Iron-moving malfunction may underlie neurodegenerative diseases, aging

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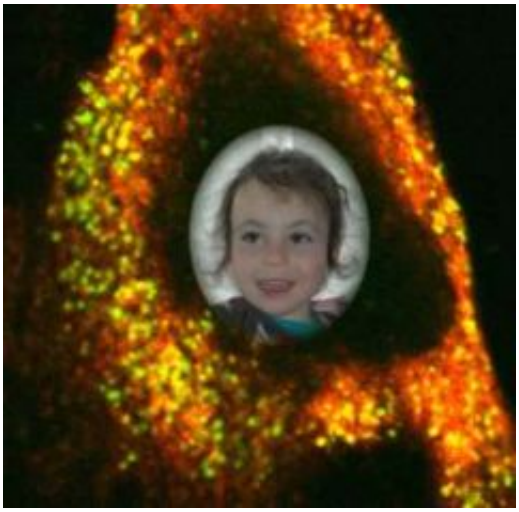

A glitch in the ability to move iron around in cells may underlie a disease known as Type IV mucolipidosis (ML4) and the suite of symptoms—mental retardation, poor vision and diminished motor abilities—that accompany it, new research at the University of Michigan shows.

The same deficit also may be involved in aging and neurodegenerative diseases such as Alzheimer's and Parkinson's, says lead author Haoxing Xu, an assistant professor of molecular, cellular and developmental biology.

The findings are scheduled to be published online Sept. 14 in the journal *Nature*.

An interest in iron transport led Xu to investigate ML4, another symptom of which is iron-deficiency anemia. Perhaps, he and his collaborators reasoned, impaired iron transport could explain both the anemia and the other problems that go hand-in-hand with ML4, a genetic disorder that mainly affects Jews of Eastern European background. Children with ML4 begin showing signs of developmental delay and eye problems during the first year of life and typically fail to progress beyond the level of a 15-month-old. Although the disease is rare, recent discovery of some children with milder forms of the condition raises the possibility of additional mild, undiagnosed cases.

To explore the possible role of iron transport in the disease, Xu's group focused on a protein called TRPML1. A mutation in the gene that produces TRPML1 is known to cause ML4, so the protein seemed like a logical starting point for investigating mechanisms responsible for the disease, even though TRPML1 had never been shown to be involved in iron transport. The only protein with that distinction was DMT1, which facilitates iron uptake in the gut and in cells that will become red blood cells, but not in most other cell types.

"Essentially all cells, including nerve cells and muscle cells, need iron," Xu said. "We wondered what happens in those cells where DMT1 isn't found, and we thought there must be an unidentified iron transporter protein, possibly TRPML1."

Unfortunately, TRPML1 isn't the easiest protein to study. Instead of residing in the cell's easily-accessed outer membrane, where many other proteins nestle, it hides in a tiny, interior pocket called lysosome. To probe the protein, Xu's group had to modify a technique known as the patch clamp, in which a micropipette and electrodes are attached to a

cell membrane to record the activity of individual or multiple proteins that serve as channels for charged particles (ions) moving in and out of cells. With their modification, which they call the lysosome patch clamp, Xu's group was able to record TRPML1 activity in the tiny lysosome.

They found that TRPML1 was indeed capable of ferrying iron out of the lysosome. But was there any evidence that interfering with that ability might result in ML4 symptoms? To address that question, Xu's group studied defective TRPML1 proteins bearing the same mutations as those found in ML4 patients. Mutations associated with severe symptoms were the least adept at shuttling iron, while those associated with milder symptoms were more proficient, although still not fully functional.

Further experiments confirmed that when TRPML1 is defective, iron becomes trapped in the lysosome. One result of the buildup is formation of a brownish waste material, lipofuscin, known as the "aging pigment." In skin cells, lipofuscin is the culprit responsible for the dreaded liver spots that appear with increasing age, but in nerve, muscle and other cells, its accumulation has more serious consequences.

"How lipofuscin causes problems in neurons and muscles is not clear, but it's believed that this is garbage that, in time, compromises the normal function of the lysosome," Xu said. "And we know the lysosome is important for all kinds of cell biology, particularly the recycling of intracellular components, so if it's damaged, the cell is going to suffer." Indeed, abnormal accumulation of lipofuscin is associated with a range of disorders including Alzheimer's disease, Parkinson's disease, and macular degeneration (a degenerative disease of the eye) and also contributes to the aging process.

"In a sense we can think of ML4 as really early onset of aging," Xu said.

Now that the connections among TRPML1, iron and lipofuscin are

coming into focus, researchers have new avenues to explore for potential treatments, not only for ML4 but also for more common neurodegenerative conditions.

"If we can somehow manipulate the lysosome iron level, we probably can provide a treatment for the patient," Xu said. "We're not far enough along for those kinds of experiments yet, but now we know enough to work toward that goal."

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