Novel miRNA and Protein Therapeutic Targets to Reduce Atherosclerosis

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As microRNAs (miRs) regulate multiple pathways, Dr. Hussain's lab hypothesized that there are microRNAs in nature that simultaneously regulate high plasma LDL-cholesterol (LDL-c) and low plasma HDL-cholesterol (HDL-c) levels in reciprocal manner. To test this, they screened a microRNA library and identified a primate-specific miR, miR-541-3p, that simultaneously reduces apoB and increases apoA1 secretion in hepatoma cells.

Mechanistic studies showed that miR-541-3p diminishes apoB secretion by reducing the expression of ZNF101 transcription factor that is an enhancer of APOB gene expression. They also discovered that miR-541-3p increases APOA1 gene expression by reducing the expression of CASZ1 transcription factor that represses APOA1 gene. Moreover, they provided evidence that knockdown of Zfp961 (a mouse orthologue of human ZNF101) reduces plasma apoB and LDL-c levels in mice. In addition, we showed that knockdown of Casz1 in mice increases apoA1 and HDL-c levels. These augmentations were associated with increases in cholesterol efflux capacity.

Simultaneous knockdown of both Zfp961 and Casz1 had additive effect resulting in reductions in LDL-c and increases in HDL-c levels. The group also studied the effects of knockdown of Zfp961 and Casz1 on atherosclerosis in mice and found that individual and combined knockdown of Zfp961 and Casz1 significantly reduces atherosclerosis.

Background

High plasma LDL-cholesterol (LDL-c) and low plasma HDL-cholesterol (HDL-c) levels are risk factors for heart disease. Available drugs separately modulate LDL and HDL levels. We are unaware of any drug that simultaneously regulates both plasma LDL-c and HDL-c levels.

Applications

- MicroRNA-541-3p overexpression can be used to lower plasma apoB-containing atherogenic lipoproteins, such as LDL, and to increase anti-atherogenic HDL in primates. These changes will have beneficial effects on plasma lipid profile and reduce the risk for atherosclerosis.
- Inhibition of ZNF101 can be used to reduce LDL-c and atherosclerosis.
- Inhibition of CASZ1 can be used to increase HDL-c and reduce atherosclerosis.

Advantages

- Unlike any existing drug, the novel microRNA described here can modulate both plasma LDL-c and HDL-c levels.
- Knockdowns of the target genes showed an additive effect that can be used to better control cholesterol plasma levels.

IP Status

Provisional patent application pending