National Aeronautics and
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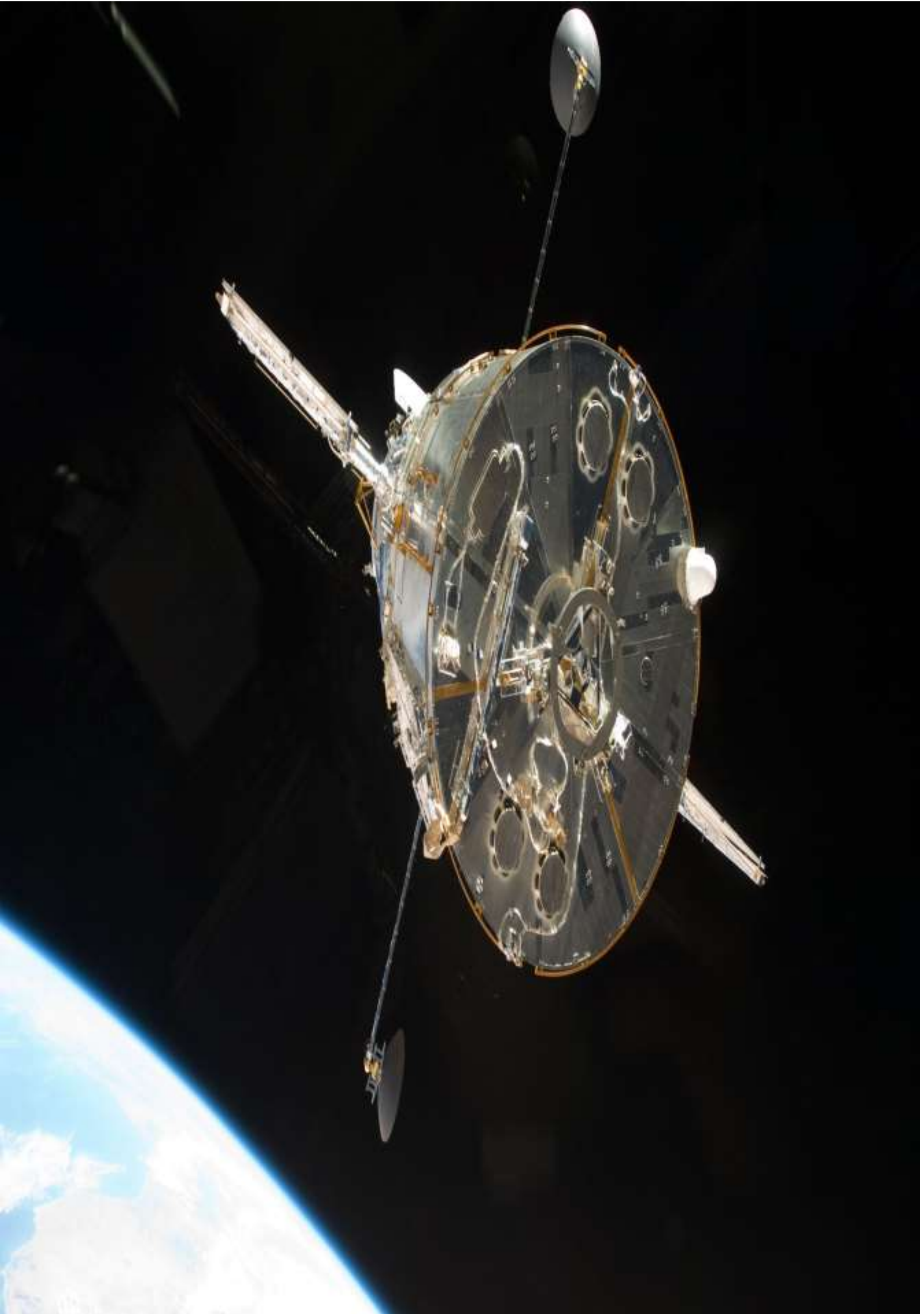

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Medical innovations: Space Flight

Future long-duration spaceflights are now being planned to the Moon and Mars as a part of the "Vision for Space Exploration" program initiated by NASA in 2004. NASA's plans for space exploration include a return to the Moon to stay-boots back on the lunar surface with an orbital outpost. This station will be a launch point for voyages to destinations further away in our solar system, including journeys to the red planet Mars. A strategic use of resources is essential to achieving long-duration space travel and understanding the human physiological changes in space, including the roles of food and nutrition in space.

