Muscle gene linked to type 2 diabetes

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People with type 2 diabetes tend to have poorer muscle function than others. Now a research team at Lund University in Sweden has discovered that in type 2 diabetes, a specific gene is of great importance for the ability of muscle stem cells to create new mature muscle cells. The findings are published in *Nature Communications*.

"In people with type 2 diabetes, the VPS39 gene is significantly less active in the muscle cells than it is in other people, and the stem cells with less activity of the gene do not form new muscle cells to the same degree. The gene is important when muscle cells absorb sugar from blood and build new muscle. Our study is the first ever to link this gene to type 2 diabetes," says Charlotte Ling, professor of epigenetics at Lund University who led the study.

In type 2 diabetes, the ability to produce insulin is impaired, and patients have chronically elevated blood sugar. Muscles are generally worse at absorbing sugar from food, and muscle function and strength are impaired in patients with type 2 diabetes.

A muscle consists of a mixture of fiber types with different properties. Throughout life, muscle tissue has the ability to form new muscle fibers. There are also immature muscle stem cells that are activated in connection with, for example, injury or exercise. In the current study, the researchers wanted to investigate whether epigenetic patterns in muscle stem cells can provide answers to why impaired muscle function occurs in type 2 diabetes.

Two groups were included in the study: 14 participants with type 2 diabetes and 14 healthy people in a control group. The participants in the groups were matched by age, gender and BMI (body mass index). The researchers studied epigenetic changes in the muscle stem cells in both groups, and under exactly the same conditions, they also extracted mature muscle cells and compared them. In total, they identified 20 genes , including VPS39, whose gene expression differed between the groups in both immature muscle stem cells and mature muscle cells. The researchers also compared the epigenetic patterns of muscle cells before and after cell differentiation in both groups.

"Despite the fact that both groups' muscle stem cells were grown under identical conditions, we saw more than twice as many epigenetic changes in the type 2 diabetes group during the differentiation from muscle stem cell to mature muscle cells. Muscle-specific genes were not regulated normally, and epigenetics did not function in the same way in cells from people with type 2 diabetes," says Charlotte Ling.

"The study clearly showed that muscle stem cells that lack the function of the gene VPS39, which is lower in type 2 diabetes, also lack the ability to form new mature muscle cells. This is because muscle stem cells that lack VPS39 due to altered epigenetic mechanisms cannot change their metabolism in the same way as muscle stem cells from controls—the cells therefore remain immature or break down and die," says Johanna Säll Sernevi, postdoc researcher at Lund University.

To confirm the findings, the researchers also used animal models with mice that had a reduced amount of the VPS39 gene, to mimic the disease. The mice subsequently had altered gene expression and reduced uptake of sugar from blood into the muscle tissue, just like the individuals with type 2 diabetes.

The comprehensive study is a collaboration between Swedish, Danish and German researchers, who believe that the findings open up new avenues for treating type 2 diabetes.

"The genome, our DNA, cannot be changed, although epigenetics in effect does. With this new knowledge, it is possible to change the dysfunctional epigenetics that occur in type 2 diabetes. For example, by regulating proteins, stimulating or increasing the amount of the VPS39 gene, it would be possible to affect the muscles' ability to regenerate and absorb sugar," concludes Charlotte Ling.

More information: Cajsa Davegårdh et al. VPS39-deficiency observed in type 2 diabetes impairs muscle stem cell differentiation via altered autophagy and epigenetics, *Nature Communications* (2021). DOI: 10.1038/s41467-021-22068-5

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