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A little less protein may be the answer in neurodegenerative disorders

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In some neurodegenerative diseases, and specifically in a devastating inherited condition called spinocerebellar ataxia 1 (SCA1), the answer may not be an "all-or-nothing," said a collaboration of researchers from Baylor College of Medicine, the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital and the University of Minnesota in a report that appears online in the journal *Nature*. The problem might be solved with just a little less.

"If you can only decrease the levels of ataxin-1 (the protein involved in SCA1) by 20 percent, you can reduce many symptoms of the disease," said Dr. Huda Zoghbi, professor of molecular and human genetics and pediatrics at BCM and director of the Neurological Research Institute. She is also a Howard Hughes Medical Institute Investigator.

Her long-time colleague Dr. Harry Orr, director of the University of Minnesota Institute for Translational Neuroscience, echoed that sentiment: "Perhaps, if you decrease the levels of the protein, you will decrease the severity of the disease." In this report, the laboratories of Zoghbi, Dr. Juan Botas, also of BCM and the Neurological Researcher Institute, Dr. Thomas Westbrook, assistant professor of molecular and human genetics at BCM, and Orr identified a molecular pathway in the cell (RAS/MAPK/MSK1) with components that can be modulated slightly to reduce the levels of defective ataxin-1, the protein that causes disease in patients with the disorder.

Spinocerebellar ataxia 1 occurs when the ataxin-1 gene is mutated, with

three letters of the DNA alphabet repeating many, many times. The abnormal protein that results cannot fold correctly and piles up in the cell, eventually killing it. As with many neurodegenerative disorders, the process can take over a decade. A person usually does not develop symptoms of this form of ataxia until he or she is 30 years old or older. The person develops gait problems, eventually loses the ability to speak and function and dies. Zoghbi and Orr teamed to find the gene associated with the disorder in 1993. Their work on the disease has spanned 20 years.

Totally eliminating the protein would not work. Mice that lack the gene have problems with learning and memory, indicating that ataxin-1 plays a role in those activities. Reducing the levels of ataxin-1 does not cure the disease, but it can significantly delay onset.

A Collaborative Innovation Award from the Howard Hughes Medical Institute enabled Zoghbi to put together the team that could screen for the genes or the gene pathway that could be manipulated to result in less ataxin-1.

"Harry and I had studied the disease and we had animal models. Botas, professor of molecular and human genetics at BCM, had a fruit fly model and Dr. Westbrook had a nice technology that enabled us to monitor ataxin-1 levels."

They began with a screen for genes that could affect the levels of ataxin-1 produced in the cell, said Dr. Ismail Al-Ramahi, a postdoctoral fellow in the lab of Botas. Dr. Jeehye Park, a post-doctoral fellow in Zoghbi's laboratory, and Al-Ramahi are co-first authors of the report. Park and her colleagues carried out the screen in human cell lines and Al-Ramahi and his colleagues carried out the screen in fruit flies (Drosophila melanogaster).

The screen in human cells focused on forms of enzymes called kinases because they are susceptible to the effects of drugs. Using a special technique called RNA silencing, they targeted each known human kinase. At the same, Botas and Al-Ramahi screened kinase genes in fruit flies with a form of SCA1. When the two laboratories compared results, they found 10 genes in common that when inhibited could reduce the levels of ataxin-1 as well as the toxicity associated with it. The genes were part of the RAS/MAPK/MSKI signaling cascade within the cell.

Then the researchers focused on one protein in this pathway called MSK1 and found that when its levels were decreased in mice that were laboratory models of SCA1, the levels of ataxin-1 dropped and the animals improved. That was the final experiment that proved that reducing levels of the protein could stave off the disease.

"We want to look for more pathways," said Zoghbi. If they find more pathways, they may be able to reduce toxicity. "If you have a pain and you take acetaminophen all the time, you have a risk of toxicity. Similarly, if you took a nonsteroidal anti-inflammatory all the time, you would have another toxicity. If you alternate between them, there is less toxicity. If we hit only one pathway with a big inhibition, we risk some toxicity. If we find two or three pathways and hit each only a little, the rest of the body should not be hurt. Each little hit should help us reduce ataxin-1 by a respectable amount."

"I think what is novel about this paper is the integration of the screen in cells that was done in Huda's lab and the screen in fruit flies done in our lab to look for targets for genes about which we knew nothing ahead of time," said Botas.

While the finding in spinocerebellar ataxia 1 is exciting, its potential application in other diseases is even more provocative.

"Now that we know that it works with ataxin-1, we can revisit many proteins whose levels drive neurodegeneration in sporadic and inherited diseases such as Alzheimer's, Parkinson's, Huntington's and other neurological disorders," said Zoghbi. "This is a pilot study and the results from it are as important as a new pathway in neurodegenerative disease research."

"These are diseases that take a long time to develop," said Park. "Most Alzheimer's occurs after the age of 85. If we could delay it until age 95, that would be very helpful."

"This is getting us really close, not only for SCA1, but I think it's going to be a guidepost for work on a lot of other neurodegenerative diseases," said Orr. "It sets us a beautiful research strategy to get at that goal."

More information: Paper: dx.doi.org/10.1038/nature12204

Provided by Baylor College of Medicine

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