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Press release

Deutsches Zentrum für Neurodegenerative Erkrankungen e.V. (DZNE)
Dr. Marcus Neitzert

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"Prelude" to Neuromuscular Disease SMA May Offer Chances for Better Treatment

Spinal muscular atrophy (SMA) is a severe neurological disease for which there is presently no cure, although current therapies can alleviate symptoms. In the search for better treatment options, scientists at DZNE and the Dresden University of Technology are now drawing attention to previously unnoticed abnormalities in embryonic development. They base their argument on studies of so-called organoids: Laboratory-grown tissue cultures that can reconstruct disease processes. Their findings are published in the journal "Cell Reports Medicine".

In SMA, neurons in the spinal cord degenerate, leading to paralysis and muscle wasting. The disease usually manifests in childhood and affects an estimated 1,500 individuals in Germany. Defects in a specific gene are considered to trigger SMA. These mutations result in a deficiency of the so-called SMN protein (Survival of Motor Neuron protein), which is critical for neurons involved in motor control. Since a few years, medical treatments have been available to address the protein deficiency by means of gene therapy. Intervention can begin within a few days after birth. However, while this approach can alleviate disease symptoms, experience to date indicates that it provides no cure.

A so far unknown prelude

Now, scientists in Dresden, Germany, are suggesting broadening the perspective in the search for better therapies. "The current perception of SMA focuses on the disease after birth, when the basic framework of the nervous system is mostly formed. This view ignores that phenomena relevant to the disease could occur much before, when the nervous system is still developing. In fact, our studies suggest that SMA is associated with anomalies in the embryonic development not known until now. We therefore believe that there is a hitherto unrecognised prelude to this disease, and that interventions are needed that go beyond existing therapies", says Dr. Natalia Rodríguez-Muela, a research group leader at DZNE's Dresden site and at the Center for Regenerative Therapies Dresden (CRTD) of Dresden University of Technology.

Tiny pieces of tissue

For their studies, Rodríguez-Muela and colleagues created "organoids" that recapitulate key features of both spinal cord and muscle tissue. These complex, albeit tiny samples of artificially generated tissue, each of them about the size of a grain of rice, were grown from human induced pluripotent stem cells. These had in turn been obtained by reprogramming skin cells of individuals affected by SMA. "It is the first time that organoids of this complexity have been generated for studying SMA", Rodríguez-Muela says. "Although these are model systems that have certain limitations, they come quite close to the real situation, because they comprise a diversity of cell types and tissue structures that occur in the human body." As the organoids matured over time, the scientists were able to study various developmental stages. "The earliest phase we can emulate with our organoid model corresponds to that of a human embryo a few weeks old. However, we only replicate the spinal cord and muscle tissue. Starting from the early developmental phase,

we can go up to the situation after birth, in particular as it is observed in patients with SMA", Rodríguez-Muela explains.

Cellular aberrations

When the scientists compared organoids with SMA pathology with healthy specimens, they found significant differences: Specifically, stem cells in SMA organoids tended to develop prematurely into spinal cord neurons. In addition, there was a distortion in the cell population, i.e., less neurons than normal, which also were highly vulnerable, and more muscle cells derived from the stem cells. Rodríguez-Muela and coworkers observed similar effects in mouse embryos with SMA-like pathology, supporting the findings in organoids. These tissue cultures also yielded another important result. "When we corrected the genetic defect associated with SMA, we still observed developmental abnormalities, although to a lesser extent", says Rodríguez-Muela. "This suggests that restoring the gene, as current therapies kind of do, is most likely not enough to completely amend SMA pathology. This is in line with clinical experience to date. Thus, I believe, we need to address the developmental abnormalities, if we want to improve treatment for SMA."

Spotlight on regulation

Rodríguez-Muela suspects that the cause for the observed developmental defects could lie in impaired gene regulation. "It may not only be a question of whether the gene producing the SMN protein is defective or not. Perhaps it is also relevant, if the deficiency of this protein impacts other genes critical for the embryo's early development. There could be a regulatory effect. The fact is that we still don't know, but it is a plausible possibility", she says. "I believe that this idea should be explored further. In the long term, this may lead to improved therapies that combine existing approaches with drugs targeting gene regulation. That is, they would have to act on what is called "epigenetics". In order to minimize the developmental abnormalities, such treatment would most likely need to be applied in early pregnancy. If prenatal testing indicates SMA, this could be a therapeutic option."

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About Deutsches Zentrum für Neurodegenerative Erkrankungen, DZNE (German Center for Neurodegenerative Diseases): DZNE is a research institute for neurodegenerative diseases such as Alzheimer's, Parkinson's and ALS, which are associated with dementia, movement disorders and other serious health impairments. To date, there are no cures for these diseases, which represent an enormous burden for countless patients, their families and the healthcare system. The aim of DZNE is to develop and translate into practice novel strategies for prevention, diagnosis, care and treatment. DZNE comprises ten sites across Germany and collaborates with numerous universities, university hospitals, research centers and other institutions in Germany and throughout the world. It is state-funded and a member of the Helmholtz Association and of the German Centers for Health Research. https://www.dzne.de/en

About the Center for Regenerative Therapies Dresden (CRTD)
The Center for Regenerative Therapies Dresden (CRTD) of TUD Dresden University of Technology is an academic home for scientists from more than 30 nations. Their mission is to discover the principles of cell and tissue regeneration and leverage this for the recognition, treatment, and reversal of diseases. The CRTD links the bench to the clinic, scientists to clinicians to pool expertise in stem cells, developmental biology, gene-editing, and regeneration towards innovative therapies for neurodegenerative diseases such as Alzheimer's and Parkinson's disease, hematological diseases such as leukemia, metabolic diseases such as diabetes, bone and retina diseases. The CRTD was founded in 2006 as a research center of the German Research Foundation (DFG) and funded until 2018 as a DFG Research Center, as well as a Cluster of Excellence. Since 2019, the CRTD is funded by the TU Dresden and the Free State of Saxony.
The CRTD is one of three institutes of the central scientific facility Center for Molecular and Cellular Bioengineering (CMCB) of the TU Dresden.
https://www.tud.de/crtd
https://tu-dresden.de/cmcb

Original publication:
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Tobias Grass et al., Cell Reports Medicine (2024), DOI: 10.1016/j.xcrm.2024.101659

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