Universität Zürich[UZH]

ZIHPNews

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Sirtuins - «magic bullets» against atherosclerosis and diabetes?

Atherosclerosis and diabetes are among the most frequent causes of death. Researchers of the ZIHP joined forces to better understand these diseases.

Christina Giger and Magdalena Seebauer

Heart attack and stroke result from atherosclerosis, a disease induced by lipid depositions in the arterial wall – called plaques – with subsequent occlusions of the blood vessels supplying the heart and brain.

Diabetes mellitus is a metabolic disease characterized by elevated blood sugar (glucose) levels. The reason is that the body produces insufficient amounts of the hormone insulin (type 1 diabetes) or becomes resistant to it (type 2 diabetes). Insulin is needed to take up glucose into cells in order to generate energy. Without insulin glucose remains in the blood stream and is excreted with the urine.

High-fat diet as an important risk factor

A couple of years ago, researchers from different fields of expertise came together with the financial support of the ZIHP to better understand the causes of atherosclerosis and diabetes. Their hypothesis was that a high-fat diet would disturb the metabolic balance in the body and thus favor the development of these diseases. Indeed, they could prove this in a mouse model.

Protection by sirtuins

These findings set the basis for a subsequent, ZIHP-financed cooperative project: The researchers characterized a family with a mutation in a certain gene – called sirtuin 1 (SIRT1). Affected family members were suffering from diabetes or a severe inflammatory bowel disease. They also found that mice with dysfunctional SIRT1 showed similar symptoms as did the patients with the SIRT1 mutation. Additionally, mice in which SIRT1 was only partially active developed increased atherosclerosis. Conversely, pharmacological SIRT1 activation in mice decreased atherosclerosis induced by a cholesterol-rich diet. But first, the researchers had to identify the reactions induced by a high-fat diet that created pathology in cells and tissues.

Inflammation is a crucial factor in diabetes

Inflammation is a natural reaction of the body to eliminate or deter endogenous or exogenous stimuli that might be dangerous. This may occur in response to pathogens or – using similar pathways – as a reaction to excessive caloric intake. However, an overreaction of the immune system can be harmful.

Researchers of the ZIHP discovered that interleukin-1 and interleukin-6 – both mediators of inflammation – play an important role in the development of type 2 diabetes. Since obesity is a chronic inflammatory disease with excessive immune reaction in the fat tissue, the researchers from the cooperative project wanted to find out whether inflamed fat deposits in the body lead to the onset of type 2 diabetes and whether the localization of the deposit is important.

Therefore, the consortium transplanted fat tissue into the abdomen of mice. They placed the fat in a way that it was drained into the portal vein, which transports blood from the gut to the liver. The transplanted mice developed insulin resistance in the liver, a characteristic of type 2 diabetes. Why did this occur? The transplanted fat tissue became inflamed and produced increasing levels of interleukin-6 that were transported by the blood to the liver, where they caused insulin resistance. Intriguingly, transplanted fat from genetically modified mice that could not produce interleukin-6 did not confer insulin resistance.

... and also in atherosclerosis

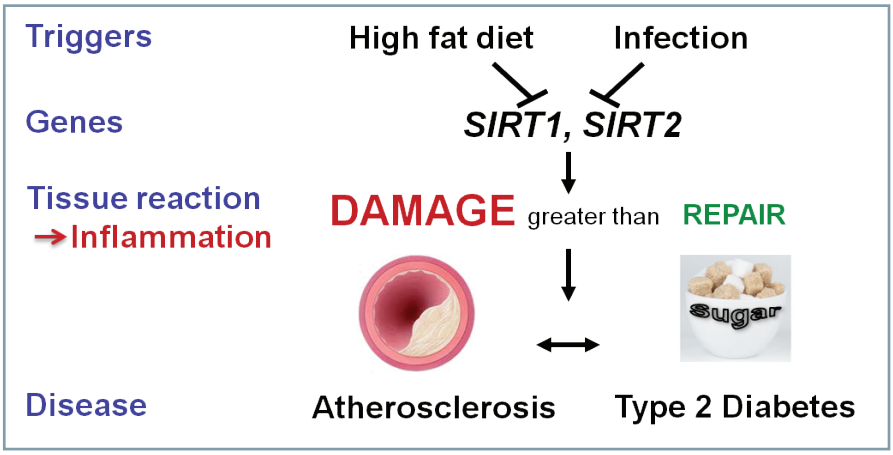
Inflammation also plays a central role in the development of atherosclerosis. In this case, macrophages are of critical importance. These immune cells «swallow» and digest foreign material in the body.

Exposed to a high-fat diet, the body takes up cholesterol, which is needed for building cell membranes. Nevertheless, an excess of blood cholesterol needs to be lowered. To achieve that, cholesterol can be bound to a certain transport molecule, the «high-density lipoprotein (HDL)». However, if it is bound to the «low-density lipoprotein (LDL)», it will remain in the body and can be harmful. LDL-cholesterol is therefore often referred to as the «bad cholesterol».

