

Supplementary Materials

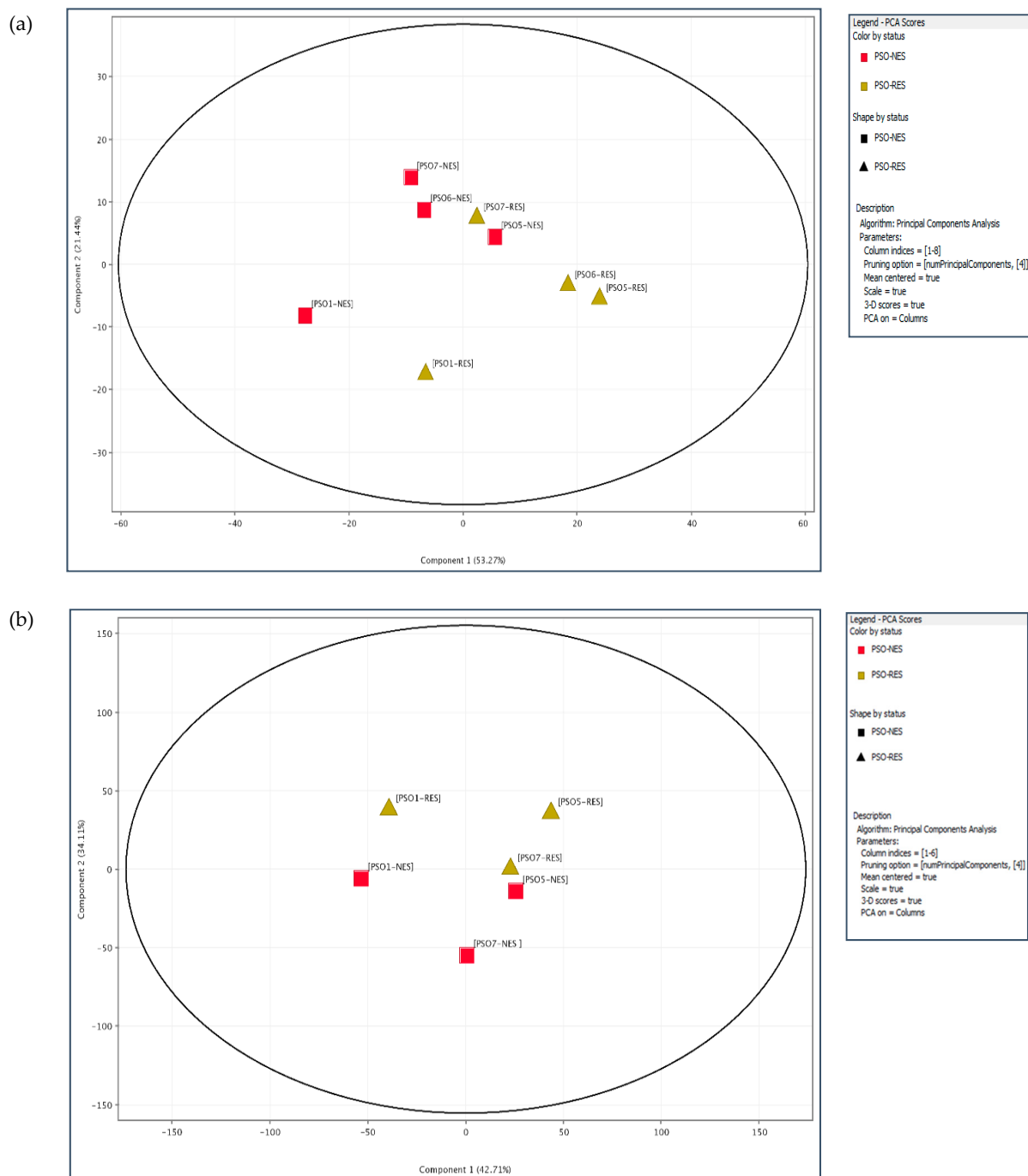


Figure S1. Principal component analysis (PCA). PCA plots of (a) epidermal and (b) dermal paired never-lesional and resolved samples. PCA was performed on resolved *vs.* never-lesional DEGs. Each point represents an experimental sample; colors and shapes indicate different types of samples. Abbreviations: RES, resolved skin; NES, never-lesional skin; DEG, differentially expressed genes.

