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Mitochondria Gone Bad

Problems in the cell's energy factories power new ideas on disease and aging

By Laura Beil • Illustration by Nicolle Rager Fuller

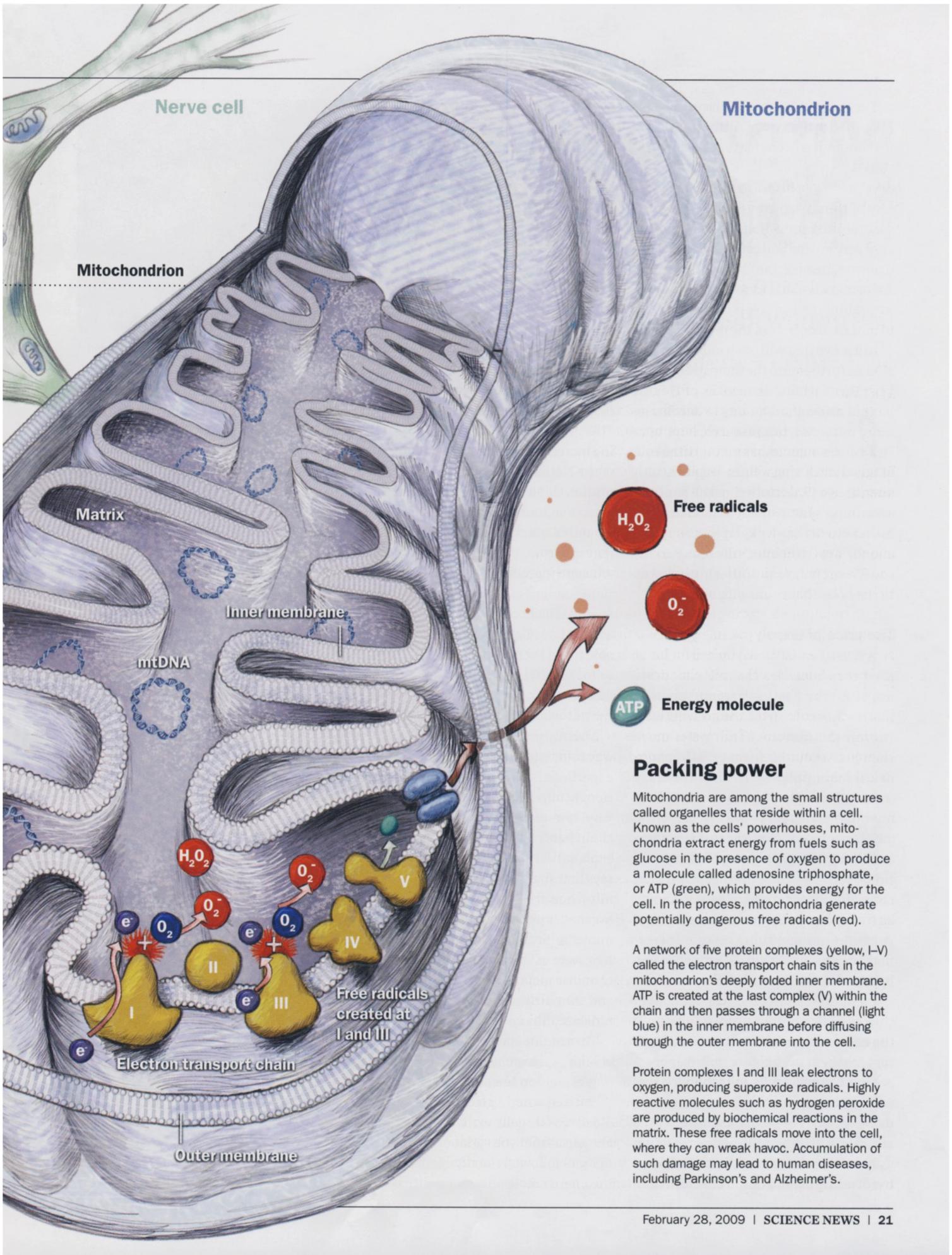
The patient, known as only “MBM,” was just 7 years old the first time doctors saw her. She had always been prone to night sweats, but now excessive perspiration was forcing her to change clothes several times a day. She was endlessly thirsty, fatigued and losing weight despite a voracious appetite. A dozen years later, at age 19, doctors checked her into a hospital, thinking she had some kind of unusual metabolic condition. After aggressive treatment with drugs, her symptoms improved, but only for a short time, and the next year surgeons removed most of her thyroid. When she was 35 — gaunt, weak and losing hair — doctors began searching every tissue of her body for a diagnosis.

