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Effects of Sex and Gender on Adaptation to Space: Immune System

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Abstract

This review is focused on sex and gender effects on immunological alterations occurring during space flight. Sex differences in immune function and the outcome of inflammatory, infectious, and autoimmune diseases are well documented. The work of the Immunology Workgroup identified numerous reasons why there could be sex and/or gender differences observed during and after spaceflight, but thus far, there has been very little investigation in this area of research. In most cases, this is due to either a low total number of subjects or the minimal number of female flight crew members available for these studies. Thus, the availability of a sufficient number of female subjects to enable statistical analysis of the data has been a limiting factor. As the inclusion of female crew members has increased in the recent past, such studies should be possible in the future. It is very difficult to obtain immunologic and infectious data in small animals that can be usefully extrapolated to humans undergoing spaceflight. Thus, it is recommended by the Immunology Workgroup that a greater emphasis be placed on studying astronauts themselves, with a focus on long-term evaluations of specific, known infectious risks.

Women demonstrate a stronger immune response to immunological stimuli, ranging from allergens and pathogens to self-antigens. This enhanced response has been observed as an increased response to pathogens and higher antibody responses upon immunization with a variety of antigens.[1,2] There is also an increased incidence of autoimmunity.[3] About 70% of people with autoimmune diseases are women, the incidence of multiple sclerosis and rheumatoid arthritis is 2–3 times higher, and the prevalence of systemic lupus erythematosis is nine times higher in women than men.[4]

Men and women can differ in the intensity, prevalence, and pathogenesis of infections.[2] Although behavioral factors can influence exposure to pathogens, the results of several studies illustrate that physiological differences between men and women cause differences in immune responses to infection as well as the development of autoimmune diseases.[2] As a result of heightened immunity to invading pathogens, both the intensity (i.e., pathogen load within an individual) and incidence of infections are often lower for women than men. There is growing awareness that some infectious diseases are associated with aberrant host inflammatory responses.[4,5] Consequently, heightened antiviral/antibacterial, inflammatory, and cellular immune responses in women might underlie increased disease symptom development following infection among women as compared with men. The mechanisms mediating these sex-based differences in infectious and autoimmune diseases remain to be established.

Effects of Spaceflight and/or Radiation on Susceptibility to Microbial Infection and Immune Responses: Implications for Sex-Based Difference

Spaceflight takes place in an extreme environment where multiple variables have the potential to alter immune responses.[6]

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These variables include microgravity, physiological stress, radiation, isolation, and circadian misalignment. Prolonged exposure to a spaceflight environment with limited clinical care capability—for example, deep space exploration-class missions—may increase crew risk for adverse health events such as infectious disease, hypersensitivities, autoimmunity, and malignancy.[7]

One of the critical factors to ensuring crew health, safety, and performance is anticipating the risk for infectious disease during human space exploration and habitation. This consideration is critical to address, as the crew will interact with microbial flora (both pathogens and commensals) from themselves, other crewmembers, their food, and the environment that could compromise their health. Moreover, it has been shown that spaceflight and spaceflight analogue culture conditions globally alter gene expression, virulence, and/or virulence-related phenotypes of obligate and opportunistic bacterial pathogens.[9–13]

While preflight countermeasures (such as National Aeronautics and Space Administration's Health Stabilization Program) have decreased the incidence of infectious disease during spaceflight missions, a significant number of incidences have been well documented that range from minor infections to potentially incapacitating or life threatening conditions, including a debilitating dental infection and an incapacitating urinary tract infection.[10,14,15] In addition, spaceflight has been shown to reactivate latent viral infections in astronauts.[16–18] These observations indicate that the crew may be exposed to obligate and opportunistic pathogens. This risk is expected to increase with longer mission durations and increased use of regenerative life support systems. While evaluations of microbial ecology aboard the Mir and International Space Station suggest a predominance of common environmental and commensal flora, clear pathogen transmission routes have been identified, including opportunistic pathogens carriage and in-flight exchange of intestinal microbial flora by the crew.[8,19,20] Evaluation of spaceflight food prior to shipment for in-flight consumption indicates that most foods do not contain medically significant organisms, but pathogens like Salmonella have been detected and have disqualified that production lot.[21] It is noteworthy that spaceflight culture has shown significant increases in the virulence of Salmonella, which is a pathogen that has been previously recovered from crew refuse.[9]

