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Early research shows promise for therapeutics that delay type 2 diabetes

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Vanderbilt researchers have discovered a unique pathway that initiates islet β cell inflammation—a hallmark of type 2 diabetes—putting them a step closer to developing targeted therapeutics for the disease that

affects one in 10 Americans.

The article, "RIPK3-mediated inflammation is a conserved β-cell response to ER stress" was published in the journal *Science Advances* on Dec. 18.

Type 2 diabetes is caused when islet β cells in the pancreas fail to produce a sufficient amount of insulin—the hormone that maintains normal blood sugar levels in the body. Before they fail completely, islet cells become stressed and inflamed. The phenomenon of islet inflammation is well known, and the disease's pathogenesis has been of interest to Wenbiao Chen, associate professor of molecular physiology and biophysics, throughout his career.

Chen's lab found a protein—receptor-interacting protein kinase 3—that mediates islet inflammation and the consequent failure and death of β cells. To better understand the pathogenesis of type 2 diabetes, the researchers developed a zebrafish that is predisposed to developing the disease. In the zebrafish model, the researchers found that overeating causes an initial increase in islet β cells, but by the fourth day one-third of the β cells die, and the fish becomes diabetic.

"After screening a variety of chemicals for β cell protective drugs, we focused on a drug that inhibits RIPK3. While this protein is best known for cell death, we were surprised to learn that its function in islet β cells is to cause inflammation," Chen said. They found RIPK3 is activated in the β cells by overeating and also found evidence that a similar response occurs in human β cells.

"It is well recognized that islet inflammation is a critical factor in the pathogenesis of type 2 diabetes, and now we have figured out one of the mechanisms that provoke this inflammation," Chen said.

RIPK3 is present in many tissues and organs throughout the body, and in some tissues, it seems to produce an anti-inflammatory response. Through deeper understanding of how RIPK3 works in β cells, researchers can work on developing drugs that specifically target islet cells and that don't compromise the benefits of RIPK3 elsewhere. Chen also intends to test whether the inhibitor drug they identified slows down diabetes development in other commonly used models.

More information: Bingyuan Yang et al. RIPK3-mediated inflammation is a conserved β cell response to ER stress, *Science Advances* (2020). DOI: 10.1126/sciadv.abd7272

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