Dynamic changes in DNA linked to human diabetes

September 1 2009

A study in the September issue of *Cell Metabolism,* a Cell Press publication, may give new meaning to the adage, "You are what you eat."

The DNA isolated from the muscles of people with diabetes bears chemical marks not found in those who respond normally to rising blood sugar levels, according to the report. The epigenetic marks in question are specifically found on a gene that controls the amount of fuel, in the form of glucose or lipids, that cells burn. Those marks also show up in the skeletal muscle of people with prediabetes, suggesting that the DNA modification might be an early event in the development of the disease.

Those changes rapidly reprogram the gene's activity without altering the underlying DNA sequence at all. They suggest a way that environmental factors—what we eat or how active we are—may perhaps influence our genes, for better or for worse.

Indeed, the researchers show that the hypermethylation of the gene known as PGC-1{alpha} for short (peroxisome proliferator-activated receptor coactivator-1{alpha}) also takes place in isolated muscle fiber cells when they are exposed to an inflammatory factor or to free fatty acids.

"These changes take place when you expose muscle to systemic factors that mimic the diabetic condition," said Juleen Zierath of the Karolinska Institutet in Sweden.

Such changes to the epigenetic imprint have been seen before, explain Zierath and Romain Barrčs, the study's first author. For instance, chemical modification of genes are responsible for developmental changes that take place as cells differentiate. They are the reason that keratin is produced in the skin but not in blood, for instance. In contrast, the changes they've now revealed take place in cells of the body that are fully mature.

"It's a much more dynamic process than we thought," Zierath said. "The genetic causes of diabetes are important, but this shows us that epigenetic changes, which take place on top of our genes, can alter our physiology in critical ways."

Evidence that dietary factors might influence epigenetic gene control in diabetes had been suggested previously by a generational study in humans, which showed that the nutritional status of the grandparent is closely linked to an increased risk of diabetes-associated mortality in their grandkids. In mice, researchers have demonstrated the crossgenerational effects of nutrition on DNA methylation status directly.

Whether epigenetic modifications could have more immediate effects in other tissues of the body wasn't clear before now. The researchers say they don't yet know whether these epigenetic changes are reversible, but they do have evidence that they might be prevented.

They were able to block hypermethlyation of PGC-1? by silencing a gene that encodes one of a few enzymes that transfer extra methyl groups to DNA. Drugs that prevent hypermethlyation might find clinical use, they say, particularly if they could be made to work only on specific tissues.

"There's room for this in terms of drug discovery," Zierath said.

In a broader sense, the discovery shows that we are not "victims of our genes," she adds. "It's exciting because there may be ways for us to lower disease risk if physical activity or other lifestyle factors can positively influence our epigenome and improve metabolism."

Further studies are needed to see whether different diets or exercise habits can alter DNA methylation in beneficial ways, she said.

More information: "Non-CpG Methylation of the PGC-1α Promoter through DNMT3B Controls Mitochondrial Density", Romain Barrčs, Megan E. Osler, Jie Yan, Anna Rune, Tomas Fritz, Kenneth Caidahl, Anna Krook and Juleen R. Zierath, Cell Metabolism, 2 September 2009.

Source: Cell Press (news : web)