Space Life Sciences Research Highlights

Studying Infections in Space to Help Provide Better Medicine Back on Earth

To gain insight into how microbes cause disease, NASA-funded microbiologist Cheryl Nickerson studies the interactions between pathogen and host in the microgravity environment. By decreasing the physical stresses of gravity on cells, she discovered unique molecular genetic and phenotypic changes that take place during infection. Such research could one day lead to new strategies for treatment and prevention of deadly diseases.

Bacteria and other microbes are all around us, even living inside our bodies. Most are harmless; some are essential for life. Others can infect a person and may cause a disease, but not always.

"It's a very dynamic dance between the host that gets infected and the pathogen that infects the host in terms of who wins," says microbiologist Cheryl Nickerson, professor of life sciences at the Biodesign Institute at Arizona State University. "It's like a high-stakes poker game."

To better understand that dynamic dance, Nickerson has been studying these interactions in the absence of one constant for life on Earth—gravity. "It's amazing how powerful the force of gravity can be," she says, "in preventing us from observing key cellular responses" important for microbial virulence (disease-causing potential).

Since first being funded by NASA in 1998, while at Tulane University, Nickerson (*http://sols.asu.edu/people/cheryl-nickerson*) and her colleagues have conducted experiments both in a simulated microgravity environment in the lab and in the spaceflight environment on Space Shuttle and International Space Station (ISS) missions. This work is unraveling the complex cellular and molecular responses of both pathogen and host and may have translational Earth benefits.

A Master Switch for Virulence

Infectious disease is a significant health problem in the United States and globally. The major food-borne bacterial pathogen *Salmonella*, for instance, causes some 1.2 million Americans to sicken each year, resulting in about 19,000 hospitalizations and 380 deaths, according to the U.S. Centers for Disease Control and Prevention. In Nickerson's early NASA-sponsored research, she discovered that this pathogen becomes more virulent after culture in the microgravity environment of spaceflight or time in a bioreactor that simulates that environment. The finding has major implications for anyone headed into space.

But what was happening inside the pathogen that made it more virulent? To find out, Nickerson's team compared gene expression in *Salmonella* cultures grown during spaceflight with otherwise identical controls on Earth. They discovered that in microgravity culture, genes important for the virulence of *Salmonella* were not being regulated as when this same organism is grown on Earth. The activity of about one-third of those genes was controlled by a single "master switch," a small protein called Hfq.

Microbiologist Cheryl Nickerson of the Biodesign Institute at Arizona State University, whose work has been funded by NASA for more than a decade, studies the cellular and molecular underpinnings of how pathogens behave in the absence of gravity. Credit: Nick Meek

In addition to controlling virulence, Hfq is known to regulate ion response pathways. Armed with that information and other knowledge, "we had a clue that if we changed the salt concentration in the culture medium in which we grew *Salmonella*, we might be able to turn off that increased virulence," Nickerson recalls. When her team did that, the bacteria lost their extra disease-causing ability in response to spaceflight culture. Such research could lead to the development of effective countermeasures that could, for instance, reduce or prevent the impact of severe food poisoning.

Hfq is not unique to *Salmonella*. This master switch can be found in many other pathogens and the Nickerson team showed that this switch also controlled the spaceflight and spaceflight-analogue response of *Pseudomonas aeruginosa*, a bacterium that causes urinary tract, lung, eye, and wound

The tiny nematode worm Caenorhabditis elegans *is often used as a stand-in for humans in research. In January 2015, Nickerson's team infected worms with* Salmonella *in space and in a lab on Earth to study how microgravity impacts the infection process.*

infections. In addition, her collaborative studies with NASA Johnson Space Center scientists showed that Hfq also regulates the spaceflight-analogue response of methicillin-resistant *Staphylococcus aureus* (MRSA), a bacterium that has become increasingly resistant to common antibiotics. Currently, our understanding of the response of MRSA to true spaceflight culture is unknown.

Nickerson has also uncovered changes in gene expression when the fungal pathogen *Candida albicans*, which causes oral and genital infections, was cultured in spaceflight. In microgravity, 452 genes differed in their expression. About a third were regulated by a different master switch, the protein Cap1. Also, the team found that these fungal cells began to aggregate into string-like filaments, a precursor to forming a biofilm and an important part of the infection process on Earth.

Each pathogen's response to microgravity was somewhat different, Nickerson notes. But they all unveiled novel clues as to how they cause disease in the body that could not have been observed with conventional experimental conditions.

The First Experimental Infection in Space

In space, infections can become serious, as was demonstrated during the 1970 Apollo XIII mission when an astronaut contracted a *P. aeruginosa* urinary tract infection. Illness can negatively impact both mission success and the health of the astronaut. So there is considerable incentive for avoiding even the simplest of infections.

For the first-ever experiment to profile the entire infection process in a living organism in real time in spaceflight, Nickerson turned to a well-studied organism that is a frequent human stand-in for research—a tiny nematode worm called *Caenorhabditis elegans*. In January 2015, she and her colleagues, including Mark Ott of the Johnson Space Center and John Alverdy of the University of Chicago, sent a small cadre of these worms up to the ISS, where astronauts infected them with *Salmonella*.

The infections were monitored in real time using video imaging downlinked to Nickerson's team. Other samples were fixed for subsequent gene expression and immune response profiling upon return to Earth. Some worms were also given phosphate as a nutritional countermeasure in an attempt to protect against the infection. The team simultaneously performed the same set of experiments on the ground under otherwise identical conditions to provide a control, so they will be able to tease out the effects of the microgravity environment on the infection process. Nickerson needed five years to prepare for the experiment—one of the most complex biological experiments ever done in space—and the data is currently being analyzed back on Earth.

Nickerson's work has already yielded important discoveries and new tools for studying human health and disease. For example, her lab has used NASA microgravity analogue bioreactors to develop advanced three-dimensional models of human tissues that closely mimic those in the body. She has shown that these models respond to challenge with pathogens, toxins, and drugs in key ways that reflect the process in the body, and cannot be observed using traditional cell culture approaches.

The spaceflight environment enables scientists to conduct biomedical research in ways that are not possible on Earth. Such studies have become more important than ever, Nickerson says, because right now, in the war between humans and the microbes that can harm us, microbes and the infectious diseases they cause are on the winning side.

Further Reading

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