New chemical tool kit manipulates mitochondria, reveals insights into drug toxicity

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Why do nearly 1 million people taking cholesterol-lowering statins often experience muscle cramps? Why is it that in the rare case when a diabetic takes medication for intestinal worms, his glucose levels improve? Is there any scientific basis for the purported health effects of green tea?

A new chemical toolkit provides the first clinical explanation for these and other physiological mysteries. The answers, it turns out, all boil down to mitochondria, those tiny organelles floating around in cellular cytoplasm, often described as the cell's battery packs.

A research team led by Harvard Medical School assistant professor and Broad Institute associate member Vamsi Mootha has developed a toolkit that isolates five primary aspects of mitochondrial function and analyzes how individual drugs affect each of these areas. These results are published online February 24 in *Nature Biotechnology*.

Over the last few decades, mitochondria have increasingly been understood as a key determinant of cellular health. On the other hand, mitochondrial dysfunction can lead to many neurodegenerative conditions as well as metabolic diseases such as diabetes. Since mitochondria are responsible for turning the food we eat into the energy that drives our bodies, these and other connections are logical. Nevertheless, there has not yet been a systematic method for thoroughly

interrogating all facets of mitochondrial activity.

“Historically, most studies on mitochondria were done by isolating them from their normal environment,” says Mootha, who is also a member of the Center for Human Genetic Research at Massachusetts General Hospital. “We wanted to analyze mitochondria in the context of intact cells, which would then give us a picture of how mitochondria relate to their natural surroundings. To do this we created a screening compendium that could then be mined with computation.”

In order to thoroughly analyze these organelles, Mootha and his team zeroed in on five basic features of mitochondria activity, looking at how a library of 2,500 chemical compounds affected mitochondrial toxic byproducts (like all “chemical factories” mitochondria produce their own toxic waste), energy levels, speed with which substances pass through these organelles, membrane voltage, and expression of key mitochondrial and nuclear genes. (Mitochondria contain their own genome, consisting of approximately 37 genes in humans.)

“It’s just like taking your car in for an engine diagnostic,” explains Mootha. “The mechanic will probe the battery, the exhaust system, the fan belt, etc., and as a result will then produce a read-out for the entire system. That’s analogous to what we’ve done.”

As a result of these investigations, Mootha and his group produced three major findings.

First, the team discovered a pathway by which the mitochondria and the cell’s nuclear genome communicate with each other. They found this by discovering that certain drugs actually broke communication between these two genomes. By reverse engineering the drugs’ toxic effects, they may be able to reconstruct normal function.

Second, the team looked at a class of the cholesterol-lowering drugs called statins. Roughly 100 million Americans take statins, and among that group, about 1 million experience muscle cramping and aches. Previous studies suggested that mitochondria were involved, but clinical evidence remained conflicting. Mootha and his colleagues found that three out of the six statins (Fluvastatin, Lovastatin, and Simvastatin) interfered with mitochondria energy levels, as did the blood-pressure drug Propranolol. When combined, the effect was worse.

“It’s likely that a fair number of patients with heart disease are on one of these three statins as well as Propranolol,” says Mootha, “Our cellular studies predict that these patients might be at a higher risk for developing the muscle cramps. Obviously, this is only a hypothesis, but now this is easily testable.”

The third and arguably most clinically relevant finding builds on a paper Mootha coauthored in 2003, a paper that demonstrated how type 2 diabetes was linked to a decrease in the expression of mitochondrial genes. A subsequent and unrelated paper showed a relationship between type 2 diabetes and an increase in mitochondrial toxic byproducts. Mootha’s group decided to query their toolkit and see if there were any drugs that affected both of these functions, drugs that could boost gene expression while reducing mitochondrial waste.

Indeed, they found six compounds that did just that, five of which were known to perturb the cell’s cytoskeleton, that is, the scaffolding that gives a cell its structure.

“Our data shows that when we disrupt the cytoskeleton of the cell, that sends a message to boost the mitochondria, turning on gene expression and dropping the toxic byproducts,” says Mootha. “The connection between the cytoskeleton and mitochondrial gene expression has never been shown before and could be very important to basic cell biology.”

Of the five drugs that did this, one, called Deoxysappanone, is found in green tea and is known to have anti-diabetic effects. Another, called Mebendazole, is used for treating intestinal worm infections. This connection gives a rationale to case reports in which diabetics treated with Mebendazole have described improvements in their glucose levels while on the drug.

The researchers intend to further investigate some of the basic biological questions that this study has raised, foremost being the relationship between the cytoskeleton and mitochondria. They also plan on using this toolkit to develop strategies for restoring normal mitochondrial function in certain metabolic and neurodegenerative conditions where it has broken down.

Source: Harvard Medical School