# Intestinal epithelial cells adapt to chronic inflammation through partial genetic reprogramming.

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## Supplementary Materiel and Methods

### *In silico* analysis for validation of the experimental OSAP

Raw data from CEL files were processed using quantile normalization and the robust multi-array average (RMA) algorithm, and were log2 transformed[1]. In order to improve the precision and accuracy the probe set estimates used for our analysis[2,3], updated Affymetrix probe set definitions of the CDF file version 18 (released on Jan 23, 2014) available on the BrainArray web database were downloaded. Gene annotation corresponding to the NCBI ("Entrez Gene")[4] was used. Hierarchical Clustering Analysis and Principal Component Analysis (PCA) were performed using expression data in order to provide an overview of the data, especially to visualize the distribution of both samples according to the expression of OSAP. Unsupervised hierarchical clustering using the Pearson correlation and Ward linkage method was computed. The 2 first components of PCA were used. The single-sample GSEA (ssGSEA) projection methodology from GenePattern[5], an extension of GSEA that enabled the computing of separate enrichment scores for sample/signature pair (e.g., tumor versus normal), was also used. The gene expression values for a given sample were rank-normalized, and an enrichment score was produced using the Empirical Cumulative Distribution Functions (ECDF) of the genes in the signature and the remaining genes[6,7]. Before running ssGSEA, we used the "Collapse Dataset" module from GenePAttern, in order to collapse all probe set

expression values for a given gene into a single expression value (according to the median). Using the human expression datasets downloaded from public repositories, the OSAP scores were calculated for each sample. The immune signature[8] and the two intestinal stem cell signatures Lgr5-GFP$^{high}$ and EphB2$^{high}$ [9] were similarly scored in each sample and the correlation between these signatures and the assessed OSAP was assessed using a Spearman correlation. The Spearman Correlation Coefficient (r) was also estimated to measure the strength of an association between two continuous variables. The Spearman correlation coefficient r can take a range of values from +1 (positive association) to -1 (negative association). Stem-like signature was defined on the basis of the 177 genes enriched in the Stem-like (expression value >0.2) subgroup with respect to the inflammatory, goblet-like, enterocyte and TA molecular subgroups.

**Nuclear extractions**

Cells were washed with 1X PBS and resuspended in 200 µL of a 10 mM Hepes pH 7.5, 10 mM KCl, 0.1 mM EDTA, 0.5% NP40 buffer supplemented with protease inhibitors (Roche). After 20 min in ice, cells were pelleted by centrifugation and the supernatant defined as the cytoplasmic fraction. After an additional wash in the extraction buffer, cell pellets were resuspended in 100 µL of a 20 mM Hepes pH 7.5, 400 mM NaCl, 1 mM EDTA supplemented with protease inhibitors. After 30 min in ice, samples were sonicated and cleared by centrifugation. Supernatants constitute the nuclear fraction. α-tubulin and phosho-Serine 10 histone H3 were used as cytoplasmic and nuclear protein control, respectively.

**List of primers used to assess gene expression by qRT-PCR**

| ID | Name | Sequence |
|---|---|---|
| NM_000041 | *APOE* | 5'-TGGACAAGTCTGGGATCCTT-3' |
| | | 5'-CATCTTCCTGCCTGTGATTG-3' |
| NM_014298 | *QPRT* | 5'-GTCACCATGGACGCTGAA-3' |
| | | 5'-GAGCCAGCTGTCACCAG-3' |
| NM_000194.1 | *HPRT1* | 5'-TGACCTTGATTTATTTTGCATACC-3' |
| | | 5'-CGAGCAAGACGTTCAGTCCT-3' |
| NM_000474.3 | *TWIST1* | 5'-GGCTCAGCTACGCCTCTC-3' |
| | | 5'-CCTTCTCTGGAAACAATGACATCT-3' |
| NM_057179 | *TWIST2* | 5'-CATGTCCGCCTCCCACTA-3' |
| | | 5'-GCATCATTCAGAATCTCCTCCT-3' |
| NM_001128128.1 | *ZEB1* | 5'-AACTGCTGGGAGGATGACAC-3' |
| | | 5'-TCCTGCTTCATCTGCCTGA-3' |
| NM_014795.2 | *ZEB2* | 5'-AAGCCAGGGACAGATCAGC-3' |
| | | 5'-GCCACACTCTGTGCATTTGA-3' |
| NM_005985 | *SNAI1* | 5'-GCTGCAGGACTCTAATCCAGA-3' |
| | | 5'-ATCTCCGGAGGTGGGATG-3' |
| NM_003068 | *SNAI2* | 5'-TGGTTGCTTCAAGGACACAT-3' |
| | | 5'-GTTGCAGTGAGGGCAAGAA-3' |
| NM_011546 | *Zeb1* | 5'-GCCAGCAGTCATGATGAAAA-3' |
| | | 5'-TATCACAATACGGGCAGGTG-3' |
| NM_015753 | *Zeb2* | 5'-CCAGAGGAAACAAGGATTTCAG-3' |
| | | 5'-AGGCCTGACATGTAGTCTTGTG-3' |

**Supplementary references**


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**Supplementary Figure legend**

**Figure S1:**

**A. Confirmation of the ectopic expression of murine Zeb transcripts by qRT-PCR**

Analysis of the ectopic expression of murine *Zeb1* and *Zeb2* in transduced HCEC-hTERT cells. Left panel: ectopic expression was assessed by qRT-PCR (Ct values are presented). Student's t-test, mean and SD of one experiment performed in triplicates are shown. Right panels: analysis of ectopic ZEB1 or ZEB2 protein by Western blot. Immortalized human mammary epithelial cells transduced with *Zeb2* were used as a positive protein detection control (*).

