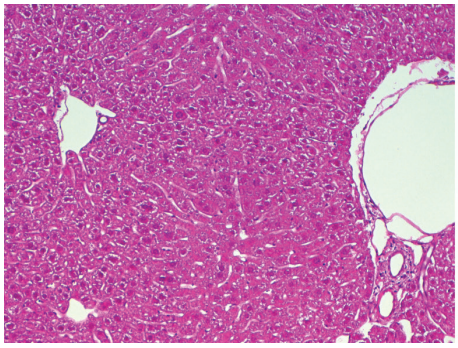
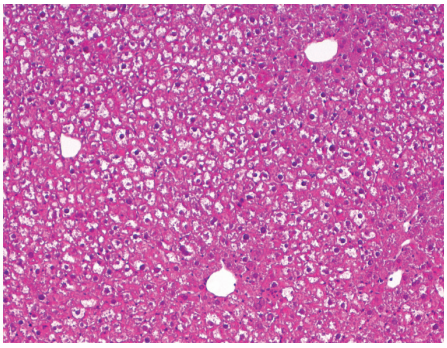
For **millions of people** their liver metabolism no longer responds to insulin. How this happens is the subject of study from the **scientists of the "LiverX"-Team** – Sugar is just not always sweet …

By Matthias Scholer

Now that we have consumed a delightful butter croissant with honey or a sumptuous serving of pasta, the thus incorporated carbohydrate are absorbed in the intestines and broken down into sugar. This then passes into the bloodstream and leads to a corresponding rise in blood sugar concentration. Faced with this increase, the pancreas responds by releasing the hormone insulin. "Among other things, the insulin binds to the liver cells that then turn their metabolism around by 180 degrees" says Prof. Wilhelm Krek, director of the RTD project LiverX. Because, "the liver ensures that the body has enough sugar to produce energy, day and night". Thanks to the blood sugar, the energy that the tissues need is available 'on tap'. "The liver cells hold the blood sugar level constant. If the level sinks, the liver cells produce sugar or reduce the stored sugar, the so-called glycogen. If the body is fed sugar after eating, however, the liver cells turn round the metabolism and store it," summarizes cell biologist Krek when asked about the regulatory processes in the liver. Thanks to a sophisticated interplay of energy supply and storage, the liver can keep blood sugar levels constant during the day-night rhythm.



Normal diet (healthy liver).



High-fat diet (fatty liver).

Disturbed signal transmission

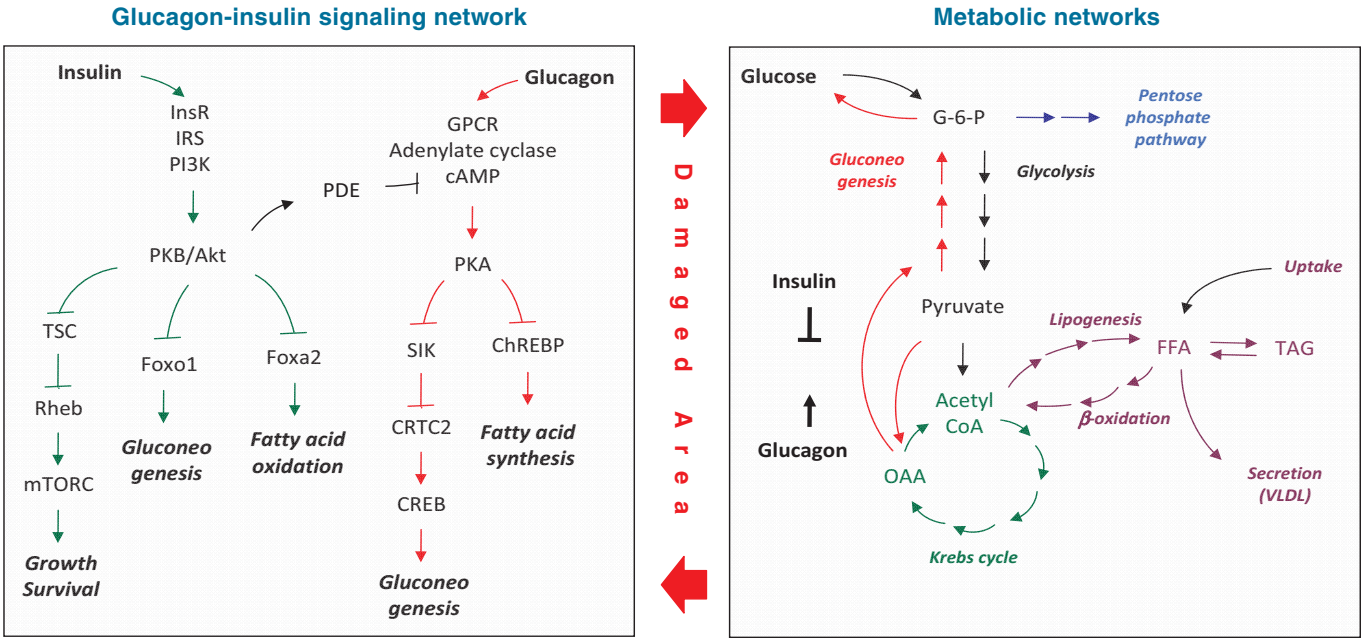
For more than 220 million people worldwide, however, this mechanism has broken down and, as a consequence, they suffer from diabetes. Fully 90% of sufferers have a so-called type II diabetes. With Type II, in contrast to Type I, enough of the insulin hormone is produced but has little or no effect on the metabolism of liver cells. For this reason, type II diabetes is also spoken of as an insulin resistance condition. "In this context, resistance does not mean that the hormone cannot latch onto the receptor. But with these patients it takes a multiple of the normal hormone levels to activate even approximately-metabolic conversion in the liver cells". This is why diabetic patients have to inject the missing insulin as soon as their blood sugar levels rise too high.

