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Study identifies potential drug target for Huntington's disease

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An enzyme known to be critical for the repair of damaged cells and the maintenance of cellular energy may be a useful target for new strategies to treat Huntington's disease (HD) and other disorders characterized by low cellular energy levels. In the August issue of *Chemistry & Biology*, a research team from the MassGeneral Institute for Neurodegenerative Disease (MIND) describes their discovery of a novel inhibitor of Poly (ADP-ribose) polymerase (PARP1) and their findings that PARP1 inhibitors can protect HD-affected cells from damage in laboratory assays.

"While PARP1 is essential for the repair of damaged DNA, we also know that, if overactivated, it can cause cell death by excessive energy depletion," says Aleksey Kazantsev, PhD, director of the MIND High Throughput Drug Screening Laboratory, who led the current study. "It has recently been shown that neurons from patients with Huntington's appear to be energy-deficient, so we hypothesized that modest stresses that would be tolerated by healthy cells could send HD cells below a viable energy threshold and that blocking PARP1 activation could be protective."

To test this hypothesis the MIND researchers first ran a computer search of their small-molecule library for potential novel inhibitors of PARP1, searching for those with structural similarities to known inhibitors. "Safety and efficacy of human drugs depends on many factors, so it's hard to predict which inhibitor would be most effective against a specific disorder. The more diverse novel inhibitors can be identified,

the more chances there are of developing safe and effective drugs," Kazantsev explains.

Two candidate molecules were identified as potential PARP1 inhibitors based on their structure, and both of them were confirmed to inhibit the enzyme's activity in an in vitro assay. However, when tested using cultured human and rat cells, only one of the candidate molecules, K245-14, successfully prevented the death of cells in which PARP1 had been overactivated.

The next assays examined whether blocking PARP1 activity with K245-14 could reduce energy depletion in cells with the HD genetic mutation. Using cells from human HD patients and from a mouse model of the disorder, the MIND researchers compared the reactions of HD cells to oxidative stress caused by the application of hydrogen peroxide with the reactions of normal cells. Although all of the cells reacted with a loss of ATP, a key source of cellular energy, the HD cells – which had much lower ATP levels to begin with – were much more vulnerable to stress-induced energy loss. Inhibiting PARP1 by means of K245-14 reduced ATP loss in all tested cells and significantly protected against both energy loss and cell death in the HD cells.

"While we were pleased to observe these predicted protective effects in our experiments, validation of PARP1 as a useful HD drug target will require the testing of inhibitors in animal trials," Kazantsev explains. "The process of identifying the best candidates for trials will be very complex, since any drug treating a central nervous system disorder needs to penetrate the blood-brain barrier. We will be working with our collaborators at the Scripps Research Institute – world leaders in computational chemistry – to conduct a more comprehensive virtual screen and select additional promising candidates for drug development.

"Inhibition of PARP1 activity is thought to be potentially beneficial for

treatment of cancer, neurodegenerative conditions such as Parkinson's disease, and over twenty other human disorders," he adds. "We envision broad therapeutic applications for small molecule inhibitors of PARP1." Kazantsev is an assistant professor of Neurology at Harvard Medical School.

Source: Massachusetts General Hospital

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