**B. NF-κB is aberrantly activated in parental HCEC-hTERT cells**

Analysis of the subcellular distribution of p65 NF-κB (p65) in parental HCEC-hTERT cells as assessed by Western blot. The significant detection of p65 in the nuclear compartment indicates an elevated NF-κB activity level at the steady state. Distribution of α-tubulin and phospho-Serine 10 histone H3 (PSer10-H3) is used as internal controls of the quality of the cytoplasmic and nuclear fractionation. C: cytoplasmic compartment, N: nuclear compartment.

**Figure S2**. **Several OSAP-associated proteins contribute to cell adaptation to stress**

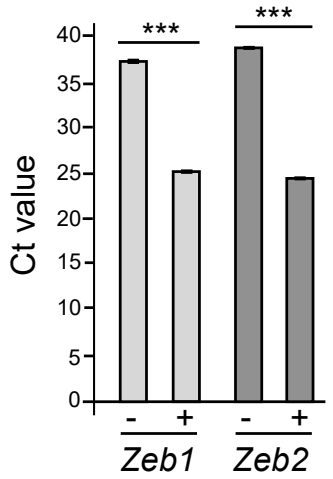
(**A**) Ectopic expression of *QPRT* or *APOE* facilitates the escape from chronic inflammation-induced (+ AMS, left panel) or chemical peroxide-induced (+ TBHP, right panel) senescence, as assessed in a crystal violet assay (top panels). (**B**) Analysis of ectopically produced QPRT

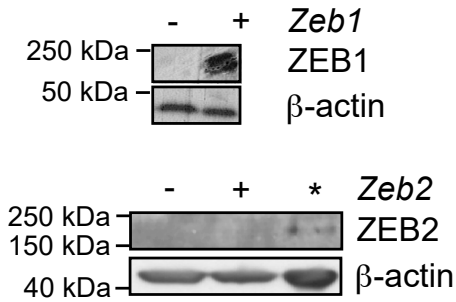
and APOE proteins in HCEC-hTERT cells transduced with *APOE* or *QPRT* respectively by Western-blot.

**Table S1:** Enriched GOBP pathways from OSAP down-regulated genes

**Table S2:** Enriched GOBP pathways from OSAP up-regulated genes

A.


***
***
40
35
30
25
20
15
10
5
0
Ct value
-
+
-
+
Zeb1
Zeb2


-
+
Zeb1
250 kDa
ZEB1
50 kDa
β-actin
-
+
*
Zeb2
250 kDa
150 kDa
ZEB2
40 kDa
β-actin

B.

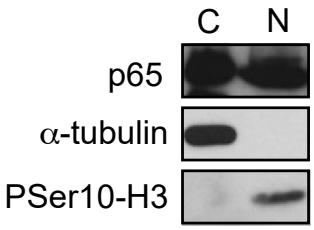
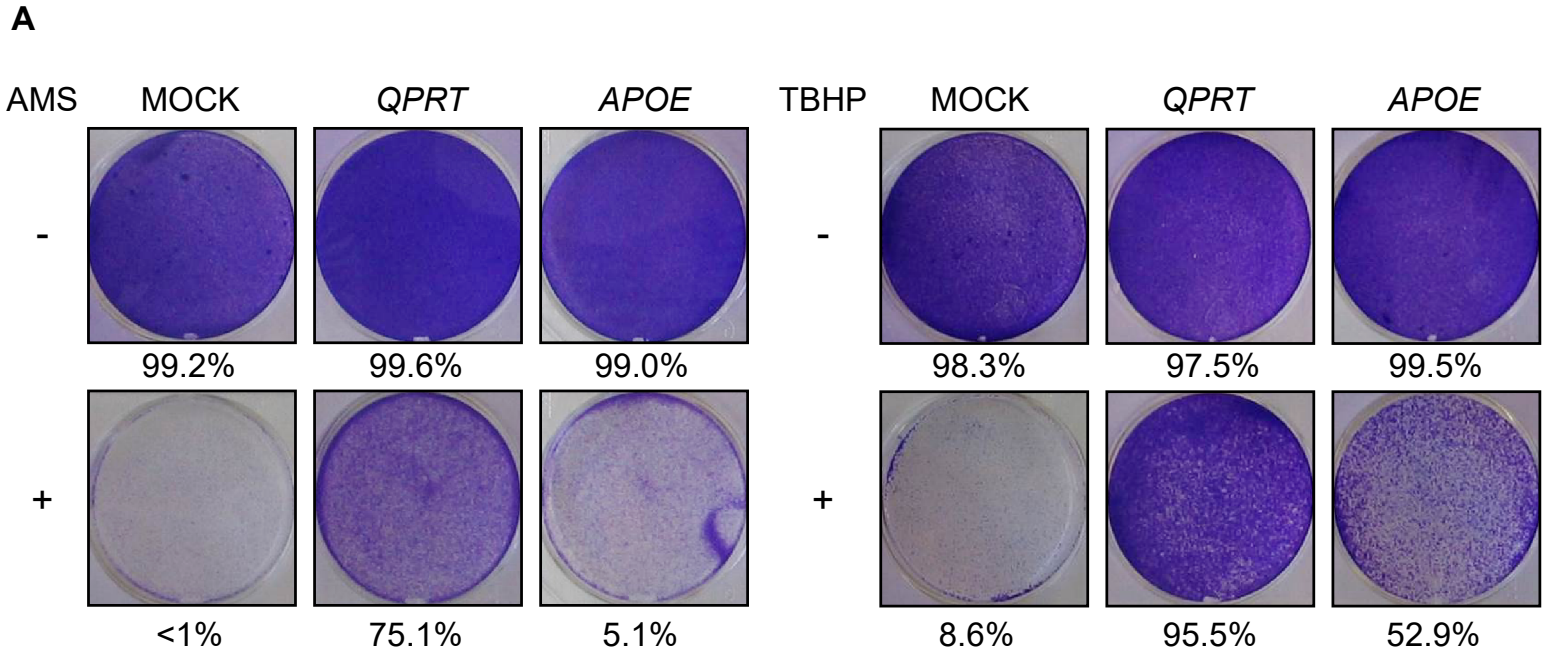

