New study may lead to improved treatment of type 2 diabetes

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Adrian Liston (VIB/KU Leuven). Credit: ©VIB

Worldwide, 400 million people live with diabetes, with rapid increases projected. Patients with diabetes mostly fall into one of two categories, type 1 diabetics, triggered by autoimmunity at a young age, and type 2 diabetics, caused by metabolic dysfunction of the liver. Despite being labeled a "lifestyle disease", diabetes has a strong genetic basis. New research under the direction of Adrian Liston (VIB/KU Leuven) has discovered that a common genetic defect in beta cells may underlie both forms of diabetes. This research was published in the international scientific journal *Nature Genetics*.

Adrian Liston (VIB/University of Leuven): "Our research finds that genetics is critical for the survival of beta cells in the pancreas - the cells that make insulin. Thanks to our genetic make-up, some of us have beta cells that are tough and robust, while others have beta cells that are fragile and can't handle stress. It is these people who develop diabetes, either type 1 or type 2, while others with tougher beta cells will remain healthy even in if they suffer from autoimmunity or metabolic dysfunction of the liver."

Different pathways to diabetes development

Diabetes is a hidden killer. One out of every 11 adults is suffering from the disease, yet half of them have not even been diagnosed. Diabetes is caused by the inability of the body to lower blood glucose, a process normally driven by insulin. In patients with type 1 diabetes (T1D), this is caused by the immune system killing off the beta cells that produce insulin. In patients with type 2 diabetes (T2D), a metabolic dysfunction prevents insulin from working on the liver. In both cases, left untreated, the extra glucose in the blood can cause blindness, cardiovascular disease, diabetic nephropathy, diabetic neuropathy and death.

In this study, an international team of researchers investigated how genetic variation controls the development of diabetes. While most previous work has focused on the effect of genetics in altering the immune system (in T1D) and metabolic dysfunction of the liver (in T2D), this research found that genetics also affected the beta cells that produce insulin. Mice with fragile beta cells that were poor at repairing DNA damage would rapidly develop diabetes when those beta cells were challenged by cellular stress. Other mice, with robust beta cells that were good at repairing DNA damage, were able to stay non-diabetic for life, even when those islets were placed under severe cellular stress. The same pathways for beta cell survival and DNA damage repair were also found to be altered in diabetic patient samples, indicating that a genetic predisposition for fragile beta cells may underlie who develops diabetes.

Adrian Liston (VIB/University of Leuven): "While genetics are really the most important factor for developing diabetes, our food environment can also play a deciding role. Even mice with genetically superior beta cells ended up as diabetic when we increased the fat in their diet."

A new model for testing type 2 diabetes

treatments

Current treatments for T2D rely on improving the metabolic response of the liver to insulin. These antidiabetic drugs, in conjunction with lifestyle interventions, can control the early stages of T2D by allowing insulin to function on the liver again. However during the late stages of T2D, the death of beta cells means that there is no longer any insulin being produced in the pancreas. At this stage, antidiabetic drugs and lifestyle interventions have poor efficacy, and medical complications arise.

Dr Lydia Makaroff (International Diabetes Federation, not an author of the current study): "The health cost for diabetes currently exceeds US$600 billion, 12% of the global health budget, and will only increase as diabetes becomes more common. Much of this health care burden is caused by late-stage type 2 diabetes, where we do not have effective treatments, so we desperately need new research into novel therapeutic approaches. This discovery dramatically improves our understanding of type 2 diabetes, which will enable the design of better strategies and medications for diabetes in the future".

Adrian Liston (VIB/University of Leuven): "The big problem in developing drugs for late-stage T2D is that, until now, there has not been an animal model for the beta cell death stage. Previously, animal models were all based on the early stage of metabolic dysfunction in the liver, which has allowed the development of good drugs for treating early-stage T2D. This new mouse model will allow us, for the first time, to test new antidiabetic drugs that focus on preserving beta cells. There are many promising drugs under development at life sciences companies that have just been waiting for a usable animal model. Who knows, there may even be useful compounds hidden away in alternative or traditional medicines that could be found through a good testing program. If a drug is found that stops late-stage diabetes, it would really be a major medical breakthrough!"

More information: Genetic predisposition for beta cell fragility underlies type 1 and type 2 diabetes, *Nature Genetics*, DOI: 10.1038/ng.3531

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