Little-known protein found to be key player

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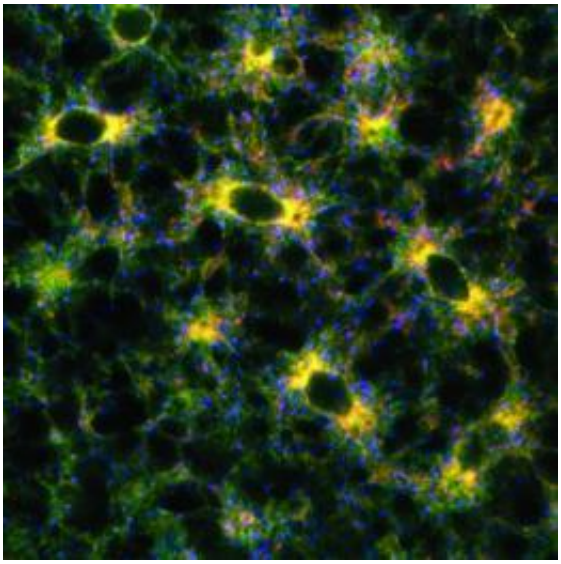

Fluorescent markers show the interconnected web of tubes and compartments in the endoplasmic reticulum, the critical part of cells that the protein atlastin helps build and maintain. Credit: A. Daga/Medea Scientific Institute

(PhysOrg.com) -- Italian and U.S. biologists this week report that a little-understood protein previously implicated in a rare genetic disorder plays an unexpected and critical role in building and maintaining healthy cells. Even more surprising, their report in the journal *Nature* shows that the protein, called "atlastin," does its work by fusing intracellular membranes in a previously undocumented way.

"If you'd asked me a year ago whether this was possible, I would have said, 'No,'" said study co-author James McNew, associate professor of

biochemistry and cell biology at Rice University. "In fact, that's exactly what I told (co-author) Andrea Daga when we first spoke about the idea a year ago."

McNew has spent the past 15 years studying SNARE proteins, a specialized family of proteins that carries out membrane fusion. It's a vital process that happens thousands of times a second in every cell of our bodies.

"It is fitting that the discovery of a new protein capable of fusing membranes comes 10 years after the demonstration that SNAREs can fuse lipid bilayers," said Daga, a researcher at the Eugenio Medea Scientific Institute in Conegliano, Italy.

In the new study, Daga's and McNew's research teams used fruit flies to study how atlastin functions. The atlastin in fruit flies is very similar to the human version of the protein and serves the same function.

"Prior to this, there were only two defined ways in which you could take biological membranes and put them together in a specific way," said McNew, a faculty investigator at Rice's BioScience Resesarch Collaborative. "Atlastin is the third, and it's the only one that requires enzymatic activity, so it's distinctly different."

Using a range of tests on purified proteins, live fruit flies and cell cultures, the Italian and U.S. teams examined the effect of both an overabundance and a scarcity of atlastin on cell function and on fruit fly development. They also created mutant versions of the protein to see how it functioned -- or failed to function -- when some parts were disabled.

The tests showed that cells with extra atlastin had an overdeveloped endoplasmic reticulum (ER), a system of interconnected membrane

tubes and chambers that's critical for normal cell function. The tests also showed too little atlastin led to a fragmented ER. Flies with defective atlastin were sterile and short-lived.

"The endoplasmic reticulum is an ever-changing environment," McNew said. "It grows. It retracts. It expands. It collapses. It's highly dynamic, and for that to be the case, there has to be a mechanism by which it can grow new pieces and connect those pieces together. That's where the fusion comes in."

Daga said the discovery will lay the foundation for a deeper understanding of both basic biological processes and disease.

"We hope the findings lead to a better understanding of hereditary spastic paraplegia (HSP), the genetic disorder that atlastin has been linked with," Daga said.

HSP is a rare genetic condition that affects fewer than one million people worldwide. It's marked by a partial paralysis of the lower extremities due to defects in the body's longest cells, the neurons that run from the spine through the legs.

Daga said atlastin's role in building and maintaining a healthy ER may help HSP researchers better understand why neurons are affected first.

"This is the first clue," Daga said. "We have the definition of what the protein does. Now we need to explore how it does that, and what it means."

Source: Rice University (news : web)