'Tiny but mighty' gene fragments are crucial for maintaining blood glucose levels, shows study

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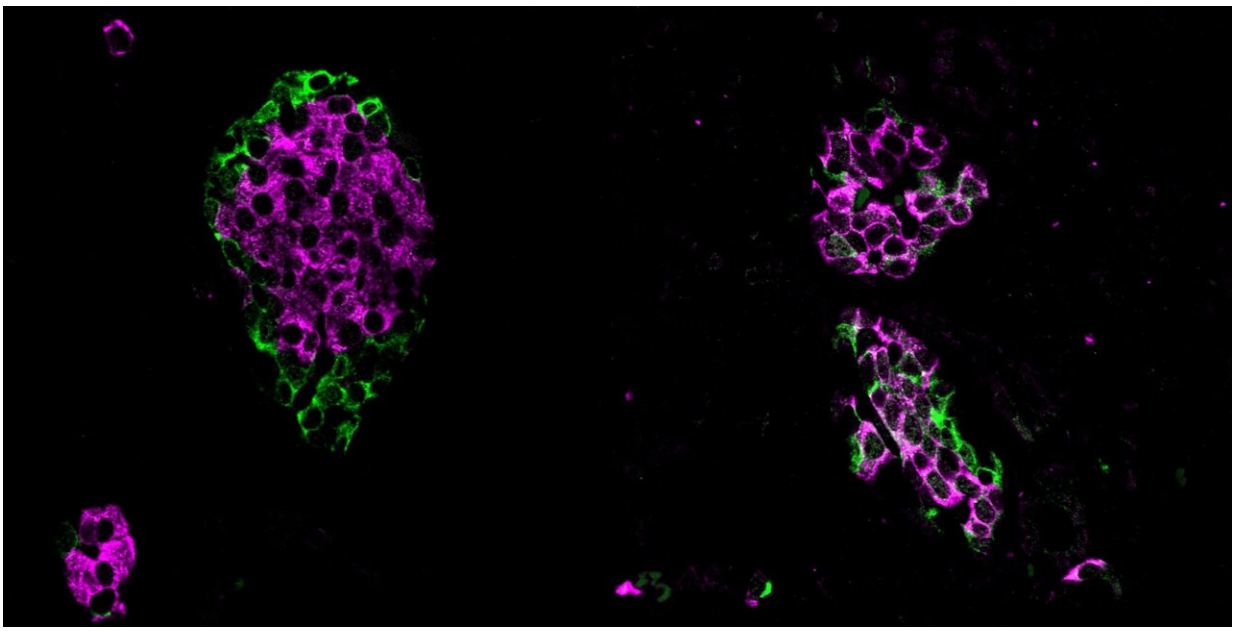

Pancreatic islets in mice, specialized tissues that host beta cells. On the left, a healthy pancreatic islet is shown with its typical morphology with alpha cells in the periphery and beta cells in the core of the islet. On the right, mice with a mutation in Srrm3 that knock out the cells' ability to regulate microexon inclusion results in islets with altered morphology and cell identity. This and other functional alterations ultimately impacts on the release of insulin and the ability to control blood glucose levels. Credit: Jonas Juan Mateu/Centre for Genomic Regulation

When cells copy DNA to produce RNA transcripts, they include only some chunks of genetic material known as exons and throw out the rest. The resulting product is a fully-mature RNA molecule, which can be used as a template to build a protein.

One of the features of gene expression is that, through a process known as alternative splicing, a cell can select different combinations of exons to make different RNA transcripts. Like movie producers creating a regular and director's cut of a film, including or excluding a single exon can result in the production of proteins with different functions.

Living organisms use alternative splicing to enable complex functions. Different types of cells in different kinds of tissues produce different RNA transcripts from the same gene. Understanding how this process works provides new clues about human development, health and disease and paves the way for new diagnostic and therapeutic targets.

In recent years, researchers have discovered microexons, a type of protein-coding DNA sequence. At just 3 to 27 nucleotides long, microexons are much shorter than the average exon, the average size of which is around 150 nucleotides. The existence of microexons across many different species ranging from flies to mammals suggest they have an important function because they have been conserved by natural selection for hundreds of millions of years.

In humans, most microexons are exclusively found in neuronal cells, where the tiny gene fragments exert a mighty role. For example, recent studies show that they are crucial for the development of photoreceptors, a specialized type of neuron in the retina. Research has also shown that alterations to microexon activity are common in autistic brains, suggesting that the tiny gene fragments play an important role in the clinical characteristics of the condition.

