Tiny antisense molecules increase 'good cholesterol' levels in obese primates

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A strategy developed by Massachusetts General Hospital (MGH)-based investigators to increase levels of beneficial high-density lipoprotein (HDL) has been shown for the first time to be effective in non-human primates. The approach uses tiny antisense sequences to block the action of microRNAs that would otherwise inhibit a protein required for generation of HDL, the "good cholesterol" that helps remove harmful lipids from the body. The report appears in the November 20 *Science Translational Medicine*.

"We have found that targeting both members of the miR-33 microRNA family with a tiny, 8-nucleotide anti-microRNA can increase HDL levels by almost 40 percent," says Anders Näär, PhD, of the MGH Center for Cancer Research, who led the study. "This sets the stage for new therapeutic strategies to treat cardiovascular disease in humans and provides a template for targeting other disease-associated microRNA families."

Major regulators of gene expression, microRNAs are segments made up of 20- to 24-nucleotides that bind to complementary strands of messenger RNA, blocking their translation into proteins. A 2010 study led by Näär identified two related microRNAs – miR-33a and miR-33b – that inhibit a protein called ABCA1, which is essential for both the generation of HDL and for the transport of lipids to the liver. Treatment with miR-33-blocking antisense molecules was able to increase HDL levels in mice, but rodents have only one form of the microRNA. If the two versions of miR-33 carried by humans and other primates have

redundant effects – that is if they both act to inhibit ABCA1 – blocking only a single version would be ineffective.

An earlier study by Näär's team showed that use of an 8-nucleotide anti-microRNA targeting only the "seed" sequence that is shared among related microRNAs could inhibit all members of a family. Before investigating the use of such an approach in humans, the researchers tested its feasibility in 20 obese and insulin resistant African green monkeys. The animals were divided into four groups, three of which received weekly injections of anti-microRNAs targeting either miR-33a, miR-33b or the seed sequence shared by both versions. The fourth group received inert control injections.

After nearly four months, HDL levels in animals receiving anti-microRNA targeting the seed sequence shared between both miR-33a and miR-33b had increased by almost 40 percent. For comparison, current therapies designed to increase HDL levels produce increases of 25 percent or less. Examination of the animals' livers showed increased expression of ABCA1 and other proteins known to be inhibited by miR-33 family members. Animals receiving anti-microRNA that targeted only miR-33a or miR-33b showed no increase in HDL levels, confirming that the two related microRNAs do have redundant effects. No adverse effects were seen in any of the animals.

"In addition to supporting this strategy for the treatment of cardiovascular disease, our study shows the importance of targeting multiple microRNA family members that may act redundantly to achieve therapeutic efficacy," says Näär, who is a professor of Cell Biology at Harvard Medical School. "We will be conducting required toxicology studies in rodents and non-human primates prior to a human Phase I safety trial."

More information: "Pharmacological Inhibition of a microRNA

Family in Nonhuman Primates by a Seed-Targeting 8-Mer AntimiR," by V. Rottiers et al. *Science Translational Medicine*, 2013.

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