C
N
p65
α-tubulin
PSer10-H3

Figure S1


A
AMS
MOCK
QPRT
APOE
TBHP
MOCK
QPRT
APOE
-
99.2%
99.6%
99.0%
98.3%
97.5%
99.5%
+
<1%
75.1%
5.1%
8.6%
95.5%
52.9%

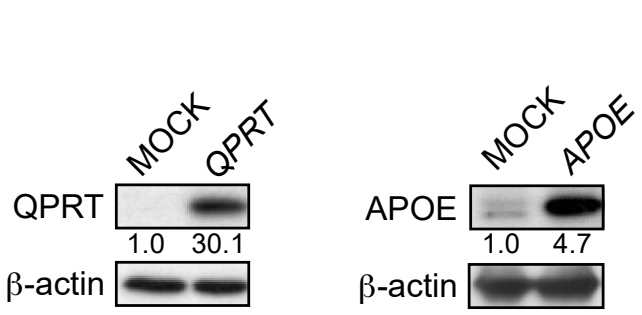

B
MOCK
QPRT
QPRT
1.0
30.1
β-actin
MOCK
APOE
APOE
1.0
4.7
β-actin

Figure S2

**Table S1**

| | Description | BgRatio | p.adjust |
|---|---|---|---|
| GOBP_RESPONSE_TO_MOLECULE_OF_BACTERIAL_ORIGIN | GOBP_RESPONSE_TO_MOLECULE_OF_BACTERIAL_ORIGIN | 354/17872 | 1.83E-06 |
| GOBP_CYTOKINE_MEDIATED_SIGNALING_PATHWAY | GOBP_CYTOKINE_MEDIATED_SIGNALING_PATHWAY | 485/17872 | 1.42E-05 |
| GOBP_CELLULAR_RESPONSE_TO_MOLECULE_OF_BACTERIAL_ORIGIN | GOBP_CELLULAR_RESPONSE_TO_MOLECULE_OF_BACTERIAL_ORIGIN | 229/17872 | 1.55E-05 |
| GOBP_CELLULAR_RESPONSE_TO_BIOTIC_STIMULUS | GOBP_CELLULAR_RESPONSE_TO_BIOTIC_STIMULUS | 256/17872 | 2.50E-05 |
| GOBP_I_KAPPAB_KINASE_NF_KAPPAB_SIGNALING | GOBP_I_KAPPAB_KINASE_NF_KAPPAB_SIGNALING | 288/17872 | 4.46E-05 |
| GOBP_NEUTROPHIL_CHEMOTAXIS | GOBP_NEUTROPHIL_CHEMOTAXIS | 105/17872 | 9.73E-05 |
| GOBP_LEUKOCYTE_CHEMOTAXIS | GOBP_LEUKOCYTE_CHEMOTAXIS | 236/17872 | 1.57E-04 |
| GOBP_GRANULOCYTE_CHEMOTAXIS | GOBP_GRANULOCYTE_CHEMOTAXIS | 127/17872 | 1.57E-04 |
| GOBP_NEUTROPHIL_MIGRATION | GOBP_NEUTROPHIL_MIGRATION | 128/17872 | 1.57E-04 |
| GOBP_LEUKOCYTE_MIGRATION | GOBP_LEUKOCYTE_MIGRATION | 385/17872 | 1.57E-04 |
| GOBP_CHRONIC_INFLAMMATORY_RESPONSE | GOBP_CHRONIC_INFLAMMATORY_RESPONSE | 17/17872 | 2.36E-04 |
| GOBP_GRANULOCYTE_MIGRATION | GOBP_GRANULOCYTE_MIGRATION | 154/17872 | 2.99E-04 |
| GOBP_POSITIVE_REGULATION_OF_NF_KAPPAB_TRANSCRIPTION_FACTOR_ACTIVITY | GOBP_POSITIVE_REGULATION_OF_NF_KAPPAB_TRANSCRIPTION_FACTOR_ACTIVITY | 154/17872 | 2.99E-04 |
| GOBP_REGULATION_OF_DNA_BINDING_TRANSCRIPTION_FACTOR_ACTIVITY | GOBP_REGULATION_OF_DNA_BINDING_TRANSCRIPTION_FACTOR_ACTIVITY | 451/17872 | 3.21E-04 |
| GOBP_ANTIMICROBIAL_HUMORAL_IMMUNE_RESPONSE_MEDIATED_BY_ANTIMICROBIAL_PEPTIDE | GOBP_ANTIMICROBIAL_HUMORAL_IMMUNE_RESPONSE_MEDIATED_BY_ANTIMICROBIAL_PEPTID | 79/17872 | 4.83E-04 |
| GOBP_CELL_CHEMOTAXIS | GOBP_CELL_CHEMOTAXIS | 315/17872 | 4.88E-04 |
| GOBP_RESPONSE_TO_CHEMOKINE | GOBP_RESPONSE_TO_CHEMOKINE | 96/17872 | 9.26E-04 |
| GOBP_MYELOID_LEUKOCYTE_MIGRATION | GOBP_MYELOID_LEUKOCYTE_MIGRATION | 230/17872 | 1.52E-03 |
| GOBP_ANTIMICROBIAL_HUMORAL_RESPONSE | GOBP_ANTIMICROBIAL_HUMORAL_RESPONSE | 123/17872 | 2.20E-03 |
| GOBP_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY | GOBP_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY | 126/17872 | 2.30E-03 |
| GOBP_POSITIVE_REGULATION_OF_DNA_BINDING_TRANSCRIPTION_FACTOR_ACTIVITY | GOBP_POSITIVE_REGULATION_OF_DNA_BINDING_TRANSCRIPTION_FACTOR_ACTIVITY | 264/17872 | 2.52E-03 |
| GOBP_HUMORAL_IMMUNE_RESPONSE | GOBP_HUMORAL_IMMUNE_RESPONSE | 312/17872 | 5.16E-03 |
