MedicalXpress

Four microRNAs identified as playing key roles in cholesterol, lipid metabolism

October 26 2015

Four tiny segments of RNA appear to play critical roles in controlling cholesterol and triglyceride metabolism. In their report receiving advance online publication in *Nature Medicine*, a Massachusetts General Hospital (MGH)-based research team describes finding how these microRNAs could reduce the expression of proteins playing key roles in the generation of beneficial HDL cholesterol, the disposal of artery-clogging LDL cholesterol, control of triglyceride levels and other risk factors of cardiovascular disease.

"While we and others have recently identified microRNAs that control cholesterol and fat metabolism and trafficking, no studies to date have systematically looked at all non-coding factors - such as microRNAs - in genetic studies of human diseases and other traits," says Anders Näär, PhD, of the MGH Center for Cancer Research, corresponding author of the current study. "Using human genetic data from almost 190,000 individuals, we have linked 69 microRNAs to increased genetic risk for abnormal cholesterol and triglyceride levels, and showed that four of these act to control proteins we know are involved in those metabolic activities."

Less than 2 percent of human DNA represents genes that code for the production of proteins. While it was originally hypothesized that the other 98 percent had no function - leading to the term "junk DNA" - it has now become apparent that these DNA sequences play essential roles in determining how, when and where protein-coding DNA is expressed. One such control mechanism is through single-stranded microRNAs,

which block the expression of protein-coding genes by binding to messenger RNAs and preventing their translation into protein. In previous studies, Näär and his colleagues found that a microRNA called miR-33 suppresses production of beneficial HDL cholesterol and that antisense blocking of miR-33 increased HDL levels in an animal model.

The current study began with analysis of genome-wide association studies involving more than 188,000 individuals, which identified 69 microRNAs located near gene variants previously associated with lipid abnormalities. Using a tool that predicts the targets of microRNAs based on matches between their nucleotide sequences and those of protein-coding genes and a database of identified gene functions, the researchers arrived on four microRNAs that appear to control genes involved in cholesterol and triglyceride levels and in other metabolic functions, such as glucose metabolism. Two of these - miR-128-1 and miR-148a - were found to control the expression of proteins essential to the regulation of cholesterol/lipid levels in cells and in animal models; miR-128-1 was also found to regulate fatty liver deposits, insulin signaling and maintenance of blood sugar levels.

"We are following up these findings with studies to address whether antisense blocking of these microRNAs could decrease atherosclerosis, cardiovascular disease and inflammatory fatty liver diseases in animals," says Näär, a professor of Cell Biology at Harvard Medical School and an MGH research scholar. "We hope these findings will lead to new, more effective ways of treating or even preventing cardiovascular disease and other metabolic disorders."

More information: Genome-wide identification of microRNAs regulating cholesterol and triglyceride homeostasis, DOI: 10.1038/nm.3980

Provided by Massachusetts General Hospital