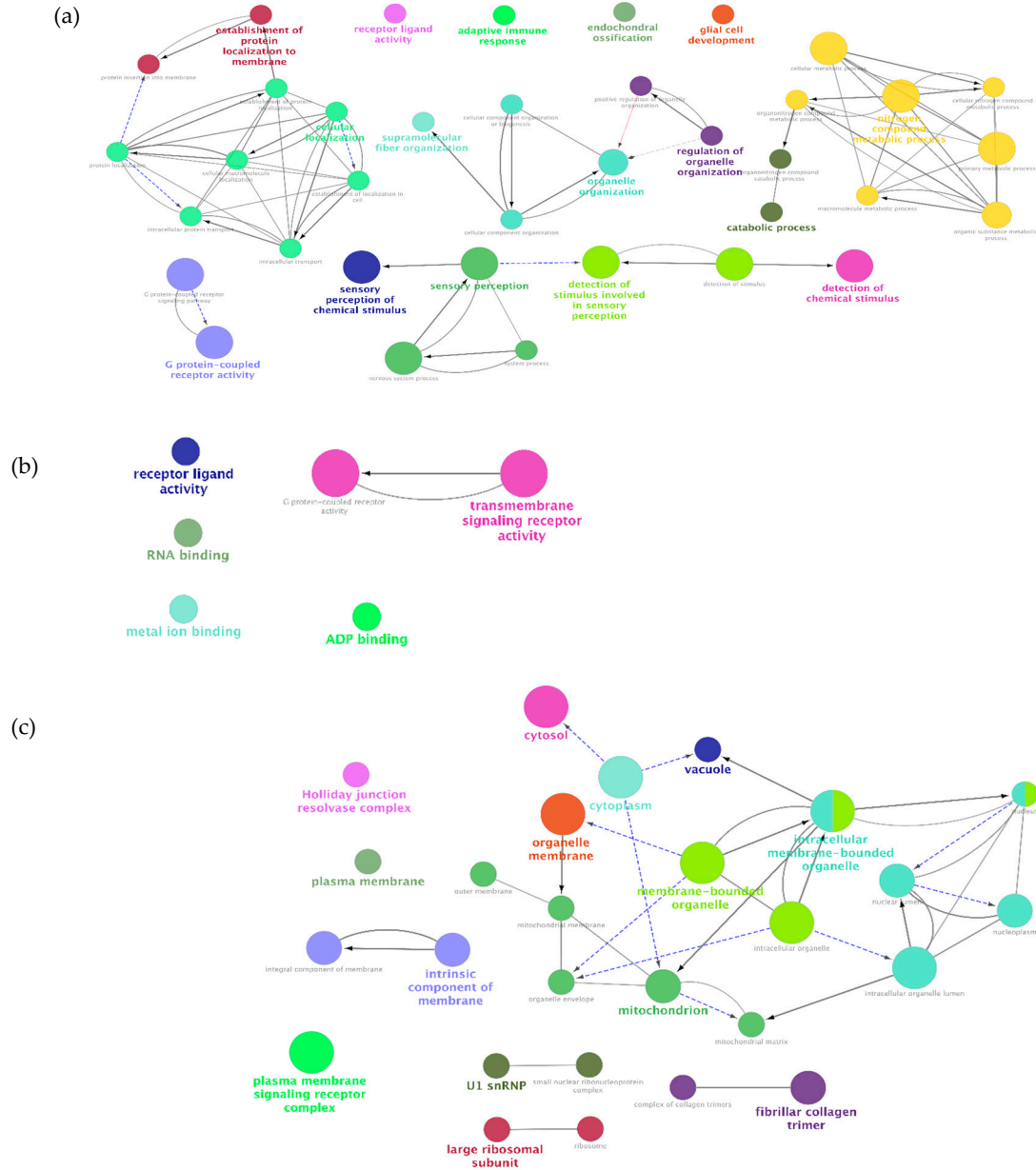


Figure S2. GO enrichment analysis of resolved *vs.* never-lesional DEGs in dermal compartments. Enrichment shows only significant (a) BPs, (b) MFs, and (c) CCs with $p < 0.05$. Node color represents the specific functional class, biological processes, and cellular components involved in the enrichment analysis of the identified DEGs. Bold fonts indicate the major BPs, MFs, or CCs that define the names of each group. Abbreviations: DEG, differentially expressed genes; BPs, biological processes; MFs, molecular functions; CCs, cellular components.

