Space Life Sciences Research Highlights

Microgravity Offers a Unique Opportunity to Study Human Immune Function

Keeping astronauts healthy is an essential and non-trivial task. In the microgravity of spaceflight, human immune functions are altered, but the mechanisms by which this occurs are not well understood. To determine what is happening at the molecular and cellular levels, former astronaut Millie Hughes-Fulford of the University of California, San Francisco, studies T cells—a type of immune cell—that have been sent into space or have been exposed to space-like conditions. Her work will provide insights that may not only improve space-traveler health but also the health of people who have never left Earth.

Before NASA started quarantining astronauts prior to flight, space travelers often got sick. In 1975, NASA physicians Willard Royce Hawkins and John Zeiglschmid reported that more than half of the Apollo astronauts experienced bacterial or viral infections during flight or within a week of landing. While quarantines have since reduced infections, astronauts still experience many negative effects from spaceflight, including altered immune function. Keeping astronauts healthy requires a better understanding of how spaceflight affects the immune system's ability to protect against infection.

Millie Hughes-Fulford's studies provide better understanding of this problem by examining T cells in spaceflight. T cells come in several types that play roles primarily in adaptive immune responses. Hughes-Fulford, a professor in the Department of Medicine at the University of California, San Francisco, brings a unique perspective to her work. In 1991, she spent nine days in space as a payload specialist on the Space Shuttle *Columbia*, which carried the first Spacelab mission dedicated to medicine and life sciences.

"Certain things don't work in the absence of [normal] gravity," she says. "I'm using the International Space Station (ISS) as a platform to understand the immune system." Such work will not only make for healthier space travelers, but could also help treat the diseases of people on Earth.

Former astronaut Millie Hughes-Fulford no longer goes into space. Instead, she studies T cells that have made the trip. Credit: ESA

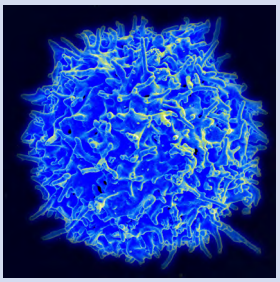
Studying T Cells in Microgravity

Decades of human and animal research have revealed that spaceflight not only decreases T-cell activation, but alters the gene- and protein-expression patterns of these cells as well. Hughes-Fulford has recently found that changes extend beyond protein-coding genes to those that encode microRNAs (miRNAs), which are short, non-coding RNA molecules that attach to messenger RNAs (mRNAs) and prevent these transcripts from being translated into proteins. The cell's use of miRNAs to regulate protein production occurs in situations where gene expression needs to be abruptly changed, such as when turning off an immune response.

Hughes-Fulford and her team made this novel discovery while conducting experiments originally designed to examine how spaceflight induces changes in gene expression patterns within primary cultures of human T-cells. To accomplish this, cells were placed in chambers inside cassettes that were sent to the ISS to incubate in microgravity, and were subsequently treated using methods that mimic pathogenic infection. As a control, comparable cassettes were placed on the ISS into a centrifuge that replicated Earth's gravity (1*g*) or one-half Earth's gravity (0.5*g*). Once samples were back on the ground, the researchers isolated RNA from the cells and analyzed it with microarrays and quantitative PCR.

Differences between the RNA expression profiles of cells subjected to microgravity and those of the centrifuged 1*g* controls were detected as early as 1.5 hours after activation. As expected, microgravity suppressed the expression of genes involved in T-cell activation and proliferation, Hughes-Fulford's team reported in 2012 in the *Journal of Leukocyte Biology*. While analyzing the list of affected RNA transcripts, however, they discovered that miR-21, a key immune regulatory miRNA, was also suppressed by microgravity. This finding presents the first piece of evidence that, in addition to altering mRNA transcription from genes, gravity (or its effective absence) alters immune responses by influencing mRNA translation into proteins! An even more surprising aspect of this observation is that miR-21 plays a role in normal immune function and that its expression levels paralleled that of the T-cell-activating mRNA transcripts it suppresses. This concept at first was confusing to the research team, as the effect would seem analogous to pressing the gas pedal and the brake in a car at the same time.

But Hughes-Fulford realized that it's not exactly how it works. It takes days for miR-21 to build up in the cell and finally be able to turn off genes. "It's like a built-in regulatory system," she says. Rather than being applied simultaneously with the gas, "the brake is being built … as the car is accelerating." When miR-21 accumulates above a threshold concentration, this "brake" becomes mature and stops the "car" by shutting off gene expression. This previously unknown mechanism, termed "self-limiting induction," also works to control the immune response here on Earth.



