



The impact of long duration spaceflight on the function of plasma cells

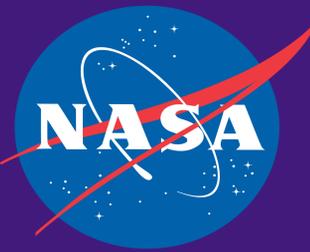
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Abstract

Long duration spaceflights have been associated with profound dysregulation of the immune system, which could jeopardize crew safety and mission success. Recent studies have examined the impact of long-duration spaceflight on specific markers of adaptive and innate immunity, but no study to date has characterized humoral immunity and serological markers of B-cell function. **Purpose:** The aim of this study was to characterize acute and chronic changes in polyclonal Free Light Chains (FLC) and in Immunoglobulin class switching, indicative of overall B-cell function, by retrospectively analyzing archived plasma samples collected during long-duration spaceflight studies. **Methods:** Plasma samples were collected before flight, during ("Early flight", "Mid-flight" and "Late flight"), immediately upon return and during a recovery period (R+18, R+33 and R+66) from 23 astronauts and 6 age/gender-matched healthy ground-based controls. Plasma Kappa and Lambda Free Light Chains were measured using commercially available ELISA kits (Abingdon Health, Oxford, UK), and changes in renal function were identified by calculating Cystatin C-derived estimates of Glomerular Filtration Rate (eGFR). Finally, Immunoglobulin isotype switching was assessed by measuring changes in total plasma IgA, IgG and IgM throughout the mission using ELISA kits (eBioscience, San Diego, CA, USA). Maximum likelihood linear mixed models (LMM) were used to determine main effects of time on the concentration of serum FLC, Immunoglobulins and Cystatin C. **Results:** There was no difference in serum Kappa and Lambda FLC between pre-flight samples and either in-flight or recovery samples (p>0.05). Furthermore, serum levels of IgA, IgG and IgM remained unchanged during and after spaceflight, when compared to pre-flight values (p>0.05). Finally, there was no difference in eGFR (p>0.05) between before, during and after flight, suggesting that kidney function was not affected by spaceflight. **Conclusion:** These preliminary findings indicate that free light chains and whole immunoglobulin output from plasma cells are unaffected by long-duration spaceflight, indicating that plasma cell immune competency is maintained in microgravity and risk of infection does not appear to be magnified.

Introduction

•Astronauts are subjected to increased physical and psychological stressors during long-term Spaceflight missions, such as increased radiation exposure, microgravity and disrupted circadian rhythm.

•Such Physical and Psychological Stressors are known to be associated with immune dysregulation

•Infectious episodes have been reported among crewmembers aboard the Mir station (i.e. conjunctivitis, acute respiratory and dental infections).

•Recent scientific projects entitled "*Salivary Markers*" (MTL # 725) and "*Integrated Immune*" (SMO-015) were conducted to assess the impact of a 6-month mission in the ISS on aspects of innate and adaptive immune function.

•These studies however they did not characterize humoral immunity and serological markers of B-cell function. Consequently it remains unknown whether spaceflight impacts overall B-cell function, and subsequently expose astronauts to increased risk for infection

•The purpose of this study is to advance the findings from two ISS flight studies ("Integrated Immune" and "Salivary Markers") by characterizing acute and chronic changes in polyclonal Free Light Chains (FLC), and in Immunoglobulin (Ig) class switching, indicative of a state of chronic inflammation and overall B-cell function.

Methods

Astronauts: A total of 29 Astronauts from NASA and ESA (N "integrated immune"= 23; N "salivary markers"=6) of various nationalities who spent 6 months in the International Space Station took part in this study. Additionally, samples from 6 ground-based controls from the "Salivary Markers" study were analyzed.

Samples: Salivary Markers: Baseline plasma and saliva samples were taken 5 month before launch and throughout the mission from the 6 Astronauts and their associated ground-based control subjects as described in Figure 1.

Integrated Immune: Baseline plasma samples were taken 5 month before launch from the 23 Astronauts (10 Rookies and 13 Veterans). Additional samples were collected 45 Days before launch, three times during the mission (FD-10 "Early", FD-90 "Mid" and R-1 "Late"), immediately upon return, and after 30 days back on Earth.

