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Scientists identify switch for brain's natural anti-oxidant defense

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Scientists at Dana-Farber Cancer Institute report they have found how the brain turns on a system designed to protect its nerve cells from toxic "free radicals," a waste product of cell metabolism that has been implicated in some degenerative brain diseases, heart attacks, strokes, cancer, and aging.

Potentially, the researchers say, it may be possible to use drugs to strengthen the anti-oxidant system in the brain as a treatment for presently incurable diseases like Parkinson's, Huntington's, and Alzheimer's and possibly other maladies.

Dana-Farber's Bruce Spiegelman, PhD, and colleagues, using a mouse model, discovered that a regulatory protein, PGC-1a, switches on the anti-oxidant system when free radicals, or reactive oxygen species, begin to accumulate. It's believed that some brain diseases involve a failure of the protective system, and the authors report that turning on PGC-1a to high levels in cultured cells protected them against nerve toxins. The findings will be reported in the Oct. 20 issue of the journal *Cell*.

"This could have broad implications for the many diseases in which reactive oxygen species are implicated," said Spiegelman. Anti-oxidant supplements have been used with some success in patients with neurodegenerative diseases, but Spiegelman noted that the process sparked by PGC-1a "is how nature does it."

Researchers currently are screening drugs in search of compounds that

could spur PGC-1a expression in brain cells, as well as exploring whether any harmful side effects might result. PGC-1a is a transcriptional co-activator discovered in Spiegelman's Dana-Farber laboratory in 1998. It has subsequently been found to play a master regulatory role in metabolic processes and muscle function, as well as being a culprit in diabetes.

The report establishes for the first time that PGC-1a both drives the mitochondria to make energy and triggers the cleanup of toxic free radicals that accumulate in the cell as byproducts. As excess free radicals build up, their toxicity places the cell under "oxidative stress," which prompts the cell to produce more PGC-1a, which in turn spurs the anti-oxidant defenses into action.

"With this mechanism, the body can speed up mitochondrial formation and at the same time suppress the creation of reactive oxygen species, which are known to be terribly damaging to the cell," explains Spiegelman, who is also a professor of cell biology at Harvard Medical School. In this respect, the cell could be compared to a self-cleaning oven -- but one that becomes less efficient with age and in certain diseases.

Therefore, the new finding of a specific regulator of the body's own anti-oxidant system could lead to more-effective treatments for a number of diseases, and might even retard some of the effects of aging, the researchers say.

In previous experiments, Spiegelman and others had bred mice that lacked the PCG-1a gene. As would be expected, the absence of PCG-1a caused the mice to have abnormalities in their metabolism -- they had less exercise capacity and were extremely sensitive to cold. But what the scientists hadn't predicted was that the mice had neurodegenerative lesions in their brains and behaved abnormally: This was a clue that

without PGC-1a, the cells' "self-cleaning" mechanism wasn't activated properly, leaving the mice more vulnerable to brain damage from renegade free radicals.

In the current research, Spiegelman and his colleagues exposed normal mice and rodents lacking PGC-1a to a nerve toxin that accelerates the production of free radicals. Mice without PGC-1a suffered more brain damage because they couldn't turn on their anti-oxidant defenses.

Finally, to investigate whether increasing PGC-1a activity in the brain would protect against oxidative stress, the scientists caused mouse brain cells and human brain cells in the laboratory to make 40 times as much PCG-1a as normal. They exposed the cells to increasing amounts of paraquat or hydrogen peroxide, chemicals that cause oxidative stress and cell damage. The result: many more brain cells survived the assault than did cells without the extra PGC-1a activity to augment their defenses.

Because PGC-1a has now been shown both to rev up energy production in the mitochondria and to suppress the resulting free radicals, "this is an almost ideal protein to control or limit the damage seen in neurodegenerative diseases that have been associated with defective mitochondrial function," the authors wrote. As a result, finding drugs that increase PGC-1a in the brain "could represent a new mode of therapy for a set of diseases that are both common and have only marginal therapies at this moment."

Source: Dana-Farber Cancer Institute