



Space Life Sciences Research Highlights

Space Flies Model How Gravity Affects the Human Immune System

A growing body of evidence has shown that a space traveler's immune system is affected by microgravity. Studying these changes at the molecular level in humans is difficult because few individuals get to go to space, but finding such mechanisms is the first step to mitigating risks to astronauts. NASA-funded researchers Kathleen Beckingham of Rice University and Deborah Kimbrell of the University of California, Davis, instead turned to the fruit fly to tackle this problem. Their work is helping to illuminate the ways that the immune system responds to altered gravity.

Astronauts have to be hale and hearty before they are sent on a mission, but by the time they return home, that trip to space has taken a toll on their immune system. To find out why the immune system exhibits signs of altered function, scientists need to understand the mechanistic causes at a cellular and molecular-genetic level.

To better understand how gravity affects immunology, NASA Space Biology researchers Kathleen Beckingham, a professor at Rice University, and Deborah Kimbrell, an associate research geneticist at the University of California, Davis, have turned to the fruit fly, *Drosophila melanogaster*. Flies may seem an unexpected choice for studying human immunology, but many of the genes responsible for human development and physiology have been conserved across evolution and are present in *Drosophila*, Beckingham notes. “This organism allows us to study—in a way we can never study in ourselves—the function of these genes,” she says.

Kimbrell, Beckingham, and their colleagues have studied fruit flies raised in the microgravity of spaceflight and in hypergravity, which can be achieved through the use of centrifuges. Studying how these flies respond to infectious agents has provided insight into what may be happening with the human immune system.

Genes, Gravity, and Space Pioneers

Beckingham and her team started their search for mutant flies with altered responses to gravity using a device called a “gravitaxic maze.” Flies walking through the maze encounter eight consecutive T-branch points at which they must choose between two paths. They thus leave the maze at one of nine exits. When the maze is horizontal, normal flies randomly choose to go right or left at each junction. However, when the maze is vertical and flies have to go up or down at the junctions, they show a slight tendency to emerge at the highest and lowest exits. The research team selected for further study mutant flies with a much stronger preference for going up or down. Eventually Beckingham and her group identified many genes that might affect sensing and reacting to gravity, five of which were novel and named after space pioneers: *yuri gagarin*, *alan shepard*, *john glenn*, *jim lovell*, and *neil armstrong*.



By analyzing fruit flies, Kathleen Beckingham (left) and Deborah Kimbrell (right) studied how the immune system responds to altered gravity.

Credit: Courtesy of K. Beckingham and D. Kimbrell

The gene *yuri gagarin* proved to be an important tool for future work. This gene is expressed in a specialized neural structure in the fly antenna called Johnston's organ. The Johnston's organ is thought to sense gravity and is analogous to the human inner ear, which allows a person to know up from down.

Flies in Space

Kimbrell was one of the earliest researchers to study innate immunity in *Drosophila* and recognized its potential for modeling the effects of altered gravity on the immune system of astronauts. Kimbrell then brought together collaborators to form a diverse research team that would investigate how the fruit fly immune response changes in microgravity and hypergravity. “Beckingham's mutant defective in gravitaxis was perhaps the best way to analyze” the effects, says Kimbrell. “So we took advantage of putting our two systems together.”

Kimbrell and colleagues began their microgravity work on the Space Shuttle *Discovery* (STS-121) in July 2006. During the 12-day trip, eggs laid at the beginning of the journey developed into adult flies. Upon return to the Kennedy Space Center in Florida, the flies (space flies) were divided

into three groups. One was left as a control, another was infected with the common bacterium *Escherichia coli*, and the last was infected with the fungal pathogen *Beauveria bassiana*. The experiment was repeated on another set of flies that had never left the ground (Earth flies).

Transcriptional profiling of the genes expressed in these space and Earth flies revealed striking differences in the response to infection. Space and Earth flies infected with bacteria responded the same, with a typically robust reaction to *E. coli*. But space flies were not able to respond normally to the fungus. The difference likely occurred because *Drosophila* responds to the two pathogens with separate pathways, only one of which was affected by spaceflight.

