Mechanism for potential Friedreich's ataxia drug uncovered

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Using clever chemistry, a Scripps Research team has pinpointed the enzyme target of a drug group that stops the progression of the devastating disease Friedreich's ataxia in mice and may do the same for humans. The findings, developed in collaboration with scientists from Repligen Corporation, help advance this treatment approach one step closer toward human clinical trials, which will be a welcome event for disease sufferers who currently have few treatment options.

The work, reported as the cover article of the September 25, 2009 issue of the journal *Chemistry & Biology*, could also lead to treatments for related conditions such as Huntington's disease and the spinocerebellar ataxias.

"It will be very rewarding if our work actually leads to a therapy for Friedreich's," says Joel Gottesfeld, a professor in the Department of Molecular Biology and leader of the Scripps Research team that discovered the potential treatment. "This is a horrible disease."

Friedreich's ataxia, which afflicts about one of every 20,000 to 50,000 people in the United States, is caused by inadequate production of the protein frataxin, which leads to degeneration of nerve tissue and an array of associated complications including heart disease and scoliosis. In most cases, sufferers are ultimately confined to a wheelchair and many die as young adults.

Researchers have tied this low frataxin production to a large repetition

of a specific triplet DNA pattern in the frataxin gene. Though many questions remain open, it appears that the unusual DNA structure resulting from these repetitions somehow attracts enzymes known as histone deacetylases (HDACs). These enzymes alter the packaging of the DNA in chromosomes in a way that inactivates the expression of the frataxin gene, though it remains intact.

In 2006, the Gottesfeld team reported the discovery of a compound simply called 4b that blocked HDAC activity, jumpstarting frataxin production in white blood cells from Friedreich's patients. Later work showed that a close derivative of 4b increased the level of frataxin production in a mouse model for Friedreich's ataxia.

But researchers remained unsure of how these molecules work, and understanding a drug's activity is critical to moving forward with drug development, as well as to gaining better understanding of a disease.

To answer that question, Chunping Xu, a postdoctoral research associate in Gottesfeld's lab, drew on work by Scripps Research Professors Barry Sharpless and Ben Cravatt and their groups. Using a technique referred to as "click chemistry" and other methods, Xu combined 4b with a fluorescent tag, resulting in a compound called 1-BP. She then incubated this creation with samples of various HDACs. If the enzyme or enzymes targeted became fluorescent, she would know it was due to binding with 1-BP.

The results were unequivocal. "This molecule has just an astonishing preference for HDAC3 over any of the other HDAC enzymes," says Gottesfeld.

Related experiments with 1-BP and extracts from Friedreich's patients' cells, and other tests done by Repligen confirmed HDAC3 as the target.

HDAC3 is part of a whole family of HDACs (at least 18) that could have been involved. By identifying the one that's playing a key role, the scientists have revealed the path, or at least a path, that can control the production of the frataxin protein. With that identified, the scientists are better positioned to understand what's causing the disease.

Having such information about the mechanism of a potential drug treatment is also critical to understanding what effects a drug might have on patients. The Gottesfeld team's work was completed in collaboration with researchers from Repligen Corporation, based in Waltham, MA, which is pursuing a Friedreich's treatment suitable for human clinical trials.

But the Scripps Research team's work isn't done. Gottesfeld and his colleagues will continue to study HDAC3 and its inhibitors in hope of identifying exactly how this enzyme controls frataxin production, and whether it directly or indirectly inactivates the frataxin gene. Such work could help researchers better understand how Friedreich's and similar diseases such as Huntington's progress, improving the chances of effective treatments.

"When you delve deeper into the mechanisms," says Gottesfeld, "You never know if you might uncover new targets and new therapeutic interventions that are even better than what you're working with."

More information: "Chemical probes identify a role for histone deacetylase 3 in Friedreich's ataxia gene silencing," *Chemistry & Biology*

Source: The Scripps Research Institute (news : web)

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