Radiation affects numerous immune system parameters, thought to be primarily due to its cell-killing effects in hematopoietic/immune system cells. As radiation effects represent a major hazard for space travel, sex differences in sensitivity to radiation effects are an important consideration for future missions because they will result in considerably higher radiation doses than those received by astronauts participating in the relatively short missions of the past. It is reported that women are more susceptible to radiation-induced cancer than men; both cancer incidence and mortality rates are 50% higher for women.[22] While radiation-induced breast cancer contributes to this increased risk for women, there is also an increased risk for other major types of radiation-induced cancer in women compared with men. The mechanism(s) involved in sex-specific, radiation-induced cancer incidence and mortality rates are not known, although numerous differences exist for sex-specific changes related to radiation-induced carcinogenesis.

Studies Carried Out in the Past 10 Years Covering Sex-Based Differences in the Effects of Spaceflight on the Immune System

It is established that alterations of the human immune system are an in-flight *in vivo* phenomenon.[8] The effects of spaceflight on the immune system are well characterized[7] and include changes in cytokine production, leukocyte subset distribution, and antibody production.[7] There have been, however, limited studies carried out to determine whether there are differential effects of spaceflight on the immune systems of men and women.[7,23] Many studies carried out both in ground-based models and during actual spaceflight indicate that short- and long-term spaceflight conditions induce changes in primarily cell-mediated immune responses of hosts.[7] Effects of spaceflight on antibody production, particularly in non-mammals, are also noted.[24] Additionally, instances of issues with infection are reported during spaceflight, *Pseudomonas aeruginosa* is one example of a pathogen that caused a serious, life-threatening infection.[8]

There are a variety of reasons why there have not been studies to determine sex-based differences in spaceflight effects on the immune system. In human and primate studies, the availability of a sufficient number of subjects to enable statistical analysis of the data has been a limiting factor.[7] In rodent studies, female subjects have primarily been used, because their behavioral characteristics minimize conflicts and fighting.[7]

Unfortunately, according to information available from recent spaceflight studies, sex-based analyses were largely not performed. In most cases, this is due to either a low total number of subjects or the minimal number of female flight crew members available for these studies.[7] It should be possible to perform some additional sex-based assessments for more recent flight experiments, including in-flight immune studies[8] that had female inclusion rates of 17%–26%. Future International Space Station studies are expected to have improved access to female crew members, and current crew selections support this.

Potential Future Approaches to Determine Sex-Based Differences in Effects of Spaceflight on the Immune System

Determining the effect of short- and long-term spaceflight on humans with attention to possible differences between men and women presented challenges with respect to immune function and susceptibility to microbial infection, autoimmune diseases, and cancers. Most of what is known about the effects of spaceflight on human immunity and resistance and susceptibility to infection has not been—and generally cannot easily be—broken down by sex, in part because women have to date made up a minority of space travelers and animal experiments in relevant models have been uncommon. In the few studies in which sex is specified, the number of women was too small to analyze outcome data separately (typically $< 10\%$ of total subjects).

Perhaps the most obvious gap in published spaceflight health risk data is long-term prospective astronaut follow-up using periodic intensive post-flight evaluations. Such studies cannot easily detect health risk for uncommon conditions unless large numbers of people are followed for long periods of time, but they are nevertheless the gold standard of health

evaluation to detect risk and it would seem hard to justify not obtaining these types of data. Typical challenges to conducting such studies also include difficulties in retired subject follow-up and reduced cooperation over time, but many prospective cohort studies have overcome these barriers.

Another important type of study not found in the literature is regular in-flight screening of both the individual microbiome and host response genes to look at coincident changes in the organism-host environment. While such studies are complicated to conduct and interpret, they are critical components of any study designed to dissect the role of sex-based differences on immune responses and corresponding infectious disease risks, as they allow critical linkage between immune parameter and microbial changes.

In summary, because of the difficulty obtaining immunologic and infectious data in small animals that can be usefully extrapolated to humans undergoing spaceflight, it is essential that a greater emphasis be placed on studying astronauts themselves, with a focus on long-term evaluations of specific known infectious risks. These include risks specific to, or elevated in, female astronauts that include but are not limited to mucosal immune responses and infections of the reproductive tract (e.g., human papillomavirus, herpes simplex virus, and bacterial infections).

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