When a fly encounters Gram-negative bacteria, such as *E. coli*, the Immune Deficiency (Imd) pathway activates. “That pathway is highly similar to the human tumor-necrosis-factor pathway,” notes Kimbrell. When infected with fungus, another key immune response pathway, the Toll pathway, activates. This too has a mammalian counterpart, mediated by a variety of Toll-like receptors that recognize a broad range of pathogens and other molecules. Toll-like receptors are “critical in humans,” Kimbrell says. In the fungus-infected space flies, the response was completely abnormal, and the Toll pathway did not activate genes, such as the antimicrobial peptides *Drosomyacin* and *Metchnikowin*, to fight the infection.

Beckingham’s *yuri gagarin* mutants were essential for testing the other extreme of gravity—hypergravity. When flies were in centrifuges that increased gravity, the Toll pathway seemed to get a boost and fungus resistance increased. But *yuri* mutants did not experience this same boost, providing further evidence of a connection between gravity and the immune system. The reduced Toll response in microgravity and the enhanced response in hypergravity (the latter mitigated by loss of the gravity-sensing gene *yuri*) provided evidence that some aspects of the innate immune system have a dependence on gravity. Gravity seemed to work as a continuum, where increased gravity had a positive effect on the immune response and decreased gravity had a negative effect.

The researchers have some hypotheses about why the Toll pathway was more affected by microgravity than the Imd pathway. It might be due to the Toll pathway’s complexity, requiring several extracellular steps and the use of endocytosis mechanisms for signaling. Stress conditions may affect pathways with several components on the surface and outside of the cell—like the Toll pathway—more strongly than those like Imd where the extracellular steps are limited to the pathogen products directly binding the receptor.



A fruit fly infected with fungus. Credit: D. Kimbrell

This difference between the effect of stress on extracellular and intracellular space could be a factor in many gravity responses to spaceflight, Kimbrell says.

Transcriptional profiles of the uninfected space and Earth flies also showed large differences in the genes being activated. “When you look at the gene expression, you see a lot of activation of stress response genes in the space flies,” Kimbrell says. Thus the space flies showed abnormal gene expression not only with a fungal infection, but also without any infection at all. Harkening back to their hypothesis about the Toll pathway, the stress response genes included those for

heat shock proteins, which interact with Toll receptors to modulate the immune response in mammals. So they may be playing a role in the fungus-infected space flies. It is possible that microgravity is contributing to an unfolded protein response (resulting in heat shock protein upregulation) or problems with the endocytic machinery, and that these issues are in turn antagonized by hypergravity.

These experiments also point to some areas of human research that could be pursued. The link between Toll receptors and heat shock proteins “should be looked at in astronauts,” Beckingham says. And the juxtaposition of the microgravity and hypergravity results suggests that during space travel some form of artificial gravity, like a spinning spacecraft or “a centrifuge in space might really help make people healthier,” she says.

In the interest of pursuing open data and encouraging the mining of NASA experiments by both professional and amateur biologists, the transcription data from Kimbrell’s spaceflight team are available on the public NASA Genelab site (<http://genelab.nasa.gov/>). The information obtained and provided by these researchers provides translational insights that could mean a better understanding of the human immune system both amongst the stars and here on Earth.

Further Reading

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Texada MJ, Simonette RA, Johnson CB, Deery WJ, Beckingham KM. *yuri gagarin* is required for actin, tubulin and basal body functions in *Drosophila* spermatogenesis. J Cell Sci. 2008 Jun 1;121(Pt 11):1926-36.

Armstrong JD, Texada MJ, Munjaal R, Baker DA, Beckingham KM. Gravitaxis in *Drosophila melanogaster*: a forward genetic screen. Genes Brain Behav. 2006 Apr;5(3):222-39.