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Invited Review

Terrestrial stress analogs for spaceflight associated immune system dysregulation

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ABSTRACT

Recent data indicates that dysregulation of the immune system occurs and persists during spaceflight. Impairment of immunity, especially in conjunction with elevated radiation exposure and limited clinical care, may increase certain health risks during exploration-class deep space missions (i.e. to an asteroid or Mars). Research must thoroughly characterize immune dysregulation in astronauts to enable development of a monitoring strategy and validate any necessary countermeasures. Although the International Space Station affords an excellent platform for on-orbit research, access may be constrained by technical, logistical vehicle or funding limitations. Therefore, terrestrial spaceflight analogs will continue to serve as lower cost, easier access platforms to enable basic human physiology studies. Analog work can triage potential in-flight experiments and thus result in more focused on-orbit studies, enhancing overall research efficiency. Terrestrial space analogs generally replicate some of the physiological or psychological stress responses associated with spaceflight. These include the use of human test subjects in a laboratory setting (i.e. exercise, bed rest, confinement, circadian misalignment) and human remote deployment analogs (Antarctica winterover, undersea, etc.) that incorporate confinement, isolation, extreme environment, physiological mission stress and disrupted circadian rhythms. While bed rest has been used to examine the effects of physical deconditioning, radiation and microgravity may only be simulated in animal or microgravity cell culture (clinorotation) analogs. This article will characterize the array of terrestrial analogs for spaceflight immune dysregulation, the current evidence base for each, and interpret the analog catalog in the context of acute and chronic stress.

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1. Introduction

One of the primary goals of the international space life-sciences community is to perform research, both clinical/descriptive and mechanistic studies, to determine the effects of spaceflight on human physiology. Spaceflight is not simply defined as prolonged microgravity exposure, but the summation of all variables that exert influence on Astronauts. Such other variables include increased radiation, physiological stress, prolonged confinement and psychological stress, disrupted circadian rhythms, altered nutrition, and an altered microbial ecosystem. Studies conducted over the last decades have demonstrated that orbital spaceflight does have negative health effects (Blaber et al., 2010). These include dysregulation of bone homeostasis, muscle loss via hypokinesis, vision impairment in some subjects, and persistent reactivation of latent herpesviruses. Anecdotal information from astronauts suggests that despite ultimate isolation from terrestrial pathogens, there is incidence infectious disease and increased hypersensitivity reactions during orbital flight (Mermel, 2013; Ilcus et al., 2009).

Dysregulation of the human immune system has long been known to be present as an acute stress-induced post-landing phenomenon (Gueguinou et al., 2009). Recently, immune system dysregulation has been demonstrated to occur during flight

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(Crucian et al., 2013a) and persist during 6-month orbital spaceflight (Mehta et al., 2013; Crucian et al., 2013b). The dysregulation occurs concurrently with persistent reactivation and shedding of latent herpesviruses. The nature of immune dysregulation during flight is currently being investigated, and studies to date have demonstrated altered peripheral leukocyte distribution, reduced function of specific leukocyte sub-populations, altered cytokine profiles. Recently, Mehta et al. (2012) positively correlated cytokine alterations with viral shedding in specific crewmembers, and postulated a Th2 shift associated with flight. It is therefore assumed that there is a cause/effect relationship between dysregulation of immunity (reduced function of cytotoxic T lymphocytes), followed by viral reactivation.

Any health risks to astronauts associated with spaceflight would be expected to increase during deep space, exploration-class missions. This is primarily due to prolonged mission duration, increased radiation exposure (both duration and magnitude), and limited clinical care combined with absence of a rapid return option. Given the very tight constraints associated with in-flight assessments, it is both practical and attractive to first engage ground-based analog studies whenever possible. Ground analog work is applicable for mechanistic studies that may not be practical for an in-flight study (due to hardware or funding constraints) or for preliminary studies that may serve to focus future in-flight work. Ground analogs for immunity fall into three general categories: human analogs (remote deployment or test subject); animal analogs (hindlimb suspension, etc.); or cell culture analogs (bioreactor, clinostat). The best human analog for immune dysregulation would replicate as many as possible of the causal factors except for microgravity and radiation. A summary of ground based spaceflight analogs in the context of specific in-flight factors is presented in Table 1. Human deployment analogs (Antarctica winterover, undersea, etc.) typically consist of stress, extreme environment, isolation and circadian misalignment. These analogs usually have associated health risks, in their own regard. Animal models are important in that they afford variables unavailable using human subjects, such as radiation treatment or stress-inducement. Animal models also make available critical tissue samples, such as spleen and thymus, unavailable from human subjects. Cell culture analogs typically replicate microgravity via rotation by constantly varying the gravity vector. Such a culture system has been shown to replicate the cellular immune suppression observed on-orbit. The cell culture analog is important to derive the intracellular mechanisms by which in vivo immune dysregulation may occur on orbit, such as gravi-sensitive genes or intracellular signaling defects.

