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Researchers at Freiburg University help to discover new effect of insulin

Newly discovered role in ageing

Freiburg, Germany, March 20, 2008 – Researchers of the Albert-Ludwigs-Universität Freiburg, in a research collaboration with their colleagues of Harvard Medical School in Boston, USA, discover a novel function of insulin that affects ageing and longevity.

The study that will be published in the March 21 issue of the science magazine *Cell* describes how insulin, through the activity of an enzyme recently described by the Freiburg research team, blocks one of the most important cellular stress regulators, a protein called SKN-1. Increasing the activity of SKN-1 extends lifespan. SKN-1 controls a genetic network called the phase-2-detoxification pathway that helps to protect cells and tissues against damage through oxidative stress. Oxidative stress is the consequence of increased levels of the so called free radicals, generated as byproducts of the cellular metabolism and also through environmental toxins. This latest discovery was the result of experiments performed in the intestinal tract of the nematode *C. elegans*, a model organism frequently used to study aspects of human age-related disorders.

Only recently, the Freiburg research team led by Ralf Baumeister had shown that an enzyme called SGK-1 in the insulin signaling pathway helps to control lifespan. „At the same time our colleagues at the Joslin Diabetes Center of Harvard Medical School discovered another gene affecting longevity, encoding the stress regulator SKN-1“, explains Prof. Baumeister, an author of the recent Cell publication. „The most obvious thing to do was to compare our data and collaborate. We discovered that we had approached the same phenomenon from two sides“.

Taking into account the many roles of insulin in the organism this novel function of insulin may require close attention. The publication suggests that insulin, under certain circumstances, might reduce the cellular defense against oxidative stress more than previously anticipated.

One of the expectations now is that, through activating SKN-1, the organismal resistance against chronic diseases and longevity can be increased. The research could be equally

important for a better understanding of diabetes and many of its complications, some of the most prominent are atherosclerosis and renal defects.

„But the most significant impact of our findings will be that on ageing research", both research teams agree. „Although we already know since 1993 of the importance of insulin singaling for the control of organismal ageing, most of its details are still enigmatic", explains Baumeister. Until now, the researchers focused on a single genetic swich, the transcription factor FOXO, as the most important factor controlling lifespan. FOXO is switched off under normal conditions by insulin, and is equally important for the diabetes metabolism, stem cell maintenance, and tumor suppression. FOXO also regulates genes of the oxidative stress response. Reduced insulin signaling in *C. elegans*, for example through manipulating SGK-1, also activates a FOXO factor called DAF-16 that helps to protect against stress and expands lifespan.

This novel study now revealed the existence of SKN-1 as a second genetic switch that is also inhibited by insulin, but independent of FOXO. The data also suggest that SKN-1 controls a distinct genetic program of stress defence and anti-aging. „We felt like archaeologists discovering a secret treasure chamber. Activating SKN-1 was all that was needed to increase longevity of the worm, and this will open an entirely new research field", says Baumeister, who iass Director of the Freiburg Center for Systems Biology ZBSA aims at understanding the details of this complex regulatory network of ageing.

It will be important now to repeat the experiments in higher organisms. In mammals, insulin and the related insulin-like growth factor are both involved in an intricate network that is not yet understood in detail. However, as both teams agree, novel findings discovered in *C. elegans* could frequently be reproduced in mice and humans.

The Freiburg research team uses *C. elegans* as an animal model for a number of human age-related diseases. Their work in the past repeatedly helped to a better understanding of Alzheimer's and Parkinson's Disease, and also contributed to research in muscular dystrophies.
The study conducted at the University of Freiburg was financially supported by the German Ministery of Research (BMBF), a Landesstiftung grant of the State Baden-Württemberg, the Fonds der Chemischen Industrie Germany, the German Research Council, and the European Community.

About ZBSA – The Freiburg Center of Systems Biology
ZBSA is an interdisciplinary research center funded by the State Baden-Württemberg and the Albert-Ludwigs-Universität Freiburg. This interdisciplinary center is supported by all science faculties of the university. In its brand-new facilities, experimental scientists from Biology and Medicine and theoretical scientists from Physics and Mathematics collaborate with robotics and computer specialists for a better understanding of the complex interplay of genes and proteins in the organism and during diseases. ZBSA is the central facility for the scientific projects that are funded by the German Excellence Initiative as the result of a national competition.

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SUMMARY
Insulin/IGF-1-like signaling (IIS) is central to growth and metabolism and has a conserved role in aging. In *C. elegans*, reductions in IIS increase stress resistance and longevity, effects that require the IIS inhibited FOXO protein DAF-16. The *C. elegans* transcription factor SKN-1 also defends against oxidative stress by mobilizing the conserved phase 2 detoxification response. Here we show that IIS not only opposes DAF-16 but also directly inhibits SKN-1 in parallel. The IIS kinases AKT-1, -2, and SGK-1 phosphorylate SKN-1, and reduced IIS leads to constitutive SKN-1 nuclear accumulation in the intestine and SKN-1 target gene activation. SKN-1 contributes to the increased stress tolerance and longevity resulting from reduced IIS and delays aging when expressed transgenically. Furthermore, SKN-1 that is constitutively active increases life span independently of DAF-16. Our findings indicate that the transcription network regulated by SKN-1 promotes longevity and is an important direct target of IIS.