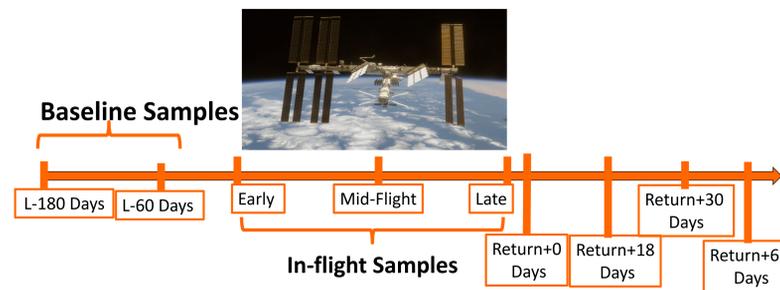


Fig 1. Plasma, Saliva and Urine Sampling Timeline

Kidney Function: Serum Cystatin C was measured in the stored samples to evaluate renal function in the Astronauts and ground-based controls using Enzyme Linked Immunosorbent Assays.

Immunoglobulin Measurements: Total IgA, IgM and IgG were measured in a total of 150µL of thawed plasma sample from all astronauts and corresponding controls using commercially available ELISA kits.

Plasma and Salivary FLC: Plasma and Saliva samples were thawed and analyzed using Enzyme Linked Immunosorbent Assays (Abingdon Health, Oxford, UK)

Statistical analysis: Multilevel, mixed models were utilized throughout this study to evaluate the effect of spaceflight on FLC and Immunoglobulin levels. Statistical significance was set at p<0.05.

Results

Table 1. Changes in plasma IgA, IgM and IgG in Astronauts and Ground-based Controls before, during and following 6 months in the ISS. (n=23 Astronauts and 6 Controls). Results are presented ± SD. Significant Differences between Pre-Flight values (* p<0.05)

		L-180	L-45	Early-Flight	Mid-Flight	Late-Flight	R+0	R+18	R+33	R+66
IgA (mg/L) ± SD	Astronauts	131.51 ± 63.73	112.73 ± 49.64	126.60 ± 58.05 *	136.38 ± 68.12 *	140.58 ± 75.08 *	126.64 ± 59.56	103.14 ± 32.67	112.46 ± 55.11 *	101.73 ± 27.51
	Ground-based Controls	147.94 ± 81.99	148.87 ± 105.63	143.09 ± 96.25	145.91 ± 102.42	162.79 ± 98.85	151.16 ± 93.82	153.74 ± 104.33	169.38 ± 119.47	160.59 ± 108.91
IgG (mg/L) ± SD	Astronauts	1218.41 ± 231.66	1190.41 ± 253.88	1181.47 ± 310.80	1235.41 ± 277.07	1249.98 ± 298.99	1184.38 ± 209.64	1359.33 ± 304.05 *	1226.67 ± 399.88	1267.50 ± 255.92
	Ground-based Controls	1068.10 ± 219.10	1069.10 ± 244.06	1058.05 ± 147.85	1087.63 ± 259.60	1202.83 ± 262.66	1099.23 ± 259.36	1141.05 ± 350.65	1167.62 ± 320.70	1140.10 ± 280.17
IgM (mg/L) ± SD	Astronauts	373.51 ± 546.67	408.84 ± 530.97	476.08 ± 665.62	422.57 ± 476.36	410.57 ± 491.51	346.95 ± 360.77	651.04 ± 751.93 *	295.78 ± 268.07	471.20 ± 324.15
	Ground-based Controls	857.08 ± 481.50	981.47 ± 815.83	729.53 ± 469.36	747.77 ± 556.78	735.10 ± 702.13	880.23 ± 872.10	682.82 ± 402.01	809.12 ± 489.81	977.72 ± 650.42

