

When blood turns sweet

Heinrich Wieland Prize winner Markus Stoffel sheds light on causes of diabetes

Scientists are on the verge of decoding the basic principles of molecular mechanisms that cause diabetes mellitus. The Zurich based medical researcher Prof. Markus Stoffel, who received this year's prestigious Heinrich Wieland Prize, has made significant contributions to answer important questions in this research area. He discovered two signaling pathways of human body cells that, when they malfunction, can lead to type 2 diabetes, by far the most frequent form of diabetes which comprises about 90 percent of all diabetic patients. With his research, Prof. Markus Stoffel, the Cologne born researcher from the Eidgenoessische Technische Hochschule (ETH) in Zurich, has marked decisive milestones in explaining the mechanisms leading to type 2 diabetes. He has also shed new light on the important role that so-called microRNAs play in the human body.

Diabetes is spreading quickly in the Industrialized Western World. In Germany alone, over 5 million patients are treated for the condition – worldwide some 180 million people are afflicted. Those numbers are expected to double by 2030. Heart attacks, strokes, blindness, kidney damage and impotence are only a few of the potential serious consequences of diabetes.

Diabetic patients suffer from chronically elevated blood sugar levels. Their bodies are either unable to produce the blood sugar reducing hormone insulin (type 1 diabetes) or progressively lose this ability during their lifetime (type 2 diabetes).

The body uses the biochemical signaling pathways discovered by Prof. Stoffel to regulate blood sugar levels and fat metabolism. In type 2 diabetes patients, this mechanism is impaired. One of the signaling pathways depends on a class of molecules, microRNAs, that were discovered 15 years ago. MicroRNAs are involved in the release of insulin by the pancreas and thereby in the maintenance of a constant level of blood sugar in the body. The second pathway depends on the protein Foxa2, which serves as an insulin sensor in the liver.

MicroRNAs were first discovered in certain type of worms, the nematodes, in 1993 but are present in almost all species. It was only in 2001 that they were termed 'microRNAs', since their function remained unclear for a long time. Today, experts know they regulate translation, the protein biosynthesis based on the read-out of the genetic code. Hence, microRNAs play a crucial role for the production of proteins in the body and therefore for most functions of the organism. Over 300 different microRNAs have been identified in the human body. The Wieland Prize winner was the first to explain the function of a particular microRNA in the human organism: "miR375" helps to regulate the release of insulin from the islets of Langerhans in the pancreas.

MicroRNAs attach themselves to messenger RNA, which is a single strand copy of the genetic code that cells use to produce proteins. In this way, they can inhibit or even block the translation of a gene into its respective protein: Since the composite of microRNA and messenger RNA can no longer be used for protein biosynthesis, it is destroyed by the cell. "Uncovering the precise mode of operation of the microRNA miR375 opens new avenues to developing innovative drugs

in the treatment of diabetes.” says Prof. Stoffel, explaining the relevance of his discovery.

The second signaling pathway discovered by Prof. Stoffel and his team also relates to gene activity, but via a completely different mechanism involving the protein Foxa2. When glucose passes from the intestine into the blood after a meal, the pancreas secretes insulin. This hormone ensures that the body temporarily stores glucose from the blood in liver, muscular and fatty tissue as energy reserves. Once the blood sugar level in the body drops and additional energy is needed, the liver mobilizes sugar and fat from the depot tissues to supply the body with the needed energy.

Foxa2 plays a pivotal role in the activation of these reserves, says Prof. Stoffel. It activates genes in liver cells to produce enzymes that biochemically alter fats and fat-like substances, allowing the stored energy to be set free. Foxa 2, however, is blocked by insulin when high levels of blood sugar provide an ample supply of energy, so fat reserves are not activated. Already in early stages of type 2 diabetes, Foxa2 is permanently inactive and consequently liver cells are not activated to metabolize fat. Available fat accumulates, resulting in a so called fatty liver. Subsequently, the sensitivity of liver cells to insulin is permanently reduced, causing diabetes to develop, even though the insulin level actually present in the body would be adequate when liver function would not be impaired.

Markus Stoffel, born in 1962, is Professor for Molecular Systems Biology at the Eidgenössische Technische Hochschule Zürich. He graduated in medicine after studying in Cambridge, United Kingdom, and Bonn, Germany. Following two-years at the Eppendorf University Hospital in

Hamburg, he held different positions at the University of Chicago for three years. In 1995, he was appointed full professor at the Rockefeller University in New York. In 2006 he joined the ETH in Zurich, and established a research team that focuses on the regulation of glucose and lipid levels in the blood. In 2006, Prof. Stoffel received the Distinguished Achievement Award of the American Diabetes Association and was appointed a member of the German Academy of Sciences 'Leopoldina'.

With the Heinrich Wieland Prize, Prof. Stoffel was awarded one of the most prestigious scientific distinctions in metabolic diseases research. The prize is named after the German chemist, lipid researcher and Nobel Prize winner Heinrich Otto Wieland (1877-1957). Since 1964, the prize is awarded annually and is endowed with a prize money of EUR 50,000. Boehringer Ingelheim, a pharmaceutical company that Heinrich Wieland was closely associated with is the sole sponsor of the research recognition. Heinrich Wieland founded the first scientific research department of the globally operating company at the beginning of the twentieth century, laying the cornerstone for the company's research activities.

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