

PRESS RELEASE

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Regeneration of insulin-producing cells in diabetic mice

Professor Pedro Herrera's team in Switzerland reveals how new beta-cells can be converted from another mature and entirely different type of cell population from the pancreas

Type 1 diabetes, one of the most frequent chronic diseases in children, is characterized by a near complete destruction of insulin-producing cells in the pancreas, the beta-cells, through an autoimmune mechanism. Until now, it was not known whether this organ was able to regenerate new beta-cells in such a case, either in a spontaneous or induced way. Pedro Herrera's team, from the University of Geneva (UNIGE), has now provided an answer to this question, thanks to transgenic mice they created. The scientists demonstrate in the April 4th on line edition of *Nature* that rodents affected with this type of diabetes are able to generate new insulin-producing cells. Surprisingly, most of them derive from a population of differentiated cells that was formerly synthesizing glucagon, a hormone whose properties are opposite to those of insulin. Such spontaneous cell conversion could be harnessed to develop methods of producing beta-cells for diabetes therapies.

Type 1 diabetes is the most common cause of diabetes in children, although it may occur at any age. Also called juvenile diabetes, this pathology usually results from autoimmune destruction of insulin-producing cells of the pancreas. The subsequent lack of insulin, a hormone necessary to convert sugar, starches and other food into energy needed for daily life, leads to a rapid starvation of cells throughout the body. The only existing treatment for this condition relies on chronic and burdensome injections of insulin. Nevertheless, the lack of fine-tuning often leads to excess of sugar in blood and to life-threatening complications such as kidney failure, blindness or gangrene.

In healthy conditions, pancreatic insulin-producing cells, called beta-cells, have a long lifespan and replicate little during their lifetime. After extreme loss of beta-cells, such as seen in diabetes, the question arises as to whether a process of regeneration occurs. If such is the case, it may be overshadowed by the concomitant destruction of newly formed insulin-producing cells by the autoimmune mechanism.

ON THE BRINK OF DESTRUCTION, CELLS CAN STILL REGENERATE

The regenerative potential of the pancreas in adult organisms was investigated by prof. Pedro Herrera's team, from the Faculty of medicine of the UNIGE and the Swiss *Frontiers in Genetics* program. An important part of their project was devoted to developing a mouse model of inducible diabetes. The researchers generated transgenic mice in which beta-cells could be ablated in a selective way, upon induction. "We wanted to study the capacity of the pancreas to produce new beta-cells after their near-total loss, a condition close to Type 1 diabetes, but without autoimmunity", explains prof.Herrera.

The scientists discovered that rodents subjected to selective extreme cell destruction were indeed able to generate new insulin-producing cells from other sources than pre-existing beta-cells. In order to investigate the origin of the newly formed cells, regeneration was studied in mice in which different pancreatic cell types were labeled, so that their fate could be monitored. “We were surprised to find that production of new beta-cells results mainly from the spontaneous conversion of a completely different type of cells, the so-called alpha-cells. The latter are indeed programmed to synthesize glucagon, a hormone whose function is opposite to that of insulin”, explains Pedro Herrera.

Occasional beta-cells are found scattered in the pancreas of patients who have been afflicted with Type I diabetes for a long time. “Whether this is the consequence of a continuous regeneration of new beta-cells, as we have seen in mice, or persistence of few beta-cells, which have escaped autoimmunity, is not known”, says Fabrizio Thorel, the first author of the article. These new observations in mice should encourage attempts of treatment by inducing and enhancing regeneration after controlling the autoimmune aggression.

CELL PLASTICITY IN ADULT INDIVIDUALS HOLDS HIGH POTENTIAL

The plasticity of the pancreas could be used for developing new treatments for diabetes. These observations also raise issues about regenerative recovery from disease. Indeed, alpha-cells were never considered previously as a potential source of cells for beta-cell therapy for diabetics. This spontaneous glucagon-to-insulin cell conversion, which relates to a process called “cell reprogramming” or “transdifferentiation”, was observed only after the near total insulin cell loss. “The amount of beta-cell destruction thus appears to determine whether regeneration occurs. Moreover, it influences the degree of cell plasticity and regenerative resources of the pancreas in adult organisms”, reports Pedro Herrera.

Until now, the notion that a mature cell in an adult organism can change and become a different type of cell has had little experimental support from mouse models. The findings of prof. Herrera’s team suggest that the production of new experimental models for selective and total cell ablation could pave the way to further discoveries about regeneration induction and cell plasticity in other organs in various pathological conditions, including cancer. ■

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