"A microexon is a short fragment of DNA that codes for a few amino acids, the building blocks of proteins. Though we don't know the exact mechanisms of action involved, including or excluding just a handful of these amino acids during splicing sculpts the surfaces of proteins in a highly precise manner. Therefore, microexon splicing can be seen as a way to perform microsurgery of proteins in the nervous system, modifying how they interact with other molecules in the highly-specialized synapses of neurons," explains ICREA Research Professor Dr. Manuel Irimia, a researcher at the Center for Genomic Regulation (CRG) who explores the functional role of microexons.

A research team led by Dr. Irimia and ICREA Research Professor Juan Valcárcel at the CRG has now discovered that microexons are also found in another type of cell that carries out highly-specialized functions within complex tissues and organs—endocrine cells in the pancreas. Microexon splicing is prevalent in pancreatic islets, tissues that host beta cells which make the hormone insulin. The findings are published today in the journal *Nature Metabolism*.

The researchers came across the discovery while they were studying the role of alternative splicing in the biology of pancreatic islets and maintenance of blood sugar levels. They studied RNA sequence data from different human and rodent tissues, specifically looking for exons that are differentially spliced in pancreatic islets compared to other tissues.

The data revealed that half the exons specifically enriched in pancreatic islets were microexons, almost all of which were also found in neuronal cells. The finding is in line with the idea that pancreatic islet cells have evolved by borrowing regulatory mechanisms from neuronal cells.

From the more than one hundred pancreatic islet microexons found, the majority were located on genes critical for insulin secretion or linked to

type-2 diabetes risk. The research also revealed that microexon inclusion in RNA transcripts was controlled by SRRM3, a protein that binds to RNA molecules and is encoded by the SRRM3 gene. The authors of the study showed that high blood sugar levels induced both the expression of SRRM3 and the inclusion of microexons, hinting at the possibility that the regulation of microexon splicing could play a role in maintaining blood sugar levels.

To further understand the impact of islet microexons, the researchers carried out various functional experiments using human beta cells grown in the laboratory, as well as in vivo and ex vivo experiments with mice lacking the SRRM3 gene.

They found that depleting SRRM3 or repressing single microexons lead to impaired insulin secretion in beta cells. In mice, alterations to microexon splicing changed the shape of pancreatic islets, ultimately impacting the release of insulin.

The researchers teamed up with Dr. Jorge Ferrer's research group, also at the CRG, to study genetic and RNA transcript data from diabetic and non-diabetic individuals and explore possible links between microexons and human metabolic disorders. They found that genetic variants which affect microexon inclusion are linked to variations in fasting blood sugar levels and also type-2 diabetes risk. They also found that type-2 diabetes patients have lower levels of microexons in their pancreatic islets.

The findings of the study pave the way to explore new therapeutic strategies to treat diabetes by modulating splicing. "Here we show that islet microexons play important roles in islet function and glucose homeostasis, potentially contributing to type-2 diabetes predisposition. For this reason, microexons may represent ideal therapeutic targets to treat dysfunctional beta cells in type-2 diabetes," explains Dr. Jonas Juan Mateu, first author of the study and postdoctoral researcher at the CRG.

"A wide range of splicing modulators are available to treat a variety of human diseases. When I first started studying splicing in pancreatic islets eight years ago, I wanted to find out whether existing splicing modulators could be repurposed for diabetes. I think we're one step closer to that," adds Dr. Juan Mateu.

While the work shows microexons are important new players in pancreatic islet biology, further work will be needed to determine their precise impact during the tissue's development. Researchers also lack mechanistic insight on how each individual microexon alters protein function and affects key pathways in islet cells. Understanding this will shed light on their exact physiological role in diabetes and other metabolic diseases linked to pancreatic islets.

The study adds to a growing body of evidence that microexons play crucial roles in human development, health and disease. "Less than 10 years after we first reported on their existence, we are seeing how microexons are key elements that modify how proteins interact with each other in cells with functions that require a high degree of specialization, such as neurotransmitter or insulin release and light transduction," explains Dr. Irimia.

"Consequently, we expect mutations in microexons to lead to diseases whose genetic causes we have not yet understood. We are beginning to search for these mutations in patients with neurodevelopmental and metabolic disorders as well as retinopathies, to then devise possible interventions to treat them," he concludes.

More information: Jonàs Juan-Mateu, Pancreatic microexons regulate islet function and glucose homeostasis, *Nature Metabolism* (2023). DOI: 10.1038/s42255-022-00734-2.
www.nature.com/articles/s42255-022-00734-2

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