| GOBP_POSITIVE_REGULATION_OF_HEPATOCYTE_PROLIFERATION | GOBP_POSITIVE_REGULATION_OF_HEPATOCYTE_PROLIFERATION | 10/17872 | 5.16E-03 |
| GOBP_REGULATION_OF_CHRONIC_INFLAMMATORY_RESPONSE | GOBP_REGULATION_OF_CHRONIC_INFLAMMATORY_RESPONSE | 10/17872 | 5.16E-03 |
| GOBP_LIPOPOLYSACCHARIDE_MEDIATED_SIGNALING_PATHWAY | GOBP_LIPOPOLYSACCHARIDE_MEDIATED_SIGNALING_PATHWAY | 62/17872 | 5.53E-03 |
| GOBP_POSITIVE_REGULATION_OF_CELL_CELL_ADHESION_MEDIATED_BY_CADHERIN | GOBP_POSITIVE_REGULATION_OF_CELL_CELL_ADHESION_MEDIATED_BY_CADHERIN | 11/17872 | 5.71E-03 |
| GOBP_INTERLEUKIN_6_PRODUCTION | GOBP_INTERLEUKIN_6_PRODUCTION | 172/17872 | 5.71E-03 |
| GOBP_POSITIVE_REGULATION_OF_MONONUCLEAR_CELL_MIGRATION | GOBP_POSITIVE_REGULATION_OF_MONONUCLEAR_CELL_MIGRATION | 66/17872 | 5.95E-03 |
| GOBP_POSITIVE_REGULATION_OF_HAIR_FOLLICLE_DEVELOPMENT | GOBP_POSITIVE_REGULATION_OF_HAIR_FOLLICLE_DEVELOPMENT | 12/17872 | 6.12E-03 |
| GOBP_PATTERN_RECOGNITION_RECEPTOR_SIGNALING_PATHWAY | GOBP_PATTERN_RECOGNITION_RECEPTOR_SIGNALING_PATHWAY | 180/17872 | 6.12E-03 |
| GOBP_POSITIVE_REGULATION_OF_CHEMOKINE_PRODUCTION | GOBP_POSITIVE_REGULATION_OF_CHEMOKINE_PRODUCTION | 70/17872 | 6.40E-03 |
| GOBP_REGULATION_OF_NUCLEOTIDE_BINDING_OLIGOMERIZATION_DOMAIN_CONTAINING_SIGNALING_PATHWAY | GOBP_REGULATION_OF_NUCLEOTIDE_BINDING_OLIGOMERIZATION_DOMAIN_CONTAINING_SIGN | 13/17872 | 6.58E-03 |
| GOBP_POSITIVE_REGULATION_OF_I_KAPPAB_KINASE_NF_KAPPAB_SIGNALING | GOBP_POSITIVE_REGULATION_OF_I_KAPPAB_KINASE_NF_KAPPAB_SIGNALING | 188/17872 | 6.58E-03 |
| GOBP_REGULATION_OF_SECONDARY_METABOLIC_PROCESS | GOBP_REGULATION_OF_SECONDARY_METABOLIC_PROCESS | 14/17872 | 7.13E-03 |
| GOBP_REGULATION_OF_VASCULAR_WOUND_HEALING | GOBP_REGULATION_OF_VASCULAR_WOUND_HEALING | 14/17872 | 7.13E-03 |
| GOBP_REGULATION_OF_HEPATOCYTE_PROLIFERATION | GOBP_REGULATION_OF_HEPATOCYTE_PROLIFERATION | 15/17872 | 7.99E-03 |
| GOBP_L_GLUTAMATE_IMPORT_ACROSS_PLASMA_MEMBRANE | GOBP_L_GLUTAMATE_IMPORT_ACROSS_PLASMA_MEMBRANE | 16/17872 | 8.80E-03 |
| GOBP_RESPONSE_TO_VIRUS | GOBP_RESPONSE_TO_VIRUS | 391/17872 | 8.80E-03 |
| GOBP_REGULATION_OF_INFLAMMATORY_RESPONSE | GOBP_REGULATION_OF_INFLAMMATORY_RESPONSE | 397/17872 | 9.20E-03 |
| GOBP_LEUKOCYTE_MIGRATION_INVOLVED_IN_INFLAMMATORY_RESPONSE | GOBP_LEUKOCYTE_MIGRATION_INVOLVED_IN_INFLAMMATORY_RESPONSE | 19/17872 | 1.11E-02 |
| GOBP_REGULATION_OF_HAIR_FOLLICLE_DEVELOPMENT | GOBP_REGULATION_OF_HAIR_FOLLICLE_DEVELOPMENT | 19/17872 | 1.11E-02 |
| GOBP_REGULATION_OF_INNATE_IMMUNE_RESPONSE | GOBP_REGULATION_OF_INNATE_IMMUNE_RESPONSE | 230/17872 | 1.11E-02 |
| GOBP_REGULATION_OF_CYSTEINE_TYPE_ENDOPEPTIDASE_ACTIVITY | GOBP_REGULATION_OF_CYSTEINE_TYPE_ENDOPEPTIDASE_ACTIVITY | 232/17872 | 1.11E-02 |
| GOBP_POSITIVE_REGULATION_OF_JNK_CASCADE | GOBP_POSITIVE_REGULATION_OF_JNK_CASCADE | 95/17872 | 1.11E-02 |
| GOBP_RESPONSE_TO_MURAMYL_DIPEPTIDE | GOBP_RESPONSE_TO_MURAMYL_DIPEPTIDE | 20/17872 | 1.11E-02 |
