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What drives inflammation in type 2 diabetes? Not glucose, says new research

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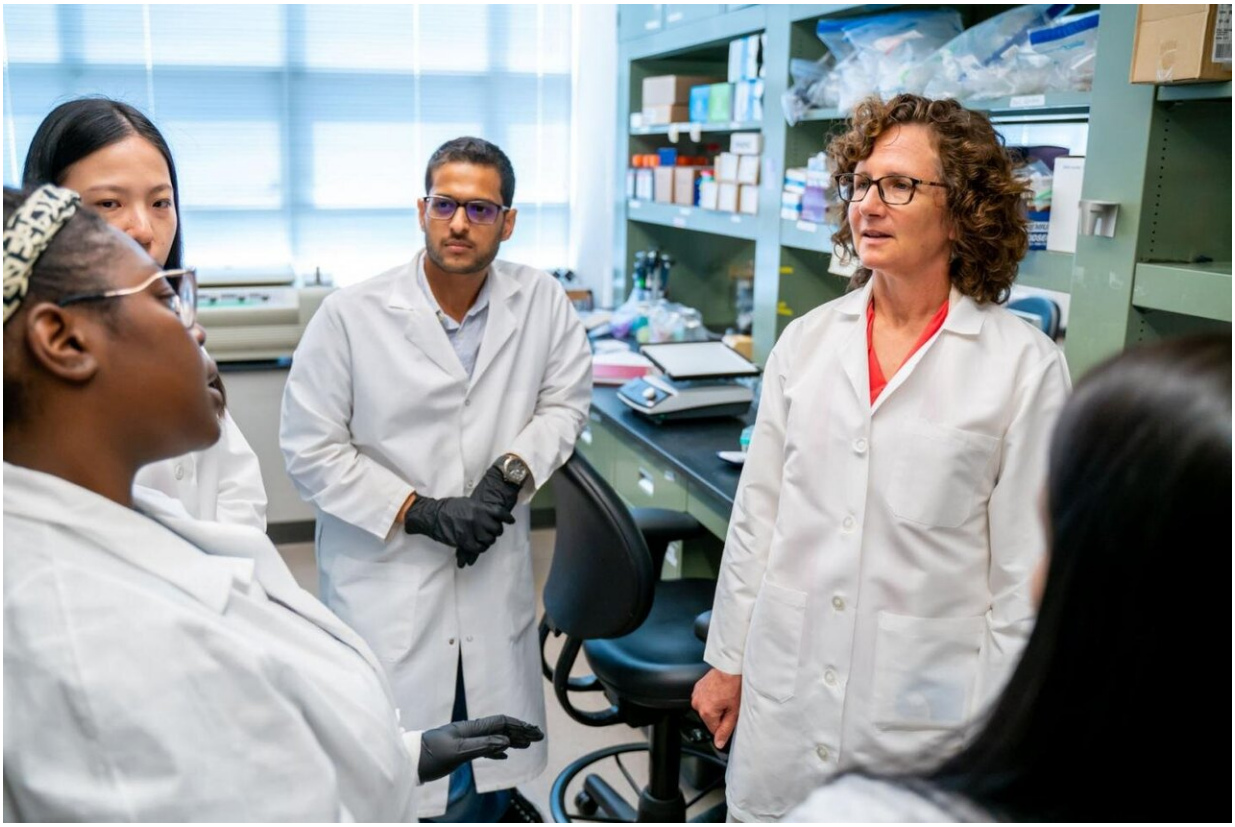

Research led by Barbara Nikolajczyk, Ph.D., disproved the conventional wisdom that glucose was the primary driver of chronic inflammation in type 2 diabetes. Credit: University of Kentucky Office of Research Communications

To date, the underlying causes of inflammation in obesity and type 2

diabetes mellitus (T2DM) have been poorly understood, which has hampered efforts to develop treatments to prevent complications from a disease that is the third leading cause of death in the United States.

But new research at the University of Kentucky shows that changes to mitochondria—the powerhouse of cells—drive chronic inflammation from cells exposed to certain types of fats, shattering the prevailing assumption that glucose was the culprit.

Chronic inflammation fuels many of the devastating complications of type 2 diabetes, including cardiovascular, kidney, and periodontal diseases, and is thus one of the key targets for therapy development. This new data may enlighten the conversation about tight glycemic control as the dominant treatment goal for people with diabetes.

The research was recently published in *Cell Metabolism* by a team led by Barbara Nikolajczyk (UK Barnstable Brown Diabetes Center, Department of Pharmacology and Nutritional Sciences) and Douglas Lauffenberger (MIT Department of Biological Engineering).

Nikolajczyk and Lauffenberger didn't set out to disprove the glucose-inflammation causation theory. Based on the importance of glycolysis—a 10-reaction sequence that produces energy—in other types of inflammation, the team hypothesized that immune cells from patients with type 2 diabetes would produce energy by burning glucose. "We were wrong," Nikolajczyk said.

"We exclusively used immune cells from human subjects for all of the work, " Nikolajczyk explained, noting that humans, but not animal models of type 2 diabetes, have the specific pro-inflammatory T cell profile her team had identified in earlier research.

The team was surprised to find that glycolysis wasn't driving chronic

inflammation. Instead, a combination of defects in mitochondria and elevated fat derivatives were responsible.

Nikolajczyk said she sees applications for this research in both basic and clinical sciences. She hopes to precisely define pro-inflammatory lipid types and explore associations between circulating and/or tissue-associated lipids and insulin resistance, one key feature of Type 2 diabetes. She is also interested in contributing to the development of new analytical approaches, spearheaded by Dr. Lauffenburger's team, that leverage ongoing lipid-related findings into a new understanding of pathology in type 2 diabetes.

"Aggressive blood glucose control to lower the risk of diabetic complications has been the goal for most people with Type 2 Diabetes for decades," Nikolajczyk said. "Our data provide an explanation for why people with tight glucose control can nonetheless have disease progression."

More information: Dequina A. Nicholas et al, Fatty Acid Metabolites Combine with Reduced β Oxidation to Activate Th17 Inflammation in Human Type 2 Diabetes, *Cell Metabolism* (2019). DOI: 10.1016/j.cmet.2019.07.004

Provided by University of Kentucky