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Potential treatment target identified for rare form of diabetes, other disorders

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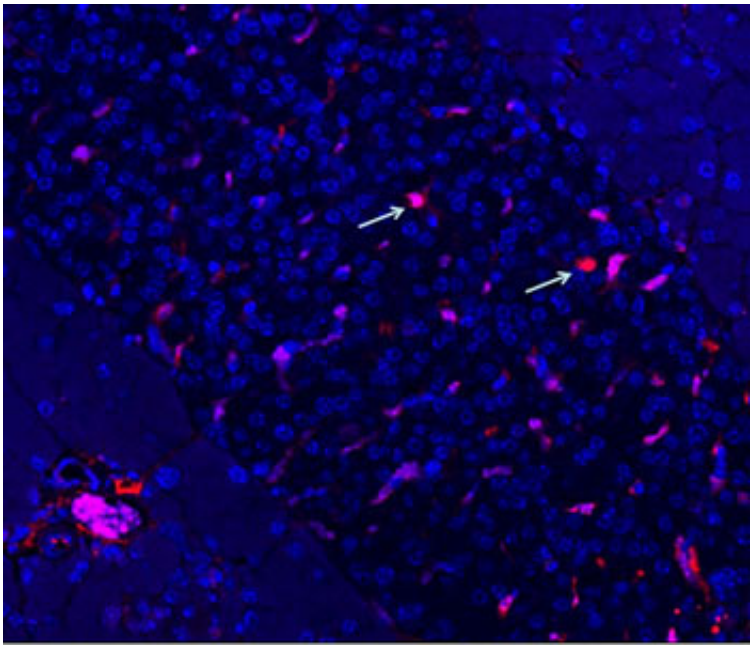

This microscopic image shows dying insulin-secreting cells (red) from a diabetic mouse pancreas. A cell-death cascade was set off by a process that occurs when harmful molecules spill from one part of the cell into other areas where they don't belong. Credit: Urano laboratory-Washington University

Cell death can trigger numerous diseases, including a rare and severe form of diabetes known as Wolfram syndrome. The cascade of cell death occurs when molecules spill from one part of a cell into another where they don't belong.

Now, scientists working to find treatments for Wolfram syndrome have identified a gatekeeper that prevents those harmful molecules from spilling and triggering cell death. The researchers, at Washington University School of Medicine in St. Louis, also have found that the gatekeeper—an enzyme—may be a good treatment target not only for diabetes but for some heart problems, Parkinson's disease and other disorders caused by the same type of cellular stress that can lead to cell death.

The findings are available June 23 in the journal *Science Signaling*.

'The type of cell stress involved in Wolfram syndrome, as well as more common forms of diabetes, can contribute to multiple diseases,' said principal investigator Fumihiko Urano, M.D., Ph.D., the Samuel E. Schechter Professor of Medicine. 'We believe the enzyme we identified may provide us with a target to protect many types of cells from a death cascade that leads to those different, seemingly unrelated disorders.'

Studying cells from mice, the research team found that the gatekeeper enzyme—known as IRE1—beefed up the membrane of a cellular structure called the endoplasmic reticulum, preventing damaging molecules from spilling into other parts of the cell.

'These molecules are supposed to stay in specific locations,' Urano said. 'Sometimes a molecule may travel to different parts of the cell to perform a function, but it needs to return to the place it resides, or big problems can result.'

Cell death can result if there are inadequate levels of the enzyme that keeps potentially harmful molecules in the proper place.

Urano explained that if cells experiencing stress related to dysfunctional IRE1 enzymes are insulin-secreting cells, a person will develop diabetes.

If cardiac cells experience that problem, an individual may develop heart disease, he said. And if the cells experiencing such stress are in the brain, disorders such Parkinson's disease or the neural damage related to Wolfram syndrome may occur.

Urano's team found that by replacing or enhancing the enzyme in mouse cells, they strengthened the cellular membrane, stopped molecules from leaking into other parts of a cell and prevented cell death. Now they want to prove that the enzyme plays an identical role in human cells.

He said it may be possible to treat Wolfram syndrome and other disorders with compounds that target the enzyme.

'It's clear from our experiments that this enzyme can keep the membrane in the cell from becoming permeable and leaking,' Urano said. 'We think it may be possible to prevent Wolfram syndrome and other diseases related to this type of cellular stress by targeting the enzyme to make the membrane stronger.'

Later this summer, Washington University and St. Louis Children's Hospital will host the sixth annual Wolfram syndrome clinic for patients from around the world. Urano and his colleagues will collect and test blood samples to see whether they can find markers of IRE1 dysfunction in patients with the disorder.

More information: Kanekura K, Ma X, Murphy JT, Zhu LJ, Diwan A, Urano F. IRE1 prevents endoplasmic reticulum membrane permeabiliation and cell death under pathological conditions. *Science Signaling*, vol 8 (382), published online June 23, 2015.

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