress. At the KEGG pathway level, our results indicated alterations in IL-17, TNF, MAPK and the AGE-RAGE signaling pathways.

Conclusion

We have shown in previous studies that donor simvastatin treatment induces protective effects against IRI in heart transplant recipients. In this study, we were able to detect significantly differentially expressed genes related to effects of simvastatin treatment. In order to single out genes that show beneficial effects of simvastatin treatment, further analysis will be conducted by exploring gene expression changes in specific biological functional categories, such as interleukin signaling and neutrophil degranulation. The complete analysis will be presented at the ISHLT 2019 congress.