| GOBP_TOLL_LIKE_RECEPTOR_3_SIGNALING_PATHWAY | GOBP_TOLL_LIKE_RECEPTOR_3_SIGNALING_PATHWAY | 20/17872 | 1.11E-02 |
| GOBP_POSITIVE_REGULATION_OF_INTERLEUKIN_6_PRODUCTION | GOBP_POSITIVE_REGULATION_OF_INTERLEUKIN_6_PRODUCTION | 97/17872 | 1.11E-02 |
| GOBP_CHEMOKINE_PRODUCTION | GOBP_CHEMOKINE_PRODUCTION | 98/17872 | 1.12E-02 |
| GOBP_REGULATION_OF_CELL_CELL_ADHESION_MEDIATED_BY_CADHERIN | GOBP_REGULATION_OF_CELL_CELL_ADHESION_MEDIATED_BY_CADHERIN | 21/17872 | 1.17E-02 |
| GOBP_RESPONSE_TO_TUMOR_NECROSIS_FACTOR | GOBP_RESPONSE_TO_TUMOR_NECROSIS_FACTOR | 248/17872 | 1.23E-02 |
| GOBP_VASCULAR_WOUND_HEALING | GOBP_VASCULAR_WOUND_HEALING | 22/17872 | 1.23E-02 |
| GOBP_LIVER_MORPHOGENESIS | GOBP_LIVER_MORPHOGENESIS | 23/17872 | 1.31E-02 |
| GOBP_TUMOR_NECROSIS_FACTOR_MEDIATED_SIGNALING_PATHWAY | GOBP_TUMOR_NECROSIS_FACTOR_MEDIATED_SIGNALING_PATHWAY | 107/17872 | 1.31E-02 |
| GOBP_SECONDARY_METABOLITE_BIOSYNTHETIC_PROCESS | GOBP_SECONDARY_METABOLITE_BIOSYNTHETIC_PROCESS | 25/17872 | 1.51E-02 |
| GOBP_MOLTING_CYCLE | GOBP_MOLTING_CYCLE | 114/17872 | 1.52E-02 |
| GOBP_REGULATION_OF_MONONUCLEAR_CELL_MIGRATION | GOBP_REGULATION_OF_MONONUCLEAR_CELL_MIGRATION | 116/17872 | 1.55E-02 |
| GOBP_NUCLEOTIDE_BINDING_DOMAIN_LEUCINE_RICH_REPEAT_CONTAINING_RECEPTOR_SIGNALING_PATHWAY | GOBP_NUCLEOTIDE_BINDING_DOMAIN_LEUCINE_RICH_REPEAT_CONTAINING_RECEPTOR_SIGNAL | 26/17872 | 1.55E-02 |
| GOBP_CELLULAR_RESPONSE_TO_INTERFERON_GAMMA | GOBP_CELLULAR_RESPONSE_TO_INTERFERON_GAMMA | 117/17872 | 1.55E-02 |
| GOBP_POSITIVE_REGULATION_OF_CYTOKINE_PRODUCTION_INVOLVED_IN_INFLAMMATORY_RESPONSE | GOBP_POSITIVE_REGULATION_OF_CYTOKINE_PRODUCTION_INVOLVED_IN_INFLAMMATORY_RESI | 27/17872 | 1.61E-02 |
| GOBP_CELL_CELL_ADHESION_MEDIATED_BY_CADHERIN | GOBP_CELL_CELL_ADHESION_MEDIATED_BY_CADHERIN | 28/17872 | 1.68E-02 |
| GOBP_REGULATION_OF_HAIR_CYCLE | GOBP_REGULATION_OF_HAIR_CYCLE | 28/17872 | 1.68E-02 |
| GOBP_GLAND_MORPHOGENESIS | GOBP_GLAND_MORPHOGENESIS | 123/17872 | 1.68E-02 |
| GOBP_POSITIVE_REGULATION_OF_DEFENSE_RESPONSE | GOBP_POSITIVE_REGULATION_OF_DEFENSE_RESPONSE | 288/17872 | 1.71E-02 |
| GOBP_L_GLUTAMATE_TRANSMEMBRANE_TRANSPORT | GOBP_L_GLUTAMATE_TRANSMEMBRANE_TRANSPORT | 29/17872 | 1.71E-02 |
| GOBP_REGULATION_OF_EPITHELIAL_CELL_MIGRATION | GOBP_REGULATION_OF_EPITHELIAL_CELL_MIGRATION | 291/17872 | 1.74E-02 |
| GOBP_INTERLEUKIN_1_PRODUCTION | GOBP_INTERLEUKIN_1_PRODUCTION | 130/17872 | 1.84E-02 |
| GOBP_ANGIOGENESIS_INVOLVED_IN_WOUND_HEALING | GOBP_ANGIOGENESIS_INVOLVED_IN_WOUND_HEALING | 31/17872 | 1.84E-02 |
| GOBP_POSITIVE_REGULATION_OF_T_CELL_MIGRATION | GOBP_POSITIVE_REGULATION_OF_T_CELL_MIGRATION | 31/17872 | 1.84E-02 |
| GOBP_POSITIVE_REGULATION_OF_STRESS_ACTIVATED_PROTEIN_KINASE_SIGNALING_CASCADE | GOBP_POSITIVE_REGULATION_OF_STRESS_ACTIVATED_PROTEIN_KINASE_SIGNALING_CASCADE | 133/17872 | 1.89E-02 |
