Medical Xpress

Answering questions about effects of microgravity on human body

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When the space shuttle Atlantis touched down in the summer of 2011 at Cape Canaveral, closing the book on the U.S. shuttle program, a team of U.S. Army researchers stood at the ready, eager to get their gloved hands on a small device in the payload that housed a set of biological samples. On Monday, April 22, at the Experimental Biology 2013 conference in Boston, the team will present the results of nearly two years' worth of study on those samples, results that shed light on how the human immune system responds to stress and assaults while in space – and maybe here on Earth.

"Weakening of the immune system associated with spaceflight is an area that needs a thorough investigation," said Marti Jett, director of the Integrative Systems Biology Program at the U.S. Army Medical Command. "Astronauts subjected to microgravity have shown a significant immune weakening. Furthermore, microgravity has been shown to enhance bacterial virulence while depressing the immune response."

Among the tasks completed by the four-person crew of the orbiter Atlantis were experiments on human cells using a common component of an Earth-dwelling microorganism that plays a role in septic shock. The experiments were designed, overseen remotely and replicated on Earth under normal gravity conditions by the army team, led by Rasha Hammamieh, deputy director of the Integrative Systems Biology Program, which is based at the U.S. Army Center for Environmental Health Research at Fort Detrick in Maryland.

"There's an increased risk of infection due to altered bacterial growth in microgravity. Wounds heal poorly in microgravity. So the question investigated was 'In what way does the host response to pathogen differ in microgravity versus on Earth?'" Hammamieh explained. The research team set out to investigate the molecular cascade of events that occur in human endothelial cells in response to exposure to the endotoxin lipopolysaccharide, or LPS, from the cell wall of gram-negative bacteria.

The cells hung out in space for six days before the astronauts applied the LPS to them, but even during that untouched period they showed genomic responses typical of immune dysfunction to the zero-gravity conditions. "And so, when we added the agonist, they didn't respond very well," Jett said. The cells were so busy dealing with the gravity situation that they barely put up a fight against the bacteria. The cells' poor response "suddenly reminded us of something we'd seen previously," Jett said.

The research team previously had conducted a study of Army Rangers. The scientists took blood samples from the special forces at the beginning, middle and end of their intensive training program and exposed those samples to pathogens to see if battlefield conditions affected immune responses. That work was published in the journal *Genes & Immunology* last year.

"We found that they weren't responding normally at all. We saw what maybe one could guess in retrospect that you would see, which was that the immune system was involved in the stress of being a Ranger, and when we added these pathogens – the virus, bacteria and toxin – in separate experiments, they didn't respond to them. And we saw something very similar to that in space. The cells were probably preoccupied with the response to microgravity, and, therefore, when exposed to LPS, yes, there was a response, but it certainly wasn't comparable to what we were seeing on the ground."

The team determined that, in the samples that went to space, there was a diminished capability of the cells to activate the normal immune response in terms of pathogen processing. Reduced gravity also altered angeogenesis and vasculogenesis and promoted genes involved in rheumatoid arthritis, tumor growth and wound repair. This could suggest an elevated risk of neurological degeneration and other problems as a result of microgravity.

Jett said the results of both the spaceflight study and Rangers study have drawn the interest of those studying immune response in people exposed to other high-stress conditions, such as Wall Street executives and CEOs. "The core motivation was to try to understand why there is not a good immune response in terms of healing and preventing illness in space – why healing is compromised – and it just ends up coming back to maybe broader strokes to what we see on Earth as well," Jett said.

About the team's toxin of choice

The research team decided to use LPS in space because it's the most common endotoxin and because it impairs the wound-healing process. When left untreated, Gram-negative bacteria infection can cause septic shock, or sepsis.

"Every year, severe sepsis strikes about 750,000 Americans. It's been estimated that between 28 and 50 percent of these people die � far more than the number of U.S. deaths from prostate cancer, breast cancer and AIDS combined," Hammamieh said.

Sepsis cases are on the rise in the U.S, and about $17 billion is spent annually to treat it. LPS-induced endotoxemia is the most common form of infection after burns, and it's the leading cause of postsurgical deaths.

"Our research seeks diagnostic, therapeutic and prognostic markers of

LPS infection in the healthy cells and the cells immunocompromised by microgravity. Our high-dimensional, -omics approach results in deluge of data," explained Hammamieh, which promises to hold the key to therapy of this complex disease.

Jett added that, because reduced gravity enhances bacterial activity, it's possible that "the host responses in microgravity may adapt novel healing mechanisms, or the assaults may find unconventional pathways to trigger the damage. The understanding of these paradigms can potentially enlighten the ground-based LPS therapy."

Doing biological science in space

After securing funding for the research project in early 2011, the team had only six months to prepare for the launch. But, having conducted systems biology work since the late 1990s, the team was a well-oiled machine. Jett said she and her colleagues had a workable plan in mind "but it was a matter of adapting to make it work in space." That was easier said than done.

"One of the complexities was to be prepared to repeat the entire setup in case the launch did not occur on the designated day. Because our cell cultures required three days to prepare for launch, we had to have cultures ready for the backup dates even while preparing as the shuttle was on the launch pad," she said. "Our technical staff got just two hours of sleep the night before the launch, since they had to prepare for the next two launch dates in case of delay. It was exhausting, exciting and an unbelievable experience."

When it was time for Atlantis to return to Earth, the logistics were equally challenging. Uncertain whether the landing would take place in Florida or California, the team dispatched a member to each coast.

"We had one person in the air going to Cape Canaveral. Dr. Hammamieh was in the airport ready to step on the plane to go to L.A. and asked, 'If I hear it's landing at Cape Canaveral, can I step off?' And then, just before she stepped through the door of the plane and they were going to close it, she got the message 'It's landing at Cape Canaveral!' and she got off. It was a crazy time. It was really fun."

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