Spaceflight shown to alter ability of bacteria to cause disease

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Space flight has been shown to have a profound impact on human physiology as the body adapts to zero gravity environments. Now, a new study led by researchers from the Biodesign Institute at Arizona State University has shown that the tiniest passengers flown in space—microbes—can be equally affected by space flight, making them more infectious pathogens.

“Space flight alters cellular and physiological responses in astronauts including the immune response,” said Nickerson, who led a project aboard NASA’s space shuttle mission STS-115 (September 2006) involving a large, international collaboration between NASA, ASU and 12 other research institutions. “However, relatively little was known about microbial changes to infectious disease risk in response to space flight.”

Cheryl Nickerson and lead author James Wilson, both professors in ASU’s School of Life Sciences, have performed the first study of its kind to investigate the effect of space flight on the genetic responses and disease-causing potential, or virulence, of Salmonella typhimurium, the main bacterial culprit of food poisoning. Their results, published in the journal *Proceedings of the National Academy of Sciences*, reveal a key role for a master regulator, called Hfq, in triggering the genetic changes that show an increase in the virulence of Salmonella as a result of spaceflight. The results of these studies hold potential to greatly advance infectious disease research in space and here on Earth, and may lead to the development of new therapeutics to treat and prevent infectious

disease.

To study the effects of space flight, Nickerson and colleagues sent specially contained tubes of Salmonella in an experimental payload aboard the Space Shuttle Atlantis. The tubes of bacteria were placed in triple containment for safety and posed no threat to the health and safety of the crew during or after the mission.

During the flight, astronaut Heidemarie M. Stefanyshyn-Piper activated growth of the bacteria in sealed hardware and 'fixed' the cultures after a day of growth to determine changes in gene and protein expression levels.

"The bacterial cultures were taken up into space and activated to grow in a separate compartment of the tubes called the growth chamber," said Nickerson. "The bacteria didn't have access to the growth chamber until Heide pushed down on a plunger which introduced the bacteria into the growth media. Then they were grown for 24 hours, and at the end of 24 hours, Heide pushed down on the plunger again, which either "fixed" the bacteria with chemicals that preserved the gene expression message, or else introduced fresh media to keep the bacteria growing to perform the virulence studies."

As a synchronous control experiment back on Earth, Nickerson's team grew an identical set of bacteria in the same type of tubes used for flight and incubated them in a special room at the NASA Kennedy Space Center called the orbital environmental simulator. "This simulator is linked in real-time to the shuttle, and duplicates the exact temperature, humidity and growth conditions of the shuttle, with the exception that they are not flying in space," said Nickerson. "In addition, we were also linked via real-time telecommunications with the shuttle crew when they were activating and terminating our experiments in flight, and we did the exact same things at the same time to the ground samples that the

astronauts did to the flight samples – thus we had perfectly matched synchronous ground controls."

After the bacteria returned to Earth, the group performed the first global analysis of Salmonella to measure the effect of space flight on gene and protein expression and virulence. By measuring the gene and protein patterns, the researchers could hone in on the key molecular players necessary for virulence from among thousands of potential candidates.

"We chose to measure gene expression at the mRNA level since the technique to do this, called microarray analysis, is a highly advanced and convenient way to quantitatively measure the expression of every gene in a single experiment," said Wilson, who coordinated the team's molecular profiling efforts for the Nickerson lab, and played a central role in the performance of these experiments, including data analysis. "It is a very powerful technique that was very applicable to the spaceflight experiment. The isolation of mRNA poses particular challenges since it is very sensitive to degradation, but we designed the experiment using a fixative that preserved the mRNA very well."

After logging in millions of miles in space, the invaluable and well-traveled bacterial samples were analyzed back on Earth, and for the protein profiling studies, were taken to the University of Arizona's core proteomics facility at its Center for Toxicology to measure the level of every protein that had been subjected to space flight.

"Working with the UA group was great and we obtained very nice data that complemented the microarray analysis very well," said Wilson. "Keep in mind also that our body of mRNA and protein expression data from this experiment is precious, since comprehensive analysis of an organism's molecular genetic response to space flight is very rare."

Compared to bacteria that remained on earth, the space-traveling

Salmonella had changed expression of 167 genes. After the flight, animal virulence studies showed that bacteria that were flown in space were almost three times as likely to cause disease when compared with control bacteria grown on the ground.

The study discovered that an important regulatory protein, Hfq, may be a key molecule responsible for the increased virulence due to space flight. “Hfq is a protein that binds to and regulates a number of regulatory RNAs, which in turn, control gene expression,” said Nickerson. “Our studies suggest that there may be a role for these regulatory RNAs in the cellular response to the physical and mechanical forces found in spaceflight, which are relevant to conditions that cells encounter here on Earth during the normal course of their lifecycles.”

These results have important implications for human health since Salmonella (and other gut-related bacterial pathogens) are a leading cause of food-borne illness and infectious disease, especially in the developing world. Nickerson’s group further highlights Hfq as a potential therapeutic target, since no vaccine currently exists for Salmonella food-borne infections in humans. In addition, the space flight studies may shed new light on why Salmonella has become increasingly resistant to antibiotic treatment.

“We also studied the morphology of the bacteria in response to space flight, and the change that we observed is consistent with what looks like formation of a biofilm. The ground grown samples did not show biofilm formation. Biofilms are associated with increased pathogenicity because the immune system can’t clear the bacteria effectively and antibiotics don’t treat them effectively.”

The group will embark on another space shuttle mission likely next year to further understand the risks and mechanisms of infectious disease agents during space flight and how microbes cause infections on Earth.

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