

Accelerated search identifies drug targets for neurodegenerative disease

July 17 2013

(Medical Xpress)—Like Huntington's disease, Parkinson's disease, and Alzheimer's disease, spinocerebellar ataxia type 1 (SCA1) is a devastating neurodegenerative disease caused when a toxic protein accumulates inside nerve cells, clogging normal function. The coordination and balance problems caused by SCA1 make it difficult for patients to speak, breathe, and swallow.

Now, a research team led by Howard Hughes Medical Institute (HHMI) investigator Huda Y. Zoghbi at Baylor College of Medicine has identified a cell signaling pathway that affects the levels of the [toxic protein](#) responsible for SCA1. When Zoghbi and her colleagues inhibited the pathway in a mouse model of the disease, they reduced the toxic protein, ataxin-1, and limited neural damage. Their results were published May 29, 2013, in the journal *Nature*.

Zoghbi and her collaborators used large-scale [genetic screens](#) in fruit flies and human cells to zero in on this pathway as a potential target for treating SCA1. Their findings demonstrate that their approach is a rapid and effective method to identify genes that contribute to the buildup of toxic proteins. Setting up the genetic screens took about two years, Zoghbi says, making it much more efficient than a traditional drug discovery approach, in which [candidate genes](#) are tested one by one.

Zoghbi and her colleagues, including Juan Botas at Baylor and Harry Orr at the University of Minnesota, already knew that they could decrease symptoms in a mouse model of SCA1 by genetically decreasing the level

of ataxin-1. Their goal was to identify genes and proteins that they could target with potential drugs to achieve the same effects.

They knew it would take time to comprehensively screen for genes that influence ataxin-1 levels, and there was no guarantee that the team would turn up viable drug targets for the disease. "Projects like this are sometimes called 'fishing expeditions,'" Zoghbi says. "But we knew that if what we were testing worked, it would be great."

Zoghbi applied for a Collaborative Innovation Award from HHMI, a program designed to support HHMI investigators and scientists outside HHMI in undertaking new projects that are so large in scope that they require collaborators with a range of expertise. The award enabled her to bring in the expertise of Thomas Westbrook, a colleague at Baylor who uses high-throughput screening to find genes involved in cancer. For his genetic experiments, Westbrook uses RNA molecules called short interfering RNAs, which attach to specific genes and shut them off. Adopting this technology enabled the team to rapidly evaluate how hundreds of different genes affected ataxin-1 levels in nerve cells.

As a proof of principle, the team focused their search on the approximately 600 genes that encode kinases – enzymes that attach a phosphate group to other proteins. Ataxin-1 needs to have a phosphate group attached to it at a specific location in order to cause damage, and kinase function can often be blocked by small molecules, making these enzymes promising candidates as drug targets.

The team examined every kinase-producing gene in both human [nerve cells](#) and fruit fly SCA1 models. Among the genes that they tested, ten successfully lowered the amount of ataxin-1 in both [fruit flies](#) and [human cells](#).

When the researchers examined the signaling pathways that each of

these genes participated in, they converged on a single network, known as the RAS-MAPK-MSK1 pathway. They found that by inhibiting this pathway in mouse models of SCA1, they could lower ataxin-1 and reduce neurodegeneration.

The RAS, MAPK, and MSK1 signaling molecules are known to influence gene expression and cells' response to stress response in a wide range of tissues. This means that drugs that inhibit the RAS-MAPK-MSK1 pathway may decrease neural damage in patients with SCA1, but could also have unwanted side effects in other parts of the body. Zoghbi says a next step will be to search for inhibitors of the pathway with more specific effects.

Meanwhile, the team will expand its search to see if they can find other targets that can be pharmacologically manipulated to reduce ataxin-1 in their models. Identifying a rich pool of potential drug targets increases the likelihood of eventual clinical success, she says. "We want to look for other relevant pathways now, because if we can find two or three pathways that are important in SCA1 and inhibit them just a little bit, we may be able to avoid toxicity," she explains.

Provided by Howard Hughes Medical Institute

Citation: Accelerated search identifies drug targets for neurodegenerative disease (2013, July 17) retrieved 10 April 2024 from

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