Genomics in Space Life Sciences

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Since the early days of manned spaceflight, hazardous effects of the space environment on living organisms have been disputed. With the continuous manning of the International Space Station, the planned Chinese space station, and renewed interest in returning to the Moon and sending manned flights to Mars, identifying and addressing the potential outcomes of long-term space exposures is critically important.

Space-flown and ground-based research

Much progress has been made towards the understanding of the effect of space environmental factors, especially microgravity and radiation, on living organisms. During the space exploration of the 1970s, physiological changes in several organ systems due to weightlessness were identified. Some of the adverse effects are a decline in cellular immune responses (*1–3*), cardiovascular deconditioning (*4*), bone deterioration (*5*), and muscular atrophy (*6*). Furthermore, simulated microgravity studies have shown increased virulence in microorganisms (*7*). Over the past 30 years, a number of *in vitro* studies have been carried out in space. However, the cost and logistics of conducting space-flown studies have not allowed in-depth interpretation of the data because of small sample sizes (*8*). Therefore, ground-based research has become common in space life sciences. Those simulated microgravity studies include head-down bed rest for humans (*9*), tail suspension for rodents (*10*), and cell and microorganism cultures with high aspect ratio vessel (HARV) bioreactors (*11*, *12*) and random positioning machine (RPM) (*13*).

Previous efforts on ground-based research

First, it has been found that bed rest with the head tilted down at $\sim 6^{\circ}$ induces physiological alterations similar to those experienced in the space environment. Second, tail suspension for mice and rats presents physiological effects analogous to those observed in a microgravity environment. Third, HARV and RPM were developed to simulate microgravity by mimicking a weightless state. The HARV bioreactor rotates cells in a zero head space suspension culture that keeps the cells in a near free fall state. The RPM constantly changes its rotational orientation at a variable speed. Either system does not eliminate gravity, but it makes a time-averaged g-vector close to zero (*14*). Namely, both devices do not allow the cells to receive gravitational loads in any fixed direction. The development of ground-based bioreactors has enabled extensive time course studies without including other environmental factors such as radiation.

New direction towards genome-wide expression studies

Recent biotechnological advancements have allowed us to gain substantial knowledge on the cellular and molecular mechanisms underlying microgravity-induced physiological effects. Initially, gravitational force was considered too weak to induce any detectable effect at a molecular level (*15*). However, it is now apparent that understanding gene and protein expression is a key to evaluate potential problems in microgravity and develop effective countermeasures. Evidence has accumulated that a sudden change in gravity indeed alters the mRNA levels of various genes as shown in this issue. Since most alterations in physiological activities most likely result from changes in gene expression, genome-wide expression studies may lead to identification of "space genes" that could play critical roles in the response to weightlessness.

Results from recent microarray studies

To date, only a handful of DNA microarray based studies on microgravity effects have been documented. First, bone loss and muscle atrophy have been identified as potential hazards. Several microarray based studies have identified a set of genes that

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are potentially responsible for those problems. It has been observed that microgravity down-regulates alkaline phosphatase and the genes involved in bone formation (*11*, *16*). Studies using rat cells have also identified altered expression of mitochondrial genes as well as cytoskeletal genes, which may be responsible for muscle atrophy (*17*, *18*). Second, DNA microarray analyses have revealed that microgravity increases the virulence of bacteria including *Salmonella* (*19*, *20*), *Escherichia coli*, *S. typhimurium* (*21*), and yeast (*22*). Third, a recent microarray study (*23*) has shown that microgravity reduces immune responses and could potentially make astronauts more susceptible to infection.

From molecular, cellular to tissue responses

To eventually develop effective countermeasures for microgravity effects, it is essential to understand the responses at varying levels. Since astronauts experience whole-body exposure to microgravity, all the organ systems are potentially affected and altered in their physiological equilibrium. The different organ systems may react differently, while a common set of genes may preferentially be altered in many organs. It is therefore important to evaluate responses to microgravity using cells derived from various organs. The identification of the common set of gravity sensitive genes may allow us to define "space genes" that may play a check-and-balance role in response to microgravity conditions.

Articles in this issue

In this issue, we have a collection of articles that examine the diverse aspects of genomic research in space life sciences. (1) The mini-review by Zhang *et al* at Indiana University introduces the current gene expression research for understanding the mechanism underlying unloading-driven bone adaptation. (2) Jade Clement's group at Texas Southern University employed microarrays to study the effects of simulated microgravity on a keratinocyte cell line. They identified 162 genes that were differentially regulated in the HARV bioreactor system. Their time course profiling results showed that cells exposed to a shorter time (3 or 4 d) to microgravity returned to virtually no differences in gene expression after a recovery period of 15 d under normal gravity, but cells exposed to a longer time (9 or 10 d) in microgravity exhibited substantial alterations in gene expression even after a much longer recovery time ($\geq$ 50 d). The results suggest that longer exposure to microgravity tends to have lasting effects on gene expression alterations. (3) Eugenia Wang's research group at the University of Louisville has examined the effects of microgravity on WI-38 human fibroblasts. Those fibroblast cells were flown on the STS-93 space shuttle mission. Two cDNA libraries were constructed and processed for suppression subtractive hybridization to identify the genes affected by microgravity. Their data show that spaceflight activated a group of genes involved in oxidative stress, DNA repair, and fatty acid oxidation. (4) Linda Hyman's group at the University of Montana characterized microgravity-enhanced pathogenicity. Using simulated microgravity induced by HARV, they show that a conserved response exists among yeast, and the pathogenicity of *Candida albicans* is enhanced by simulated microgravity. (5) The article by Lu *et al* presents research on mutations in rice seeds that were flown on a recoverable satellite JB-1 for 15 d. After spaceflight, the seeds were bred on the ground and four mutants were generated. Using two-dimentional gel electrophoresis and reverse phase liquid chromatography, they show that the contents of albumin, globulin, and prolamine in mutant seeds revealed significant changes, and the changes were stably inherited from 8^{th} to 9^{th} generation.

In summary, this is the first special issue of the GPB journal to bring together articles on the topic of genomic and proteomic research in space life sciences. The tools in genomics and proteomics are very well suited for unraveling the effects of microgravity on living organisms. Their usage in space life sciences is, however, in its infancy. It is our desire that the collection of studies in this issue will open a new chapter in space life sciences.

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