Supplementary Information

Transcriptomics Analysis Reveals Molecular Alterations Underpinning Spaceflight Dermatology

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Supplementary Table 1. Curated pathways for directed pathway analysis. Pathway lists used in our analysis for **Figs. 5 – 7**.

Curated skin health pathways:

HP_ABNORMALITY_OF_SKIN_PHYSIOLOGY
HP_ABNORMALITY_OF_SKIN_ADNEXA_PHYSIOLOGY
HP_ABNORMALITY_OF_EPIDERMAL_MORPHOLOGY
GOBP_EPIDERMIS_MORPHOGENESIS
GOBP_REGULATION_OF_EPIDERMIS_DEVELOPMENT
GOBP_NEGATIVE_REGULATION_OF_EPIDERMIS_DEVELOPMENT
GOBP_REGULATION_OF_KERATINOCYTE_DIFFERENTIATION
GOMF_KERATIN_FILAMENT_BINDING
REACTOME_KERATINIZATION
REACTOME_COLLAGEN_BIOSYNTHESIS_AND_MODIFYING_ENZYMES
GOBP_ELASTIN_CATABOLIC_PROCESS
GOBP_ELASTIN_METABOLIC_PROCESS
HP_DERMAL_ATROPHY
HP_ABNORMAL_ELASTICITY_OF_SKIN
HP_THIN_SKIN
HP_THICKENED_SKIN
ENK_UV_RESPONSE_EPIDERMIS_DN
DURCHDEWALD_SKIN_CARCINOGENESIS_DN
ENK_UV_RESPONSE_KERATINOCYTE_DN
GOBP_REGULATION_OF_WATER_LOSS_VIA_SKIN

Curated DNA damage & repair pathways:

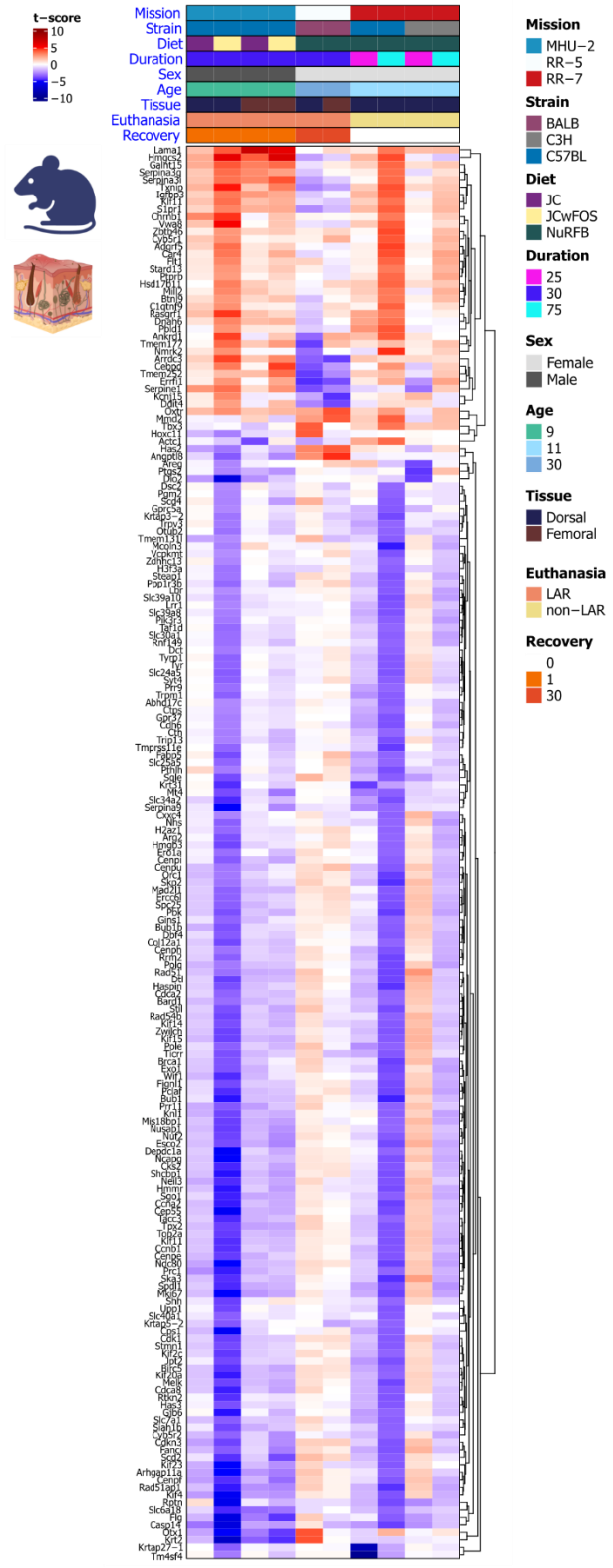
Pathway	Category
GOBP_BASE_EXCISION_REPAIR	Base Excision Repair
GOBP_BASE_EXCISION_REPAIR_AP_SITE_FORMATION	Base Excision Repair
GOBP_BASE_EXCISION_REPAIR_GAP_FILLING	Base Excision Repair
KEGG_BASE_EXCISION_REPAIR	Base Excision Repair
REACTOME_BASE_EXCISION_REPAIR	Base Excision Repair
REACTOME_BASE_EXCISION_REPAIR_AP_SITE_FORMATION	Base Excision Repair
REACTOME_DISEASES_OF_BASE_EXCISION_REPAIR	Base Excision Repair