Excess LDL-cholesterol can be modified and oxidized in the body. Oxidized LDL-cholesterol can be recognized by macrophages as «foreign», and swallowed and digested. Doing so, macrophages will change their appearance and function and become so-called foam cells. Upon decay, they burst and release their oxidized LDL-cholesterol into the arterial wall. These lipid depositions attract additional inflammatory cells that form plaques leading to progression of atherosclerosis. If we eat too much cholesterol-rich food, excess amounts of LDL-cholesterol have to be eliminated from the body. Hence, more foam cells are formed and the risk for atherosclerosis rises.

The positive influence of SIRT1

The consortium of the cooperative project found that SIRT1 decreases the uptake of LDL-cholesterol into macrophages. Macrophages cannot recognize oxidized LDL-cholesterol any longer and therefore remain functional without transforming into foam cells. Interestingly, mice with partially deficient SIRT1 function develop increased atherosclerosis.



Complementarily, the researchers performed pharmacological experiments: They fed atherosclerotic mice with a cholesterol-rich diet and a SIRT1-activating drug. This decreased the amount of blood LDL-cholesterol, foam cell formation and diminished atherosclerosis. In addition, these experiments uncovered a novel mechanism involved in lowering blood cholesterol levels.

In summary, a high fat or cholesterol-rich diet activates the immune system. Physiologically, SIRT1 serves as a guard to control the body's immune reactions. However, if we eat too much fat or cholesterol, endogenous SIRT1 is unable to keep immune reactions balanced.

Similar effects occur if SIRT1 function is impaired by a mutation. Chronic inflammatory diseases such as atherosclerosis or type 2 diabetes may be the consequence. It is therefore very promising to aim for a pharmacologic SIRT1 activation that would generate several beneficial effects. Human studies are planned.

The ZIHP continues to support research on inflammatory diseases

Currently, researchers of the ZIHP are investigating the role of sirtuins in other chronic inflammatory diseases, such as inflammatory bowel disease or osteoporosis. Hints for an involvement of sirtuins were given by the finding that mice unable to produce SIRT1 develop a severe version of inflammatory bowel disease.

Apart from that, other approaches exist that aim for improved mechanistic insight or therapeutic applications. In a completed cooperative project, researchers showed that muscle training increases insulin sensitivity: Even small amounts of insulin are sufficient to convert glucose to energy. In another ongoing cooperative project, researchers examine the involvement of deoxysphingobases – waste products of cell membranes – in the development of diabetes.

Only the close interactions between experts from different research fields in basic and clinical science enable them to solve complex research questions. The ZIHP aims to facilitate such integrative projects also in the future through its financial support.

→ Sirtuins in the immune system: From physiology to auto-inflammatory and auto-immune disease
Consortium members: Christian Matter, Adriano Fontana, Peter J. Richards, Steffen Gay, Michael Hottiger, Gerhard Rogler
Project duration: January 2010 – December 2012
Supported PhD students: 3 (all within the → imMed PhD Program)

→ Role of inflammatory mediators in metabolic stress: from physiology to pathology
Consortium members: Marc Donath, Arnold von Eckardstein, Thomas Lutz, Christian Matter, Burkhard Becher, Daniel Konrad, Christoph Handschin
Project duration: January 2007 – December 2009
Supported PhD students: 5 (3 of them within the → imMed PhD Program)

ZIHP cooperative projects

→ all current projects

→ all completed projects

→ call for applications for new projects

«The most important things are communication, fairness, and trust»

What are the benefits of such a cooperative approach, what are the limitations?
Christian Matter: I very much appreciate the concept of the ZIHP cooperative projects. The idea to bring together experts from different research fields who strive to answer a question of common interest is what makes research exciting and successful. It's also the different approaches – whether you look at a human being, an experimental animal or deep into molecular mechanisms – that provides true added value and integrative answers.

Of course, like in every «cooperation» in life, be it partnership, friendship, research or company teamwork, you aim for optimal synergies, and you have to agree to compromises. All in all, I think we did well. It also provides an opportunity, especially for PhD students, to formulate own ideas and integrate other ones, accept challenges and solve them.

How did the cooperation evolve, how did it take place?
Matter: Many years ago, I met with Marc Donath. We were excited that inflammatory pathways in obesity and type 2 diabetes share many aspects with those driving atherosclerosis. We decided that it would be very rewarding to further investigate these phenomena together. The basis for a ZIHP cooperative project with many perspectives and much enthusiasm was laid.

«We could profit from each other's scientific networks.»
Christian Matter, project coordinator

During the cooperation, I think the most important things besides enthusiasm and expertise are communication, fairness, and trust. Therefore, the consortium met several times per year with the PhD students to set strategic goals, streamline reports and finances. Moreover, the principal investigators within each subproject met to present their latest findings, to prioritize ideas, and choose the most suitable approaches. Last but not least, also the PhD students met on an individual basis to fine-tune technical questions of their experiments and exchange ideas.

What was the specific benefit for the researchers and PhD students?
Matter: One big benefit for our consortium was that we could take advantage from each other's scientific networks that include many renowned scientists from all over the world. Thanks to the ZIHP as a main coordinating center we were able to invite such scientists to ZIHP symposia or seminars and to discuss our research face to face. This created valuable novel and exciting ideas.

With the SIRT1 project, we could engage in a fruitful collaboration with Sirtris, the company that produces SIRT1 activators. Bearing in mind that the activator once may be used for treatment of atherosclerosis, obesity or type 2 diabetes, such collaborations are essential to translate our experimental findings into a clinically relevant context.