| GOBP_NEGATIVE_REGULATION_OF_CELL_JUNCTION_ASSEMBLY | GOBP_NEGATIVE_REGULATION_OF_CELL_JUNCTION_ASSEMBLY | 32/17872 | 1.91E-02 |
| GOBP_NEURON_DEATH_IN_RESPONSE_TO_OXIDATIVE_STRESS | GOBP_NEURON_DEATH_IN_RESPONSE_TO_OXIDATIVE_STRESS | 33/17872 | 2.00E-02 |
| GOBP_RESPONSE_TO_INTERFERON_GAMMA | GOBP_RESPONSE_TO_INTERFERON_GAMMA | 139/17872 | 2.06E-02 |
| GOBP_POSITIVE_REGULATION_OF_LEUKOCYTE_MIGRATION | GOBP_POSITIVE_REGULATION_OF_LEUKOCYTE_MIGRATION | 141/17872 | 2.09E-02 |
| GOBP_REGULATION_OF_JNK_CASCADE | GOBP_REGULATION_OF_JNK_CASCADE | 141/17872 | 2.09E-02 |
| GOBP_POSITIVE_REGULATION_OF_INFLAMMATORY_RESPONSE | GOBP_POSITIVE_REGULATION_OF_INFLAMMATORY_RESPONSE | 145/17872 | 2.23E-02 |
| GOBP_POSITIVE_REGULATION_OF_CYSTEINE_TYPE_ENDOPEPTIDASE_ACTIVITY | GOBP_POSITIVE_REGULATION_OF_CYSTEINE_TYPE_ENDOPEPTIDASE_ACTIVITY | 146/17872 | 2.24E-02 |
| GOBP_POSITIVE_REGULATION_OF_LYMPHOCYTE_MIGRATION | GOBP_POSITIVE_REGULATION_OF_LYMPHOCYTE_MIGRATION | 37/17872 | 2.32E-02 |
| GOBP_CELLULAR_RESPONSE_TO_CHEMICAL_STRESS | GOBP_CELLULAR_RESPONSE_TO_CHEMICAL_STRESS | 334/17872 | 2.42E-02 |
| GOBP_REGULATION_OF_RESPONSE_TO_BIOTIC_STIMULUS | GOBP_REGULATION_OF_RESPONSE_TO_BIOTIC_STIMULUS | 350/17872 | 2.84E-02 |
| GOBP_NEURON_DEATH | GOBP_NEURON_DEATH | 352/17872 | 2.86E-02 |
| GOBP_ASTROCYTE_DEVELOPMENT | GOBP_ASTROCYTE_DEVELOPMENT | 43/17872 | 2.94E-02 |
| GOBP_POSITIVE_REGULATION_OF_JUN_KINASE_ACTIVITY | GOBP_POSITIVE_REGULATION_OF_JUN_KINASE_ACTIVITY | 43/17872 | 2.94E-02 |
| GOBP_DEFENSE_RESPONSE_TO_BACTERIUM | GOBP_DEFENSE_RESPONSE_TO_BACTERIUM | 361/17872 | 3.00E-02 |
| GOBP_REGULATION_OF_T_CELL_MIGRATION | GOBP_REGULATION_OF_T_CELL_MIGRATION | 44/17872 | 3.00E-02 |
| GOBP_AMINO_ACID_IMPORT_ACROSS_PLASMA_MEMBRANE | GOBP_AMINO_ACID_IMPORT_ACROSS_PLASMA_MEMBRANE | 45/17872 | 3.10E-02 |
| GOBP_TISSUE_MIGRATION | GOBP_TISSUE_MIGRATION | 368/17872 | 3.13E-02 |
| GOBP_JNK_CASCADE | GOBP_JNK_CASCADE | 175/17872 | 3.19E-02 |
| GOBP_ACID_SECRETION | GOBP_ACID_SECRETION | 47/17872 | 3.19E-02 |
| GOBP_MEMBRANE_PROTEIN_ECTODOMAIN_PROTEOLYSIS | GOBP_MEMBRANE_PROTEIN_ECTODOMAIN_PROTEOLYSIS | 47/17872 | 3.19E-02 |
| GOBP_PHENOL_CONTAINING_COMPOUND_BIOSYNTHETIC_PROCESS | GOBP_PHENOL_CONTAINING_COMPOUND_BIOSYNTHETIC_PROCESS | 47/17872 | 3.19E-02 |
| GOBP_SENSORY_PERCEPTION_OF_MECHANICAL_STIMULUS | GOBP_SENSORY_PERCEPTION_OF_MECHANICAL_STIMULUS | 177/17872 | 3.25E-02 |
| GOBP_REGULATION_OF_RESPONSE_TO_CYTOKINE_STIMULUS | GOBP_REGULATION_OF_RESPONSE_TO_CYTOKINE_STIMULUS | 178/17872 | 3.27E-02 |
| GOBP_PROGRAMMED_NECROTIC_CELL_DEATH | GOBP_PROGRAMMED_NECROTIC_CELL_DEATH | 49/17872 | 3.32E-02 |
| GOBP_RESPONSE_TO_NICOTINE | GOBP_RESPONSE_TO_NICOTINE | 49/17872 | 3.32E-02 |
| GOBP_REGULATION_OF_MORPHOGENESIS_OF_A_BRANCHING_STRUCTURE | GOBP_REGULATION_OF_MORPHOGENESIS_OF_A_BRANCHING_STRUCTURE | 51/17872 | 3.55E-02 |