REACTOME_PCNA_DEPENDENT_LONG_PATCH_BASE_EXCISION_REPAIR	Base Excision Repair
REACTOME_POLB_DEPENDENT_LONG_PATCH_BASE_EXCISION_REPAIR	Base Excision Repair
WP_BASE_EXCISION_REPAIR	Base Excision Repair
GOBP_CELLULAR_RESPONSE_TO_DNA_DAMAGE_STIMULUS	DDR
GOBP_DNA_DAMAGE_INDUCED_PROTEIN_PHOSPHORYLATION	DDR
GOBP_DNA_DAMAGE_RESPONSE_DETECTION_OF_DNA_DAMAGE	DDR
GOBP_DNA_DAMAGE_RESPONSE_SIGNAL_TRANSDUCTION_BY_P53_CLASS_MEDIATOR	DDR
GOBP_DNA_DAMAGE_RESPONSE_SIGNAL_TRANSDUCTION_RESULTING_IN_TRANSCRIPTION	DDR
GOBP_G2_DNA_DAMAGE_CHECKPOINT	DDR
GOBP_INTRA_S_DNA_DAMAGE_CHECKPOINT	DDR
GOBP_INTRINSIC_APOPTOTIC_SIGNALING_PATHWAY_IN_RESPONSE_TO_DNA_DAMAGE	DDR
GOBP_INTRINSIC_APOPTOTIC_SIGNALING_PATHWAY_IN_RESPONSE_TO_DNA_DAMAGE_BY_P53_CLASS_MEDIATOR	DDR
GOBP_MITOTIC_G2_DNA_DAMAGE_CHECKPOINT	DDR
GOBP_NEGATIVE_REGULATION_OF_DNA_DAMAGE_CHECKPOINT	DDR
GOBP_NEGATIVE_REGULATION_OF_DNA_DAMAGE_RESPONSE_SIGNAL_TRANSDUCTION_BY_P53_CLASS_MEDIATOR	DDR
GOBP_NEGATIVE_REGULATION_OF_INTRINSIC_APOPTOTIC_SIGNALING_PATHWAY_IN_RESPONSE_TO_DNA_DAMAGE	DDR
GOBP_NEGATIVE_REGULATION_OF_RESPONSE_TO_DNA_DAMAGE_STIMULUS	DDR
GOBP_POSITIVE_REGULATION_OF_INTRINSIC_APOPTOTIC_SIGNALING_PATHWAY_IN_RESPONSE_TO_DNA_DAMAGE	DDR
GOBP_POSITIVE_REGULATION_OF_RESPONSE_TO_DNA_DAMAGE_STIMULUS	DDR
GOBP_PRE_REPLICATIVE_COMPLEX_ASSEMBLY_INVOLVED_IN_CELL_CYCLE_DNA_REPLICATION	DDR
GOBP_REGULATION_OF_DNA_DAMAGE_CHECKPOINT	DDR
GOBP_REGULATION_OF_DNA_DAMAGE_RESPONSE_SIGNAL_TRANSDUCTION_BY_P53_CLASS_MEDIATOR	DDR