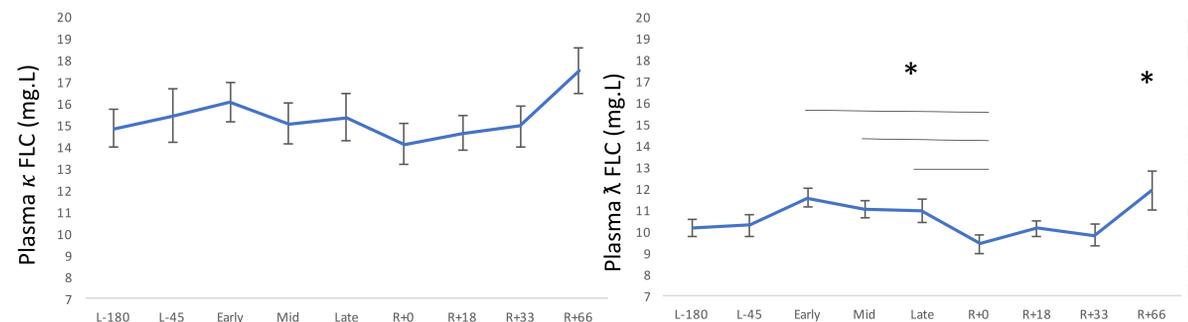


Figure 2. Changes in plasma Kappa FLC and Lambda FLC in all Astronauts before, during and following 6 months in the ISS. (n=23 Astronauts). No change was observed in the ground-based controls (data not presented). Results are presented ± Standard Deviation. Significant Differences between Post-flight value (R+0) (* p<0.05)

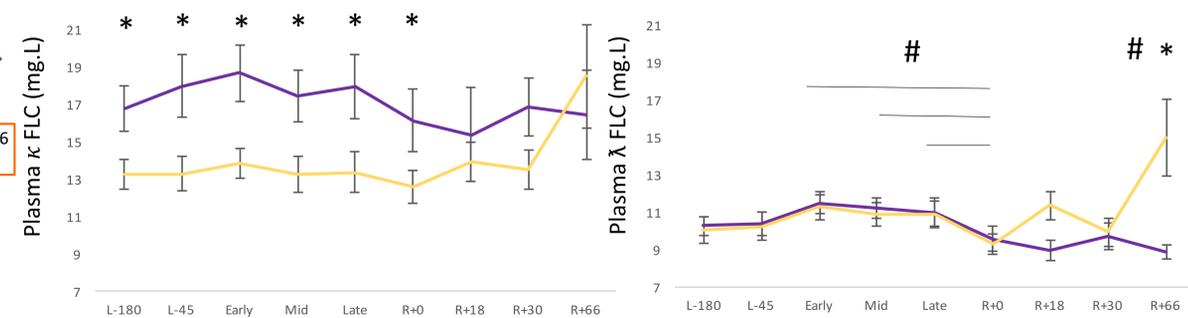


Figure 3. Impact of Astronaut's experience (Rookie in Purple n=10 - Veterans in Gold n=13) on plasma FLC concentrations before, during and following 6 months in the ISS. Results are presented ± Standard Deviation. Significant Differences between Experience (* p<0.05). Significant Differences between Post-flight value (R+0) # p<0.05)

Conclusion

- Plasma IgA concentrations were elevated in astronauts during flight (early, mid-flight and late-flight) when compared to pre-flight values, but no significant difference was observed in plasma IgA in the ground-based controls. Plasma IgG and IgM were elevated in astronauts upon return on Earth (R+18) when compared to pre-flight values.
- Plasma Lambda FLC concentrations were elevated in astronauts during flight (early, mid-flight and late-flight) when compared to post-flight values (R+0). Plasma Kappa FLC concentrations remained stable throughout the mission. After controlling for Astronaut's Experience (first mission vs one or more mission), Rookie astronauts had an increase in plasma Kappa FLC during flight, but not veteran astronauts.
- In-flight Herpesvirus reactivation (CMV, EBV and VZV) did not impact Immunoglobulins and FLC levels in astronauts.
- These results suggest that while astronauts who are flying in the ISS for the first time may exhibit greater plasma cell activation than their more experienced counterparts, overall free light chains and whole immunoglobulin output from plasma cells appear to be relatively unaffected by long-duration spaceflight, indicating that plasma cell immune competency is maintained in microgravity and risk of infection does not appear to be magnified.

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