MedicalXpress

Moonlighting enzyme linked to neurodegenerative disease

April 24 2007

Friedreich's ataxia is one of those diseases few have heard of unless you know someone with the condition. For that individual -- usually a child or teenager -- it is devastating. Symptoms are mild at first: muscle weakness in the arms and legs, vision impairment and slurred speech, but eventually the symptoms progress and most patients become wheelchair-bound and succumb to heart failure later in life. There is no cure at this time, but Mayo Clinic researchers have identified mutations in an enzyme that may contribute to the disease.

"Children and teens want to be on top of the world and having a disease like this is devastating for them and their families in so many different respects," says Grazia Isaya, M.D., Ph.D., senior author of the study and a basic scientist at Mayo Clinic who specializes in Friedreich's ataxia. "Their cognitive functions are not impaired so they understand exactly what is happening to them."

Friedreich's ataxia is an inherited neurodegenerative disease of children and teens and is considered an orphan disease by the National Institutes of Health because of its rarity -- affecting one in 40,000. It is associated with a deficiency of frataxin, a protein that balances iron in mitochondria, which are the structures that convert nutrients into energy for cells. A new Mayo Clinic study published in the April issue of the Proceedings of the National Academy of Sciences (PNAS) shows that mutations in a moonlighting enzyme, dihydrolipoamide dehydrogenase (DLD), are responsible for decreasing the enzyme's primary role as a metabolizer, while increasing its role in breaking down frataxin, its

second job.

Moonlighting proteins and enzymes are molecules that perform two or more different functions. These proteins are thought to have evolved because they can provide cells with significant advantages, namely, the ability to increase the spectrum of metabolic activities without increasing the number of protein-coding genes, and the ability to coordinate different metabolic pathways.

Mutations in DLD have been linked to severe metabolic disorders in humans, but it wasn't known that DLD was a moonlighting enzyme with two jobs: regulating metabolism and breaking down proteins.

The PNAS study describes how Mayo investigators identified DLD's role in reducing the amount of frataxin that is produced.

"These findings reveal a previously unrecognized mechanism by which certain DLD mutations can simultaneously induce the loss of a primary metabolic activity and the gain of a moonlighting proteolytic (breaking down enzymes) activity. The latter could contribute to the metabolic derangement associated with DLD deficiency and represent a target for therapies of this condition," the authors write.

Like all proteins, frataxin is continuously synthesized, and it carries out its function before it breaks down. Some proteins degrade more rapidly than others, but frataxin degrades at a much more rapid pace than other proteins. "We observed this degradation years ago and in doing so, we decided to go after the enzyme responsible for the degradation thinking it probably might play an important role in the regulation of frataxin and could represent a target therapy for Friedreich's ataxia," says Dr. Isaya.

The severity of Friedreich's ataxia is proportional to the decrease in the levels of frataxin: the lower the frataxin, the more severe the disease.

"Yet, this correlation does not completely explain the clinical variability because even within the same family we may see individuals with different phenotypes -- one more severe than the other," Dr. Isaya says.

In Friedreich's ataxia, clinicians have long hypothesized the existence of gene modifiers -- genes that can influence the outcome of other gene mutations. "We believe that the enzyme we've identified is most likely a modifier of Friedreich's ataxia because mutations in that gene could increase or decrease the levels of frataxin in patients," she says.

Identifying and confirming the role of this moonlighting enzyme could aid in the development of new therapies for patients with Friedreich's ataxia. In addition, further study could confirm the presence of mutations in the enzyme that could explain, in part, differing clinical phenotypes among patients.

Dr. Isaya says: "Understanding protein function is central to being able to provide individualized clinical care to patients who may, for example, carry different mutations of this enzyme and express different clinical phenotypes."

Source: Mayo Clinic