GOBP_REGULATION_OF_INTRINSIC_APOPTOTIC_SIGNALING_PATHWAY_IN_RESPONSE_TO_DNA_DAMAGE	DDR
GOBP_REGULATION_OF_INTRINSIC_APOPTOTIC_SIGNALING_PATHWAY_IN_RESPONSE_TO_DNA_DAMAGE_BY_P53_CLASS_MEDIATOR	DDR
GOBP_REGULATION_OF_RESPONSE_TO_DNA_DAMAGE_STIMULUS	DDR
GOBP_SIGNAL_TRANSDUCTION_IN_RESPONSE_TO_DNA_DAMAGE	DDR
GOBP_SIGNAL_TRANSDUCTION_INVOLVED_IN_G2_DNA_DAMAGE_CHECKPOINT	DDR
GOBP_TELOMERE_MAINTENANCE_IN_RESPONSE_TO_DNA_DAMAGE	DDR
GOBP_UV_DAMAGE_EXCISION_REPAIR	DDR
GOCC_SITE_OF_DNA_DAMAGE	DDR
GOMF_DAMAGED_DNA_BINDING	DDR
KYNG_DNA_DAMAGE_BY_4NQO	DDR
KYNG_DNA_DAMAGE_BY_4NQO_OR_GAMMA_RADIATION	DDR
KYNG_DNA_DAMAGE_BY_4NQO_OR_UV	DDR
KYNG_DNA_DAMAGE_BY_GAMMA_AND_UV_RADIATION	DDR
KYNG_DNA_DAMAGE_BY_GAMMA_RADIATION	DDR
KYNG_DNA_DAMAGE_BY_UV	DDR
KYNG_DNA_DAMAGE_DN	DDR

KYNG_DNA_DAMAGE_UP	DDR
REACTOME_DNA_DAMAGE_BYPASS	DDR
REACTOME_DNA_DAMAGE_REVERSAL	DDR
REACTOME_DNA_DAMAGE_TELOMERE_STRESS_INDUCED_SENESCENCE	DDR
REACTOME_G1_S_DNA_DAMAGE_CHECKPOINTS	DDR
REACTOME_G2_M_DNA_DAMAGE_CHECKPOINT	DDR
REACTOME_INHIBITION_OF_REPLICATION_INITIATION_OF_DAMAGED_DNA_BY_RB1_E2F1	DDR
REACTOME_RECOGNITION_OF_DNA_DAMAGE_BY_PCNA_CONTAINING_REPLICATION_COMPLEX	DDR
REACTOME_SUMOYLATION_OF_DNA_DAMAGE_RESPONSE_AND_REPAIR_PROTEINS	DDR
REACTOME_TP53_REGULATES_TRANSCRIPTION_OF_DNA_REPAIR_GENES	DDR
WP_DNA_DAMAGE_RESPONSE	DDR
WP_DNA_DAMAGE_RESPONSE_ONLY_ATM_DEPENDENT	DDR
WP_DNA_IRDAMAGE_AND_CELLULAR_RESPONSE_VIA_ATR	DDR
WP_MIRNA_REGULATION_OF_DNA_DAMAGE_RESPONSE	DDR
