

PRESS RELEASE

False alarm of the immune system during muscle disease

New findings on the link between myotonic dystrophy 2 and autoimmune diseases

Bonn / Dresden, February 21 - Researchers at the University Hospitals of Dresden and Bonn of the DFG Transregio 237 and from the Cluster of Excellence ImmunoSensation2 at the University of Bonn have made progress clarifying why patients with myotonic dystrophy 2 have a higher tendency to develop autoimmune diseases. Their goal is to understand the development of the disease, and their research has provided new, potential therapeutic targets. The results of the study have now been published in the renowned journal "Nature Communications".

Myotonic dystrophy 2 (DM2) is a form of muscular dystrophy, a disease that leads to progressive muscle degeneration. It is caused by the expansion of a repetitive DNA sequence containing multiple CCTG bases in the CNBP gene. In general, the sequence of nucleobases in the DNA carries the genetic information. Patients suffer from muscle weakness that is more pronounced in the area of the muscles close to the trunk, as well as sustained muscle stiffness and pain. Although DM2 occurs in roughly one out of 10,000 people in Germany, there are no targeted therapies. In initial studies, Prof. Claudia Günther and her team at the Carl Gustav Carus University Hospital at the Technical University of Dresden also observed that patients with DM2 suffer more from autoimmune diseases with an increased production of antibodies in the blood than the general population. However, the underlying mechanism for these symptoms was previously unknown.

Anti-viral response without a virus

In addition to the higher rates of autoimmunity, i.e. impaired tolerance to certain endogenous substances, Günther's team observed an unusual gene signature in cells derived from DM2 patients. "There were genes upregulated in the patient cells that are normally there to combat viruses," says first author Sarah Rösing, a doctoral student in Prof. Günther's Dresden research group. "We quickly realized that this was an important discovery. While this type of immune response helps to combat viral infection, chronic activation is often connected to autoimmunity, so we really needed to understand where it comes from". In order to elucidate the link between the expanded DNA repeats (CCTG)_n found in DM2 patients, the antiviral response and autoimmune diseases, scientists from the DFG-funded

Medical Director and Chairman of the Board

Tel: +49 228 287-10900
Fax: +49 228 287-9010900
wolfgang.holzgreve@ukbonn.de

Communication and media

Viola Röser
Management

Tel: +49 228 287-10469
viola.roeser@ukbonn.de

Bonn University Hospital
Communication and media
Venusberg Campus 1
Geb. 02
53127 Bonn

Transregio 237 "Nucleic Acid Immunity" at the University Hospitals of Dresden and Bonn and the Cluster of Excellence ImmunoSensation2 at the University of Bonn collaboratively investigated the molecular signature in cells from patients with DM2.

DM2 cells are under chronic stress from junk proteins

In close collaboration, the researchers in Dresden and Bonn showed that in the cells of DM2 patients, the DNA repeats (CCTG)_n are translated into toxic nonsense proteins. Their formation leads to a chronic form of stress of endoplasmic reticulum (ER), a branched duct system as an extension of the nuclear membrane, which is where many proteins are folded. This ER Stress causes, in turn, chronic damage to the mitochondria, the energy powerhouse of the cells. "Mitochondrial damage and ER stress in our cells are clear signals that something is wrong," comments Prof. Eva Bartok, one of the senior authors of the publication from the University Hospital Bonn and the University of Bonn, "this type of stress can definitely look like a viral infection and trigger an antiviral response".

Cellular stress triggers the immune response

These "stressed mitochondria" release small amounts of DNA within the cell, which are then recognized as a danger signal by the innate immune system. This is because cGAMP synthase (cGAS), an important innate immune receptor for DNA, recognizes this mitochondrial DNA and thus triggers an alarm state in the host by inducing release of the key antiviral mediator, type I interferon. "That was our 'aha' moment," says Prof. Günther, corresponding author of the publication. "We have identified a mechanism and a pathway that now open up new possibilities for targeted therapies of the disease."

Confirmation through studies and outlook

These important findings offer new potential therapeutic targets to suppress the development of the autoimmune disease in these patients. "Our data provides an important rationale for inhibiting cGAS and the type I interferon pathway in myotonic dystrophy 2," comments Prof. Bartok. "It is very exciting to see how the results of our basic research could potentially improve the care of these patients," concludes Prof. Günther.

Publication: Sarah Rösing, Fabian Ullrich, Susann Meisterfeld, Franziska Schmidt, Laura Mlitzko, Marijana Croon, Ryan Natrass, Nadia Eberl, Julia Mahlberg, Martin Schlee, Anja Wieland, Philipp Simon, Daniel Hilbig, Ulrike Reuner, Alexander Rapp, Julia Bremser, Peter Mirtschink, Stephan Drukewitz, Thomas Zillinger, Stefan Beissert, Katrin Paeschke, Gunther Hartmann, Aleksandra Trifunovic, Eva Bartok and Claudia Günther; Chronic endoplasmic reticulum stress in myotonic dystrophy type 2 promotes autoimmunity via mitochondrial DNA release; Nature Communications; DOI: <https://doi.org/10.1038/s41467-024-45535-1>

Scientific contact:

Prof. Dr. Eva Bartok

Institute for Experimental Hematology and Transfusion Medicine
University Hospital Bonn

Cluster of Excellence ImmunoSensation2, University of Bonn

phone: +49-228-287-16730

e-mail: ebartok@uni-bonn.de

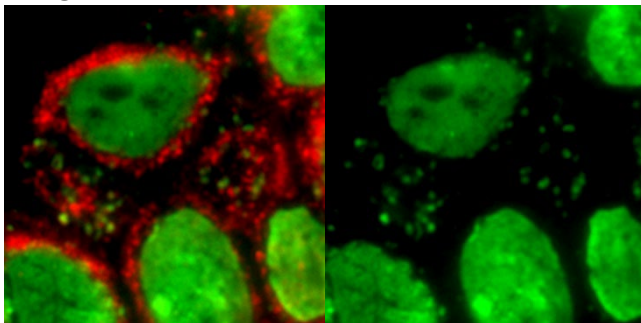
Prof. Dr. Claudia Günther

Klinik und Poliklinik für Dermatologie

E-Mail: Claudia.Guenther@ukdd.de

University Hospitals Dresden

Image material:



Caption: DNA (green) leaked into the cytoplasm colocalises with the DNA sensor cGAS (red) in the skin of patients with myotonic dystrophy type 2.

Picture credits: University Hospitals Dresden / Sarah Rösing



Caption: Together, Prof. Claudia Günther (left) from Dresden Prof. Eva Bartok and (right) from Bonn are investigating the connection between myotonic dystrophy and autoimmune diseases.

Picture credits: University Hospitals Dresden & University Hospital Bonn

Press contact:

Dr. Inka Väth

Deputy Press Officer at the University Hospital Bonn (UKB)

Communications and Media Office at Bonn University Hospital

Phone: (+49) 228 287-10596

E-mail: inka.vaeth@ukbonn.de

About University Hospital Bonn: The UKB treats around 500,000 patients per year, employs around 9,000 staff and has total assets of 1.6 billion euros. In addition to the 3,500 medical and dental students, 550 people are trained in numerous healthcare professions each year. The UKB is ranked first among university hospitals (UK) in NRW in the science ranking and in the Focus clinic list and has the third highest case mix index (case severity) in Germany. In 2022 and 2023, the F.A.Z. Institute recognized the UKB as the most desirable employer and training champion among public hospitals in Germany.