Medical Xpress

High-resolution 3D images reveal the muscle mitochondrial power grid

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A new study overturns longstanding scientific ideas regarding how energy is distributed within muscles for powering movement. Scientists are reporting the first clear evidence that muscle cells distribute energy primarily by the rapid conduction of electrical charges through a vast, interconnected network of mitochondria—the cell's "powerhouse"—in a way that resembles the wire grid that distributes power throughout a city. The study offers an unprecedented, detailed look at the distribution system that rapidly provides energy throughout the cell where it is needed for muscle contraction.

The scientists accomplished the results using state-of-the-art imaging technologies at the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI) at the National Institutes of Health in Bethesda, Maryland. This new information may lead to a better understanding of many diseases linked to energy utilization in the heart and skeletal muscle such as heart disease, mitochondrial diseases, and muscular dystrophy, they say.

"The discovery of this mechanism for rapid distribution of energy throughout the muscle cell will change the way scientists think about muscle function and will open up a whole new area to explore in health and disease," says Robert S. Balaban, Ph.D., scientific director of NHLBI's Division of Intramural Research and chief of NHLBI's Laboratory of Cardiac Energetics. Dr. Balaban is the study's co-leader along with Sriram Subramaniam, Ph.D., a researcher with NCI's Laboratory of Cell Biology. This landmark study is the featured cover article in the July 30 print issue of the journal *Nature*.

For the current experiments, the NIH scientists collaborated in a detailed study of the mitochondria structure, biochemical composition, and function in mouse skeletal muscle cells. The researchers used 3D electron microscopy as well as super-resolution optical imaging techniques to show that most of the mitochondria form highly connected networks in a way that resembles electrical transmission lines in a municipal power grid.

The movement of muscles, from flexing your arms to the pumping of the heart, requires lots of energy that must be distributed throughout the cell. For example, the skeletal muscle rate of energy utilization can increase 100-fold with strenuous exercise. As a result, muscle cells contain many mitochondria, microscopic structures that are specially equipped to convert foods, including sugars and fats, into useable high-energy molecules, particularly adenosine triphosphate (ATP), for work. As part of this process, known as oxidative phosphorylation, the mitochondria, like small cellular batteries, use an electrical voltage across their membranes as an intermediate energy source in converting food into ATP. Thus, this mitochondrial membrane voltage can be considered one of the primary sources of energy in the cell.

Scientists have long-believed that mitochondria distribute energy to muscle cells mainly by molecular diffusion, or the slow spread of the end products of oxidative phosphorylation, including ATP and other compounds, through the crowded cell. However, recent genetic studies suggest that diffusion alone does not fully support the distribution of energy in heart and skeletal muscle cells. Researchers have suspected that a faster, more efficient energy pathway might exist but have found little proof of its existence—until now.

After using high-resolution 3D images to reveal the structure of the mitochondrial power grid, the scientists used specially designed optical probes to subsequently demonstrate that these mitochondrial "wires" were electrically conductive. Using these probes, the researchers were able to demonstrate that most of the mitochondria were in direct electrical communication through the interconnecting network, demonstrating that the mitochondria are electrically coupled and can rapidly distribute the mitochondrial membrane voltage—the primary energy for ATP production—throughout the cell.

The study provides unprecedented images of how these mitochondria are arranged in muscle. "Structurally, the mitochondria are arranged in such a way that permits the flow of potential energy in the form of the mitochondrial membrane voltage throughout the cell to power ATP production and subsequent muscle contraction, or movement," Dr. Balaban explained. Mitochondria located on the edges of the muscle cell near blood vessels and oxygen supply are optimized for generating the mitochondrial membrane voltage, while the interconnected mitochondria deep in the muscle are optimized for using the voltage to produce ATP, Balaban added.

"These observations solve the problem of how muscle rapidly distributes energy in the cell for movement," Dr. Balaban said. "The findings also challenge the older model that energy is distributed by the slow diffusion of high-energy molecules through the remarkably dense muscle cell."

The use of focused-ion beam scanning electron microscopy, called FIB-SEM, played a critical role in unraveling the 3D architecture of mitochondrial networks in these muscle cells. Dr. Subramaniam and his colleagues were the first to develop and use this imaging approach almost a decade ago to image cells and tissue.

"We originally developed these biological imaging methods to explore mechanisms of HIV-1 infection and structural changes in melanoma cells," said Dr. Subramaniam. "It is very satisfying to see how the methods are now useful in a completely different sphere of biology with this interdisciplinary collaboration."

Identifying this basic property of the muscle cell in how it distributes energy has potential implications for disease diagnosis and treatment. These findings could spark new avenues of scientific and medical research, the scientists said. In the future, scientists may use muscle biopsies or sophisticated non-invasive imaging techniques to determine how defects in mitochondrial networks impact different diseases.

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