WP_MIRNAS_INVOLVED_IN_DNA_DAMAGE_RESPONSE	DDR
GOBP_DNA_DOUBLE_STRAND_BREAK_PROCESSING	DNA DSB
GOBP_DOUBLE_STRAND_BREAK_REPAIR	DNA DSB
GOBP_DOUBLE_STRAND_BREAK_REPAIR_INVOLVED_IN_MEIOTIC_RECOMBINATION	DNA DSB
GOBP_DOUBLE_STRAND_BREAK_REPAIR_VIA_BREAK_INDUCED_REPLICATION	DNA DSB
GOBP_DOUBLE_STRAND_BREAK_REPAIR_VIA_CLASSICAL_NONHOMOLOGOUS_END_JOINING	DNA DSB
GOBP_DOUBLE_STRAND_BREAK_REPAIR_VIA_SINGLE_STRAND_ANNEALING	DNA DSB
GOBP_DOUBLE_STRAND_BREAK_REPAIR_VIA_SYNTHESIS_DEPENDENT_STRAND_ANNEALING	DNA DSB
GOBP_MEIOTIC_DNA_DOUBLE_STRAND_BREAK_FORMATION	DNA DSB
GOBP_NEGATIVE_REGULATION_OF_DOUBLE_STRAND_BREAK_REPAIR_VIA_HOMOLOGOUS_RECOMBINATION	DNA DSB
GOBP_NEGATIVE_REGULATION_OF_DOUBLE_STRAND_BREAK_REPAIR_VIA_NONHOMOLOGOUS_END_JOINING	DNA DSB
GOBP_NON_RECOMBINATIONAL_REPAIR	DNA DSB
GOBP_POSITIVE_REGULATION_OF_DOUBLE_STRAND_BREAK_REPAIR	DNA DSB
GOBP_POSITIVE_REGULATION_OF_DOUBLE_STRAND_BREAK_REPAIR_VIA_HOMOLOGOUS_RECOMBINATION	DNA DSB
GOBP_POSITIVE_REGULATION_OF_DOUBLE_STRAND_BREAK_REPAIR_VIA_NONHOMOLOGOUS_END_JOINING	DNA DSB
GOBP_REGULATION_OF_DOUBLE_STRAND_BREAK_REPAIR	DNA DSB
GOBP_REGULATION_OF_DOUBLE_STRAND_BREAK_REPAIR_VIA_HOMOLOGOUS_RECOMBINATION	DNA DSB
GOBP_REGULATION_OF_DOUBLE_STRAND_BREAK_REPAIR_VIA_NONHOMOLOGOUS_END_JOINING	DNA DSB
GOBP_REPLICATION_BORN_DOUBLE_STRAND_BREAK_REPAIR_VIA_SISTER_CHROMATID_EXCHANGE	DNA DSB
GOMF_DOUBLE_STRANDED_METHYLATED_DNA_BINDING	DNA DSB
GOMF_DOUBLE_STRANDED_TELOMERIC_DNA_BINDING	DNA DSB
REACTOME_DNA_DOUBLE_STRAND_BREAK_REPAIR	DNA DSB