| GOBP_REGULATION_OF_ADAPTIVE_IMMUNE_RESPONSE | GOBP_REGULATION_OF_ADAPTIVE_IMMUNE_RESPONSE | 188/17872 | 3.62E-02 |
| GOBP_TUMOR_NECROSIS_FACTOR_SUPERFAMILY_CYTOKINE_PRODUCTION | GOBP_TUMOR_NECROSIS_FACTOR_SUPERFAMILY_CYTOKINE_PRODUCTION | 188/17872 | 3.62E-02 |
| GOBP_DEFENSE_RESPONSE_TO_FUNGUS | GOBP_DEFENSE_RESPONSE_TO_FUNGUS | 53/17872 | 3.72E-02 |
| GOBP_AMINO_ACID_IMPORT | GOBP_AMINO_ACID_IMPORT | 54/17872 | 3.82E-02 |
| GOBP_POSITIVE_REGULATION_OF_PEPTIDASE_ACTIVITY | GOBP_POSITIVE_REGULATION_OF_PEPTIDASE_ACTIVITY | 195/17872 | 3.89E-02 |
| GOBP_MONONUCLEAR_CELL_MIGRATION | GOBP_MONONUCLEAR_CELL_MIGRATION | 199/17872 | 4.08E-02 |
| GOBP_MEMBRANE_PROTEIN_PROTEOLYSIS | GOBP_MEMBRANE_PROTEIN_PROTEOLYSIS | 58/17872 | 4.19E-02 |
| GOBP_REGULATION_OF_STRESS_ACTIVATED_PROTEIN_KINASE_SIGNALING_CASCADE | GOBP_REGULATION_OF_STRESS_ACTIVATED_PROTEIN_KINASE_SIGNALING_CASCADE | 203/17872 | 4.19E-02 |
| GOBP_RESPIRATORY_SYSTEM_DEVELOPMENT | GOBP_RESPIRATORY_SYSTEM_DEVELOPMENT | 203/17872 | 4.19E-02 |
| GOBP_NEGATIVE_REGULATION_OF_FAT_CELL_DIFFERENTIATION | GOBP_NEGATIVE_REGULATION_OF_FAT_CELL_DIFFERENTIATION | 59/17872 | 4.20E-02 |
| GOBP_POSITIVE_REGULATION_OF_NUCLEAR_DIVISION | GOBP_POSITIVE_REGULATION_OF_NUCLEAR_DIVISION | 59/17872 | 4.20E-02 |
| GOBP_SECONDARY_METABOLIC_PROCESS | GOBP_SECONDARY_METABOLIC_PROCESS | 59/17872 | 4.20E-02 |
| GOBP_REGULATION_OF_JUN_KINASE_ACTIVITY | GOBP_REGULATION_OF_JUN_KINASE_ACTIVITY | 60/17872 | 4.30E-02 |
| GOBP_POSITIVE_REGULATION_OF_EPITHELIAL_CELL_PROLIFERATION | GOBP_POSITIVE_REGULATION_OF_EPITHELIAL_CELL_PROLIFERATION | 209/17872 | 4.30E-02 |
| GOBP_WOUND_HEALING | GOBP_WOUND_HEALING | 431/17872 | 4.30E-02 |
| GOBP_CYTOPLASMIC_PATTERN_RECOGNITION_RECEPTOR_SIGNALING_PATHWAY | GOBP_CYTOPLASMIC_PATTERN_RECOGNITION_RECEPTOR_SIGNALING_PATHWAY | 61/17872 | 4.30E-02 |
| GOBP_RESPONSE_TO_OXIDATIVE_STRESS | GOBP_RESPONSE_TO_OXIDATIVE_STRESS | 436/17872 | 4.30E-02 |
| GOBP_POSITIVE_REGULATION_OF_INTERLEUKIN_1_BETA_PRODUCTION | GOBP_POSITIVE_REGULATION_OF_INTERLEUKIN_1_BETA_PRODUCTION | 62/17872 | 4.30E-02 |
| GOBP_POSITIVE_REGULATION_OF_INTERLEUKIN_8_PRODUCTION | GOBP_POSITIVE_REGULATION_OF_INTERLEUKIN_8_PRODUCTION | 62/17872 | 4.30E-02 |
| GOBP_REGULATION_OF_SYNAPSE_STRUCTURE_OR_ACTIVITY | GOBP_REGULATION_OF_SYNAPSE_STRUCTURE_OR_ACTIVITY | 213/17872 | 4.30E-02 |
| GOBP_ACIDIC_AMINO_ACID_TRANSPORT | GOBP_ACIDIC_AMINO_ACID_TRANSPORT | 63/17872 | 4.30E-02 |
| GOBP_INTERLEUKIN_2_PRODUCTION | GOBP_INTERLEUKIN_2_PRODUCTION | 63/17872 | 4.30E-02 |
| GOBP_LYMPHOCYTE_CHEMOTAXIS | GOBP_LYMPHOCYTE_CHEMOTAXIS | 63/17872 | 4.30E-02 |
| GOBP_REGULATION_OF_LYMPHOCYTE_MIGRATION | GOBP_REGULATION_OF_LYMPHOCYTE_MIGRATION | 63/17872 | 4.30E-02 |