To effectively address the challenges of space flight, the Bioastronautics Initiative, undertaken in 2001, expands extramural collaboration and leverages unique capabilities of the scientific community and the federal government, all the while applying this integrated knowledge to Earth-based problems. Integral to the National Aeronautics and Space Administration's missions in space is the reduction of risk of medical complications, particularly during missions of long duration. Cumulative medical experience and research provide the ability to develop evidence-based medicine for prevention, countermeasures, and treatment modalities for space flight.

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The microbiome and its importance in human health: Space Flight

As we travel into the extreme environment of space, our gut bacterial hitchhikers are along for the ride, whether we like it or not. Therefore, we must understand how our microscopic bacterial residents play a role in maintaining human health in space.

The microbiome can affect many physiological processes in our bodies, including immune system development, the ability to process dietary polysaccharides, vitamin and hormone production, pH regulation, processing and detoxification of environmental chemicals, and maintenance of the skin and mucosal barrier function

Our bodies consist of far more bacterial cells than human cells, and a proper balance between them can either help us stay healthy or make us ill.

In fact, we live in symbiosis with a vast population of bacteria, archaea, eukaryotes, and viruses, collectively called microbiota, that colonize different bodily parts.

The analysis of human microbiome is an exciting and rapidly expanding field of research. In the past decade, the biological relevance of the microbiome for human health has become evident. Microbiome comprises a complex collection of microorganisms, with their genes and metabolites, colonizing different body niches.

In the human body, the major niches colonized by microbes are the gut, mouth, genitals, skin, and airways. The composition of this bacterial population varies depending on the body part. For example, the human intestine is composed predominantly of Bacteroidetes and Firmicutes (90%), and complemented by Actinobacteria, Proteobacteria, and Verrucomicrobia, whereas the microbiome of the retroauricular skin crease is composed mainly of Actinobacteria followed by Firmicutes, Proteobacteria, and Bacteroidetes.

It is now well known that the microbiome interacts with its host, assisting in the bioconversion of nutrients and detoxification, supporting immunity, protecting against pathogenic microbes, and maintaining health.

Exploring these balance points and molecular changes in gut bacterial cells in stressful environments like space can help us understand how to maintain gut bacterial health in extreme environments on Earth.

