**Press Release**
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Leibniz Institute for Age Research
Fritz Lipmann Institute (FLI)

ERIBA

# Lean but sated: Molecular Switch for a Healthy Metabolism discovered

**The protein complex mTORC1 is a central regulator of cell metabolism. In the active state, it stimulates anabolic processes and increases the production and storage of proteins and lipids. Researchers from the German Leibniz Institute for Age Research in Jena and the Dutch Ageing Institute ERIBA in Groningen discovered a mechanism how mTORC1 regulates metabolism: It controls the expression of a specific variant of the transcriptional regulator C/EBPβ. Elimination of this variant in mice results in a healthy metabolism, leanness and improved insulin sensitivity. The study may provide a basis for novel strategies for the treatment of metabolic diseases such as obesity and type II diabetes.**

The mTORC1 (mammalian target of rapamycin complex 1) is a central regulator of cell metabolism and its activity is regulated by nutrient availability and growth signals. If activated, it stimulates anabolic metabolism and enhanced production of proteins and lipids. The resulting increase in biomass is a prerequisite for tissue growth. Hyper-activation of mTORC1 by overfeeding may result in obesity and is believed to promote metabolic disorders such as type II diabetes. In contrast, a calorie restricted diet decreases mTORC1 activity. This improves metabolic health and increases life span in many species up to mammals. Many researchers have focused on mTORC1 function during the past years because of its crucial role in metabolism. However, little is known about factors that are specifically controlled by mTORC1 and that are responsible for the regulation of genes that are important for metabolic adjustments.

Now, researchers from Leibniz Institute for Age Research – Fritz Lipmann Institute (FLI) in Jena, Germany, and European Research Institute for the Biology of Ageing (ERIBA) in Groningen, Netherlands, found a mechanism through which mTORC1 regulates metabolic processes. The research results were published in renowned journal *EMBO Reports*.

**Switching on and off metabolic gene transcription.**

“Researchers already know a lot about how mTORC1 is activated by nutrient supply. But little is known about the downstream factors that regulate metabolic genes and thereby determine the metabolic state of an organism”, Prof. Dr. Cornelis Calkhoven (ERIBA), former group leader at FLI, explains. A main function of mTORC1 is the stimulation of mRNA translation, which is the crucial and final process in gene expression that results in production of the biologically active proteins. “We now found a factor – C/EBPβ – which is controlled by mTORC1”, Calkhoven continues. C/EBPβ is a gene regulator that controls various metabolic genes. Within cells, there exist two kinds of C/EBPβ: the long variant is a gene activator, whereas the short variant suppresses genes.

“Our data show that mTORC1 specifically promotes the formation of the short variant of C/EBPβ”, Dr. Christine Müller (ERIBA), former researcher at FLI, states. The researchers used a mouse model in which a mutation in the C/EBPβ gene prevents the production of the short C/EBPβ variant even if mTORC1 is activated. “Intriguingly, our data show that mice with this mutation display an improved metabolic phenotype, including reduced fat metabolism and fat accumulation, and improved insulin sensitivity and glucose tolerance”, Dr. Laura Zidek, Postdoc at FLI, emphasizes the findings.

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**Healthy metabolism.**

“The healthy metabolic phenotype we observed in our mouse model is similar to what is found under calorie restriction”, Calkhoven explains. Interestingly, these positive effects can be achieved without reduction in food intake: the mice are lean but sated.

“Our study shows that the mechanism regulating the formation of C/EBPβ variants is an important molecular switch in the metabolic pathway controlled by mTORC1. Thus, pharmacological targeting of C/EBPβ isoform expression may provide a promising strategy for the treatment of metabolic diseases such as obesity and type II diabetes thereby extending health span.

**Publication.**

Zidek LM, Ackermann T, Hartleben G, Eichwald S, Kortman G, Kiehntopf M, Leutz A, Sonenberg N, Wang ZQ, von Maltzahn J, Müller C, Calkhoven CF. Deficiency in mTORC1-controlled 1 C/EBPβ -mRNA translation improves metabolic health in mice. EMBO Rep. 2015. pii: e201439837. DOI 10.15252/embr.201439837.

**Background information.**

The **Leibniz Institute for Age Research – Fritz Lipmann Institute (FLI)** is the first German research organization dedicated to biomedical aging research since 2004. More than 330 members from over 30 nations explore the molecular mechanisms underlying aging processes and age-associated diseases. For more information, please visit *www.fli-leibniz.de*.

Dutch **European Research Institute for the Biology of Ageing (ERIBA)** was founded by the **University Medical Center Groningen (UMCG)** in 2013. ERIBA is an internationally orientated research institute focusing on fundamental biological problems related to aging and age-associated diseases. See *www.umcg.nl/EN/Research/ERIBA* for more information.

The **Leibniz Association** connects 89 independent research institutions that range in focus from the natural, engineering and environmental sciences via economics, spatial and social sciences to the humanities. Leibniz Institutes address issues of social, economic and ecological relevance. They conduct knowledge-driven and applied basic research, maintain scientific infrastructure and provide research-based services. The Leibniz Association identifies focus areas for knowledge transfer to policy-makers, academia, business and the public. Leibniz Institutes collaborate intensively with universities – in the form of “WissenschaftsCampi” (thematic partnerships between university and non-university research institutes), for example – as well as with industry and other partners at home and abroad. They are subject to an independent evaluation procedure that is unparalleled in its transparency. Due to the institutes’ importance for the country as a whole, they are funded jointly by the Federation and the Länder, employing some 18,100 individuals, including 9,200 researchers. The entire budget of all the institutes is approximately 1.64 billion EUR. See *www.leibniz-association.eu* for more information.

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**Picture 1**

mTORC1 controls the expression of different variants of the gene regulator C/EBPβ. Suppression of the short variant in mice leads to a healthy metabolism, leanness and improved insulin sensitivity.

[Source: Lazare / www.pixabay.com]