This review will characterize the many diverse and unique terrestrial analogs for space immune-dysregulation. The analogs will be described as to their nature and which flight variables are replicated, the existing literature will be summarized, and proper analog use will be discussed. That this summary will support and guide future analog studies so that the most relevant and appropriate scientific products may be generated, to further aid in-flight studies and the eventual reduction in clinical risk to astronaut crewmembers related to immunosuppression.

2. Spaceflight and the stress immune spectrum

Among the myriad of factors that could affect immunity during spaceflight, physical and psychological stress are likely to play a major role. Spaceflight is associated with a number of stressful events that can be considered acute (i.e. launch/landing stress) or chronic (prolonged periods of isolation, loneliness, anxiety). From an acute stress standpoint, launch and landing in a space vehicle are high-risk events that have resulted in catastrophe (i.e. the disintegration of the Space Shuttles Challenger and Columbia in 1986 and 2003 respectively), and will undoubtedly raise crew stress levels prior to launch and landing. Moreover, exposure to high gravitational forces during launch and landing and re-adaptation to the 1G environment following prolonged periods of deconditioning imposes a large degree of physical strain on the body. Collecting biological samples for immune analysis within close proximity to these events makes it difficult to delineate the effects of the acute physiological stress response from those factors that are unique to the spaceflight environment (i.e. microgravity, radiation exposure) itself. From a chronic stress standpoint, future exploration class missions (i.e. to Mars or an asteroid) are likely to involve prolonged periods of isolation and hardship for up to 3 years. During these missions, it is also likely that crewmembers will encounter periods of acute stress while in a state of chronic stress and physical deconditioning (i.e. landing on the Martian surface following 6-months of space travel). It is important that any terrestrial analog used to determine the effects of spaceflight on immunity suitably accounts for these acute and chronic stressors that are likely to be encountered by the crew, particularly during prolonged, deep space exploration-class missions.

The duration, intensity and timing of a physiological stress response are critical factors when determining the impact of stress on immune function and health. It has been proposed that the effects of stress on the immune system can be viewed across a spectrum (Dhabhar, 2009). At one end are the effects of *acute stress* (Fig. 1). These are stressful events of short duration (order of minutes to hours) that may elicit physiological responses that prime or enhance immunity in preparation for injury or an infectious threat. A unique characteristic of acute stress is the rapid physiological response that occurs while the stressor is applied, followed by an abrupt shutdown of the response when the stressor is removed. At the other end of the spectrum are the effects of *chronic stress*. These are persistent or prolonged stressful events (order of weeks to months to years) that may result in immune dysregulation or suppression. What separates chronic from acute stress is that the physiological response can persist long after cessation of the

Table 1
Variables which influence immune homeostasis during spaceflight versus specific ground analogs. While it is generally not feasible to replicate flight specific variables terrestrially (for human subjects to a magnitude that supports space physiology research, it is possible to replicate most mission-associated variables to some degree of fidelity in a ground-analog setting.

	Spaceflight variables	Appropriate terrestrial analog (Immunity)
Spaceflight-specific variables	Radiation	Animal and cell culture irradiation modles
	Microgravity	Bed Rest (some aspects of fluid shift) Bioreactor/clinostat (cell culture)
Mission-associated variables	Physiological stress	Antarctica, Arctic, NEEMO
	Psychological stress (isolation, work schedules, perceived risk)	Antarctica, Arctic, NEEMO
	Circadian misalignment	Lab based sleep deprivation protocol
	Altered nutrition	Antarctica winterover
	Altered clinical care	None
	Environmental factors (air, water recirculation, etc.)	Can be replicated to some degree during specifically designed laboratory environments (MARS500)