| GOBP_POSITIVE_REGULATION_OF_RESPONSE_TO_EXTERNAL_STIMULUS | GOBP_POSITIVE_REGULATION_OF_RESPONSE_TO_EXTERNAL_STIMULUS | 441/17872 | 4.30E-02 |
| GOBP_RESPONSE_TO_FUNGUS | GOBP_RESPONSE_TO_FUNGUS | 64/17872 | 4.36E-02 |
| GOBP_POSITIVE_REGULATION_OF_CELL_ADHESION | GOBP_POSITIVE_REGULATION_OF_CELL_ADHESION | 446/17872 | 4.38E-02 |
| GOBP_REGULATION_OF_LEUKOCYTE_MIGRATION | GOBP_REGULATION_OF_LEUKOCYTE_MIGRATION | 219/17872 | 4.38E-02 |
| GOBP_REGULATION_OF_MORPHOGENESIS_OF_AN_EPITHELIUM | GOBP_REGULATION_OF_MORPHOGENESIS_OF_AN_EPITHELIUM | 65/17872 | 4.38E-02 |
| GOBP_POSITIVE_REGULATION_OF_ERK1_AND_ERK2_CASCADE | GOBP_POSITIVE_REGULATION_OF_ERK1_AND_ERK2_CASCADE | 223/17872 | 4.44E-02 |
| GOBP_CELLULAR_RESPONSE_TO_RETINOIC_ACID | GOBP_CELLULAR_RESPONSE_TO_RETINOIC_ACID | 67/17872 | 4.44E-02 |
| GOBP_ENDOTHELIAL_CELL_APOPTOTIC_PROCESS | GOBP_ENDOTHELIAL_CELL_APOPTOTIC_PROCESS | 67/17872 | 4.44E-02 |
| GOBP_L_ALPHA_AMINO_ACID_TRANSMEMBRANE_TRANSPORT | GOBP_L_ALPHA_AMINO_ACID_TRANSMEMBRANE_TRANSPORT | 67/17872 | 4.44E-02 |
| GOBP_NECROTIC_CELL_DEATH | GOBP_NECROTIC_CELL_DEATH | 67/17872 | 4.44E-02 |
| GOBP_T_CELL_MIGRATION | GOBP_T_CELL_MIGRATION | 67/17872 | 4.44E-02 |
| GOBP_REGULATION_OF_PEPTIDASE_ACTIVITY | GOBP_REGULATION_OF_PEPTIDASE_ACTIVITY | 457/17872 | 4.46E-02 |
| GOBP_AMYLOID_PRECURSOR_PROTEIN_CATABOLIC_PROCESS | GOBP_AMYLOID_PRECURSOR_PROTEIN_CATABOLIC_PROCESS | 68/17872 | 4.46E-02 |
| GOBP_PIGMENT_BIOSYNTHETIC_PROCESS | GOBP_PIGMENT_BIOSYNTHETIC_PROCESS | 68/17872 | 4.46E-02 |
| GOBP_L_AMINO_ACID_TRANSPORT | GOBP_L_AMINO_ACID_TRANSPORT | 69/17872 | 4.53E-02 |
| GOBP_NEGATIVE_REGULATION_OF_INTERLEUKIN_6_PRODUCTION | GOBP_NEGATIVE_REGULATION_OF_INTERLEUKIN_6_PRODUCTION | 69/17872 | 4.53E-02 |
| GOBP_REGULATION_OF_ENDOTHELIAL_CELL_MIGRATION | GOBP_REGULATION_OF_ENDOTHELIAL_CELL_MIGRATION | 231/17872 | 4.60E-02 |
| GOBP_POSITIVE_REGULATION_OF_PROTEIN_CATABOLIC_PROCESS | GOBP_POSITIVE_REGULATION_OF_PROTEIN_CATABOLIC_PROCESS | 234/17872 | 4.73E-02 |
| GOBP_POSITIVE_REGULATION_OF_INTERLEUKIN_1_PRODUCTION | GOBP_POSITIVE_REGULATION_OF_INTERLEUKIN_1_PRODUCTION | 73/17872 | 4.94E-02 |
| GOBP_IMMUNE_RESPONSE_REGULATING_SIGNALING_PATHWAY | GOBP_IMMUNE_RESPONSE_REGULATING_SIGNALING_PATHWAY | 479/17872 | 4.97E-02 |

**Table S2**

| | Description | BgRatio | p.adjust |
|---|---|---|---|
| GOBP_VASCULAR_PROCESS_IN_CIRCULATORY_SYSTEM | GOBP_VASCULAR_PROCESS_IN_CIRCULATORY_SYSTEM | 263/17872 | 1.34E-02 |
| GOBP_REGULATION_OF_VASCULAR_PERMEABILITY | GOBP_REGULATION_OF_VASCULAR_PERMEABILITY | 48/17872 | 1.34E-02 |
| GOBP_REGULATION_OF_SKELETAL_MUSCLE_ADAPTATION | GOBP_REGULATION_OF_SKELETAL_MUSCLE_ADAPTATION | 14/17872 | 3.68E-02 |
| GOBP_VASCULAR_TRANSPORT | GOBP_VASCULAR_TRANSPORT | 87/17872 | 3.68E-02 |
| GOBP_POSITIVE_REGULATION_OF_VASCULAR_PERMEABILITY | GOBP_POSITIVE_REGULATION_OF_VASCULAR_PERMEABILITY | 17/17872 | 3.68E-02 |