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*MicroRNAs from plants accumulate in mammalian blood and tissues, where they can regulate gene expression.

MicroRNAs from common plant crops such as rice and cabbage can be found in the blood and tissues of humans and other plant-eating mammals, according to a study published today in Cell Research. One microRNA in particular, MIR168a, which is highly enriched in rice, was found to inhibit a protein that helps removes low-density lipoprotein (LDL) from the blood, suggesting that microRNAs can influence gene expression across kingdoms.

"This is a very exciting piece of work that suggests that the food we eat may directly regulate gene expression in our bodies," said Clay Marsh, Director of the Center for Personalized Health Care at the Ohio State University College of Medicine who researches microRNA expression in human blood but who was not involved in the study.

MicroRNAs are, as the name implies, very short RNA sequences (approximately 22 nucleotides in length) discovered in the early 1990s. They are known to modulate gene expression by binding to mRNA, often resulting in inhibition. With the recent discovery that microRNAs circulate the blood by hitching a ride in small membrane-encased particles known as microvesicles (see our July 2011 feature on microvesicles, "Exosome Explosion"), there has been a surge of interest in microRNAs as a novel class of biomarkers for a variety of diseases.

Chen-Yu Zhang, a molecular biologist at Nanjing University in China, was studying the role of circulating microRNAs in health and disease when he discovered that microRNAs are present in other bodily fluids such as milk. This gave him the "crazy idea" that exogenous microRNAs, such as those ingested through the consumption of milk, could also be found circulating in the serum of mammals, he recalled.

To test his hypothesis, Zhang and his team of researchers sequenced the blood microRNAs

of 31 healthy Chinese subjects and searched for the presence of plant microRNAs. Because plant microRNAs are structurally different from those of mammals, they react differently to oxidizing agents, and the researchers were able to differentiate the two by treating them with sodium periodate, which oxidizes mammal but not plant microRNAs.

To their surprise, they found about 40 types of plant microRNAs circulating in the subjects' blood—some of which were found in concentrations that were comparable to major endogenous human microRNAs.

The plant microRNAs with the highest concentrations were MIR156a and MIR168a, both of which are known to be enriched in rice and cruciferous vegetables such as cauliflower, cabbage, and broccoli. Furthermore, the researchers detected the two microRNAs in the blood, lungs, small intestine, and livers of mice, in variable concentrations that significantly increased after the mice were fed raw rice (although cooked rice was also shown to contain intact MIR168a).

Next, the researchers scoured sequence databases for putative target genes of MIR156a and MIR168a and found that MIR168a shared sequence complementarity with approximately 50 mammalian genes. The most highly conserved of these sequences across the animal kingdom was the exon 4 of the low-density lipoprotein receptor adapter protein 1 gene (LDLRAP1).

LDLRAP1 is highly expressed in the liver, where it interacts with the low-density lipoprotein receptor to help remove low-density lipoprotein (LDL), aka "bad" cholesterol, from the blood.

The researchers hypothesized that MIR168a could be taken up by the epithelial cells lining the gastrointestinal tract, packaged into microvesicles, and secreted into the blood stream, where they can make their way to target organs. Once in the liver, MIR168a binds to LDLRAP1 mRNA, reducing the protein levels and ultimately impairing the removal of LDL from the blood.

To test this hypothesis in vitro, the researchers transfected synthetic MIR168a into a human epithelial cell line and collected the secreted microvesicles. When they added these microvesicles to a liver cell line called HepG2, they found that while it did not change the levels of LDLRAP1 mRNA, it did decrease the levels of the actual LDLRAP1 protein.

Likewise, the LDLRAP1 protein level decreased in the livers of live mice 3 to 7 days after eating fresh rice or being injected with synthetic MIR168a—significantly increasing LDL in the blood. When the researchers injected the mice with an RNA sequence that bound to and neutralized MIR168a, the protein and LDL levels returned to normal.

"This microRNA inhibits this protein and increased the plasma LDL levels," Zhang said. With higher levels of circulating cholesterol, "it can possibly increase the risk of metabolic

syndrome," he added. But more importantly, this research points to a "new therapeutic strategy for the treatment of diseases," based on the enhancement or inhibition of exogenous microRNAs.

Although the team has still a long way to go in elucidating the mechanisms by which plant microRNAs can regulate gene expression in humans, these initial results promise to increase the understanding of how specific ingredients in food can mediate health and disease, Marsh said.

Indeed, Zhang suspects that this is just one example of many. With time, "I'm confident other people will find more exogenous plant microRNAs that can pass through the GI tract and also have effects on the host physiology," Zhang said.

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Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA

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Our previous studies have demonstrated that stable microRNAs (miRNAs) in mammalian serum and plasma are actively secreted from tissues and cells and can serve as a novel class of biomarkers for diseases, and act as signaling molecules in intercellular communication. Here, we report the surprising finding that exogenous plant miRNAs are present in the sera and tissues of various animals and that these exogenous plant miRNAs are primarily acquired orally, through food intake. MIR168a is abundant in rice and is one of the most highly enriched exogenous plant miRNAs in the sera of Chinese subjects. Functional studies *in vitro* and *in vivo* demonstrated that MIR168a could bind to the human/mouse low-density lipoprotein receptor adapter protein 1 (LDLRAP1) mRNA, inhibit LDLRAP1 expression in liver, and consequently decrease LDL removal from mouse plasma. These findings demonstrate that exogenous plant miRNAs in food can regulate the expression of target genes in mammals.

Keywords: microRNA; MIR168a; LDLRAP1; low-density lipoprotein; microvesicle; cross-kingdom