In recent decades many scientists have devoted themselves to the study of this disease process. This has already led to a wealth of findings. So, why is the LiverX team still keenly interested in the pathogenesis of insulin resistance in diabetes type II? "We want to find out why a healthy liver cell responds to insulin and an insulin-resistant cell doesn't," is how the cell biologist sums up the main objective of the project. Because, to date, research results give no uniformly consistent answer to this question.

What is undisputed is that the binding of the hormone to the receptor triggers a signaling network in liver cells. Finally, it is this signal that activates the liver-specific metabolic network. "In diabetes patients, the signal transmission to the metabolic network is disturbed. And it's precisely these fractures in signal transmission that we want to define and explore," explains Krek. For this, the researchers are employing the latest technology and complex mathematical models. "We're focusing on the quantitative measurement of the various components involved in signal transmission and their spatial arrangement," says the scientist about the aim of the measurements.

Of mice and men

These analyses are first carried out in healthy liver cells, not in human tissues, but in mouse liver cells. These rodents are ideal for investigations. On the one hand, the knowledge thus gained enables the team to approximate processes in human cells. On the other, it is a simple affair to study the influence of circadian rhythms and food intake on the metabolic processes of the mice under controlled conditions. "And," Krek goes on to explain, "we can deliberately ensure an oversupply of energy in order to provoke obesity within a mouse population. Obesity causes diabetes type II in animals, too, and gives us the means to compare the molecular processes, as well as healthy and insulin-resistant cells." When the researchers find a difference between two cell populations that could be responsible for the defective signaling, they leave the molecular world of mouse cells. "Our goal isn't to cure diabetes in mice. Once we have a hot lead, we investigate whether we can find the same difference between healthy and insulin-resistant human liver cells. Only then do we continue to examine the point in question," says Krek. Because the researchers do not want to waste unnecessary time. "We don't want to spend years defining the fractured points in the signal transmission in mice, only to find out, somewhere down the line, that only a small number of these plays a role in



human biology," says Wilhelm Krek, explaining the team's methods. After all, the medical relevance of the research results plays a central role in LiverX. "In a first step we want to understand the mechanism of insulin resistance at the molecular level. This will create the basis to consider new approaches in the treatment of diabetes," predicts the cell biologist, giving an insight into the future.

First, however, the team is focusing on the defects in signal transmission. And head of project Krek is satisfied with the current state of LiverX. "The project has only been running for a little over two years. We've been able to adapt our methods of measuring to the demands and the corresponding examinations are on schedule. Although we haven't yet been able to define a specific breaking point, we are optimistic about the future".

We can therefore hope that sugar will be sweet for everyone in the foreseeable future.

The "**LiverX**"-Team

- **Wilhelm Krek** (ETH Zurich) is head of the LiverX project. His own area of expertise is in the analyses of signal networks and gene expression programs that are steered by hormones and nutritional components.
- **Markus Stoffel** (ETH Zurich) is a recognized expert on metabolic imbalances. His work concentrates on the identification of gene patterns that bring about insulin resistance.
- **Matthias Peter** (ETH Zurich) brings his experience of the quantitative analysis of metabolic pathways in microfluid systems to the team.
- **Joachim Buhmann** (ETH Zurich) deals with the computer simulations of the modeling of hormonally-driven dynamic processes in liver cells.
- **Giatgen Spinas** (University Hospital Zurich) and **Markus Heim** (University Hospital Basle) contribute to the project with their years of experience in endocrinology, diabetes and hepatology.

«LiverX» – at a glance

LiverX
Systems Biology of Hepatic Insulin Resistance

Principal Investigator	Prof. Wilhelm Krek (ETHZ)
Involved research groups	Prof. Peter Bühlmann (ETHZ), Prof. Ruedi Aebersold (ETHZ),
	Prof. Joachim Buhmann (ETHZ), Prof. Markus Heim (University Hospital Basel),
	Prof. Luke Lee (University of California), Prof. Holger Moch (University Hospital Zurich),
	Prof. Matthias Peter (ETHZ), Prof. Volker Roth (University of Basel),
	Prof. Markus Rudin (ETHZ), Prof. Uwe Sauer (ETHZ),
	Prof. Giatgen Spinas (University Hospital Zurich), Prof. Jörg Stelling (ETHZ),
	Prof. Markus Stoffel (ETHZ), Dr. Nicola Zamboni (ETHZ)
Number of research groups	15
Researchers: Administrators	39 : 1
Biologists: Non-biologists	1.2 : 1
Total budget (2008–2011)	CHF 13 100 000, of which CHF 6 155 000 from SystemsX.ch