They finally located the problem. It was MBM's mitochondria, the organelles that supply the energy for cells to function. Thanks to mitochondria, the sandwich you had for lunch is now powering your heart and brain. Somehow the mitochondria inside MBM's cells had gone haywire, becoming too large and too numerous. Such damage was “the first instance of a spontaneous functional defect of the mitochondrial enzyme organization.” The mysterious case of patient MBM was considered so remarkable that the *Journal of Clinical Investigation* published a description of it. That was in 1962.

Today, scientists suspect that millions of people may be suffering from mitochondria gone awry, in more subtle but nonetheless insidious forms. Evidence suggests that malfunctioning mitochondria could explain Alzheimer's disease, Parkinson's, diabetes, cardiovascular disease, obesity, cancer and other consequences of aging. Given the organelle's core function in the body, some think mitochondria might even be the biological epicenter of aging itself: If you live long enough, all your cells might experience a kind of energy crisis. “I strongly believe that mitochondrial metabolism is the key to aging,” says Hemachandra Reddy of Oregon Health & Science University in Beaverton.

Even before scientists suspected a role in common diseases, mitochondria had some biological celebrity. The sometimes tubular, sometimes bean-shaped structures are remnants of an ancient bacterium captured by a one-celled organism more than a billion years ago, experts believe. In animal cells, mitochondria are the only cellular components outside the nucleus that boast their own DNA, which is passed on from mother to child almost in its entirety. Douglas Wallace of the University of California, Irvine, a self-described “mitochondriac,” has used variations in mitochondrial DNA to help construct a global human family tree, tracing the migration of ancient humans from Africa.





Nerve cell

Mitochondrion

Mitochondrion

Matrix

Inner membrane

mtDNA

H_2O_2 Free radicals

O_2^-

ATP Energy molecule

Packing power

Mitochondria are among the small structures called organelles that reside within a cell. Known as the cells' powerhouses, mitochondria extract energy from fuels such as glucose in the presence of oxygen to produce a molecule called adenosine triphosphate, or ATP (green), which provides energy for the cell. In the process, mitochondria generate potentially dangerous free radicals (red).

A network of five protein complexes (yellow, I-V) called the electron transport chain sits in the mitochondrion's deeply folded inner membrane. ATP is created at the last complex (V) within the chain and then passes through a channel (light blue) in the inner membrane before diffusing through the outer membrane into the cell.

Protein complexes I and III leak electrons to oxygen, producing superoxide radicals. Highly reactive molecules such as hydrogen peroxide are produced by biochemical reactions in the matrix. These free radicals move into the cell, where they can wreak havoc. Accumulation of such damage may lead to human diseases, including Parkinson's and Alzheimer's.

Free radicals created at I and III

Electron transport chain

Outer membrane

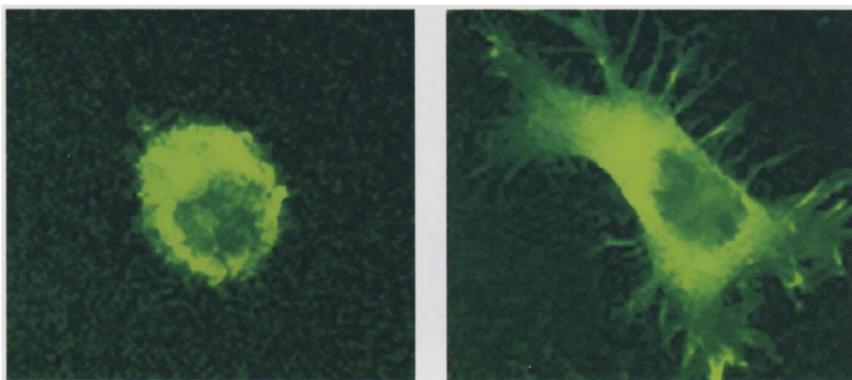
These days, however, Wallace concerns himself with the living. “All these diseases that no one has been able to solve might be solved by understanding the mitochondria,” he says. This is, he contends, a new way of thinking about illness. “Up until very recently, mitochondria were considered very arcane and certainly not part of mainstream medicine,” he says. Questions about mitochondria were mostly confined to rare brain and muscle syndromes linked to inherited defects in the organelles.

