Identification of CHROME as a Competing Endogenous RNA that Regulates Cholesterol Homeostasis

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The discovery of microRNAs (miRNA) targeting gene pathways involved in HDL and LDL metabolism illuminated the potent role of non-coding RNAs in the regulation of cholesterol homeostasis. Long non-coding RNAs (lncRNA) have also been identified as crucial regulators of gene expression; however, few have been fully characterized. Here we report a novel human lncRNA, CHROME (Cholesterol Homeostasis Regulator Of MicroRNA Expression), that functions as a competing endogenous RNA to regulate cellular cholesterol homeostasis. We show that CHROME has 7 broadly expressed variants that are transcriptionally regulated by the cholesterol-sensing liver X receptors. Computational analyses revealed that CHROME harbors binding sites for multiple (11) miRNAs involved in cholesterol homeostasis, including miR-27b and miR-33a/b, which function as hubs controlling the expression of genes involved in cholesterol efflux and HDL metabolism. Using CHROME knock-down and overexpression, we demonstrate that CHROME acts as a 'miRNA sponge' that sequesters these miRNAs, limiting their ability to repress target genes, including ABCA1, OSBPL6 and ANGPTL3. Consistent with this, we show that overexpression of CHROME increases cholesterol efflux, whereas its silencing reduces cholesterol efflux from primary human hepatocytes and macrophages. As hepatic cholesterol efflux via ABCA1 plays a central role in HDL biogenesis, we investigated the relationship of CHROME to its miRNA targets and plasma levels of HDL cholesterol in liver samples from a cohort of 200 healthy individuals. This analysis showed that CHROME is inversely correlated with miR-27b and miR-33a/b levels, and positively correlated with levels of their target genes and plasma HDL cholesterol. Collectively, these findings identify CHROME as a key regulatory component of the non-coding RNA circuitry that controls cellular cholesterol efflux and plasma HDL levels in humans.

Disclosure Block:
C. van Solingen: None. **E.J. Hennessy:** None. **M. Ouimet:** None. **K. Rinehold:** None. **M. Hussein:** None. **M.J. Garbedian:** None. **D. Teupser:** None. **L.M. Holdt:** None. **K.J. Moore:** None.