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New inhibitor for regulating the essential protein SMNDC1

The SMNDC1 gene controls key functions in the human body and is linked to diseases such as diabetes and cancer. Scientists in Stefan Kubicek's research group at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences have successfully pinpointed the exact location of the SMNDC1 protein within the cell nucleus and identified an inhibitor that opens up the potential for therapeutic applications of SMNDC1. The study has been published in Nature Communications.

(Vienna, 16 August 2023) The protein SMNDC1 is considered an essential gene in the human body, present in nearly every cell. Previous studies by Principal Investigator Stefan Kubicek's research group at CeMM had shown that knocking down SMNDC1 can stimulate alpha cells in the islets of Langerhans to produce insulin, potentially offering a new therapeutic target for treating diabetes. To better understand the function of SMNDC1, the scientists in the Kubicek group investigated its precise cellular location and its interactions with molecules.

SMNDC1 is classified as a splicing factor, meaning it is involved in the process where RNA is transformed into the final messenger RNA that carries the genetic information. This messenger RNA is essentially the blueprint for building a specific protein in a cell. Consequently, SMNDC1 influences the expression of many other proteins. Study first author Lennart Enders, a PhD student in Kubicek's lab, successfully and precisely localized SMNDC1 in the cell nucleus for the first time, explaining, "Our study has shown that SMNDC1 specifically resides within small compartments in the cell nucleus known as 'nuclear speckles,' due to their speckled appearance. These small droplets, formed through phase separation without a membrane, collect proteins with similar functions. SMNDC1 congregates with other proteins that are also thought to play a central role in the splicing process."

New inhibitor binds specifically to SMNDC1

Studies have already linked SMNDC1 to a wide variety of diseases such as liver cancer and diabetes. In light of this, Enders and his colleagues searched for an inhibitor that specifically binds to and influences SMNDC1, thereby identifying a new potential drug target. Through a comprehensive screening of about 90,000 chemical compounds in collaboration with Marton Siklos, a chemist in Kubicek's lab, key molecules were identified as inhibitors and subsequently improved in their molecular structure to ensure better and more specific binding to SMNDC1. Together with the Sattler Laboratory (TU Munich), the scientists used nuclear magnetic resonance to demonstrate precisely how the developed inhibitor binds to the SMNDC1 protein domain.

Research group leader Stefan Kubicek added, "SMNDC1 is an essential gene, and its complete loss impairs the viability of most cell types. In relation to diabetes and cancer, we see therapeutic potential in exploring new treatment avenues. Our earlier study revealed that SMNDC1 suppresses insulin transcription and PDX1 mRNA stability in alpha cells. Additionally, the loss of SMNDC1 in human pancreatic islets improves glucose sensitivity." In the next phase, the scientists intend to collaborate with partners to further investigate the therapeutic potential of SMNDC1.

Interested in partnering? Find out more about the Small Molecular Program to target SMNDC1 here.

Picture attached: First author Lennart Enders and last author Stefan Kubicek, © Anna Yuwen, CeMM

The Study "Pharmacological perturbation of the phase-separating protein SMNDC1" was published in Nature Communications on 16 August 2023, DOI: 10.1038/s41467-023-40124-0.

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Stefan Kubicek joined CeMM in August 2010. He obtained an MSc in synthetic organic chemistry from the Vienna University of Technology after writing a diploma thesis at ETH Zurich. For his PhD in Thomas Jenuwein's lab at the IMP in Vienna, he changed fields to molecular biology. He then performed postdoctoral research working on chemical biology with Stuart Schreiber at the Broad Institute of Harvard and MIT. Stefan Kubicek heads the chemical screening platform and PLACEBO (Platform Austria for Chemical Biology), a task he is well equipped for based on previous screening experience with Boehringer Ingelheim and at the Broad Institute. Stefan Kubicek has also headed the Christian Doppler Laboratory for Chemical Epigenetics and Antiinfectives, a public-private partnership between CeMM, Boehringer Ingelheim and Haplogen. The Kubicek lab is working on the role of chromatin in the definition of cell types and cell states, particularly chromatin modifying enzymes as synthetic lethal targets in cancer and chemical transdifferentiation to insulin-producing beta cells. In an ERC-funded project, the laboratory is working on metabolic enzymes in the cell's nucleus and testing the hypothesis that small molecule metabolites shape chromatin structure and thus control gene expression and cell identity.

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The **CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences** is an international, independent and interdisciplinary research institution for molecular medicine under the scientific direction of Giulio Superti-Furga. CeMM is oriented towards medical needs and integrates basic research and clinical expertise to develop innovative diagnostic and therapeutic approaches for precision medicine. Research focuses on cancer, inflammation, metabolic and immune disorders, and rare diseases. The Institute's research building is located on the campus of the Medical University and the Vienna General Hospital.
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