REACTOME_DNA_DOUBLE_STRAND_BREAK_RESPONSE	DNA DSB
REACTOME_HOMOLOGY_DIRECTED_REPAIR	DNA DSB
REACTOME_PROCESSING_OF_DNA_DOUBLE_STRAND_BREAK_ENDS	DNA DSB
REACTOME_SENSING_OF_DNA_DOUBLE_STRAND_BREAKS	DNA DSB
WP_DNA_IRDOUBLE_STRAND_BREAKS_DSBS_AND_CELLULAR_RESPONSE_VIA_ATM	DNA DSB
GOBP_DNA_DEALKYLATION_INVOLVED_IN_DNA_REPAIR	DNA Repair
GOBP_DNA_LIGATION_INVOLVED_IN_DNA_REPAIR	DNA Repair
GOBP_DNA_REPAIR	DNA Repair
GOBP_MITOCHONDRIAL_DNA_REPAIR	DNA Repair
GOBP_NEGATIVE_REGULATION_OF_DNA_REPAIR	DNA Repair
GOBP_POSITIVE_REGULATION_OF_DNA_REPAIR	DNA Repair
GOBP_REGULATION_OF_DNA_REPAIR	DNA Repair
GOCC_DNA_REPAIR_COMPLEX	DNA Repair
HP_ABNORMALITY_OF_DNA_REPAIR	DNA Repair
HP_DEFECTIVE_DNA_REPAIR_AFTER_ULTRAVIOLET_RADIATION_DAMAGE	DNA Repair
KAUFFMANN_DNA_REPAIR_GENES	DNA Repair
REACTOME_DISEASES_OF_DNA_REPAIR	DNA Repair
REACTOME_DNA_REPAIR	DNA Repair
WP_DNA_REPAIR_PATHWAYS_FULL_NETWORK	DNA Repair
GOBP_NEGATIVE_REGULATION_OF_SINGLE_STRANDED_VIRAL_RNA_REPLICATION_VIA_DOUBLE_STRANDED_DNA_INTERMEDIATE	DNA SSB
GOBP_SINGLE_STRAND_BREAK_REPAIR	DNA SSB
GOBP_MEIOTIC_MISMATCH_REPAIR	Mismatch Repair
GOBP_MISMATCH_REPAIR	Mismatch Repair
GOCC_MISMATCH_REPAIR_COMPLEX	Mismatch Repair
GOMF_MISMATCH_REPAIR_COMPLEX_BINDING	Mismatch Repair
GOMF_MISMATCHED_DNA_BINDING	Mismatch Repair
KEGG_MISMATCH_REPAIR	Mismatch Repair
REACTOME_DISEASES_OF_MISMATCH_REPAIR_MMR	Mismatch Repair
REACTOME_MISMATCH_REPAIR	Mismatch Repair
WP_DNA_MISMATCH_REPAIR	Mismatch Repair
