

Rare disease reveals crucial factor for fat digestion

Patients with congenital diarrheal disorders, a group of rare inherited diseases with largely unknown mechanisms, suffer from severe to life-threatening diarrhea and nutrient malabsorption from birth. Using state-of-the-art genetic and molecular biology analysis methods involving the revolutionary gut organoid technology, researchers from the LBI RUD and CeMM, together with the Medical University of Innsbruck and University Medical Center Utrecht identified the largest cohort of DGAT1-deficient patients to date. The scientists also unveiled the molecular mechanisms of the affected protein and discovered its crucial role in fat digestion. The results, published in *Gastroenterology*, lead to a substantial therapy improvement of the patients and displayed new fundamental features of human biology.

(Vienna, the July 6, 2018) For our body to absorb fat from our diet, a series of complex biochemical reactions take place. First, the fat molecules consisting of a glycerol bound to three fatty acids (therefore also known as triglycerides) have to be digested by various enzymes into its components prior to being absorbed by cells of the small intestine, the enterocytes. Here, they are restored into triglycerides and packed into small particles which are released into the blood stream and transported into the rest of the body. If this process of dietary fat is disturbed, it can lead to devastating conditions.

This was the case with ten children from six families, all of whom suffered since birth from extreme diarrhea and/or vomiting. After a number of conventional therapies failed, the case of the young children was reported to the team of Kaan Boztug, Director of the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI RUD) and Adjunct Principal Investigator of the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences. In collaboration with the Medical University of Innsbruck, the University Medical Center Utrecht and the Ankara University School of Medicine, the scientists performed DNA sequencing on the patients and identified mutations in the gene for a protein called diacylglycerol-acyltransferase 1 or DGAT1. The study was published in *Gastroenterology* (DOI: 10.1053/j.gastro.2018.03.040).

DGAT1 is an enzyme crucial for the terminal step of triglyceride formation in enterocytes representing cells lining the intestinal tract. The scientists showed that the mutations resulted in a reduced or total lack of DGAT1 protein in cells of the patients. In an *in vitro* experiment, those cells were not able to metabolize lipids properly. Above that, the researchers were able to establish gut organoids - miniaturized and simplified structures with organ-like properties - out of patient-derived biopsies and recapitulated the effects of the genetic defect. Excitingly,

repairing the function of DGAT1 in patient-derived fibroblast cells or inducing another enzyme called *DGAT2* restored the lipid metabolism.

“Gut organoids may serve as an excellent model system to further characterize gastrointestinal diseases”, Rico Ardo. PhD Student at LBI-RUD/CeMM and joint-first author of the study, emphasizes: “Combined with the other experimental approaches, they enabled us to elucidate the genetic cause and molecular mechanism of the patients’ symptoms. These findings indicate the importance of DGAT1 in fat metabolism in the intestinal epithelium.”

The study highlights the importance of genetic diagnosis of patients with early onset diseases as a crucial step for developing a proper care and therapy. At the same time, this work once again shows the general relevance of research on rare diseases, which in many cases not only helps affected patients, but also provides new insights into human biology.

“Studying such rare diseases pinpoint core homeostatic processes in human physiology and enable us to find therapies where conventional approaches fail”, Kaan Boztug adds. “The DGAT1-deficient patients have been commenced in a fat-free diet as a first line of therapy, which is proving effective, and LBI-RUD researchers are exploring the development of more specific and precise personalized therapies”.

Attached pictures: Immunofluorescent images of DAPI (blue) and LD540 (yellow) staining of organoids 1a&b) from healthy control 2a&b) from DGAT1-deficient patient. Adapted from *Gastroenterology*, picture by Jorik M van Rijn.

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Authors: Jorik M van Rijn[#], Rico Chandra Ardy[#], Zarife Kuloğlu[#], Bettina Härter[#], Désirée Y. Van Haaften-Visser[#], Hubert van der Doef, Marliek van Hoesel, Aydan Kansu, Anke H.M. van Vugt, Marini Thian, Freddy T.M. Kokke, Ana Krolo, Meryem Keçeli Başaran, Neslihan Gürcan Kaya, Aysel Ünlüsoy Aksu, Buket Dalgıç, Figen Ozcay, Zeren Baris, Renate Kain, Edwin C.A Stigter, Klaske D. Lichtenbelt, Maarten P.G. Massink, Karen J Duran, Joke B.G.M Verheij, Dorien Lugtenberg, Peter G.J Nikkels, Henricus G.F. Brouwer, Henkjan Verkade, Rene Scheenstra, Bart Spee, Edward E.S. Nieuwenhuis, Paul J. Coffey, Andreas R Janecke, Gijs van Haaften, Roderick H.J. Houwen, Thomas Müller^{*}, Sabine Middendorp^{*} and Kaan Boztug^{*} ([#]shared first authors, ^{*}shared senior authors).

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Kaan Boztug studied human medicine in Düsseldorf, Freiburg and London, after which he graduated with Ian Campbell at the Scripps Research Institute (La Jolla, US). He completed his clinical training and postgraduate research with Christoph Klein at Hannover Medical School prior to his first appointment as an independent group leader in 2011 at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences. Since 2011, he holds a dual appointment as Associate Professor at the Department of Paediatrics and Adolescent Medicine at the Medical University of Vienna. Since 2016, Kaan Boztug is director of the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases. He is furthermore director of the CeRUD Vienna Center for Rare and Undiagnosed Diseases as well as the Jeffrey Modell Diagnostic and Research Center Vienna at the Medical University of Vienna and the St. Anna Childrens' Hospital.

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For **further information** please contact

Mag. Wolfgang Däuble

Media Relations Manager

CeMM

Research Center for Molecular Medicine
of the Austrian Academy of Sciences

Lazarettgasse 14, AKH BT 25.3

1090 Vienna, Austria

Phone +43-1/40160-70 057

Fax +43-1/40160-970 000

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wdaeuble@cemm.oeaw.ac.at

www.cemm.at