Missing MicroRNAs may be significant in resisting obesity

September 6 2012

(Medical Xpress)—Tiny strands of RNA affect how our cells burn fat and sugar—a finding that gives biologists a place to start in the quest for therapies to treat obesity and related health problems, said scientists at Virginia Tech and the University of Texas Southwestern Medical Center at Dallas.

Mice on high fat diets are resistant to obesity when two mini-molecules called microRNAS are missing from their genetic makeup, according to a study this week in the Proceedings of the National Academy of Sciences.

The discovery suggests that treatments targeting these two specific microRNAs may help stem the nation's obesity epidemic. More than one-third of adults in the United States and about 17 percent of the nation's children are obese, increasing their risk for type 2 diabetes, heart disease , stroke, liver disease, and some cancers, according to the National Institutes of Health.

"Scientists know the best health solution for obesity involves eating less and exercising more," said Matthew W. Hulver, Ph.D., an associate professor with the Department of Human Nutrition, Foods, and Exercise in the College of Agriculture and Life Sciences at Virginia Tech. "But in cases when people can't or won't exercise, if we can identify what is contributing to the regulation of our metabolic circuits, we can target it with a drug or pharmacologic solution."

Once considered to be little more than scrap DNA, scientists now know microRNAs have an important role in regulating how genes shape human health and behavior. They have been linked to heart disease, diabetes, hepatitis C, leukemia, lymphoma, and breast cancer.

Although microRNAs previously have been linked to obesity, the new findings are the first to establish a connection between microRNAs and cellular metabolism.

MicroRNA biologists at UT Southwestern Medical Center modified mice to be genetically unable to produce microRNA-378 and its cousin miR-378*, resulting in relatively trim animals with metabolisms that quickly convert cellular food into energy.

"We did not know the function of this pair of microRNAs, but were intrigued because they arose from a gene connected with metabolism, and they are expressed in a variety of tissues, such as muscle, fat, and liver," said Eric N. Olson, Ph.D., a professor and the chairman of molecular biology at UT Southwestern and senior author of the study. "When we modified mice so that they were missing these microRNAs, it permitted their cells to burn more energy and have greater obesity resistance than those of their untreated litter mates. This pair of microRNAs seems to function as key regulators of metabolism, suggesting that a drug designed to inhibit them would have a positive effect against obesity."

Olson's lab has examined the results of microRNA changes on various disease states, including heart disease and amyotrophic lateral sclerosis—also known as Lou Gehrig's disease.

In the current study, Virginia Tech scientists, including Madlyn I. Frisard, Ph.D., an assistant professor of Human Nutrition, Foods, and Exercise, and Hulver, director of the Metabolic Phenotyping Core at

Virginia Tech, isolated mitochondria—the furnaces within cells that turn fat and other fuel into energy—from liver and skeletal muscle.

When they measured mitochondrial use of fatty acids, they found that a chemical process that releases energy called oxidation was increased, supporting the discovery that loss of the microRNAs results in increased energy expenditure and resistance to obesity, even with a high-fat diet.

"The take home message is microRNAs potentially are a magic bullet against obesity. This is a surprising finding that sheds light on how the body processes food and, in this case, how mice are able to withstand a fat-laden diet and stay skinny," said Gerald W. Dorn II, M.D., the Philip and Sima K. Needleman professor of Medicine at Washington University School of Medicine in St. Louis, who did not participate in the research. "In perspective, people evolved to be able to survive starvation, but as a culture, we're never much farther than a quarter a mile away from McDonald's. It would be nice to tinker with the metabolic gene program, and this research provides a single target that affects how the body deals with energy."

Provided by Virginia Tech