GOBP_GLOBAL_GENOME_NUCLEOTIDE_EXCISION_REPAIR	Nucelotide Excision Repair
GOBP_NUCLEOTIDE_EXCISION_REPAIR	Nucelotide Excision Repair
GOBP_NUCLEOTIDE_EXCISION_REPAIR_DNA_DAMAGE_RECOGNITION	Nucelotide Excision Repair
GOBP_NUCLEOTIDE_EXCISION_REPAIR_DNA_DUPLEX_UNWINDING	Nucelotide Excision Repair
GOBP_NUCLEOTIDE_EXCISION_REPAIR_DNA_GAP_FILLING	Nucelotide Excision Repair
GOBP_NUCLEOTIDE_EXCISION_REPAIR_DNA_INCISION	Nucelotide Excision Repair

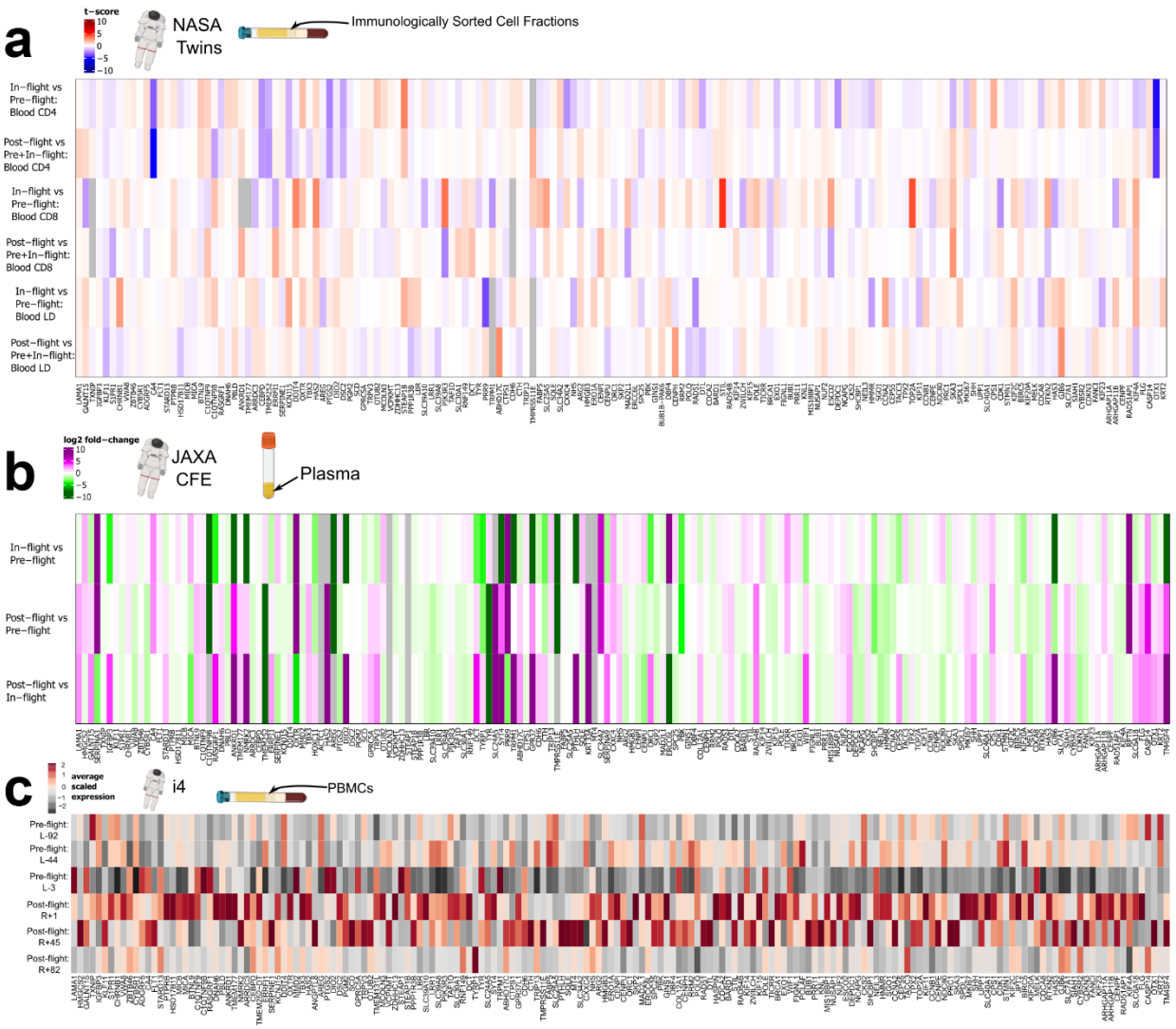
GOBP_NUCLEOTIDE_EXCISION_REPAIR_PREINCISION_COMPLEX_ASSEMBLY	Nucelotide Excision Repair
GOBP_NUCLEOTIDE_EXCISION_REPAIR_PREINCISION_COMPLEX_STABILIZATION	Nucelotide Excision Repair
GOBP_TRANSCRIPTION_COUPLED_NUCLEOTIDE_EXCISION_REPAIR	Nucelotide Excision Repair
GOCC_NUCLEOTIDE_EXCISION_REPAIR_COMPLEX	Nucelotide Excision Repair
KEGG_NUCLEOTIDE_EXCISION_REPAIR	Nucelotide Excision Repair
REACTOME_DNA_DAMAGE_RECOGNITION_IN_GG_NER	Nucelotide Excision Repair
REACTOME_GAP_FILLING_DNA_REPAIR_SYNTHESIS_AND_LIGATION_IN_GG_NER	Nucelotide Excision Repair
REACTOME_GLOBAL_GENOME_NUCLEOTIDE_EXCISION_REPAIR_GG_NER	Nucelotide Excision Repair
REACTOME_NUCLEOTIDE_EXCISION_REPAIR	Nucelotide Excision Repair
REACTOME_TRANSCRIPTION_COUPLED_NUCLEOTIDE_EXCISION_REPAIR_TC_NER	Nucelotide Excision Repair
WP_NUCLEOTIDE_EXCISION_REPAIR	Nucelotide Excision Repair

Curated/custom mitochondrial pathways:

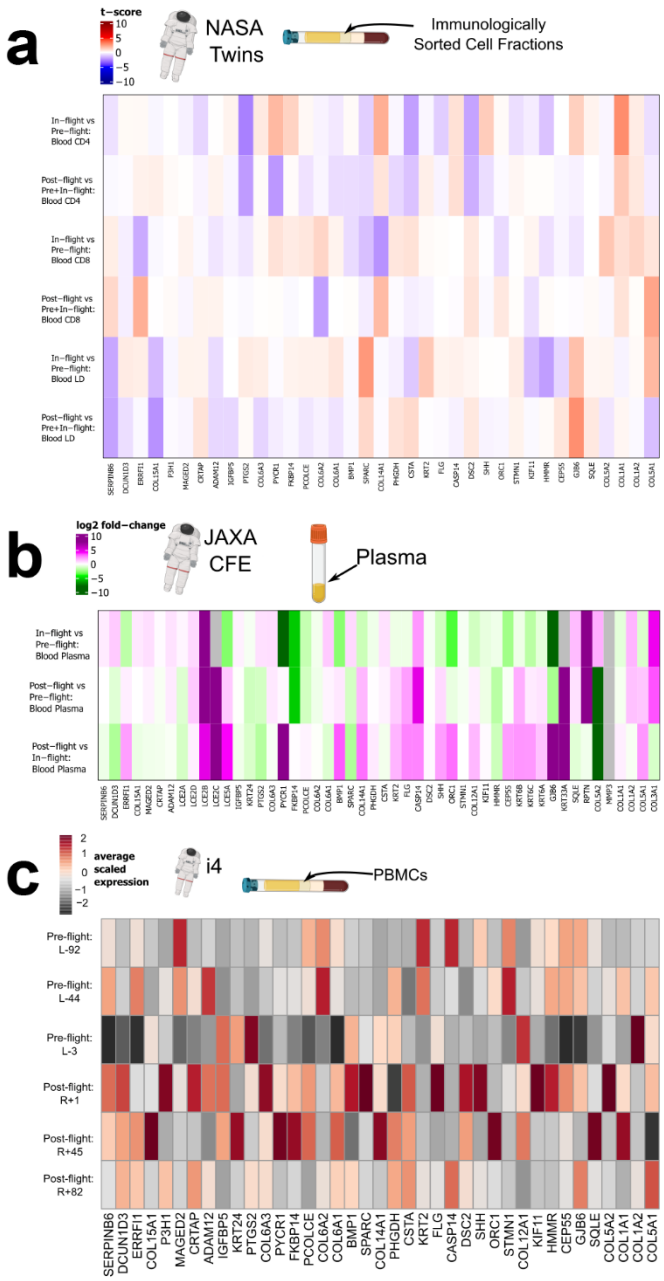
Pathway	Genes