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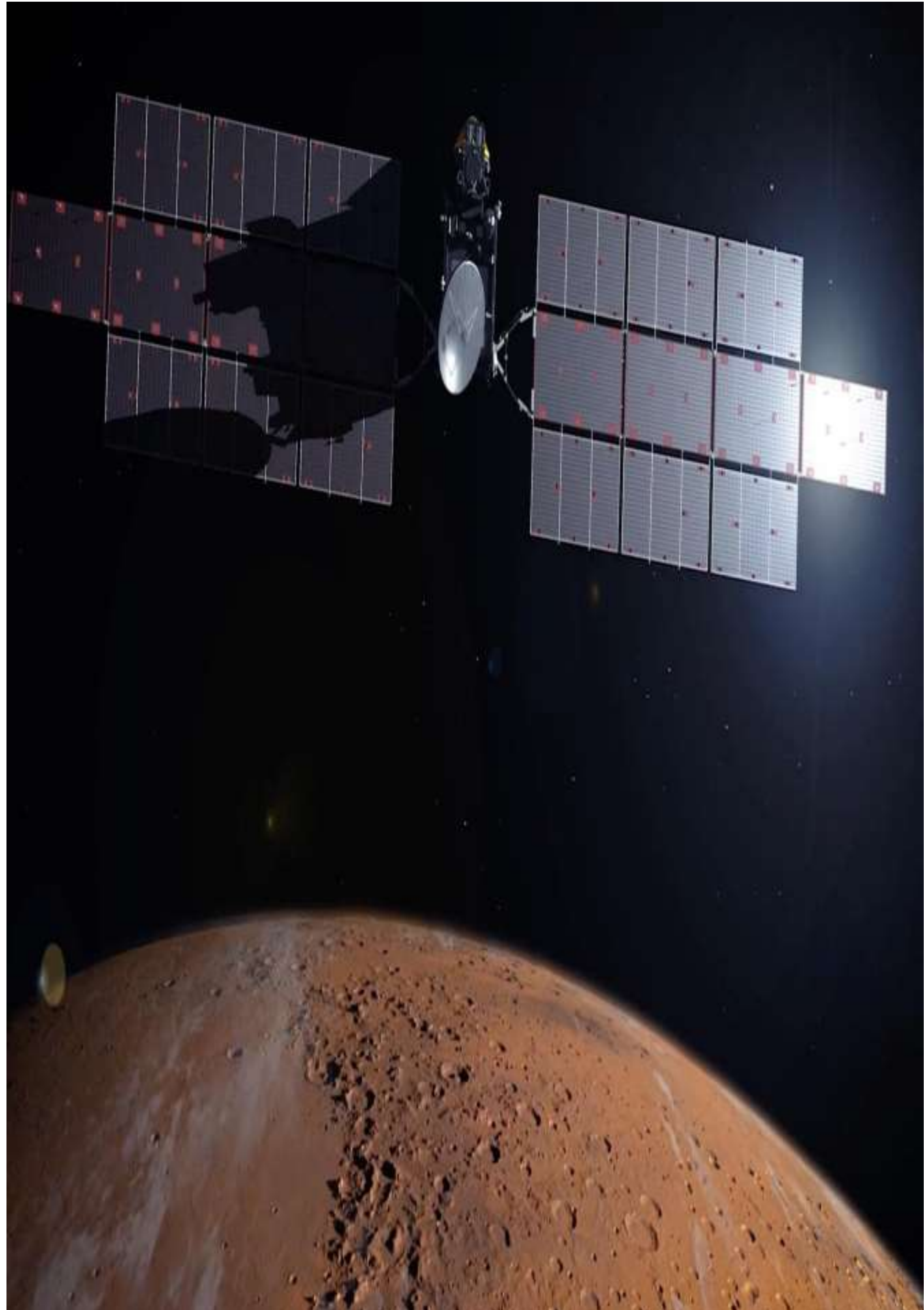


Fundamental biological features of spaceflight: gut microbiome

The study by Liu et al. was the first to show the effect of short-term spaceflight missions on the human gut microbiome. Microgravity environments are known to cause a plethora of stressors to astronauts. They found that microgravity appeared to shift the gut microbiome in a way that fostered an unhealthy microbial environment rather than a healthy one.

Probiotics can be used both to prevent the onset of dysbiosis when the patient is exposed to predisposing conditions prolonged antibiotic therapies, intense physical or mental stress, chronic debilitating diseases.

Bacteria can survive the harsh conditions of space. Bacteria from aggregates at least half a millimeter in diameter survived three years of exposure to space, and were capable of repairing the genetic damage they suffered. The results show that bacteria could survive space long enough to make the trip between Mars and Earth.

Since the early 1960s, some of these stressors have been shown in both animal and human studies to promote gut microbiota dysbiosis, which may drive gastrointestinal disease and metabolic imbalances, as well as changes in bacterial physiology in the spaceflight environment and ground-based analogue studies.

The study of off planet/extraterrestrial, space vehicle and spacecraft microbiomes provides insight on the impact of space travel on human health, characterization of how the environment impacts microbial communities in space vehicles/spacecraft and microbiota dynamics of space-built environments.

The features include oxidative stress, DNA damage, mitochondrial dysregulation, epigenetics (including gene regulation), telomere length alterations, and microbiome shifts.

Previous inflight studies have shown that astronauts have reported a range of health issues ranging from GI distress, respiratory illness and skin irritation and infections.