In a move that will push mitochondria studies further into the mainstream, this year the National Institutes of Health has put aside grant money to encourage more mitochondria research, hoping to “transform our understanding of the role of this critical organelle in human health and disease,” according to the funding announcement. Already scientists have found clues that link defects in mitochondria to Alzheimer’s disease, Parkinson’s, heart failure and other breakdowns in the body that come with age.

The price of energy

While scientists have theorized for at least three decades that mitochondria might be the basis for aging, renewed interest has come from the growing realization that a mitochondrion is more than just a cellular furnace. Mitochondria’s main purpose is indeed energy production — they make molecules of adenosine triphosphate, or ATP, the gasoline of a cell. But these energy factories also flip the levers on other functions, such as protecting against highly damaging incarnations of oxygen known as free radicals, orchestrating chemical communication within a cell and triggering the natural death of cells that become broken down or aged. Still, skeptics point out that there’s not enough evidence yet to conclude whether mitochondria are the causes of illness, the victims of it or just innocent bystanders.

Free radical damage has long been suspected as a culprit in aging, and mitochondria are both the primary source of free radicals in a cell and the main protection against them. “As you get older, the number of mitochondria that are not function-



In nerve cells, mitochondria are key to the growth of axons and dendrites, which send and receive signals from other cells. Antioxidants that target mitochondria may protect cells and spur axon and dendrite development: An untreated mouse nerve cell (left) shows less growth than does a cell treated with the antioxidant MitoQ (right).

ing increases,” says Mark Mattson, chief of the National Institute on Aging’s Laboratory of Neurosciences in Baltimore. Over time, mutations accumulate in mitochondrial genes. These and other changes may cause the power plants to work less efficiently, producing less energy for the same amount of glucose — the way a less energy-efficient car travels fewer miles on a tank of gas. Cells eventually become less able to rid themselves of these defective mitochondria. As life goes on, the body moves closer to a brownout — or so says the mitochondrial aging theory.

Mattson points out that the only known way to extend life span, at least in animal experiments, is through calorie restriction. Studies have found that mice fed very-low-calorie diets live longer than their better-fed brethren. While the explanation is still under study, Mattson says that such food restriction may affect mitochondria most acutely, putting the organelles under stress. The stress forces mitochondria to operate more efficiently. In a state of slight starvation, “the mitochondria maintain their function longer, and they also seem to produce less free radicals,” he says.

To examine the efficiency of old mitochondria, researchers from the University of Washington Medical Center in Seattle measured whether mitochondria from older muscle cells work as well as mitochondria from younger ones. The investigators followed the production of ATP, the energy molecule, along with oxygen

consumption. In the body, food is broken down into sugar molecules called glucose; mitochondria use oxygen to convert glucose into ATP. Older muscles seem to struggle with ATP production, the scientists reported in 2007 in *Proceedings of the National Academy of Sciences*.

“In aging muscles, there is a mitochondria dysfunction,” says Seattle researcher David Marcinek. “They produce less ATP for the same amount of oxygen consumed.”

In Mattson’s view, and that of other researchers who suspect that people are only as young as their mitochondria, mild amounts of stress force mitochondria to make better use of the glucose available — whether that stress is from calorie restriction or another source. Stress also causes cells to produce proteins that protect the mitochondria from free radical damage. And Mattson points out that other conditions that strain energy production — such as physical and mental activity — also appear to strengthen tissues at the same time.

He points to other lines of evidence linking mitochondria to aging. For example, mice bred to have deletions in a gene called *PolgA*, which encodes an enzyme critical for the replication of mitochondrial DNA, experience accelerated aging, including hair loss, weight loss and curvature of the spine. More recently, in the journal *Science*, Wallace and his colleagues reported that a mutation in the mitochondrial genes of mice led to heart

failure, a disease that becomes more common with age, even when the DNA in the cell nucleus remained unaffected.

Death in the brain

If mitochondria are the architects of aging, they may also be responsible for some of the most notorious afflictions of old age. Mitochondria aren't distributed evenly in the body. A cell may have a few dozen of them or a few thousand, depending on the energy demand. Not surprisingly, the diseases most under scrutiny for a mitochondrial origin are those involving tissues that consume a lot of energy, and therefore maintain small armies of mitochondria. And a particularly greedy organ — consuming about 20 percent of the body's energy — is the brain.