Table S1. List of the 102 overlapped genes between resolved *vs.* never-lesional DEGs and lesional *vs.* healthy DEGs in the epidermis.

| <i>Number</i> | <i>Gene symbol</i> | <i>Gene ID</i> | <i>P-value</i> | <i>Regulation</i> | <i>FC</i> | <i>Description</i> |
|---------------|--------------------|-----------------|----------------|-------------------|-----------|---|
| 1 | CACNA2D1 | ENSG00000153956 | 0.0029 | down | -2.49 | calcium voltage-gated channel auxiliary subunit alpha2delta 1 |
| 2 | ODF3L1 | ENSG00000182950 | 0.0290 | down | -2.05 | outer dense fiber of sperm tails 3 like 1 |
| 3 | WNT2 | ENSG00000105989 | 0.0430 | down | -2.03 | Wnt family member 2 |
| 4 | LIF | ENSG00000128342 | 0.0372 | down | -1.88 | leukemia inhibitory factor |
| 5 | TPPP | ENSG00000171368 | 0.0014 | down | -1.83 | tubulin polymerization promoting protein |
| 6 | LRRRC8C | ENSG00000171488 | 0.0100 | down | -1.69 | leucine rich repeat containing 8 family member C |
| 7 | ANKRD33B | ENSG00000164236 | 0.0040 | down | -1.66 | ankyrin repeat domain 33B |
| 8 | KLF11 | ENSG00000172059 | 0.0349 | down | -1.63 | Kruppel like factor 11 |
| 9 | MLXIP | ENSG00000175727 | 0.0133 | down | -1.57 | MLX interacting protein |
| 10 | PAMR1 | ENSG00000149090 | 0.0500 | down | -1.57 | peptidase domain containing associated with muscle regeneration 1 |
| 11 | CERS6 | ENSG00000172292 | 0.0155 | down | -1.56 | ceramide synthase 6 |
| 12 | ATP2B1 | ENSG00000070961 | 0.0383 | down | -1.50 | ATPase plasma membrane Ca2+ transporting 1 |
| 13 | HSF2 | ENSG00000025156 | 0.0101 | down | -1.50 | heat shock transcription factor 2 |
| 14 | ABCA3 | ENSG00000167972 | 0.0074 | down | -1.48 | ATP binding cassette subfamily A member 3 |
| 15 | CNTNAP3 | ENSG00000106714 | 0.0304 | down | -1.47 | contactin associated protein-like 3 |
| 16 | RHOBTB3 | ENSG00000164292 | 0.0378 | down | -1.45 | Rho related BTB domain containing 3 |
| 17 | CDON | ENSG00000064309 | 0.0271 | down | -1.45 | cell adhesion associated, oncogene regulated |
| 18 | DUSP10 | ENSG00000143507 | 0.0085 | down | -1.44 | dual specificity phosphatase 10 |
| 19 | CLDN8 | ENSG00000156284 | 0.0171 | down | -1.44 | claudin 8 |
| 20 | ZNF614 | ENSG00000142556 | 0.0108 | down | -1.43 | zinc finger protein 614 |
| 21 | EDIL3 | ENSG00000164176 | 0.0090 | down | -1.43 | EGF like repeats and discoidin domains 3 |
| 22 | ESPN | ENSG00000187017 | 0.0245 | down | -1.42 | espin |
| 23 | RASAL2 | ENSG00000075391 | 0.0326 | down | -1.42 | RAS protein activator like 2 |
| 24 | ZXDB | ENSG00000198455 | 0.0343 | down | -1.41 | zinc finger, X-linked, duplicated B |
| 25 | N4BP2L1 | ENSG00000139597 | 0.0185 | down | -1.40 | NEDD4 binding protein 2 like 1 |
| 26 | RNF217 | ENSG00000146373 | 0.0019 | down | -1.40 | ring finger protein 217 |
| 27 | EEF2K | ENSG00000103319 | 0.0131 | down | -1.39 | eukaryotic elongation factor 2 kinase |
| 28 | FCER1A | ENSG00000179639 | 0.0003 | down | -1.38 | Fc fragment of IgE receptor Ia |