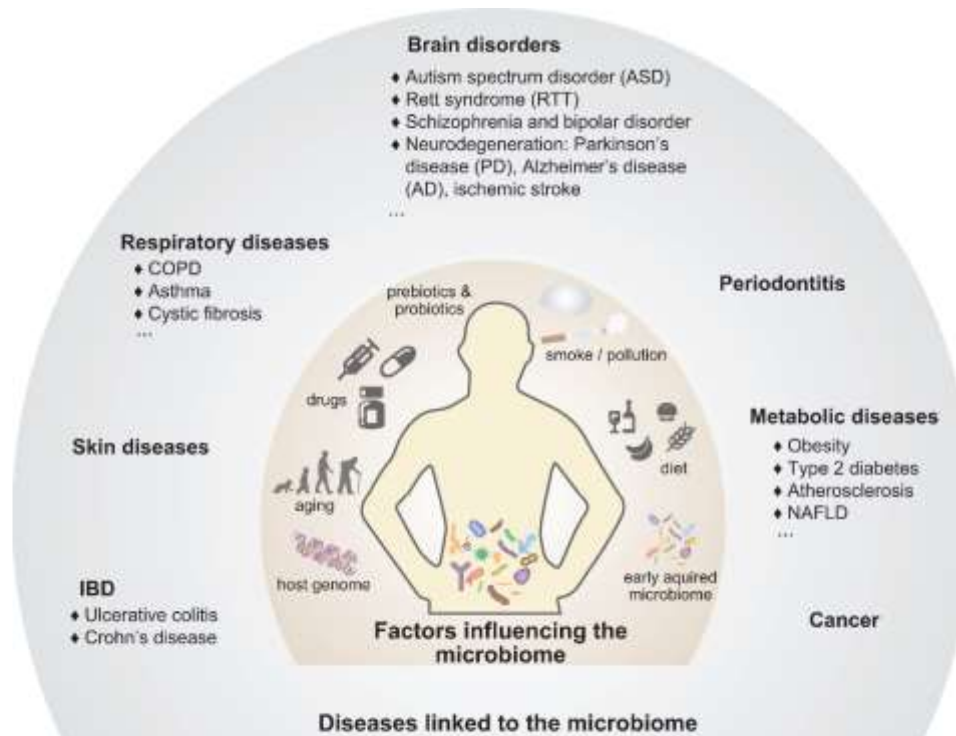
Many of these symptoms have been associated with a weakening of the immune function as shown by reactivation of Epstein Bar Virus (EBV), and Varicella Zoster Virus (VZV) during space flight. Altered production of cytokines including increases in white blood cell counts have been measured during space flight and associated with altered adaptive immunity.

That is why scientists use the International Space Station as a testing ground to study how to keep astronauts safe and healthy on long-duration missions. These studies also benefit humans on Earth by providing a better understanding of how microbes behave in a sanitized, isolated, and confined environment.

The Astronaut Microbiome project is a large study currently underway that seeks to employ culture-independent methods for studying the microbiome of astronauts, surfaces, and water at the International Space Station - NASA (ISS).

In view of the effects on immunity, the use of prebiotics and probiotics to stimulate the production of short-chain fatty acids, would thus increase nutrient and metabolic resources and the eliminatory capacity of lymphocytes, which may limit the re-emission of latent viruses. By using probiotics, the number of short chain fatty acids (SCFAs) producing microorganisms in the gut can be increased. By doing so, this can have a beneficial effect on our immune system and maintain a healthy lifestyle.

Expedition 34 crew fruit and vegetables within a Cargo Transfer Bag. Photo Credit: NASA.



What can influence the microbiome? Factors influencing the intestinal microbial composition and the effects of dysbiosis on host health. Credit: **https://doi.org/10.1177/2397847317741 - *Exploring the microbiome in health and disease: Implications for toxicology.***

Traveling to space has been shown to reduce immune functioning in astronauts. Recently, it has become apparent that gut microbiome composition of astronauts is altered following space travel, and this is of significance given the important role of the gut microbiome in human health.

Long-Term Space Nutrition. Improper nutrition is not associated with caloric intake. Humans have been involved in manned spaceflight for the past five decades, with the International Space Station (ISS) as the main destination for short-term missions. Major space agencies' extensive plans for a long-term human presence in space have also motivated missions to the Moon and Mars.

During the European mission at the end of the last century, astronauts had an inadequate intake of energy, liquid, and calcium in addition to excessive sodium compared to the dietary reference intake on Earth.

During the Skylab program, astronauts were methodically sampled before, during, and after missions, and it was found that while overall gastrointestinal (GI) microbial counts went up, diversity of the GI community went down following space flight. They also found an increase in certain pathogens like Serratia marcescens and Staphylococcus. aureus after space flight, and it was shown that S. aureus was transferred from astronaut to astronaut.

Alterations in the skin microbiome that might contribute to the high frequency of skin rashes/hypersensitivity episodes experienced by astronauts in space were also observed. This analysis identified 17 gastrointestinal genera whose abundance significantly changed in space (adjusted p-value by the false discovery rate (FDR) < 0.05). Thirteen out of the 17 genera belonged to the Phylum Firmicutes, mostly to the order Clostridiales, with nine genera being part of the GI core microbiota.