Folate Metabolism	*DHFR, SHMT1, MTHFR, MTR, MTRR, MTHFD1, ALDH1L2, MTFMT, DHFR2, SHMT2, GCLC (GCS), MTHFD2, MTHFD2L, GTPBP3/MT01, TYMS, ATIC, TK1, TK2, MTHFD1L*
Glutathione Synthesis	*GCLC, GCLM, GPX1, GPX2, GPX3, GSTA1, GSTM1, GSTO1, GSTP1, GSTZ1, GSTA4, GSTA2, GSTA3, GSTM2, GSTM3, GSTM4, GSTO2, GSTT2, GSTK1*
Glycolysis	*SLC2A1, SLC2A4, HK1, HK2, HK3, GCK, GPI, PFKM, PFKL, ALDOA, GAPDH, PGK1, ENO1, PKM, LDHA, LDHB, SLC16A1, SLC16A3, SLC16A4*
Selected HIF Target Genes	*VEGFA, EPO, PDGFB, PGF, CXCL12, CXCR4, HMOX1, ID2, IGF2, TERT, POU5F1, PGM1, TGFa, GADD45A, TGFb3, IGFBP3, NOS2, NOS3, PMAIP1, GPX3, SOD2, ADM, ANGPT1, ANGPT2, NPPA, ABCG2, CP, EDN1, FECH, KDR, FLT1, LEP, SERPINE1, TF, NT5E, CCN2, ENG, TFF3, MET, NR4A1, DDIT4, RORa, AURKA, WT1, SNAI1, SNAI2, TCF3, VIM, ZEB1, ZEB2, BNIP3, NDRG4, PPP5C, MCL1, NPM1, GPI, ANGPTL4, CTSC, L1CAM, LGALS1, LOX, LOXL2, LOXL4, MMP1, MMP2, MMP9, MMP14, PLAUR, STC2, TWIST1*
mTOR pathway	*TSC1, TSC2, RHEB, RPTOR, AK1S1, MTOR, DEPTOR, MLST8, TEL2, TTI1, CLIP-170, GRB10, LIPIN1, ATG1, EIF4EBP1, RPS6KB1, MAPKAP1, RICTOR, PRR5, PRR5L, PRKAA2, PRKAB1, PRKAG1, DDIT4, AKT1, AKT2, AKT3*
Peroxisome	*PEX1, PEX2, PEX3, PEX5, PEX6, PEX7, PEX10, PEX12, PEX13, PEX14, PEX26, PHYH, CAT, AGXT, ACOX1, HSD17B4, GNPAT, ABCD1, AMACR, AGPS, TRIM37*
ISR	*EIF2A, EIF2B2, EIF2AK1, EIF2AK2, EIF2AK3, EIF2AK4, ATF3, ATF4, ATF5, ATF6, DDIT3, PPP1R15A, FGF21, GDF15, XBP1, SESN2, SCAF1*



