press release

MEDIZINISCHE UNIVERSITÄT INNSBRUCK

Tyrolean summit success: SCIENCE reports on Innsbruck research
A team from the Innsbruck Biocenter enlightens the molecular structure of a cancer-relevant protein complex

With the detailed atomic elucidation of the crystal structures of the so-called LAMTOR complex and its implications for the cellular signal transmission, a research team from the Innsbruck Biocenter headed by the scientists Lukas A. Huber (cell biology) and Klaus Scheffzek (structural biology) attracts attention within the international scientific community. The protein complex LAMTOR controls a variety of essential processes in the cell and can be interpreted as a molecular switch for signaling pathways relevant for the development of cancer and metabolic diseases. SCIENCE, one of the world's most respected science magazines, reports on this.

Innsbruck, 22.9.2017: Signal propagation in cells plays an essential role in the development of the tumor as well as in the course of the immune response and thus in the development of metabolic disorders such as diabetes and metabolic syndrome. LAMTOR, originally identified by the working group of the Tyrolean cell biologist and phsyician Lukas A. Huber amongst others consists of seven proteins (p14, p18, MP1, HBXIP, p11, also termed LAMTOR1-5) RagA and RagC). It coordinates cell division, cell growth, cell death and cell migration by recruiting the signaling proteins MAPK and mTORC to the lysosome. In a cooperation funded by the Austrian Science Funds (FWF), the research groups of Huber, Scheffzek and other colleagues at the Biocenter of the Medical University have now succeeded in elucidating the three-dimensional structure of the LAMTOR complex and its impact on signaling. Their results may open a door to the development of new therapeutic approaches. The groundbreaking findings from Innsbruck have just been published in the renowned international journal *SCIENCE*.

Zooming into the detail
The method of biomolecular crystallography established with the appointment of the structural biologist Klaus Scheffzek to the Biocenter (then under the directorship of Lukas A. Huber) enables the detailed 3-dimensional structure determination of biomolecular components and their complexes in the submicrometer range. "We see that the LAMTOR1 subunit forms the clamp that binds the other components and tethers the protein complex to the lysosome, the mobile waste disposal and signaling platform of the cell. RagA and RagC, two signal components of the G protein family, are thereby aligned with the signal path mTORC and thus dock to the lysosomal LAMTOR complex," explains Scheffzek, whose special expertise is in the area of the so called G proteins, key signal propagators in cells.
On the basis of this structural view, it was now possible to selectively insert mutations that interfere with the complex by means of the CRISPR / CAS9 gene shears into the genome of human cells in order to investigate and study their effects in cell culture. If, for example, the clip LAMTOR1 was severed at certain points, the complex was no longer functional. At the same time, those amino acid regions which are responsible for a functional assembly have been identified. "The knowledge about the critical amino acid positions gives us a preview of potential new drugs that could turn off the complex in diseases like cancer or metabolic disorders, in which the mTORC signaling pathway is overactive, explains the physician and cell biologist Huber.

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Know-how and close proximity

The new findings of the Innsbruck team are the result of a number of research years driven by relentless scientific curiosity and, last but not least, optimal campus-strategic factors. "In the course of this research, not least in view of international high-level competition, we were striving for optimal combination of scientific neighbourhood and expertise," said Scheffzek and Huber. Their study may also challenge earlier work by the American molecular biologist and discoverer of the mTORC signaling path, David Sabatini. "Now that we understand the cellular biological function of the individual components in the signal forwarding, the findings from 2012 and thus the regulation of the signal transduction by LAMTOR must also be seen in a new light," summarize Huber and Scheffzek.

Future Prospects

For the further development of the research work, Scheffzek and Huber aim to study higher order complexes involving LAMTOR. In addition, in cooperation with the Austrian Drug Screening Institute (ADSI) in Innsbruck, the structural biology insights the complex offers to be translated into chemical compounds aiming at switching off the mTORC complex that is hyperactive in certain diseases.

Press pictures to download and link to the research: https://www.i-med.ac.at/pr/presse/2017/41.html

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About Medical University of Innsbruck

Medical University of Innsbruck has approximately **1,400* employees** and around **3,000 students** and, together with the University of Innsbruck, is the largest educational and research institution in western Austria and the regional university for Tyrol, Vorarlberg, South Tyrol and Liechtenstein. The following courses are offered at Innsbruck Medical University: **Medicine and Dentistry** as the basis of an academic medical degree and a **PhD degree (PhD)** as the postgraduate aspect of scientific work. The bachelor's degree in **Molecular Medicine** is new in the curriculum since autumn 2011. There is the possibility to continue with a master degree in Molecular Medicine.
Medical University of Innsbruck is involved in numerous international educational and research programmes and networks. The research focuses on the areas **Oncology**, **Neuroscience**, **Genetics**, **Epigenetics** and **Genomics** as well as **Infectious Diseases**, **Immunology & Organ and Tissue Repair**. In addition to scientific research, Medical University of Innsbruck is also nationally and internationally very successful in the highly competitive field of research funding.

* full-time equivalent

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