Among these taxonomic groups, there was a more than five-fold inflight reduction in Akkermansia and Ruminococcus, and a ~3-fold drop in Pseudobutyrivibrio and Fusicatenibacter.

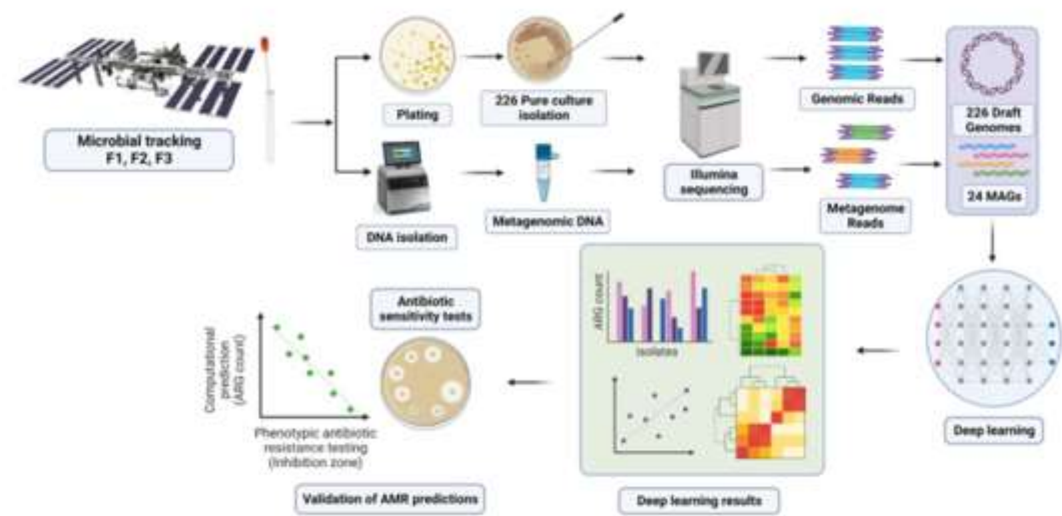
Some studies have illustrated those specific human experiences and environments can quickly and profoundly perturb the gut microbiota composition. The human gut microbiota is a large and diverse microbial community in the human gastrointestinal tract.

The interaction between humans and their gut microbiota is important in human physiology. The study showed that Bacteroides abundance increased after spaceflight, with a decrease in Lactobacillus and Bifidobacterium.

The Impacts of Microgravity on Bacterial Metabolism. Microgravity has been found to consistently increase biofilm formation in spaceflight grown bacteria, including opportunistic pathogens like Staphylcoccus aureus, Escherichia coli and Pseudomonas aeruginosa. Strangely, amino acid metabolism may impact this well-known phenomenon as well.

The composition and activity of the gut microbiota are unstable and are influenced by endogenous and environmental factors. The upcoming exploration missions will imply a much longer duration than any of the missions flown so far. In these missions, physiological adaptation to the new environment leads to changes in different body systems, such as the cardiovascular and musculoskeletal systems, metabolic and neurobehavioral health and immune function. To keep space travelers healthy on their trip to Moon, Mars and beyond and their return to Earth, a variety of countermeasures need to be provided to maintain body functionality.

STS105-308-029 (15 August 2001) --- Astronauts and cosmonauts representing three different crews are just about to share a meal in the Zvezda Service Module on the International Space Station (ISS). Photo Credit: NASA.



Overview of sample collection and data analysis for the characterization of antibiotic resistance at the ISS using deep learning. The data are processed in a step-wise fashion including data QC, mapping, quantification, and matching to time of collection and mission. The figure has been generated using BioRender (http://biorender.com) Credit: https://doi.org/10.1186/s40168-022-01332-w /Machine learning algorithm to characterize antimicrobial resistance associated with the International Space Station surface microbiome.

Targeting the gut microbiome, with specifically designed probiotics or dietary fiber, which focuses on the issues that are faced by astronauts, could potentially reduce a variety of issues. Supplementation with probiotics has been shown to have beneficial effects on human health.

Numerous studies have indicated the profound role of the gut microbiome in human health. The gut microbiome is the term given to describe the vast collection of symbiotic microorganisms in the human gastrointestinal system and their collective interacting genomes.