Supplementary Figure 1. All cross-mission genes involved in rodent skin spaceflight response. A heatmap showing regulatory changes of all cross-mission genes (genes that are significantly (FDR ≤ 0.1) differentially expressed between flight and ground control across multiple missions) within each rodent data subset.



Supplementary Figure 2. The profile of all the cross-mission genes in astronauts. a) Heatmap showing t-score in orthologs of the rodent skin cross-mission genes in astronaut blood samples from sorted cell fractions from the NASA Twin Study. **b)** Heatmap showing $\log_2$ fold-change in orthologs of the rodent skin cross-mission genes in plasma samples at different time points from the JAXA CFE astronaut study. **c)** Heatmap showing average scaled expression in orthologs of the rodent skin cross-mission genes in astronaut PBMC data from the Inspiration4 mission at different timepoints.



Supplementary Figure 3. The profile of subset of the skin health genes in astronauts. a) Heatmap showing t-score in orthologs of the rodent skin, skin health genes (from **Fig. 5**) in astronaut blood samples from sorted cell fractions from the NASA Twin Study. **b)** Heatmap showing $\log_2$ fold-change in orthologs of the rodent skin, skin health genes (from **Fig. 5**) in plasma samples at different time points from the JAXA CFE astronaut study. **c)** Heatmap showing average scaled expression in orthologs of the rodent skin, skin health genes (from **Fig. 5**) in astronaut PBMC data from the Inspiration4 mission at different timepoints.