| 29 | RICTOR | ENSG00000164327 | 0.0260 | down | -1.37 | RPTOR independent companion of MTOR complex 2 |
| 30 | ZC3H12A | ENSG00000163874 | 0.0224 | down | -1.37 | zinc finger CCCH-type containing 12A |
| 31 | GATM | ENSG00000171766 | 0.0024 | down | -1.36 | glycine amidinotransferase |
| 32 | HIVEP1 | ENSG00000095951 | 0.0471 | down | -1.35 | human immunodeficiency virus type I enhancer binding protein 1 |
| 33 | AAMDC | ENSG00000087884 | 0.0023 | down | -1.35 | adipogenesis associated Mth938 domain containing |
| 34 | TRAF6 | ENSG00000175104 | 0.0401 | down | -1.34 | TNF receptor associated factor 6 |
| 35 | EFHC2 | ENSG00000183690 | 0.0191 | down | -1.33 | EF-hand domain containing 2 |
| 36 | DIP2B | ENSG00000066084 | 0.0036 | down | -1.33 | disco interacting protein 2 homolog B |
| 37 | SIK1 | ENSG00000142178 | 0.0144 | down | -1.32 | salt inducible kinase 1 |
| 38 | TNFRSF19 | ENSG00000127863 | 0.0208 | down | -1.32 | TNF receptor superfamily member 19 |
| 39 | FGD4 | ENSG00000139132 | 0.0179 | down | -1.31 | FYVE, RhoGEF and PH domain containing 4 |
| 40 | UBN2 | ENSG00000157741 | 0.0366 | down | -1.31 | ubiquitin 2 |
| 41 | PHC3 | ENSG00000173889 | 0.0424 | down | -1.31 | polyhomeotic homolog 3 |
| 42 | CLDN1 | ENSG00000163347 | 0.0165 | down | -1.31 | claudin 1 |
| 43 | PPTC7 | ENSG00000196850 | 0.0017 | down | -1.30 | PTC7 protein phosphatase homolog |
| 44 | DZIP1L | ENSG00000158163 | 0.0243 | down | -1.30 | DAZ interacting zinc finger protein 1 like |
| 45 | ANO1 | ENSG00000131620 | 0.0170 | down | -1.30 | anoctamin 1 |
| 46 | DENND4C | ENSG00000137145 | 0.0159 | down | -1.29 | DENN domain containing 4C |
| 47 | MAP3K2 | ENSG00000169967 | 0.0164 | down | -1.29 | mitogen-activated protein kinase kinase kinase 2 |
| 48 | GPCPD1 | ENSG00000125772 | 0.0071 | down | -1.29 | glycerophosphocholine phosphodiesterase 1 |
| 49 | KLF13 | ENSG00000169926 | 0.0214 | down | -1.28 | Kruppel like factor 13 |
| 50 | ARHGAP42 | ENSG00000165895 | 0.0069 | down | -1.28 | Rho GTPase activating protein 42 |

| | | | | | | |
|-----|---------|-----------------|--------|------|-------|--|
| 51 | PHYHD1 | ENSG00000175287 | 0.0348 | down | -1.26 | phytanoyl-CoA dioxygenase domain containing 1 |
| 52 | SPATA18 | ENSG00000163071 | 0.0154 | down | -1.26 | spermatogenesis associated 18 |
| 53 | BACH1 | ENSG00000156273 | 0.0094 | down | -1.26 | BTB domain and CNC homolog 1 |
| 54 | ATG14 | ENSG00000126775 | 0.0185 | down | -1.26 | autophagy related 14 |
| 55 | CEP68 | ENSG00000011523 | 0.0305 | down | -1.25 | centrosomal protein 68 |
| 56 | TUBGCP3 | ENSG00000126216 | 0.0244 | down | -1.25 | tubulin gamma complex associated protein 3 |
| 57 | FZD1 | ENSG00000157240 | 0.0303 | down | -1.25 | frizzled class receptor 1 |
| 58 | RC3H1 | ENSG00000135870 | 0.0082 | down | -1.25 | ring finger and CCCH-type domains 1 |
