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Master gene may shed new light on lysosomal and neurodegenerative disorders

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Cells, like ordinary households, produce "garbage" – debris and dysfunctional elements – that need disposal. When the mechanism for taking out this garbage fails, rare genetic diseases called lysosomal storage disorders (including Tay-Sachs, Batten and Fabry disease) can disable and even kill the children they affect. In adults, such failure leads to neurodegenerative diseases that occur later in life, such as Alzheimer's and Parkinson's diseases.

An international partnership between researchers at the Jan and Dan Duncan Neurological Research Institute (NRI) at Texas Children's Hospital, Baylor College of Medicine and the Telethon Institute of Genetics and Medicine in Naples, Italy, led to the discovery of a master gene that controls not only the lysosomes, which destroy the debris, but also cellular compartments called autophagosomes that encapsulate the material and fuse with the lysosomes to achieve the ultimate clearance of the cell's "garbage."

This finding may cast new light on the search for ways to combat these inherited diseases and neurodegenerative diseases that start in adulthood. A report on the research, done in collaboration with scientists from the Cambridge Institute for Medical Research of the University of Cambridge in the United Kingdom, appears online in the current issue *Science Express*.

"The master gene (transcription factor EB or TEFB) that controls the function of lysosomes (organelles in the cell that break down waste and

cellular debris) also controls the function of autophagosomes," said Dr. Andrea Ballabio, scientific director at the Telethon Institute of Genetics and Medicine in Naples, Italy, and professor of molecular and human genetics at BCM and the Texas Children's Neurological Research Institute. "Defects in this process are also implicated in neurodegenerative disorders such as Alzheimer's and Parkinson's diseases."

Ballabio, who is also on the faculty of the Federico II University in Naples and senior author of the report, describes the autophagosomes as "garbage trucks" that pick up the debris and take it to the lysosomes, which "incinerate" it.

The discovery that a single master gene directs this activity "is one of the few examples of coordinated regulation of two cellular compartments," he said.

Ballabio and his colleagues had already demonstrated that TEFB regulates the genesis and formation of lysosomes, but they were considering whether they could use the gene as a switch to increase the capacity of the cell to get rid of waste products. They knew that the number of lysosomes would increase, but that would not be helpful without more autophagosomes.

"We thought there would be no point in increasing the incinerators unless we could also increase the garbage trucks," he said.

They found that TFEB controlled both activities.

"This understanding paves the way to finding drugs to activate the process," said Dr. Carmine Settembre, postdoctoral fellow at TIGEM, NRI and BCM and first author of the report. The work already done on mice and ongoing work in the laboratory is paving the way to better

understanding of the gene and possible applications in human disease.

"This gene is a wonderful tool," said Ballabio. "By modulating the activity of a single gene, we can induce the activity of a variety of other genes that are involved in the process of degradation."

"Collaborations are the best way to accelerate discovery and advance the search for ways to impact neurological disorders. This partnership between NRI, BCM and Telethon Institute of Genetics and Medicine is a fine example of the power of collaborations," said Dr. Huda Zoghbi, director of the NRI at Texas Children's Hospital, professor of neurology, neuroscience, pediatrics and molecular and human genetics at BCM and an investigator with the Howard Hughes Medical Institute.

More information: http://www.sciencemag.org/content/early/recent

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