More on noncoding RNAs: genetic associations, regulation of expression and in vitro studies show an independent role for small nucleolar RNAs in cardiovascular disease

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Topic(s):
Basic Science - Vascular Biology and Physiology: Genetics, Epigenetics, ncRNA

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Background/Introduction. We have shown that 14q32 microRNAs are highly involved in vascular remodelling and cardiovascular disease. Inhibition of 14q32 microRNAs led to increases in post-ischemic blood flow recovery and decreased atherosclerotic lesion formation, as well as increased plaque stability. Besides microRNAs however, the 14q32 locus also encodes genes for two other types of noncoding RNAs, namely 3 long noncoding RNAs (IncRNAs) and 41 small nucleolar RNAs (snoRNAs). The 14q32 IncRNAs are believed to function as regulators of the region’s imprinted expression, but the function of the 41 snoRNAs is still unknown. All 14q32 snoRNAs are so-called ‘orphan’ snoRNAs of the C/D box subtype

Purpose. We aimed to gather evidence for an independent role for 14q32 snoRNAs in cardiovascular disease.

Methods & Results. We analyzed data of a Genome Wide Association Scan (GWAS) in 5244 participants of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). Single Nucleotide Polymorphisms (SNPs) in the snoRNA-cluster were significantly associated with various cardiovascular endpoints. These snoRNA-cluster SNPs were not linked to SNPs in the microRNA-cluster or in MEG3, indicating that snoRNAs modify the risk of cardiovascular disease independently.

We looked at expression of 14q32 snoRNAs throughout the human vasculature in a biobank of 95 different vascular tissue samples, collected during general surgery. Expression profiles of the 14q32 snoRNAs appeared highly vessel-specific. When we compared expression levels of 14q32 snoRNAs in human venae saphenae magnae (VSM) with those in failed VSM-coronary artery bypass grafts, we found that 14q32 snoRNAs were upregulated. Striking were SNORD113.2 (17.3-fold upregulation) and SNORD113.9 (19.8-fold). SNORD113.2 was also upregulated twofold in plasma samples drawn from patients with ST-Elevation Myocardial Infarction (STEMI) directly after hospitalization and fourfold at days 4 and 7, compared to 30 days after start of treatment.

In vitro studies show that the 14q32 snoRNAs bind predominantly to methyl-transferase Fibrillarin, indicating that they act through canonical mechanisms, but on non-canonical RNA targets. Inhibition of the snoRNAs led to increased scratch-wound healing, whereas snoRNA upregulation has the opposite effect.

Conclusions. 14q32 snoRNAs appear to play an independent role in cardiovascular pathology. 14q32 snoRNAs are specifically regulated throughout the human vasculature and their expression is upregulated during cardiovascular disease. Our data demonstrate that snoRNAs merit increased effort and attention in future basic
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