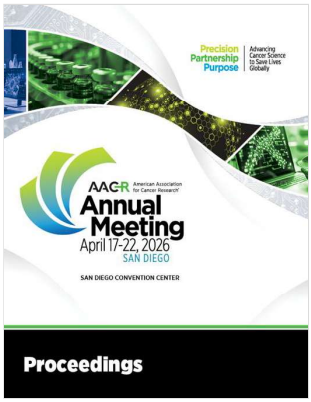
Volume 86, Issue 7_Supplement
1 April 2026



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Abstract 5273: Signaling pathway insights into spaceflight cancer risks FREE

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Cancer Res (2026) 86 (7_Supplement): 5273.
https://doi.org/10.1158/1538-7445.AM2026-5273

Abstract

Spaceflight is a stochastic risk factor for development of cancer in astronauts and experimental data beyond low earth orbit is scarce[1]. Our understanding of role of tumorigenic pathways in the context of space biology is limited. We compared differentially expressed genes (DEGs), signaling pathways, and cancer hallmarks between human tumor tissue with Spaceflight data from civilian astronauts on private missions and rodents on Space missions[2].Astronaut RNA Seq data from the Inspiration4 (I4) mission and NASA Twin study were used conjointly with data from space-flown rodents and compared to transcriptome from organ-matched human tumor counterparts from NCI Genomic Data Commons. The peripheral blood transcriptome of the I4 crew revealed a temporal trend of oncogenic gene dysregulation from pre-flight to 82 days after return to Earth (R+82). Early post-flight window showed activation of pro-tumorigenic and immune-mediated genes namely KRAS, MTOR, STAT3, RARA, and PIK3CA on R+1 (immediate post-spaceflight), of which sustained activation of key genes were observed on R+45 (45 days post return to Earth) and on R+82. DNA damage repair genes such as MRE11, ATR, ABL1, RAD51B, RAD51D, FANCA, and CREBBP were activated in parallel. Over time, most regulatory genes recovered, but therapeutic targets namely ALK, ROS1, NTRK3, POLE, RAD51D, MTAP, ESR1, FGFR3, TSC1, STK11, ABL1, CREBBP, RAF1, NRG1, BCL6, and KMT2D

were found to be upregulated post-flight after readjusting to Earth, irrespective of inter-individual variability. Sustained upregulation of stemness factors STAT3 and FOXP1 indicate adaptivity or immune system tuning post-stress but warrants attention for long term studies for potential oncogenic risks.In parallel, multi-organ sorted patient and rodent data offered staggering insights into tumorigenic roles of major signaling cascades in cancer. Significant overlaps in DEGs were observed between primary human tumors and spaceflown models notably in Breast (p 4.84E-57, OR 7.7), Colon (p 9.24E-46, OR 25), Kidney (p 9.21E-62, OR 9.3), Lung (p 1.38E-51, OR 28), and Skin (p1.23E-85, OR 119). GSEA analysis revealed pro-tumorigenic pathway enrichment. For example, in breast, we observed activation in pathways of MYC targets (NES 2.17, FDRq 0.003), mTORC (NES 2.42, FDRq 0.000), PI3K pathway (NES 1.31, FDRq 0.123), DNA damage repair (NES 1.76, FDRq 0.002), Oxidative Phosphorylation (NES 3.28, FDRq 0.000), and ROS cascades (NES 2.10, FDRq 0.000).The distinction between signaling pathway dysregulations in healthy tissue, benign tumors, stress-induced tissue, and florid malignancy remains a question. Sustained activation of pathways post-spaceflight in astronauts is a crucial finding that mirrors a cellular environment observed in human pre-malignant tissues. Simultaneously, the significant similarity in cellular pathways between tumors and spaceflight petitions cognizance of the bivalent nature of pathways in cancer[3].

Citation Format:

Anu R I, Josef Borg, JangKeun Kim, Tricia Larose, Ryan T. Scott, Joseph Borg, Christopher E. Mason, Afshin Beheshti, Kurt van der Speeten. Signaling pathway insights into spaceflight cancer risks [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2026; Part 1 (Regular Abstracts); 2026 Apr 17-22; San Diego, CA. Philadelphia (PA): AACR; Cancer Res 2026;86(7 Suppl):Abstract nr 5273.

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