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Research reveals lipids' unexpected role in triggering death of brain cells

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The lipid that accumulates in brain cells of individuals with an inherited enzyme disorder also drives the cell death that is a hallmark of the disease, according to new research led by St. Jude Children's Research Hospital investigators.

The work provides the first evidence that a lipid can initiate the suicidal, or apoptotic, response in cells. The findings involve a lipid called GM1-ganglioside. Lipids are fat-like molecules. GM1 builds up with devastating results in the brain cells of patients with GM1-gangliosidosis because they lack the enzyme required to break down that molecule.

Working in mice missing this key enzyme, researchers reported new details of how GM1 accumulation inside certain structures in brain cells disrupts their internal calcium balance. This imbalance ultimately leads to the programmed cell death known as apoptosis. The work appears in the November 13 online edition of *Molecular Cell*.

"The finding is essential for understanding the causes of progressive loss of brain cells, characteristic of this disease," said Alessandra d'Azzo, Ph.D., of St. Jude Genetics and Tumor Cell Biology. She is the senior author of the report and holds the Jewelers for Children Endowed Chair in Genetics and Gene Therapy. The work also provides hints for a strategy to intervene in the disease process.

The research led d'Azzo and her colleagues to propose that the death of brain cells and neurodegeneration that strikes GM1-gangliosidosis

patients is a two-step process. The investigators demonstrated that blocking the first step in this process prevented cells from self-destructing, which was not the case when just the second step was inhibited. They predicted the discovery might have important implications for developing new treatments for this catastrophic disease.

The findings also have implications for scientists studying other aspects of the cross-talk between intracellular compartments, involving calcium signaling.

GM1-gangliosidosis is a lysosomal storage disorder in which an essential enzyme in the lysosomes is defective and cannot break down GM1. Lysosomes serve as the cell's digestive and recycling centers, stripping proteins, fats and other molecules down to their components so they can be used to assemble new molecules. Symptoms develop in childhood, in some cases shortly after birth, and include mental retardation, seizures and other problems. The outlook for patients remains bleak.

Normally, GM1 is found in the cell membrane. But previous work from d'Azzo's laboratory has shown that in patients with GM1-gangliosidosis, this lipid accumulates in other locations within the cell, including the membrane of the endoplasmic reticulum (ER). The ER is the structure where proteins are produced. GM1 accumulation in the ER membrane depletes the ER's calcium supply, disrupting the key protein-folding process. The disruption prompts the ER to target the cell for destruction.

In the current study, investigators extended their search for answers about the neurodegeneration in GM1-gangliosidosis to the mitochondria, another intracellular compartment. Some of the mitochondria are connected to the ER via the so-called mitochondria-associated ER membranes or MAMs. MAMs function like bridges, providing a route for calcium to move out of the ER and into the mitochondria. Researchers focused on the mitochondria because one of their cellular

duties is to soak up and store excess intracellular calcium, including calcium from the ER.

Using a variety of techniques, researchers identified a region within MAMs where GM1 not only accumulates but sets the stage for step two of the calcium imbalance that triggers cellular suicide. Investigators reported that in healthy cells these regions, known as glycosphingolipid-enriched microdomains, or GEMs, include tiny amounts of GM1. But in mice lacking the enzyme to break down GM1, large amounts of this lipid build up in the GEMs, said Ida Annunziata, Ph.D., a postdoctoral fellow in d'Azzo's laboratory. She shares first authorship of the paper with Renata Sano, Ph.D., a former postdoctoral fellow in d'Azzo's laboratory, currently at the Burnham Institute for Medical Research, La Jolla, Calif.

Investigators found evidence that the build-up of GM1 changes the composition of the contact sites linking ER and mitochondria and increases their number. Within the GEMs of diseased mice, researchers found elevated levels of three proteins that play important roles in transporting calcium from the ER to the mitochondria.

Those proteins include the phosphorylated form of IP3 receptor-1 (IP3R-1), which is important for the release of calcium from the ER. Not only is there more IP3R-1, but researchers reported that the protein physically interacts with GM1. d'Azzo suggested that the interaction might promote clustering of the IP3R-1 on the ER side of the GEMs, but the structural effects of accumulated GM1 on this protein must still be determined.

"It is becoming more and more apparent that intracellular organelles, including the ER, cross-talk with each other," d'Azzo said. "Here we show that in GM1-gangliosidosis, build-up of GM1 at the MAMs/GEMs alters the normal cross-talk between the ER and mitochondria."

For patients with GM1-gangliosidosis, investigators now believe problems begin when GM1 builds-up in the ER, exhausting its calcium supply and disrupting protein folding.

The second hit comes as the mitochondria struggles and eventually fails to cope with the calcium streaming in from the ER across the GEMs. Overloaded with calcium, the mitochondrial membrane becomes leaky, and a pore, known as the permeability transition pore (PTP), opens. Eventually the mitochondria release specialized proteins, like cytochrome c and other factors, triggering a biochemical cascade that ends in the destruction of both the mitochondria and the cell itself.

Source: St. Jude Children's Research Hospital