| 59 | NIPA1 | ENSG00000170113 | 0.0310 | down | -1.24 | non imprinted in Prader-Willi/Angelman syndrome 1 |
| 60 | PAN3 | ENSG00000152520 | 0.0052 | down | -1.24 | PAN3 poly(A) specific ribonuclease subunit |
| 61 | SVIP | ENSG00000198168 | 0.0349 | down | -1.22 | small VCP interacting protein |
| 62 | MBNL1 | ENSG00000152601 | 0.0129 | down | -1.22 | muscleblind like splicing regulator 1 |
| 63 | ZFP36L2 | ENSG00000152518 | 0.0286 | down | -1.21 | ZFP36 ring finger protein like 2 |
| 64 | TBL1XR1 | ENSG00000177565 | 0.0258 | down | -1.21 | transducin beta like 1 X-linked receptor 1 |
| 65 | C1GALT1 | ENSG00000106392 | 0.0215 | down | -1.21 | core 1 synthase, glycoprotein-N-acetylgalactosamine 3-beta-galactosyltransferase 1 |
| 66 | IRF6 | ENSG00000117595 | 0.0296 | down | -1.20 | interferon regulatory factor 6 |
| 67 | LNPEP | ENSG00000113441 | 0.0403 | down | -1.19 | leucyl and cystinyl aminopeptidase |
| 68 | AKR1B10 | ENSG00000198074 | 0.0387 | up | 2.58 | aldo-keto reductase family 1 member B10 |
| 69 | FABP5 | ENSG00000164687 | 0.0198 | up | 2.09 | fatty acid binding protein 5 |
| 70 | PYDC1 | ENSG00000169900 | 0.0150 | up | 2.04 | pyrin domain containing 1 |
| 71 | WNT5A | ENSG00000114251 | 0.0132 | up | 1.92 | Wnt family member 5A |
| 72 | TMEM52 | ENSG00000178821 | 0.0177 | up | 1.62 | transmembrane protein 52 |
| 73 | SCD | ENSG00000099194 | 0.0127 | up | 1.53 | stearoyl-CoA desaturase |
| 74 | TREX2 | ENSG00000183479 | 0.0397 | up | 1.48 | three prime repair exonuclease 2 |
| 75 | ROM1 | ENSG00000149489 | 0.0256 | up | 1.47 | retinal outer segment membrane protein 1 |
| 76 | TK1 | ENSG00000167900 | 0.0441 | up | 1.47 | thymidine kinase 1 |
| 77 | PON3 | ENSG00000105852 | 0.0006 | up | 1.47 | paraoxonase 3 |
| 78 | GADD45G | ENSG00000130222 | 0.0248 | up | 1.46 | growth arrest and DNA damage inducible gamma |
| 79 | CTSB | ENSG00000164733 | 0.0235 | up | 1.45 | cathepsin B |
| 80 | TMEM64 | ENSG00000180694 | 0.0373 | up | 1.44 | transmembrane protein 64 |
| 81 | TMEM14A | ENSG00000096092 | 0.0085 | up | 1.43 | transmembrane protein 14A |
| 82 | MYO1B | ENSG00000128641 | 0.0116 | up | 1.41 | myosin IB |
| 83 | WNT10A | ENSG00000135925 | 0.0262 | up | 1.40 | Wnt family member 10A |
| 84 | RASA4 | ENSG00000105808 | 0.0411 | up | 1.40 | RAS p21 protein activator 4 |
| 85 | ZNF503 | ENSG00000165655 | 0.0010 | up | 1.37 | zinc finger protein 503 |
| 86 | GALNT6 | ENSG00000139629 | 0.0177 | up | 1.36 | polypeptide N-acetylgalactosaminyltransferase 6 |
| 87 | TNNT2 | ENSG00000118194 | 0.0274 | up | 1.35 | troponin T2, cardiac type |
| 88 | STK39 | ENSG00000198648 | 0.0300 | up | 1.35 | serine/threonine kinase 39 |
| 89 | SLX1A | ENSG00000132207 | 0.0085 | up | 1.35 | SLX1 homolog A, structure-specific endonuclease subunit |
| 90 | CRABP2 | ENSG00000143320 | 0.0207 | up | 1.34 | cellular retinoic acid binding protein 2 |
| 91 | DTYMK | ENSG00000168393 | 0.0152 | up | 1.34 | deoxythymidylate kinase |
