PLASMA CYTOKINE LEVELS DURING LONG-DURATION SPACEFLIGHT

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Could spaceflight-associated immune system weakening preclude the expansion of human presence beyond Earth's orbit?


Evidence Book

Risk of Crew Adverse Health Event Due to Altered Immune Response

June 2009

National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

HRP-147060

Immune dysregulation during deep space missions has the capacity to synergize with other variables such as oxidative damage or radiation exposure. This would further enhance clinical risk to crewmembers.
Th1 - Immunity to intracellular pathogens, viruses

*Normal Function*
- Cell Mediated ‘Inflammatory’ Response
- Fight intracellular pathogens (viruses)
- Control DTH response to skin viral/bacterial antigens
- Fight tumor formation
- Phagocyte dependent inflammation

*Disease correlations:*
Rheumatoid arthritis
organ specific immune disorders
Chohn’s disease
Sarcoidosis
Acute allograft rejection
Unexplained recurrent abortions
Multiple sclerosis

Th2 - Antibody response to extracellular pathogens, parasites

*Normal Function*
- Humoral (Antibody) Responses
- ‘Anti-Inflammatory Response

*Disease correlations:*
Rapid progression of HIV to AIDS
Chronic graft vs. host disease
Systemic autoimmune diseases
Atopic asthma
Scleroderma
Serum lupus erythematosus
Chronic allergies/sensitization
Atopic dermatitis

Cytokines: Th1/Th2

![Diagram showing cytokines and Th1/Th2 interactions](image)
<table>
<thead>
<tr>
<th>Environment</th>
<th>Response type</th>
<th>Products</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-12+IL-18 (Monocytic Inf.)</td>
<td>Th1</td>
<td>IFNγ, IL-2, TNFα, LT</td>
<td>Purpose: CMI, DTH, intracellular pathogens. Pro-inflammatory, cause organ-specific autoimmunity.</td>
</tr>
<tr>
<td>TGFβ+IL-6 (Neutrophil. Inf.)</td>
<td>Th17</td>
<td>IL-17a, f, IL-21, IL-22</td>
<td>Purpose: clear gut bacteria, other pathogens not handled by Th1/2 (citrobacter, k. pneumoniae, candida). Disease: arthritis, MS, psoriasis, EAE.</td>
</tr>
<tr>
<td>IL-4+IL-2 (Baso/Eo/Mast inf.)</td>
<td>Th2</td>
<td>IL-4, IL-5 (IL-10, 9, 12)</td>
<td>Purpose: humoral immunity, extracellular organisms. Disease: allergy, atopy.</td>
</tr>
<tr>
<td>TGFβ + IL-4</td>
<td>Th9</td>
<td>IL-9, IL-10</td>
<td>IL-9 stimulates proliferation, prevents apoptosis. Effector subset (not regulatory subset). Subset of Th2? Plastic, can switch to Th1 or Th17.</td>
</tr>
<tr>
<td>TGFβ</td>
<td>Treg</td>
<td>TGFβ</td>
<td>Natural Tregs control inflammation, secrete anti-inflammatory cytokines. Reduced Treg function associated with many autoimmune disorders. Express CD25, CD152, icFoxp3.</td>
</tr>
<tr>
<td>TGFβ+IL-27</td>
<td>Tr1</td>
<td>IL-10, TGFβ (IL-21 autoc)</td>
<td>Regulatory type 1 cell: potent immunosuppressive properties, do not express Foxp3. Main tolerance, control autoimmunity, prevent graft rejection, GVH disease</td>
</tr>
<tr>
<td>TGFβ+IL-27</td>
<td>Th3</td>
<td>TGFβ, IL-10</td>
<td>Th3 cells are involved in mucosal immunity. Mediate non-inflammatory environment. Promote switch to IgA (non-inflammatory, does not activate c', not involved with phagocytosis). Responsible for 'oral tolerance'?</td>
</tr>
<tr>
<td>IL-21</td>
<td>Tfh</td>
<td>IL-6, IL-10, IL-21</td>
<td>Folicular helper T cells. Regulate step-wise development of antigen-specific B cells in vivo. CCR5+ Deployed to B cell zones of lymphoid tissues</td>
</tr>
</tbody>
</table>
**NUTRITION**
Proper nutrition is a requirement for a normal immune response. Deficiencies in any of several dietary requirements have been linked to diminished immune function and/or clinical illness.

**RADIATION**
Immune cells generally susceptible to radiation damage. Peripheral T and B cells via apoptosis induction; and via lethal damage to marrow stem cells.

**BONE**
Within the bone marrow cavity, cytokines produced by immune cells also have important effects on regulating bone homeostasis. RANKL, M-CSF, TNF, ILs, and IFNs, affect the differentiation and activity of osteoclasts and bone resorption. During chronic inflammation, the balance of bone modeling and remodeling can be greatly affected.

