Reduced RNA editing in the failing human heart mediates alternative circular RNA splicing

K. Kokot1, J. Kneuer1, D. John2, M. Moebius-Winkler1, M. Mueller3, M. Andritschke1, S. Gaul1, B. Sheikh4, J. Haas5, H. Thiele6, F. Leuschner5, S. Dimmel2, B. Meder5, U. Laufs1, J.N. Boeckel1

1Leipzig University Hospital, Clinic and Polyclinic for Cardiology, Leipzig, Germany; 2Goethe University Hospital, Institute for Cardiovascular Regeneration, Frankfurt, Germany; 3Herz- und Diabeteszentrum NRW, Ruhr-Universitaet Bochum, Bad Oeynhausen, Germany; 4Helmholtz Institute for Metabolic, Obesity and Vascular Research (HI-MAG), Leipzig, Germany; 5University of Heidelberg, Department of Internal Medicine III, Heidelberg, Germany; 6Heart Center at University of Leipzig, Leipzig, Germany

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Background and purpose: Post-transcriptional RNA editing is an important mechanism in the development of human diseases. RNA editing can affect RNA stability and alternative splicing. The aim of our study was to characterize RNA editing and its impact on alternative RNA splicing in the healthy and failing human heart.

Methods and results: Human heart samples of heart failure (HF) patients (n=20) and controls (n=10) were analyzed using RNA sequencing with subsequent analysis of RNA editing. We identified adenosine-to-inosine (A-to-I) editing as the major form of RNA editing in human hearts, being reduced in HF patients. Consistently, we found the editing enzyme ADAR2 reduced in HF patients. A-to-I RNA editing predominantly occurred in intronic regions of protein-coding genes, specifically in repetitive, primate-specific Alu elements which can affect RNA splicing. Indeed, we found 173 circular RNAs (circRNAs) regulated by alternative mRNA splicing in the failing heart.

Loss of ADAR2 led to reduced RNA editing concomitant with an increase of circRNA, while overexpression reduced circRNA expression and enhanced RNA editing.

Conclusion: A-to-I editing is the major type of RNA editing in the human heart, being reduced in HF. We demonstrate a primate-specific alternative RNA splicing mechanism mediated by RNA editing in human hearts. The findings may be relevant to diseases with reduced RNA editing such as cancer, neurological and cardiac diseases.