| 92 | PLBD1 | ENSG00000121316 | 0.0194 | up | 1.34 | phospholipase B domain containing 1 |
| 93 | VASN | ENSG00000168140 | 0.0234 | up | 1.33 | vasorin |
| 94 | PUDP | ENSG00000130021 | 0.0446 | up | 1.32 | pseudouridine 5'-phosphatase |
| 95 | AKR1B1 | ENSG00000085662 | 0.0092 | up | 1.30 | aldo-keto reductase family 1 member B |
| 96 | ESRRA | ENSG00000173153 | 0.0385 | up | 1.30 | estrogen related receptor alpha |
| 97 | BEX3 | ENSG00000166681 | 0.0380 | up | 1.28 | brain expressed X-linked 3 |
| 98 | SRXN1 | ENSG00000271303 | 0.0201 | up | 1.28 | sulfiredoxin 1 |
| 99 | PDLIM4 | ENSG00000131435 | 0.0434 | up | 1.26 | PDZ and LIM domain 4 |
| 100 | POLL | ENSG00000166169 | 0.0259 | up | 1.26 | DNA polymerase lambda |
| 101 | CDKN1C | ENSG00000129757 | 0.0401 | up | 1.22 | cyclin dependent kinase inhibitor 1C |
| 102 | PON2 | ENSG00000105854 | 0.0194 | up | 1.21 | paraoxonase 2 |

Table S2. GO enrichment analysis of the 102 overlapped genes between resolved *vs.* never-lesional DEGs and lesional *vs.* healthy DEGs in the epidermis. We performed GO analysis on 102 overlapped genes. The results revealed 54 significant BPs ($P < 0.001$ & $FDR < 0.2$). Abbreviations: GO, gene ontology; DEGs, differentially expressed genes; BP, biological processes.

| <i>Number</i> | <i>GO Term</i> | <i>Description</i> | <i>P-value</i> | <i>FDR q-value</i> | <i>Enrichment</i> |
|---------------|----------------|--|----------------|--------------------|-------------------|
| 1 | GO:0051716 | cellular response to stimulus | 0.00000419 | 0.0644 | 2.26 |
| 2 | GO:0071560 | cellular response to transforming growth factor beta stimulus | 0.00000613 | 0.0471 | 19.19 |
| 3 | GO:0071559 | response to transforming growth factor beta | 0.0000127 | 0.0649 | 16.59 |
| 4 | GO:0048518 | positive regulation of biological process | 0.0000147 | 0.0565 | 1.67 |
| 5 | GO:1904953 | Wnt signaling pathway involved in midbrain dopaminergic neuron differentiation | 0.0000151 | 0.0465 | 58.72 |
| 6 | GO:0042221 | response to chemical | 0.0000164 | 0.042 | 2.24 |
| 7 | GO:0070887 | cellular response to chemical stimulus | 0.0000165 | 0.0362 | 2.67 |
| 8 | GO:0071310 | cellular response to organic substance | 0.0000262 | 0.0504 | 2.87 |
| 9 | GO:0071495 | cellular response to endogenous stimulus | 0.0000434 | 0.0742 | 3.73 |
| 10 | GO:0045598 | regulation of fat cell differentiation | 0.0000546 | 0.084 | 9.03 |
| 11 | GO:0048856 | anatomical structure development | 0.0000726 | 0.101 | 1.97 |
| 12 | GO:0046125 | pyrimidine deoxyribonucleoside metabolic process | 0.0000773 | 0.099 | 130.48 |
| 13 | GO:0046104 | thymidine metabolic process | 0.0000773 | 0.0914 | 130.48 |
| 14 | GO:0006796 | phosphate-containing compound metabolic process | 0.0000824 | 0.0905 | 2.34 |
| 15 | GO:0061158 | 3'-UTR-mediated mRNA destabilization | 0.0000835 | 0.0856 | 34.54 |
| 16 | GO:0006793 | phosphorus metabolic process | 0.000102 | 0.0979 | 2.31 |