**NEUROLOGY**
A reciprocal flow of information and functional connection exists between the nervous and immune systems. Communication occurs via soluble mediators and cell-cell contacts.

**MICROBIOLOGY**
Host-pathogen interactions determine susceptibility to disease. Microbial virulence in conjunction with immune status determines the magnitude and outcome of infection.

**EXERCISE**
Research is uncovering a link between moderate, regular exercise and a strong immune system. However, there is also evidence that too much intense exercise can reduce immunity and may even make you sick.
Specific Study Objectives

- Determine the in-flight status of immunity, physiological stress, viral immunity/reactivation.

- Specific measurements include leukocyte distribution, T cell function, cytokine production profiles (mRNA, intracellular, secreted, plasma), virus-specific T cell number/function, latent herpesvirus reactivation, stress hormone levels.

- Determine the clinical risk related to immune dysregulation for exploration class spaceflight, as well as an appropriate monitoring strategy for spaceflight-associated immune dysfunction, that could be used for the evaluation of countermeasures.

Determine the nutritional status of astronauts before, during, and after spaceflight ensure adequate intake of energy, protein, and vitamins during missions.

The Clinical Nutritional Status Assessment measures dietary intake, body composition, protein, bone, iron, mineral, vitamin, and antioxidant status (60 total analytes). Currently, it is a medical requirement for U.S. crewmembers on-board the ISS.

The results of data analysis are used both to understand the connections between nutrition and human health during space flight, and to develop effective dietary strategies to reduce adverse health impacts (including bone loss, loss of important vitamins and minerals, and increased genetic damage from radiation).
**SAMPLING SCHEDULE**

Early: ~2 weeks

Mid: 2-4 mos

Late: R-1-2 days

FD15  FD30  FD60  FD120  FD180

SMO-018

SMO-016
### Cytokine Categories

<table>
<thead>
<tr>
<th>INFLAMMATORY</th>
<th>ADAPTIVE/Th1</th>
<th>ADAPTIVE/Th17</th>
<th>ADAPTIVE/Th2</th>
<th>CHEMOKINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1 alpha</td>
<td>IFN-gamma</td>
<td>IL-17</td>
<td>IL-4</td>
<td>CXCL8/IL-8</td>
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<tr>
<td>IL-1 beta</td>
<td>IL-2</td>
<td></td>
<td>IL-5</td>
<td>(+/-)</td>
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<tr>
<td>TNF-alpha</td>
<td></td>
<td></td>
<td>IL-10</td>
<td>CCL2/MCP-1</td>
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<td>IL-6</td>
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<td></td>
<td>CCL3/MIP-1 alpha</td>
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<td></td>
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<td></td>
<td>CCL4/MIP-1 beta</td>
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<td></td>
<td>CCL5/RANTES</td>
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<td></td>
<td>CXCL5/ENA-78</td>
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<tr>
<td>anti-INFLAMMATORY</td>
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<tr>
<td>IL-1ra/IL-1F3</td>
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### Growth Factors

<table>
<thead>
<tr>
<th>GROWTH FACTORS</th>
<th>CHEMOKINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-CSF</td>
<td>CXCL8/IL-8</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>(+/-)</td>
</tr>
<tr>
<td>FGF basic</td>
<td>CCL2/MCP-1</td>
</tr>
<tr>
<td>Tpo</td>
<td>CCL3/MIP-1 alpha</td>
</tr>
<tr>
<td>VEGF</td>
<td>CCL4/MIP-1 beta</td>
</tr>
</tbody>
</table>

For a 22-cytokine array, assuming a qualitative data, there are **4,194,304** possible outcomes.
Plasma Cytokine Data – Inflammatory Cytokines

**IL-1a**

**IL-1b**

**IL-6**

**TNFα**

**IL-1ra**
Plasma Cytokine Data – Adaptive Immunity

**IFNγ**

**IL-2**

**IL-17**

**IL-4**

**IL-5**

**IL-10**
Plasma Cytokine Data – Growth Factors

- **G-CSF**
- **GM-CSF**
- **FGF basic**
- **Tpo**
- **VEGF**

Each graph represents the concentration levels of the respective growth factors over time, with different markers indicating significant changes.
Conclusions

• In general, levels of inflammatory and adaptive immunity cytokines are not elevated during long-duration spaceflight.

• Reduced T cell, granulocyte, NK and monocyte function have all been reported following both long and short duration spaceflight, however no systemic inflammatory or adaptive immune activation evident during spaceflight.

• Increases in growth factors and chemokines may indicate other types of adaptation occurring during spaceflight, such as attempts to overcome diminished immunocyte function.

• Are there localized inflammatory processes that result in a downstream peripheral manifestation (IL-1ra, CXCL5, IL-8)?

• There appear to be varied individual crew responses, and specific relationships between cytokines and markers of iron status and muscle turnover that warrant further evaluation.