

## The impact of long duration spaceflight on plasma Antimicrobial Proteins

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### ABSTRACT

**Introduction:** Robust immunity is essential for further human exploration of the solar system beyond Earth's orbit. Spaceflight has been associated with immune perturbations and latent viral reactivation. However, logistical constraints have restricted many of these studies to simple pre- and post-flight measures, which are greatly confounded by the stressors associated with launch, landing and re-adaptation to the 1G environment. More in-flight immune data are required particularly during long-duration (3-6 months) spaceflight missions. This study examined the effects of spaceflight on plasma antimicrobial proteins (AMPs) and reactivation of latent herpesviruses.

**Methods:** Plasma, saliva and urine samples were obtained from 20 crewmembers who spent ~6-months on the International Space Station (ISS). Samples were collected 180 and 45-days before launch, in-flight (at 'early', 'mid' and 'late' stages of the mission), immediately upon return to Earth (R+0) and 30 days following return (R+30). Plasma LL-37, HNP 1-3 and lysozyme concentrations were determined by ELISA. Saliva Epstein-Barr virus (EBV), varicella zoster virus (VZV) and urine cytomegalovirus (CMV) DNA levels were quantified by Real-Time PCR. Maximum likelihood linear mixed models (LMM) were used to determine main effects of time (pre-flight, in-flight, R+0 and R+30), and EBV, VZV and CMV viral shedding status (shedding or non-shedding) on the concentration of each AMPs. **Results:** Lower plasma levels of LL-37 were found at R+0, compared to pre-flight, in-flight and R+30 (-80.6%, -80.2% and -73.49% respectively;  $p < 0.01$ ). Plasma HNP 1-3 levels were elevated above pre-flight level during flight, at R+0 and R+30 (+24%, +40% and +17% respectively;  $p < 0.01$ ). Only those crewmembers found to shed CMV had a significant reduction in plasma LL-37 at R+0 ( $p < 0.05$ ). Similarly, crewmembers found to shed VZV at R+0 had lower HNP 1-3 concentrations than crewmembers who did not shed VZV (-68.9%;  $p < 0.01$ ). Finally, only those crewmembers who shed EBV had increased plasma levels of HNP 1-3 at R+0 ( $p < 0.01$ ). Plasma lysozyme levels were unaffected by spaceflight or latent viral shedding. **Conclusion:** Long-duration spaceflight alters plasma LL-37 and HNP 1-3 levels and are linked to the reactivation of latent herpesviruses. The in-flight changes observed for HNP 1-3 indicate that certain immune perturbations may be independent of launch/landing stress. Future studies are required to determine if spaceflight induced immune dysregulation increases the risk of an adverse health event before exploration-class planetary missions (i.e. to Mars) can be considered.