In the December issue of the journal *NeuroMolecular Medicine*, Reddy makes the case for Alzheimer's being a mitochondrial disease. For starters, it now appears that brain cells involved in Alzheimer's show damage from free radicals early in the disease process. Studies have found decreased production of mitochondrial enzymes in the brains of Alzheimer's patients. Also, one of the toxic proteins that collects in Alzheimer's-afflicted brains, called amyloid-beta, appears to conspire with mitochondrial proteins.

A study published in *Nature Medicine* in October investigated the relationship between amyloid-beta and mitochondria. Scientists from Columbia University Medical Center blocked the action of a molecule used by mitochondria, called cyclophilin D, which appears to have a role in cell death in the brains of Alzheimer's patients. That experiment, combined with other studies using mice lacking cyclophilin D, indicated that amyloid-beta and cyclophilin D may be partners in crime, working together to cause mitochondria to rupture and release their deadly contents into the cell. Without cyclophilin D, amyloid-beta wasn't as destructive, and mice with a version of Alzheimer's improved in learning and memory.

Other scientists believe that another aging-related brain disease — Parkinson's — starts and ends with mitochondria. "If you have mitochondria that are

not functioning, the first thing is you've got impaired energy production," says Claire Henchcliffe of Weill Cornell Medical College in New York City. "That could reset the threshold for a cell's demise."

In November, in *Nature Clinical Practice Neurology*, Henchcliffe described the evidence linking mitochondria to Parkinson's. Among the key points: The genes known to be associated with Parkinson's code for proteins thought to be involved in mitochondrial operation. "That's a major supportive argument," Henchcliffe says. "There seem to be functional links between all of them and the mitochondria." Also, she says, studies have found that major mitochondrial genes and proteins are depleted in the region of the brain that dies during Parkinson's disease. But she also acknowledges that mitochondrial defects have not been detected in everyone with Parkinson's, illustrating both the disease's complexity and the need to figure out how to better tailor treatments to individual patients.

Behind the power failure

Though mitochondria experts have an intense interest in neurological problems, the scope of investigation extends to almost every major human illness. Wallace investigates not only neurodegenerative and heart diseases, but also diabetes and obesity (which are ultimately energy-balance and storage issues). Other researchers are looking into cancer and muscle problems. Such an extensive list should not be surprising, Wallace says, given the mitochondrion's importance in every cell. "Energy is the one thing you can't live without," he says. Last summer, in the journal *Genetics*, Wallace wrote a commentary proposing that Asian medicine, which is directed at the mysterious energy force of living things known as "chi," might have the right idea. When mitochondria can't keep up with the body's energy demands, he says, cells die, tissues age and organs fail.

But what makes mitochondria lose steam? Some damage may come from normal wear and tear. Mitochondrial DNA gets copied a lot more often than does nuclear DNA. Mitochondrial genetic

material is more vulnerable to damage, and less able to make repairs. In many cases, mitochondria might take a hit from the environment. Parkinson's researchers cite MPTP, a contaminant that made its way into synthetic heroin in the 1970s. Users who injected the drug soon developed acute Parkinson's symptoms, including tremors and rigidity. Further tests have found that MPTP can cause damage to neurons in the substantia nigra in the brain — the dopamine-producing area that dies in Parkinson's — and can disrupt mitochondrial function. Another chemical that damages mitochondria, the pesticide rotenone, also causes Parkinson's symptoms in laboratory animals.

"Not that we are anywhere close to identifying the environmental causes of Parkinson's," Henchcliffe notes. Rather, the examples of rotenone and MPTP suggest that mitochondria might be vulnerable to environmental assaults, no matter the source. One paper, published last year in *Molecular Nutrition & Food Research*, suggested that medications — including some of the most common pills in the medicine cabinet, such as aspirin and cholesterol drugs — might harm mitochondria.

Once scientists figure out the cause of mitochondrial problems, the hope is to devise a way to prevent or repair the damage. For those with congenital mitochondrial disease, doctors have no cures, only symptom relief. But clinical trials are underway for some age-related diseases. One is looking at whether high doses of an antioxidant that acts in the mitochondria, coenzyme Q-10, might slow disease progression in Parkinson's patients.

In the case of patient MBM, researchers offer no hint about how long she survived, or how well, after doctors discovered the source of her problem. No one knows how she died, but maybe one day scientists will understand how she lived. ■

Laura Beil is a freelance science writer in Cedar Hill, Texas.

Explore more

■ Douglas C. Wallace. "Mitochondria as Chi." *Genetics*. June 2008.