Defects in mitochondria may explain many health problems observed during space travel

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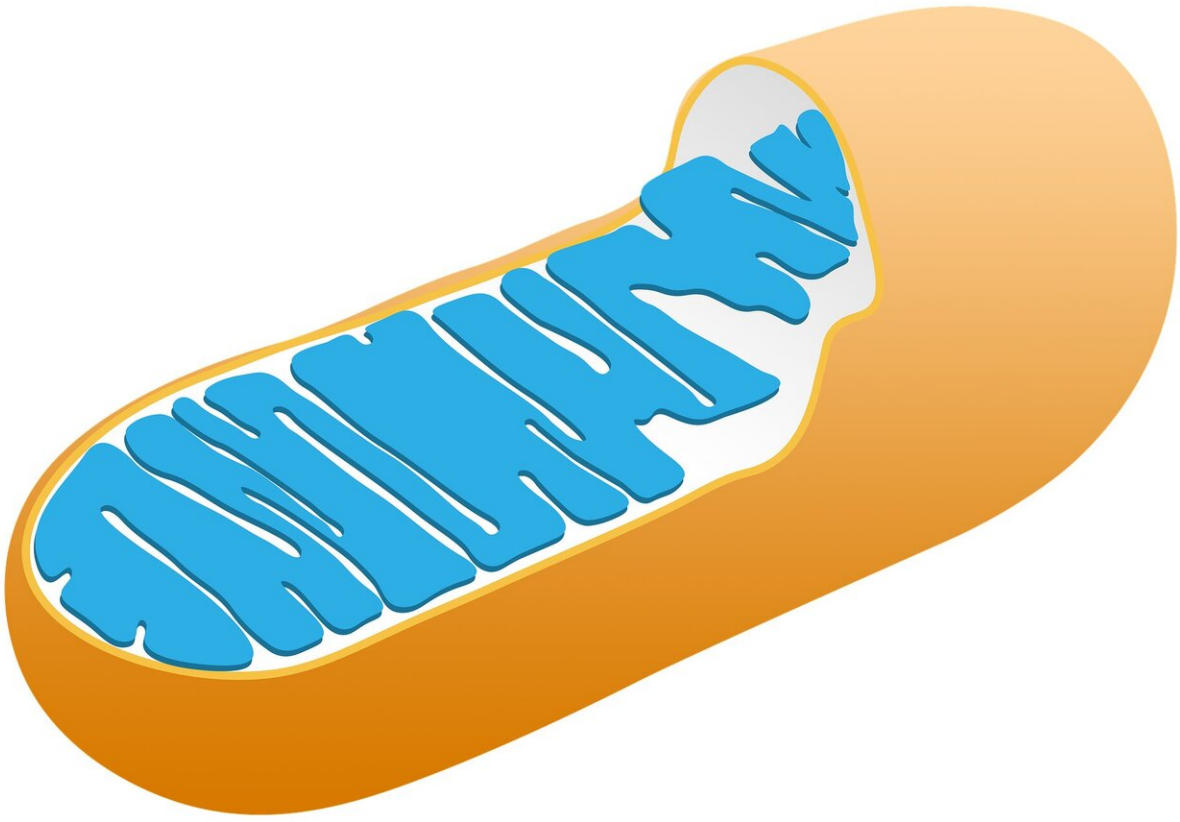

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For space exploration to be successful, it's vital to understand—and find ways to address—underlying causes of the health issues that have been observed in astronauts who have spent extended periods of time off world. These problems include loss of bone and muscle mass, immune dysfunction, and heart and liver problems. Using data collected from a number of different resources, a multidisciplinary team is reporting discovery of a common thread that drives this damage: mitochondrial dysfunction. The researchers used a systems approach to look at widespread alterations affecting biological function. The findings are reported November 25 in the journal *Cell*.

"We started by asking whether there is some kind of universal mechanism happening in the body in space that could explain what we've observed," says senior author Afshin Beheshti, a principal investigator and bioinformatician at KBR in the Space Biosciences Division of the National Aeronautics and Space Administration (NASA) at Ames Research Center in California's Silicon Valley and a visiting researcher at the Broad Institute. "What we found over and over was that something is happening with the mitochondria regulation that throws everything out of whack."

The investigators analyzed data obtained from NASA's GeneLab platform, a comprehensive database that includes data from animal studies, the NASA Twin Study, and samples collected from 59 astronauts over decades of space travel. Many of the scientists who participated in this study are involved with GeneLab's Analysis Working Groups, which draw from institutions all over the world. The platform contains a range of "omics" data related to changes in tissues and cells that occur due to the combined effects of space radiation and

microgravity, including proteomic, metabolomic, transcriptomic, and epigenomic data.

The researchers used an unbiased approach to look for correlations that could explain the widespread changes observed. "We compared all these different tissues from mice that were flown in space on two different missions, and we saw that mitochondrial dysfunction kept popping up," Beheshti says. "We looked at problems in the liver and saw they were caused by pathways related to the mitochondria. Then we looked at problems in the eyes and saw the same pathways. This is when we became interested in taking a deeper look."

He explains that mitochondrial suppression, as well as overcompensation that can sometimes occur because of that suppression, can lead to many systemic organ responses. They can also explain many of the common changes seen in the immune system.

Using their discoveries from mice as a starting point, the researchers then looked at whether the same mechanisms could be involved with humans in space. Examining data from the NASA Twins Study, in which identical twins Scott and Mark Kelly were followed over time, the former on the International Space Station and the latter on the ground, they saw many changes in mitochondrial activity. Some of these changes could explain alterations in the distribution of immune cells that occurred in Scott during his year in space. They also used physiological data and blood and urine samples that had been collected from dozens of other astronauts to confirm that mitochondria activity in different cell types had been altered.

"I was completely surprised to see that mitochondria are so important, because they weren't on our radar," Beheshti says. "We were focusing on all the downstream components but hadn't made this connection." He adds that mitochondrial dysfunction can also help explain another

common problem with extended space travel: disrupted circadian rhythms. Since the team first reported their findings within NASA, other NASA scientists have begun making connections between mitochondrial changes and common space-related cardiovascular problems as well.

The hope is that now that mitochondrial issues have been identified as a cause of so many health risks related to space travel, countermeasures could be developed to address them. "There are already many approved drugs for various mitochondrial disorders, which would make it easier to move them toward this application," Beheshti notes. "The low-hanging fruit now would be to test some of these drugs with animal and cell models in space."

More information: *Cell*, da Silveira et al.: "Multi-Omics Analysis Reveals Mitochondrial Stress as a Central Hub for Spaceflight Biological Impact" www.cell.com/cell/fulltext/S0092-8674(20)31461-6 , DOI: 10.1016/j.cell.2020.11.002

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