MedicalXpress

Gene deficiency is a protective barrier to obesity

June 26 2007

A search for the molecular clues of longevity has taken Mayo Clinic researchers down another path that could explain why some people who consume excessive calories don't gain weight. The study, which was done in laboratory mouse models, points to the absence of a gene called CD38. When absent, the gene prevented mice on high-fat diets from gaining weight, but when present, the mice became obese.

The findings were published this month in the online issue of The FASEB Journal, the journal of the Federation of American Societies for Experimental Biology. The study will appear in the November 2007 print issue of the journal.

"Obesity is a complex problem compounded by multiple factors, one of which is our genes. Genes play a role in about 50 percent of cases, and in this study, we demonstrate that CD38 regulates body weight," states Eduardo Chini, M.D., Ph.D., an anesthesiologist at Mayo Clinic and corresponding author of the study.

Identifying the signaling mechanisms that lead to obesity caused by a high-fat, high-calorie diet is a critical part of understanding and developing new treatments for obesity, Dr. Chini says.

Research in animal models has shown that caloric restriction can lower cholesterol and blood pressure -- often considered the biomarkers of aging. In addition, published research in animal models shows that caloric restriction, defined as consuming 30 percent to 40 percent less

than your average daily intake, can turn on the SIRT1 gene, one of a family of seven genes linked to longevity.

In addition, recent studies have shown that the chemical receptor PGC1 (peroxisome proliferator-activated receptor coactivator) plays a key role in the development of obesity and control of metabolism. The SIRT genes activate PGC1 and in doing so, can offset the negative effects of obesity -- at least in mice. But how the SIRT-PGC1 reaction works, hasn't quite been explained until now.

In previous laboratory studies by the Mayo Clinic research team, CD38 was shown to be involved in regulating a wide variety of signaling pathways, such as those that regulate energy metabolism. In addition, recent studies in humans also show a possible connection between CD38 and metabolism, specifically metabolic syndrome. Metabolic syndrome includes metabolic-related health issues that usually afflict people who are obese. These health issues include high blood pressure, elevated insulin levels and high cholesterol levels.

In this study, researchers investigated and confirmed that CD38 inhibits SIRT and the expression of PGC1 in mouse models and, as a result, regulates body weight. In the absence of CD38, the SIRT-PGC1 pathway was activated and protected mice models from developing obesity.

Researchers studied two groups of mice: one with the gene CD38 and the other without. Each group was fed a high-calorie diet with 60 percent of calories from fat. In a second test, each group was fed a standard diet in which 4 percent of calories came from fat.

As a result, the body fat of mice that carried CD38 and were on a high-fat diet nearly quadrupled and their body weight almost doubled. After eight weeks on a high-fat diet, mice with CD38 began to show signs of glucose intolerance, one of the first indicators of diabetes onset. In

addition, this group of mice lived for only four-to-six months compared to the second group of mice that lived for 12 months.

For the group of mice that did not carry CD38, their body fat and weight did not change even though they were on a high fat diet. These mice burned more energy, were leaner and otherwise healthy.

“These changes contributed to the ability of these mice to fend off weight gain despite a high-fat diet and lack of exercise. Together these results suggest that a CD38 deficiency has a protective effect against high-fat, diet-induced obesity,” Dr. Chini says.

Dr. Chini and colleagues also examined the effects of resveratrol in mice. Resveratrol is a naturally occurring substance found in some plants such as mulberries, peanuts and red grapes used to make wine. It has been marketed as a drug that mimics the effects of moderate exercise without the physical act of exercising and also as a longevity drug, despite the lack of evidence that resveratrol is safe and effective in humans.

Mice with CD38 were treated with 30 milligrams (mg) of resveratrol per day. And, to determine the effects of the SIRT genes on obesity, mice without CD38 received the same dose of sirtinol, a drug that shuts down the SIRT genes.

Researchers found that mice with CD38 that were treated with resveratrol for two weeks were protected from high-fat, diet-induced obesity. By contrast, the protective effect against high-fat, diet-induced obesity in the absence of CD38 in mice was invalidated by sirtinol. Mice without CD38 that were treated with sirtinol gained a statistically significant amount of weight when compared with mice without the gene who were not treated with sirtinol.

This data supports the novel notion that CD38 modulates high-fat, diet-induced obesity by a SIRT- dependent mechanism.

“Together these results identify a novel pathway regulating body weight and clearly show that CD38 is a nearly obligatory component of the cellular cascade that led to diet-induced obesity,” the authors write.

The authors say the study’s results are promising and should be explored in follow-up studies that will focus on the quality of life and longevity in mice.

Source: Mayo Clinic