Gene may 'bypass' disease-linked mitochondrial defects, fly study suggests

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By lending them a gene normally reserved for other classes of animals, researchers have shown they can rescue flies from their Parkinson's-like symptoms, including movement defects and excess free radicals produced in power-generating cellular components called mitochondria. The gene swap also protects healthy flies' mitochondria, and to a large extent the flies themselves, from the damaging effects of cyanide and other toxins, the team reports in the May issue of *Cell Metabolism*, a Cell Press publication.

The key gene (single-subunit alternative oxidase or AOX) in essence acts as a bypass for blockages in the so-called oxidative phosphorylation (OXPHOS) cytochrome chain in mitochondria. Howard Jacobs, who led the study at the University of Tampere in Finland, likens that chain to a series of waterfalls in a hydroelectric power station. Only, in the case of mitochondria, it is electrons that flow to release energy that is captured in molecular form.

"This is the first whole organism test for the idea that you can take a gene that encodes a single polypeptide and bypass OXPHOS where it is blocked," said Jacobs, emphasizing that OXPHOS includes dozens of components and hundreds of proteins. "You may lose power from one [molecular] 'turbine,' but power from the others can be restored. With a single peptide, you can bypass two-thirds of the system. That's the beauty of the idea."

Defects in mitochondrial OXPHOS are associated with diverse and

mostly intractable human disorders, the researchers said. Therefore, there's a chance that the strategy might also prove beneficial in mammals, including humans, which like arthropods have also lost the AOX gene over the course of evolution. (Arthropods are represented by insects, spiders, and crabs.)

On the other hand, most plants, animals, and fungi do possess an alternative mitochondrial respiratory chain, which can bypass the OXPHOS system under specific physiological conditions. In plants, AOX is thought to be essential for maintaining energy balance under daylight conditions. In fungi, AOX has been implicated in the control of longevity and resistance to oxidative stress. In many animals, too, including annelid worms, mollusks, and urochordates—an underwater filter-feeding sister group to vertebrates— AOX is present and is believed to provide resistance to oxidative stress.

In a previous study, Jacobs and his colleagues tested the idea that AOX might bypass the consequences of OXPHOS inhibition in human cells. They introduced the gene into human cells by inserting DNA taken from the urochordate Ciona intestinalis. Those studies found that the protein encoded by the Ciona AOX gene made its way to mitochondria, where it conferred cyanide-resistant respiration and protected against metabolic acidosis, oxidative stress, and cell death when cells were treated with OXPHOS inhibitors such as antimycin or cyanide.

Now, they've shown that the same holds true in a living animal. Importantly, ubiquitous Ciona AOX activity had no apparent ill effects for the flies. Quite the contrary, mitochondria taken from AOX-expressing flies showed significant resistance to cyanide, and the flies partially resisted both cyanide and antimycin. AOX also rescued the movement defect and excess production of reactive oxygen species by mitochondria in flies with a mutant version of a gene known as dj-1b, which is the fly equivalent to the human Parkinson's disease gene DJ1.

The findings led the researchers to conclude that "AOX appears to offer promise as a wide-spectrum therapeutic tool in OXPHOS disorders." The next step is to test whether the findings in flies will also hold true in mammals, Jacobs said. His hope is that the AOX gene might someday be delivered to humans via a suitable gene therapy, although he admits that goal assumes many things will fall into place.

"OXPHOS dysfunction is not just a problem in some rare genetic disorders or in degenerative diseases," he said. It's an issue in a very large number of pathologies—and a major cause of tissue damage after heart attack and stroke.

So, why don't we have this gene in the first place, one might ask?

Jacobs said he isn't entirely sure, but he suspects the gene renders energy production by mitochondria less efficient under normal circumstances, which isn't ideal for running fast to catch prey or avoid predators. But in today's world, he said, as people live longer and longer, it might be better to avoid the consequences of a stroke than to run a marathon.

Source: Cell Press (news : web)