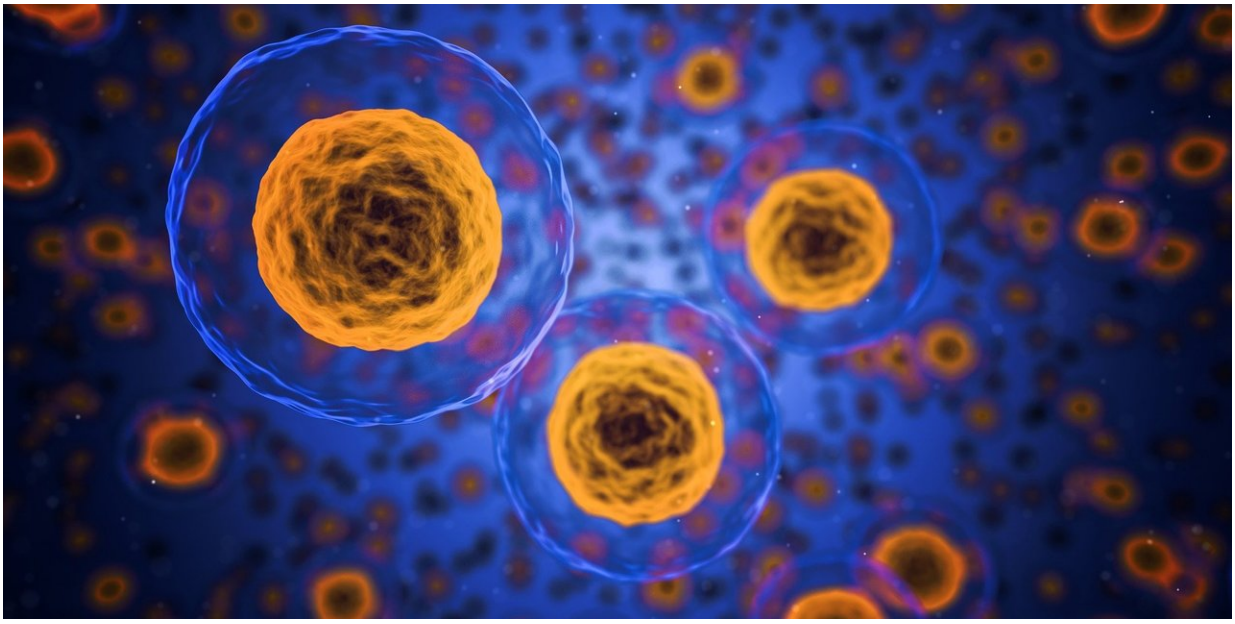
Research reveals insulin-producing beta cells may change function in diabetes

May 17 2019



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A revolutionary new study using only materials derived from humans has revealed that insulin-producing beta cells can change their function in diabetes—and that this change may be reversible.

Research led by the University of Exeter is the first to look at the cells using an entirely animal-free model, instead using a completely human cell system in laboratories for the first time. The team found that the

RNA messaging system which tells proteins how to behave in cells is different in diabetes. The changes lead to some of the beta cells no longer producing insulin which regulates blood sugar, and instead producing somatostatin, which can block the the secretion of other important hormones including insulin itself.

The research is published in *Human Molecular Genetics* and funded by Animal Free Research UK. The study may give new insights into how high blood sugar can alter the behaviour of important hormone-producing cells, and pave the way to new treatments.

Professor Lorna Harries, of the University of Exeter Medical School, who led the research, said: "These insights are really exciting. Only recently, Exeter researchers discovered that people with type 1 diabetes still retain some insulin-producing cells, but the environment produced by diabetes can be toxic for these cells that remain. Our work could lead to new changes to protect these cells, which could help people maintain some ability to make their own insulin. The method we used of creating an all-human cell system for the first time is significant—I don't think we'd have seen these changes in mouse cells."

Carla Owen, Chief Executive of Animal Free Research UK which funded the research, said: "This is pioneering research at its best—we supported the Exeter team to create a novel method to investigate how diabetes affects humans, rather than animals. Their breakthrough findings would never have been discovered in animals, highlighting the importance of using a human-relevant approach to understanding human diseases. We're proud to be supporting the next phase to take this discovery forward and closer to treatments for people living with diabetes."

The team examined what happens to human beta cells when exposed to an environment that replicated type 2 diabetes.

Beta cell loss occurs in both type 1 and type 2 diabetes. Scientists have previously assumed this was because the microenvironment around the cells causes them to die.

However, the team found for the first time that a proportion of the cells are no longer beta cells that are making insulin. They had actually started to make a different hormone called somatostatin—characteristic of a delta cell.

The team than analysed post mortem pancreas tissue from people with either type 1 or type 2 diabetes. This revealed that they have more delta cells than they should have, suggesting that diabetes might be causing some of the beta cells to turn into delta cells in people as well as in cells in the laboratory.

Similar findings have been reported in animal models, but the changes are different. In mice, most of the changes are beta to alpha cells, not delta cells. Alpha cells make a different hormone called glucagon. This means that the consequences of changes in cell type might be different between mice and humans.

In the next step, the team investigated why the cells might change from beta cells to delta cells, by looking at gene regulation. They looked at differences in the genes that make the decision as to which type of RNA message is made which helps cells to deal with their environment. In samples from the pancreas of people with type 2 diabetes, they found that about a quarter of genes show disruption to the expected pattern of messages made compared with samples from people with no diabetes. This indicates that the differences in the regulators translate to differences in messages made. The type of RNA message made controls every aspect of cell life or behaviour, and the authors speculate this could be why the treated cells behave differently.

Professor Harries said: "The really exciting finding is that in the laboratory at least, we have been able to reverse the changes—turn the delta cells back to beta cells—if we restore the environment to normal, or if we treat the cells with chemicals that restore the regulator genes and the patterns of RNA messages made to normal. That's very promising when we consider the potential for new therapeutics."

Provided by University of Exeter