The life and death of beta cells

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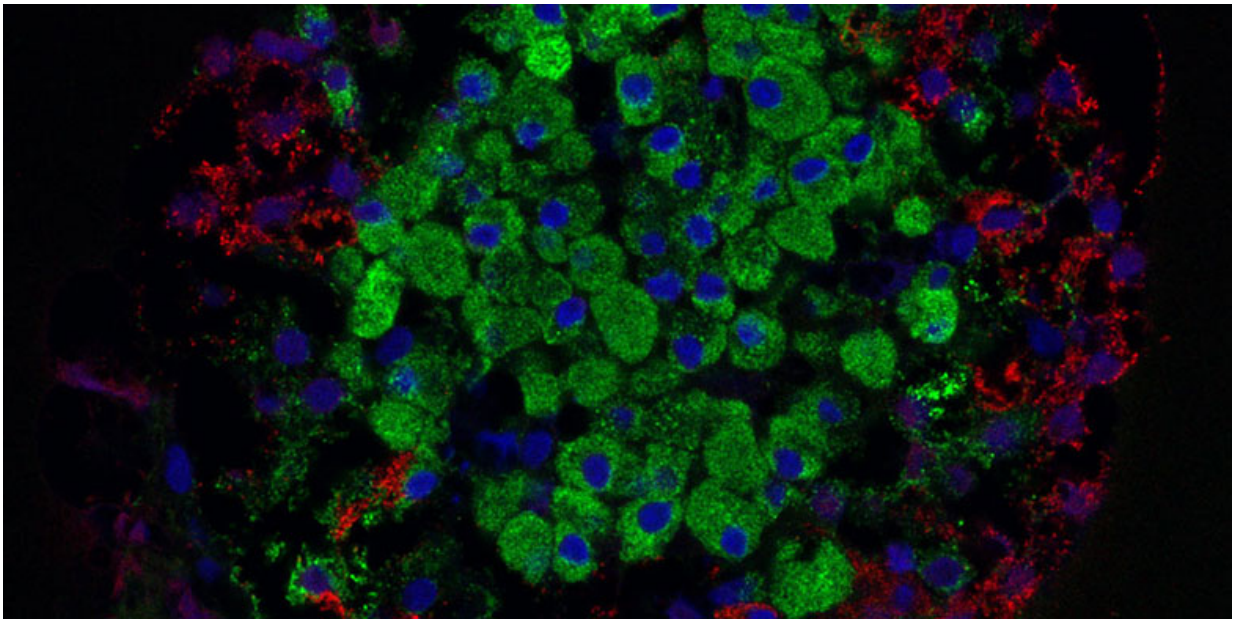

Beta cells (green) produce the hormone insulin. Credit: Masur / Wikimedia Commons

ETH researchers studying microRNA—tiny strands of ribonucleic acid—in beta cells have found a type that plays a key role in cell death under stress.

Diabetes is one of the scourges of modern society, and the number of cases is rising every year. Already, there are over 380 million diabetics around the world. The International Diabetes Foundation estimates that by 2030, over half a billion people will be suffering from type 2 diabetes

. Today, Switzerland has more than 430,000 diabetics, 40,000 of them with type 1 diabetes.

What both type 1 and type 2 diabetes have in common is a dying off of insulin-producing beta cells, which are found on the pancreas. This deprives the body of an important signalling molecule that plays an essential part in how cells absorb glucose from the blood and metabolise this fuel.

MicroRNA triggers cell death

Until now it was unclear what exactly causes the beta cells to die. Now researchers in the group headed by Markus Stoffel, a professor at ETH Zurich's Institute of Molecular Health Sciences, have discovered new mechanisms governing why these insulin-producing cells cease to function. Their death is triggered by massive overproduction of short strands of ribonucleic acid, known as microRNA (miR) 200.

The researchers discovered that production of miR-200 is greatly increased in the beta cells of diabetic mice, resulting in an excess of this particular microRNA. Using a mouse model, they were able to demonstrate that they could quickly bring about the death of beta cells—and of the mice—by forcing miR-200 production.

Conversely, the biologists were also able to use a mouse model to show that by blocking miR-200 they could guarantee the survival of beta cells, even ones under extreme stress. One example of cell stress was when the mice had problematic blood lipid levels; another was when the endoplasmic reticulum, which is where insulin is produced, was under stress.

"These observations are extremely revealing and interesting," says Stoffel. They indicate that miR-200 plays a key role in the survival of

this vital cell type. Evidently miR-200 can bring about programmed cell death, known as apoptosis, in beta cells.

Beta cells burn out

Beta cells play a major part in the onset of diabetes. One precursor of diabetes is insulin resistance. In overweight people, for instance, muscle cells react either insufficiently or not at all to insulin, the hormone produced and expressed by beta cells. This causes the beta cells to divide and grow in order to increase insulin production. After a period of working overtime, however, the beta cells are exhausted and die off. The body lacks insulin, and the result is diabetes.

"To a certain extent, the same thing happens in pregnant women, but after the pregnancy this process of cell division and increased insulin release is reversible," says Stoffel. The process is not reversible in obese people, who also have problematic blood lipid levels that put additional stress on their beta cells.

Triad of microRNAs

Stoffel's research group has recently identified several microRNAs that are related to the life and function of beta cells and hence also to diabetes. "It appears that several microRNAs act on beta cells, performing different stress-management tasks," he says.

One of the miR families they have found is central to beta cell division as a response to a need for more insulin. If this strand of RNA is not present, too few cells—if any—will divide. A further microRNA family governs how much insulin is produced and expressed. "We've now established that the third family, miR-200, is responsible for the life and death of beta cells," Stoffel summarises.

These short sequences of RNA show great therapeutic potential. Their activity can be inhibited by a corresponding strand that is perfectly complementary to the sequence—Stoffel calls these antagomirs. Antagomirs are currently undergoing Phase II clinical trials as a treatment for hepatitis C. The antagomir for miR-122 stops the hepatitis C virus from reproducing. Whether and how antagomirs might also be used to deal with the harmful microRNAs implicated in diabetes requires more research.

Essential regulation level

MicroRNAs are part of a complex hierarchical regulatory network involving interactions at several levels. Certain molecules, known as transcription factors, regulate gene activity at the DNA level, for instance by silencing a gene so that it cannot be transcribed. It is at the level of these transcriptions, known as messenger RNA, that microRNAs work - by inhibiting the translation of messenger RNA into a protein. "The fine tuning for which microRNAs are responsible has long been underestimated," says Stoffel. Tiny changes in gene regulation can have huge effects on cell behaviour. These short strands of RNA temper cells' reaction to stress, ensuring it does not get out of hand. "So microRNAs also control crisis situations," says Stoffel.

MicroRNAs have been regulating cell processes for aeons, as evidenced by phylogeny. Humans have around 21,000 genes, of which 700 to 1,000 code for microRNAs—and 300 of these genes are present in all higher life forms, from worms to humans.

More information: Belgardt B-F, Ahmed K, Spranger M, Latreille M, Denzler R, Kondratiuk N, von Meyenn F, Nunez Villena F, Herrmanns K, Bosco D, Kerr-Conte J, Pattou F, Rülicke T, Stoffel M. The microRNA-200 family regulates pancreatic beta cell survival in type 2 diabetes. *Nature Medicine*, advanced online publication, Mai 18th 2015.

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