Researchers uncover cellular mechanism involved in Krabbe disease

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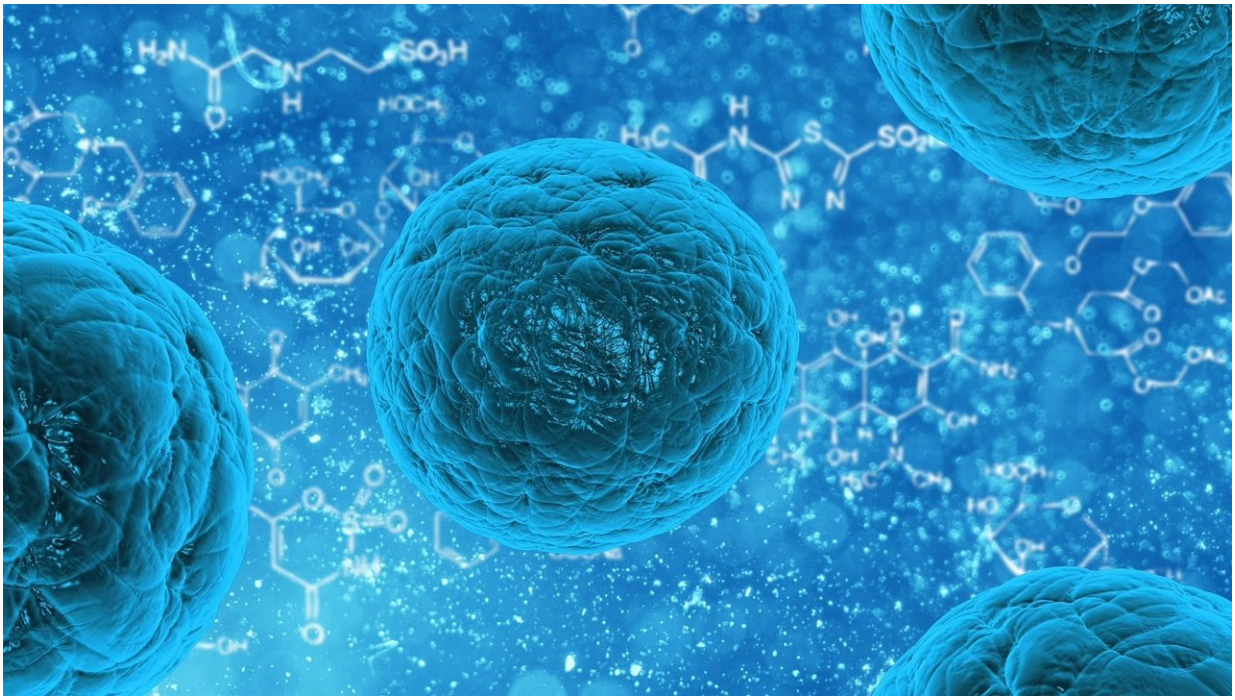

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A group of researchers at the University at Buffalo have published a paper that clarifies certain cellular mechanisms that could lead to improved outcomes in patients with globoid cell leukodystrophy, commonly known as Krabbe disease.

The paper, titled "Macrophages Expressing GALC Improve Peripheral

Krabbe Disease by a Mechanism Independent of Cross-Correction," was published today (May 5) in the journal *Neuron*.

The research was led by Lawrence Wrabetz, MD, and M. Laura Feltri, MD. Wrabetz and Feltri head the Hunter James Kelly Research Institute and both are professors in the departments of Biochemistry and Neurology in the Jacobs School of Medicine and Biomedical Sciences at UB.

The institute is named for the son of former Buffalo Bills quarterback Jim Kelly. Hunter Kelly died at age 8 in 2005 from complications of Krabbe disease.

Krabbe disease is a progressive and fatal neurologic disorder that usually affects newborns and causes death before a child reaches the age of 2 or 3.

Traditionally, hematopoietic stem cell transplantation, also known as a bone marrow transplant, has improved the long-term survival and quality of life of patients with Krabbe disease, but it is not a cure.

It has long been assumed that the bone marrow transplant works by a process called cross-correction, in which an enzyme called GALC is transferred from healthy cells to sick cells.

Using a new Krabbe disease animal model and patient samples, the UB researchers determined that in reality cross-correction does not occur. Rather, the bone marrow transplant helps patients through a different mechanism.

The researchers first determined which cells are involved in Krabbe disease and by which mechanism. They discovered that both myelin-forming cells, or Schwann cells, and macrophages require the GALC

enzyme, which is missing in Krabbe patients due to genetic mutation.

Schwann cells require GALC to prevent the formation of a toxic lipid called psychosine, which causes myelin destruction and damage to neurons. Macrophages require GALC to aid with the degradation of myelin debris produced by the disease.

The research showed that hematopoietic stem cell transplantation does not work by cross-correction, but by providing healthy macrophages with GALC.

According to Feltri, the data reveal that improving cross-correction would be a way to make bone marrow transplants and other experimental therapies such as gene therapy more effective.

"Bone marrow transplantation and other treatments for lysosomal storage disorders, such as enzyme replacement therapy, have historically had encouraging but limited therapeutic benefit," said study first author Nadav I. Weinstock, an MD-Ph.D. student in the Jacobs School. "Our work defined the precise cellular and mechanistic benefit of bone marrow transplantation in Krabbe disease, while also shedding light on previously unrecognized limitations of this approach.

"Future studies, using genetically engineered bone marrow transplantation or other novel approaches, may one day build on our findings and eventually bridge the gap for effectively treating patients with lysosomal disease," he continued.

More information: Macrophages Expressing GALC Improve Peripheral Krabbe Disease by a Mechanism Independent of Cross-Correction, *Neuron* (2020).

Provided by University at Buffalo