Role of adenosine-to-inosine RNA editing in human atherosclerosis

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Topic(s):
Atherosclerosis

Citation:
Cardiovascular Research Supplements (2016) 111 (S1), S106

Background: Adenosine to inosine (A-to-I) RNA editing is catalysed by ADARs (adenosine deaminases acting on RNA) and is an important posttranscriptional regulator of RNA metabolism. Although RNA editing is essential for life, its role in cardiovascular disease is unknown.

Methods and Results: RNA-sequencing (RNA-seq) of human endothelial cells revealed that ADAR1 is the main RNA editor in HUVECs. The vast majority of editing events are detected in Alu regions due to their ability to form double-stranded structures, a prerequisite for RNA editing. A-to-I RNA editing of the primate-specific Alu elements is observed in 25% of poly(A)+ transcripts and in 44% of ribosomal RNA-depleted transcripts. Cathepsin S (CTSS), an extracellular matrix degrading enzyme, has 3 Alu elements in its 3′-untranslated region and is among the most extensively edited mRNAs. Interestingly, ADAR1 silencing downregulates CTSS mRNA expression, whereas ADAR1 overexpression results in an increase of both CTSS RNA editing rate and CTSS mRNA expression. Mechanistically, RNA immunoprecipitation (RIP), luciferase reporter and iCLIP assays showed that A-to-I RNA editing of the Alu elements in the 3′UTR of CTSS mRNA regulates the recruitment of the stabilizing RNA-binding protein HuR to CTSS 3′UTR and, thus, controls CTSS mRNA stability and expression. CTSS Alu RNA editing is increased under hypoxic or pro-inflammatory conditions in vitro, as well as in patients with coronary or carotid atherosclerotic vascular disease. Further, the extent of CTSS Alu RNA editing rate correlated with various markers of subclinical atherosclerosis including intima-media thickness and number of atherosclerotic plaques. Importantly, ADAR1 and the extent of CTSS RNA editing correlated with CTSS expression levels in patients’ samples from 6 non-overlapping cohorts of patients with inflammatory vascular diseases (total n=366), including peripheral blood mononuclear cells, carotid atherosclerotic plaques and thoracic aortic aneurysms.

Conclusion: This study shows for the first time that Alu A-to-I RNA editing is a critical modulator of inflammatory gene expression in all stages of atherosclerotic vascular disease development.