The action of T cells is altered by spaceflight.
Credit: NIAID/NIH

Self-limiting induction may be happening in other systems in the body, she speculates. It might be, for instance, how the body keeps from growing too many skin cells—and possibly causing cancer—when patching up a scratch. And if it's true, she says, "it's a brilliant way for the body to work," and one that she doesn't think she could have discovered outside of microgravity.

The team also observed that T cells exposed to 0.5*g* produced levels of miR-21 that matched those in the 1*g* control, suggesting that partial gravity may prevent some of the biological consequences of microgravity. Thus, an easier and cheaper countermeasure against the effects of microgravity might be the use of artificial gravity at a level lower than that found on Earth, she says. "The question is, how much gravity do you need to make your immune system work properly?"

While such work provides insights into astronaut health, it also has direct significance for better understanding of the human aging process. While the two may not seem to have much in common, microgravity causes many of the same problems for the immune system as does old age. If the team can discover some missing factor that causes immune system suppression, then it may be possible to counteract that, Hughes-Fulford says, which could lead to treatments for the elderly and immune-compromised population.

Simulated Microgravity Versus the Real Thing

As a veteran of multiple flight experiments, Hughes-Fulford knows all too well that sending experiments to the ISS is very difficult and expensive, and there are limitations on what can be sent. Researchers, therefore, have developed ways to mimic the continuous "free-fall" effects of spaceflight here on Earth. A rotating wall vessel, for example, slowly rotates a cylinder to keep cells in suspension. The random positioning machine, in contrast, consists of two rotating frames. Cells are placed in the inner frame and rotated at random directions and speeds, which simulates microgravity. But Hughes-Fulford and her team wanted to know if these methods actually duplicate the effects of spaceflight.

The answer to that question is, yes, but only partially. The team compared changes in gene expression during mouse T-cell activation in both simulators with those observed in Space Shuttle experiments. They found many similarities in gene expression patterns between the environments. In particular, six early-immune genes that facilitate T-cell responses to infections were downregulated in simulated and real microgravity. While the effect was greater in cells exposed to the true microgravity of spaceflight, the observations suggest that the ground-based analogs may provide qualitative predictions of the changes in affected genes.

Nevertheless, "being in true microgravity is different," Hughes-Fulford states. She worries that while simulators can produce useful data that may help scientists design experiments for the ISS, they are not a replacement for spaceflight. "If you based everything on things on the ground, you could miss something very important."

Getting people to Mars and keeping them healthy along the way is the ultimate goal for Hughes-Fulford. Astronauts now have several ways to counteract the altered immune effects of microgravity, she notes, such as quarantines. However, better understanding of how spaceflight alters immune function and susceptibility to pathogens could either lead to the development of new countermeasures or improve those already in place.

Hughes-Fulford's most recent spaceflight experiments have not only identified an alternative molecular mechanism by which spaceflight alters immune function, but have also provided important insights into how the immune system is regulated here on Earth. Conducting experiments in space may not always be practical, but Hughes-Fulford's validation of microgravity simulations confirms that analogs may provide adequate substitutes for making initial observations and planning future spaceflight experiments.

Further Reading

Hughes-Fulford M, Chang TT, Martinez EM, Li CF. Spaceflight alters expression of microRNA during T-cell activation. FASEB J. 2015 Aug 14.

Martinez EM, Yoshida MC, Candelario TL, Hughes-Fulford M. Spaceflight and simulated microgravity cause a significant reduction of key gene expression in early T-cell activation. Am J Physiol Regul Integr Comp Physiol. 2015 Mar 15;308(6):R480-8.

Chang TT, Walther I, Li CF, Boonyaratanakornkit J, Galleri G, Meloni MA, Pippia P, Cogoli A, Hughes-Fulford M. The Rel/NF-κB pathway and transcription of immediate early genes in T cell activation are inhibited by microgravity. J Leukoc Biol. 2012 Dec;92(6):1133-45.

Hawkins W, Zieglschmid J. Clinical aspects of crew health. In Biomedical Results of Apollo, edited by R. Johnston, L. Dietlein, and C. Berry. Washington: National Aeronautics and Space Administration, 1975. pp. 43-81.