Hope for children with rare genetic defect

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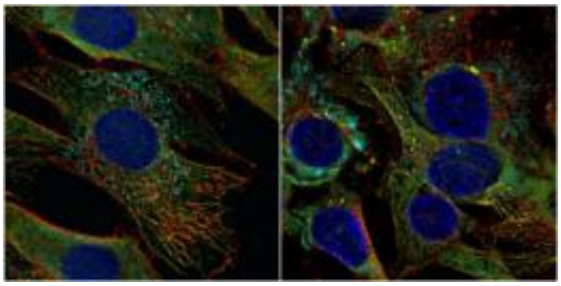

With the help of MELC microscopy, it is possible to visualize the location of large number of different proteins in the same cells by sequential staining. Compared to the healthy cells of the wild type (left), the cells of mice suffering from JNCL (right) are smaller, and the distribution of the proteins seems "disordered." Some structures are lost, others seem pathologically bloated, as can be seen in the structures colored in green. While the cells of the wild type exhibit a regular staining, large round accumulations are present in mutants. Credit: Anton Petcherski, Goethe-University.

To date, there is no therapy for Batten disease. Patients pass away in their teens or twenties. Four years ago, the working group lead by Dr. Mika Ruonala at Goethe University, Frankfurt, Germany started to study the consequences of the underlying genetic defect. In the meantime, the scientists have detected several "biomarkers" that can now be used in search for screening for potentially active drugs in cooperation with the Harvard Medical School in Boston.

It is a rare disease with devastating consequences: Around first grade, the children start experiencing vision impairments, which two to three

years later progress to complete blindness. This is the first indication of a progressive destruction of brain cells. Later on, the patients experience hallucinations, epileptic seizures, dementia and, finally, failure of all motor abilities. In this last stage, the immobile patients must be artificially ventilated. To date, there is no therapy for Juvenile Neuronal Ceroid-Lipofuscinosis (JNCL, also called Batten disease), so patients pass away in their teens or twenties. Four years ago, the working group lead by Dr. Mika Ruonala started their research at the Center for Membrane Proteomics of the Goethe University to study the consequences of the underlying genetic defect on the whole complex network of cellular proteins., In the meantime, by studying a JNCL mouse model with a novel method of fluorescence microscopy the scientists have detected several 'biomarkers' that can now be used in search for screening for potentially active drugs in cooperation with the Harvard Medical School in Boston.

"A prerequisite for a large-scale screen for active ingredients is to have an understanding of the global effects that the genetic defect has on the complex network of the cells' proteins. Consequent validation of the changes in the protein networks provides new possibilities for drug-based intervention" explains Dr. Mika Ruonala. "Analogously with the gene defect it is equally important to understand the global effect a drug has on the complete protein network. A drug that solves a problem in one area may lead to serious adverse events in other areas. It is therefore important to proof the effects of a drug with as many criteria as possible." The visualization of the protein networks is possible with the help of the Multi-Epitope-Ligand Cartography (MELC), an innovative microscopy technology that produces three-dimensional "snapshots" of the arrangement of dozens of proteins in the cell. "We now know, for example, that proteins that would never meet in a healthy nervous cell have contact in JNCL, but we also know that contacts get lost due to the disease," states Anton Petcherski. During his master's thesis in Dr. Ruonala's working group, he used MELC and found several peculiarities

in the protein constellation of cells from brains of transgenic mice that mimic the human JNCL. He then defined the particularly significant "biomarkers" that now serve as the basis of this screening.

At Harvard Medical School in Boston, the group of Dr. Susan Cotman has been occupied with JNCL for several years. Dr. Cotman is the "mother" of the genetically precise JNCL mouse model that the Frankfurt group uses. Dr. Cotman's working group had already carried out a high throughput screening for the active ingredients for the treatment of the disease – back then, however, only a few biomarkers were known. "Since there are many anomalies in the cooperation of the proteins in the case of JNCL, the disease pattern does not necessarily improve when we are able to influence one area in a correcting manner," says Ruonala. "It is also a question of hierarchy in the protein network. Some proteins are more important for the cohesion of the network than others."

Now the two working groups are going to join forces: As part of his doctoral thesis, Anton Petcherski will be going to Boston for one year in order to search for a suitable medication for JNCL in the local drug collections. The researchers limit their search to already approved drugs, since this considerably shortens the transfer of potential medication to clinical trial. In their own laboratory, the Frankfurt group already found one active ingredient that inhibits the progression of the disease in JNCL mice. According to the bench-to-bedside strategy this drug has been used for treatment of completely different diseases for a long time and the name will be revealed when the respective data have been published. Dr. Ruonala has only revealed that two international clinical studies are about to begin within the next few months.

Provided by Goethe University Frankfurt