Discovery enables clear identification of diseased beta cells in type 2 diabetes

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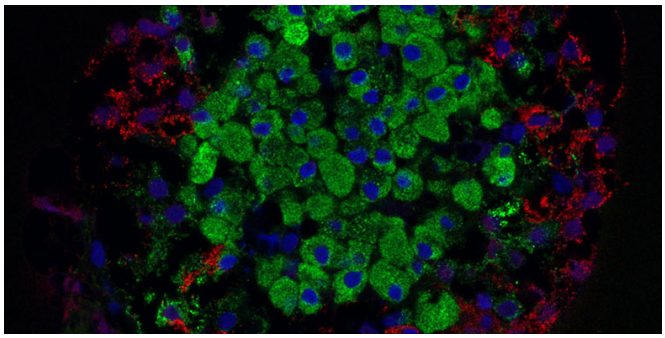

Beta cells (green) produce the hormone insulin. Raised levels of micro RNA 200 are harmful. Credit: Masur / Wikimedia Commons

Researchers at Joslin Diabetes Center, an affiliate of Harvard Medical School, have unlocked the key to clearly identifying diseased beta cells in type 2 diabetes. This discovery has both research and therapeutic implications.

Studies of diabetes rely on the ability of researchers to sort diseased cells from healthy cells. For years, researchers have noted that typical RNA sequencing analysis of these cells was poorly able to separate type 2 cells from non-diseased control cells. Researchers realized there must be a fundamental difference between diseased and healthy cells that had gone undiscovered.

Now, researchers at Joslin have uncovered that difference. They report that changes in the methylation of messenger RNAs specifically known as m6A affects how beta cells function. In the process of methylation, certain molecules interact with mRNAs in a reversible manner to turn various genetic switches on or off. Methylation works on a level above DNA—so it's not coded in the genes, but it acts based on environmental triggers.

This study, published in *Nature Metabolism*, showed that decreased levels of methylation lead to lower expression of a number of proteins needed in the development of properly functioning beta cells. The work was done in the lab of Rohit N. Kulkarni MD, Ph.D., HMS Professor of Medicine; Margaret A. Congleton Chair and co-Head of the Section on Islet Cell and Regenerative Biology.

"We identified that m6A mRNA methylation segregates human type 2 diabetes islets from controls significantly better than gene expression and that m6A is vital for beta cell biology," says Dario F. DeJesus, MSc, Ph.D., and the lead author on the study and a postdoc in the Kulkarni Lab at Joslin.

This work was made possible by improvements in technology over the last decade, allowing researchers to probe the interactions of messenger RNA with its surroundings.

After a long string of analyses, the researchers were able to track which differences in methylation occurred in type 2 diabetes islet cells, and in turn, which proteins were affected by the methylation of mRNA.

"In the case of type 2 diabetes, it appears that mRNA that is able to code for many proteins is hypomethylated, which means that the amount of methylation is lower in type 2 compared to controls," says Dr. Kulkarni. "This is important, because methylation determines what happens to the transcript [or the code the mRNA uses to produce new proteins]. But if there is a hypomethylation of the mRNA, then it might not make the protein correctly or may push it to decay."

They saw that this hypomethylation led to a reduction in the actions of a number of proteins, including three—PDX1, IGF1 receptor, and PP3CA—that are very important for normal beta cell function.

They then confirmed these observations using knockdown studies in animals, where they systematically removed from action the enzymes known to control methylation of m6A mRNA. They forced hypomethylation in non-diseased animals to see if this would trigger type 2 diabetes. They found that the mice all developed signs of type 2 diabetes, even though they were born without the disease.

"The analysis of this mouse model was very dramatic. It resembled type two diabetes. The mice were born normally, so they didn't have defects during birth, but one month after being born they had the high glucose levels which kept on increasing. Their islets showed many characteristics that resembled type two diabetes where all the beta cells were lost," says Dr. Kulkarni.

This research not only solves the problem of cell separation in the laboratory, but it helps improve our understanding of how type 2 diabetes progresses in the real world.

"This fills a gap which has been poorly understood over the last several decades. We're really excited that we were able to make this observation and we proposed a model where modulating the enzymes important for methylation could provide a new target for therapeutics," says Dr. Kulkarni.

Dr. Kulkarni and his colleagues are next investigating the effects of methylation in other metabolic tissues, and in other types of diabetes such as type 1 diabetes and Maturity-onset diabetes of the young (or MODY).

They are also looking into how they can target the methylation process for improvements, which could be translated to a treatment for type 2 diabetes.

More information: Dario F. De Jesus et al. m6A mRNA methylation regulates human ?-cell biology in physiological states and in type 2 diabetes, *Nature Metabolism* (2019). DOI: 10.1038/s42255-019-0089-9

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