DIABETES

Glucose isn't always to blame

To date, the underlying causes of inflammation in obesity and type 2 diabetes mellitus (T2DM) have remained unclear, which has hampered efforts to develop preventive treatments. Now, Barbara Nikolajczyk and Douglas Lauffenburger show that changes to mitochondria drive inflammation in cells that have been exposed to fatty acid derivatives, which are elevated in obesity and T2DM. These data provide new insights into the causes of inflammation in T2DM and suggest that lipids could continue to drive inflammation (and thus metabolic dysfunction) in patients who have responded well to treatments that target glucose levels.

"We were initially interested in investigating whether changes in the metabolism of immune cells contributed to T2DM-associated chronic inflammation," explains Nikolajczyk. "Based on the importance of non-mitochondrial glycolysis in other types of inflammation, we hypothesized that immune cells from patients with T2DM would generate ATP by burning glucose by non-mitochondrial glycolysis — we were wrong."

In their study, the investigators used immune cells from patients with T2DM. As a marker for inflammation, the authors used a specific T cell inflammatory profile, which consists of predominantly $CD4^+$ type 17 T helper cells (T_H17 cells).

Nikolajczyk and colleagues found that non-mitochondrial glycolysis failed to drive the T2DM-associated inflammatory signature. Other major pathways of ATP generation, including fatty acid oxidation and glutaminolysis, were similarly unable to activate T_H17 cells. Instead, a combination of mitochondrial defects and fatty acid derivatives associated with T2DM were the cause of inflammation. "We combined siRNA-mediated knockdown of mitochondrial transporters (which was only partially effective) with higher concentrations of fatty acid derivatives that are naturally elevated in T2DM, to partially recapitulate T_H17 function in cells from lean healthy participants," adds Nikolajczyk. "Although it seems obvious that complete knockdown of mitochondrial transporters only partially recapitulates human disease, a rather clever integration of findings in the literature led lead author Dequina Nicholas to consider the possibility that partial defects might combine to generate T cell-associated inflammation."

The team is now interested in developing new analytical approaches that leverage ongoing lipidomics findings to further understand the pathology of T2DM. "This direction might begin to address the questions in the community regarding tight glycaemic control as the treatment goal for people with T2DM," concludes Nikolajczyk.

Alan Morris

ORIGINAL ARTICLE Nicholas, D. A. et al. Fatty acid metabolites combine with reduced β oxidation to activate Th17 inflammation in human type 2 diabetes. *Cell Metab.* https://doi.org/10.1016/j.cmet.2019.07.004 (2019)

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DIABETES

New test for diabetes insipidus

New research published in *The Lancet* has described a diagnostic test for diabetes insipidus that is easier to perform and associated with fewer adverse effects than the current standard test. Bettina Winzeler and colleagues show that arginine-stimulated copeptin (which is derived from the preprohormone of arginine vasopressin) measurements have a similar diagnostic accuracy to hypertonic saline-stimulated copeptin measurements, which is presently the best test available.

Osmotic stimulation tests, such as the water deprivation test and hypertonic saline test, are currently used for the diagnosis of diabetes insipidus. The water deprivation test, however, has little diagnostic accuracy and the hypertonic saline test is challenging to perform. In the present study, Winzeler and colleagues aimed to identify other potential, simpler and more accurate tests to diagnose diabetes insipidus. "In this prospective diagnostic study, our aim was to investigate whether arginine infusion stimulates copeptin and whether it can be used as a simple test to diagnose diabetes insipidus," explains Winzeler.

DIABETES

Blood signature for β-cell autoimmunity

A clinical need exists for biomarkers for early β-cell autoimmunity, which can predict progressive β-cell destruction in type 1 diabetes mellitus (T1DM) before it actually occurs. Now, a study in *Diabetes* identifies an early peripheral blood signature in children who develop β-cell autoimmunity at a young age.

In genetically susceptible individuals, the appearance of T1DM-associated autoantibodies in serum can predict progression to T1DM. However, the presence of these antibodies is indicative of active autoimmunity and β-cell destruction. To investigate earlier predictive factors, Riitta Lahesmaa and colleagues identified 7 children who developed β-cell autoimmunity at a young age (<36 months) and 7 matched control children, from a cohort of 836 children with HLA-DR or HLA-DQ risk alleles for T1DM. From each child, longitudinally collected (at 3, 6, 12, 18, 24 and 36 months of age) peripheral blood mononuclear cell (PBMC) samples were analysed.

The researchers fractionated the PBMC samples into $CD4^+$ (a marker of T helper cells), $CD8^+$ (a marker of effector T cells) and $CD4^-CD8^-$ cellular subsets. Importantly, RNA-sequencing based transcriptomic analyses of these cellular subsets and unfractionated PBMCs revealed changes that are associated with, and precede the appearance of, β-cell autoimmunity. One upregulated example was *IL32*, which encodes a proinflammatory cytokine that has not been previously associated with β-cell autoimmunity.

Importantly, a human pancreatic β-cell line was shown to express IL-32 in response to proinflammatory cytokines. In addition, treatment of human islets obtained from cadaveric donors with coxsackie B virus (a β-cell tropic virus) induced IL-32 expression, suggesting a potential role for IL-32 in T1DM pathogenesis.