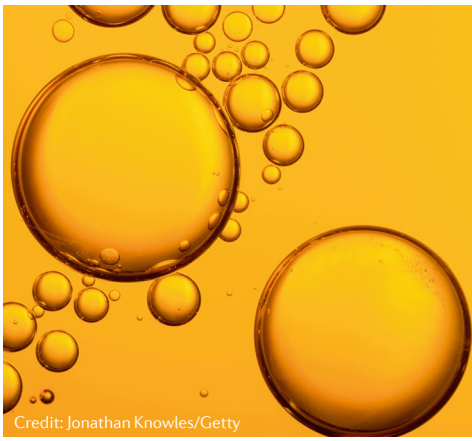
DIABETES

New approach to improving insulin sensitivity


Credit: Jonathan Knowles/Getty

Insulin resistance is a key feature of type 2 diabetes mellitus, but very few therapeutic approaches specifically target this characteristic. New research published in *Cell Metabolism* suggests that miR-690, which is derived from the exosomes of M2-polarized bone marrow-derived macrophages (BMDMs), could be used to improve insulin sensitivity.

Previous work had demonstrated that exosomes from M2-like adipose tissue macrophages in lean mice could be used to ameliorate insulin sensitivity in obese mice. However, this technique had practical limitations and so was challenging to study further. "To overcome these limitations, we treated mouse BMDMs in vitro with IL-4 and IL-13 to direct them towards an anti-inflammatory M2-like phenotype and harvested the exosomes they secreted," explain authors Jerrold Olefsky and Wei Ying.

> "miR-690 is a key insulin-sensitizing miRNA"

The researchers used the secreted exosomes to treat adipocytes, myocytes and primary mouse hepatocytes in vitro; the exosomes were also administered to mice with high-fat diet-induced obesity. Compared with control conditions, the treatment with exosomes improved insulin sensitivity.

Exosomes contain a range of factors (including miRNAs), and so, to determine which factor was key in the insulin-sensitizing effect, the researchers generated a mouse model that produced exosomes that did not contain miRNAs. When these exosomes were used to treat adipocytes, myocytes and obese mice, no insulin-sensitizing effects were seen. The researchers then conducted further experiments with the five most highly expressed miRNAs in BMDM exosomes, which revealed that miR-690 was the factor underlying the insulin-sensitizing effect of these exosomes. "We identified NADK as a mRNA target of miR-690, and the miR-690–*Nadk* axis regulates inflammation and insulin signalling," add Olefsky and Ying.

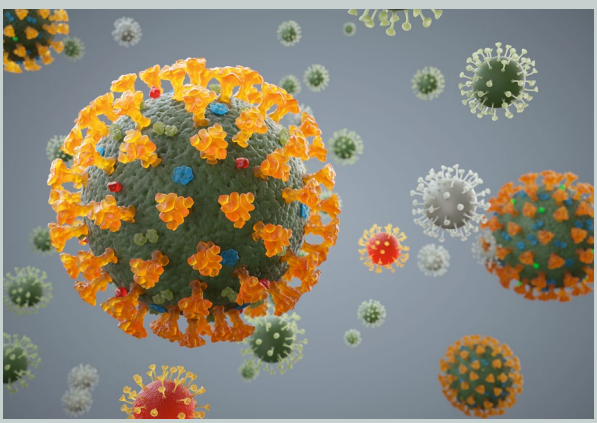
"miR-690 is a key insulin-sensitizing miRNA that is highly expressed within M2 exosomes," conclude Olefsky and Ying. "This suggests that this miRNA could become a new insulin-sensitizing agent for the treatment of metabolic diseases."

Claire Greenhill

ORIGINAL ARTICLE Ying, W. et al. MiR-690, an exosomal-derived miRNA from M2-polarized macrophages, improves insulin sensitivity in obese mice. *Cell Metab.* https://doi.org/10.1016/j.cmet.2020.12.019 (2021)

COVID-19

Effects of pancreatic SARS-CoV-2 infection identified


Credit: Andriy Onufriyenko/Getty

The pancreas is a target of SARS-CoV-2, according to a new study published in *Nature Metabolism*. The authors found that SARS-CoV-2 replicates within the islets of Langerhans and that, following infection, there are reduced numbers of insulin-secretory granules in β-cells. Importantly, the authors also show that SARS-CoV-2 infection leads to impaired glucose-stimulated insulin secretion.

In a previous study in which the authors characterized SARS-CoV-2 infection and tropism in gastrointestinal tissue, they also found that two cellular factors that are targeted by SARS-CoV-2 (ACE2 and TMPRSS2) are expressed in pancreatic tissue. Reports that identified metabolic disorders and new-onset diabetes mellitus in patients with COVID-19 spurred the authors to look into the susceptibility of islets of Langerhans to SARS-CoV-2 infection.

The authors worked with islets of Langerhans isolated from uninfected patients and exposed the islets to SARS-CoV-2. The team also applied immunohistochemistry to check for receptor expression in healthy human pancreatic tissue and for the presence of SARS-CoV-2 proteins in pancreata of four patients who had died as a result of COVID-19.

"When we checked for presence of SARS-CoV-2 in pancreatic tissues, it was astonishing that we detected infected pancreata in the biopsy samples of all four patients who died with COVID-19," adds Kleger. "What was most striking is that in our experiments, as well as in infected tissue of patients, the infected cells within the islets of Langerhans appeared insulin negative but stained positive for endocrine markers." The authors' data suggest that β-cells might lose their identity and thus their function upon infection.

> "the islets of Langerhans appeared insulin negative but stained positive for endocrine markers"

The authors now want to identify at what stage of the disease infections of the pancreas occur, whether this is a transient effect or whether patients who have had COVID-19 have pancreatic infection-induced consequences such as diabetes mellitus.

Alan Morris

ORIGINAL ARTICLE Müller, J. A. et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. *Nat. Metab.* https://doi.org/10.1038/s42255-021-00347-1 (2021)