New discovery provides insight into the development of complications in type 1 diabetes

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Joslin scientists have advanced understanding of how the cellular repair process is impaired in type 1 diabetes, which can cause cell death and lead to complications. The findings appear in the August issue of *Cell Metabolism*.

Complications are a major cause of serious diseases in type 1 diabetes, affecting the cardiovascular system, kidneys, eyes and nerves. "Even with very good glycemic control, people with type 1 diabetes can still develop complications that impact their ability to work and quality of life. If we could find therapies that detect complications at an early stage, people with diabetes could lead healthier, more productive lives," says senior author Rohit Kulkarni, M.D., Ph.D., Principle Investigator in the Section on Islet Cell and Regenerative Biology at Joslin Diabetes Center and Associate Professor of Medicine at Harvard Medical School.

Progress has been difficult in determining exactly how the body's cellular repair process malfunctions in type 1 diabetes so that effective treatments can be developed. One challenge has been the lack of animal and cellular models that can precisely replicate the human disease for scientific investigation.

In this study, induced pluripotent stem (iPS) cells, which have the potential to differentiate into any type of cell in the body, were used to model the disease. They were derived from skin cells obtained from

patients who have had type 1 diabetes for 50 years or more and are members of the Joslin 50-Year Medalist Program, and also from healthy controls. "Studying iPS cells that come directly from patients with the disease offers a major advantage over other models," says Dr. Kulkarni.

Participants were classified according to complications status: Medalist +C for severe complications and Medalist -C for absent or mild complications.

Genetic analysis of the iPS and skin cells showed "remarkable differences in expression of genes and proteins in the Medalist +C group compared to the Medalist -C group and the controls," says Dr. Kulkarni.

In the Medalist +C group, there were alterations in the DNA damage checkpoint pathway machinery that monitors the DNA repair process of the body's cells. This machinery functioned well in the Medalist -C group, ensuring that damaged cells were repaired, preventing cell death and the development of complications. Further evidence was provided by nerve cells that were differentiated from the iPS cells: nerve cells from the Medalist +C group were more prone to early death than nerve cells from the Medalist -C group.

The analysis revealed higher levels of a protein known as miR200 in the Medalist +C group than in the Medalist -C group and controls. "This is a very significant finding because miR200 plays an important role in the DNA repair process," says Dr. Kulkarni.

When the scientists reduced expression of miR200 in iPS and skin cells from the Medalist +C group, the DNA damage checkpoint pathway machinery was restored and DNA damage was reduced in the cells. This makes miR200 a promising potential target for therapeutic interventions and also a possible biomarker for early detection of the development of complications.

The Joslin researchers are continuing their investigations of miR200 and DNA repair. "We need to figure out the exact mechanisms by which miR200 regulates the DNA repair process and also determine if miR200 can be detected in the bloodstream and serve as an effective biomarker for complications," says Dr. Kulkarni.

They plan to use the iPS cells to differentiate into kidney, eye and vascular cells and learn more about how complications develop in those cells. "These differentiated cells could provide a faster and more efficient way to test which medications are most effective in different patients," says Dr. Kulkarni.

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