Decrease of RNA editing in the failing heart leads to induction of circRNAs

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Background and purpose: Adenosine-to-Inosine (A-to-I) RNA editing is a post-transcriptional modification process that affects the secondary structure of RNAs. Changes in RNA editing have been associated with human diseases. We therefore aimed to analyze editing in the healthy and failing human heart.

Methods and results: Transcriptome sequencing of human heart samples of heart failure (HF) patients (n=20) and controls (n=10) revealed A-to-I editing as the major type of editing (>80%). In HF patients, RNA editing was reduced, which was primarily attributable to Alu elements in introns of protein-coding genes. We identified 166 upregulated circRNAs in HF, with the majority showing reduced RNA editing in their parental host gene (88.3%). CircRNA expression did not correlate with their corresponding host gene (R=0.07, P<0.05), suggesting that an alternative splicing mechanism gives rise to the elevated circRNA levels in HF. The RNA editing enzyme ADAR2, which binds to RNA regions that are edited from adenosine to inosine, was decreased in failing human hearts (−68.2%). In vitro, reduction of ADAR2 increased circRNA levels suggesting a causal effect of reduced ADAR2 levels on increased circRNAs in the failing human heart. To gain mechanistic insight, we examined the formation of circRNAs on one exemplary candidate. AKAP13 was among the top edited mRNAs in the human heart and gave rise to a circular transcript, which was elevated in HF. ADAR2 reduced the formation of double-stranded structures in AKAP13 pre-mRNA, thereby reducing the stability of Alu elements and the circularization of the resulting circRNA. Overexpression of circAKAP13 impaired the sarcomere regularity of human induced pluripotent stem cell-derived cardiomyocytes (−31.0%).

Conclusion: Our study shows that ADAR2 mediates A-to-I RNA editing in the human heart. We describe an alternative splicing mechanism of circRNAs in the human heart. In the healthy human heart, A-to-I RNA editing represses the formation of dsRNA structures of Alu elements thereby favoring linear mRNA splicing. Our results contribute to a better mechanistic understanding into the human-specific regulation of circRNA formation and are relevant to diseases with reduced RNA editing and increased circRNA levels.