Systems biology approaches based on next generation 'omics' technologies are now able to describe the gut microbiome at a detailed genetic and functional (transcriptomic, proteomic and metabolic) level, providing new insights into the importance of the gut microbiome in human health, and they are able to map microbiome variability between species, individuals and populations.

Our microbial community depends on consistent rhythms to function optimally. Rhythmic Disruption, our sleep-wake cycle directly impacts our gut composition. Travel can disrupt your normal rhythms (sleep-wake and fast-eat cycles) and, in turn, disrupt your microbiome by reducing the number of healthy microorganisms and increasing the population of potentially harmful microorganisms.

Prophylactic treatments with prebiotics or probiotics (green box) could be used to counterbalance the detrimental effects of space travel on the astronauts' microbiome. While on a space mission, astronauts do not get the same replenishment of microbes that they get on Earth. The traditional view of health microbiology is that microbes make you sick and should be removed from the spacecraft environment whenever possible. Astronauts' food is specially designed to last for long periods of time and has almost no microbial content.

Failure to provide the appropriate food or to optimize resource utilization introduces the risk that an inadequate food system will hamper mission success and/or threaten crew performance. Investigators for the National Aeronautics and Space Administration (NASA) Advanced Food Technology (AFT) consider identified concerns and work to mitigate the risks to ensure that any new food system is adequate for the mission. There are three meals per day, plus snacks that can be eaten at any time, ensuring astronauts receive at least 2500 calories each day.

While keeping an extremely clean spaceship environment has been an effective preventive measure for protecting astronauts from infections caused by many dangerous pathogens, the lack of microbial intake for long periods of time may have a detrimental effect on the diversity of the crew microbiota and, therefore, on astronaut health, to a sufficient extent that it may not be a viable strategy for long-term space missions.

Aspects of immune system dysregulation associated with long-duration spaceflight have yet to be fully characterized and may represent a clinical risk to crewmembers during deep space missions.

Alterations in plasma cytokine levels are an established biomarker for many diseases. As the dysregulation of the immune system is an established postflight phenomenon, and persistent dysregulation may be a clinical risk to crewmembers, it is appropriate to survey plasma cytokine levels in astronauts during long-duration spaceflight. The utility for such models lies in the mechanistic understanding of microgravity-associated immune changes or in the evaluation of potential countermeasures.

ISS005E16336 -- View of Astronaut Peggy Whitson, flight engineer (left) and Cosmonaut Valery Korzun, commander (right), eating a meal in the Service Module (SM)/Zvezda. Tomato and hamburger are floating. Photo was taken during Expedition Five on the International Space Station (ISS). Photo Credit: NASA.

The crew shared a special Thanksgiving meal aboard the space station, a break from what can be a repetitive, limited menu. Photo Credit: NASA

No significant alterations were observed during or following spaceflight for the inflammatory or adaptive/T-regulatory cytokines: IL-1α, IL-1β, IL-2, interferon-gamma (IFN-γ), IL-17, IL-4, IL-5, IL-10, CCL3, or CCL5. This pattern of cytokine dysregulation suggests multiple physiological adaptations persist during flight, including inflammation, leukocyte recruitment, angiogenesis, and thrombocyte regulation.

Probiotics are also a promising alternative to fight microbial dysbiosis in space, particularly in situations where the GI flora has been significantly depleted of its original microbial content, for example following antibiotic treatment.

Research by:
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Medina Marco A

Human Research Program

The space station has been continuously inhabited by humans for 20 years, supporting many scientific breakthroughs. The orbiting lab provides a platform for long-duration research in microgravity and for learning to live and work in space, experience that supports Artemis, NASA's program to go forward to the Moon and on to Mars.

Protecting immune function and the gut microbiome

Immune function and the intestinal microbiota are thought to undergo changes during long-duration spaceflight. An investigation from the Japan Aerospace Exploration Agency (JAXA), Probiotics studies the effects of beneficial bacteria on immune function and intestinal microbiota of crew members. These probiotics could be incorporated into the diet on future space missions, providing basic nutrition and helping to protect overall crew member health. Results also could shed light on changes that bacteria experience during spaceflight, which could contribute to efforts to reduce infections.

John Love, ISS Research Planning Integration Scientist- Expedition 65

Editor: Ana Guzman

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