| 17 | GO:0032872 | regulation of stress-activated MAPK cascade | 0.000121 | 0.11 | 6.34 |
| 18 | GO:0070302 | regulation of stress-activated protein kinase signaling cascade | 0.000132 | 0.113 | 6.26 |
| 19 | GO:0032874 | positive regulation of stress-activated MAPK cascade | 0.000139 | 0.113 | 7.63 |
| 20 | GO:0070304 | positive regulation of stress-activated protein kinase signaling cascade | 0.00015 | 0.115 | 7.53 |
| 21 | GO:0009893 | positive regulation of metabolic process | 0.000227 | 0.166 | 1.83 |
| 22 | GO:0046328 | regulation of JNK cascade | 0.000231 | 0.161 | 6.95 |
| 23 | GO:0048522 | positive regulation of cellular process | 0.000313 | 0.209 | 1.61 |
| 24 | GO:0051239 | regulation of multicellular organismal process | 0.000341 | 0.219 | 1.87 |
| 25 | GO:0071363 | cellular response to growth factor stimulus | 0.000351 | 0.216 | 5.33 |
| 26 | GO:0009120 | deoxyribonucleoside metabolic process | 0.000383 | 0.226 | 65.24 |
| 27 | GO:0071470 | cellular response to osmotic stress | 0.000386 | 0.22 | 20.97 |
| 28 | GO:0006970 | response to osmotic stress | 0.000406 | 0.223 | 11.51 |
| 29 | GO:0060070 | canonical Wnt signaling pathway | 0.000406 | 0.215 | 11.51 |
| 30 | GO:0016310 | phosphorylation | 0.00041 | 0.21 | 2.69 |
| 31 | GO:0046330 | positive regulation of JNK cascade | 0.000438 | 0.217 | 7.89 |
| 32 | GO:0006468 | protein phosphorylation | 0.000448 | 0.215 | 2.94 |
| 33 | GO:1902105 | regulation of leukocyte differentiation | 0.000493 | 0.23 | 5.04 |
| 34 | GO:0009719 | response to endogenous stimulus | 0.000497 | 0.225 | 2.77 |
| 35 | GO:0042538 | hyperosmotic salinity response | 0.000534 | 0.234 | 55.92 |
| 36 | GO:0051173 | positive regulation of nitrogen compound metabolic process | 0.000535 | 0.228 | 1.85 |
| 37 | GO:0010033 | response to organic substance | 0.000535 | 0.222 | 2.11 |
| 38 | GO:0061157 | mRNA destabilization | 0.000576 | 0.233 | 18.35 |
| 39 | GO:0010604 | positive regulation of macromolecule metabolic process | 0.000585 | 0.23 | 1.81 |
| 40 | GO:0050896 | response to stimulus | 0.000594 | 0.228 | 1.55 |
| 41 | GO:0051254 | positive regulation of RNA metabolic process | 0.0006 | 0.225 | 2.26 |
| 42 | GO:0070848 | response to growth factor | 0.000664 | 0.243 | 4.79 |
| 43 | GO:0003056 | regulation of vascular smooth muscle contraction | 0.000709 | 0.254 | 48.93 |
| 44 | GO:0120161 | regulation of cold-induced thermogenesis | 0.000737 | 0.257 | 7.04 |
| 45 | GO:1901701 | cellular response to oxygen-containing compound | 0.000741 | 0.253 | 2.95 |
| 46 | GO:0050779 | RNA destabilization | 0.000752 | 0.251 | 16.78 |
| 47 | GO:0043506 | regulation of JUN kinase activity | 0.000789 | 0.258 | 9.67 |
| 48 | GO:0030154 | cell differentiation | 0.000802 | 0.257 | 2.15 |

| | | | | | |
|----|------------|---|----------|-------|-------|
| 49 | GO:0000288 | nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay | 0.000909 | 0.285 | 43.49 |
| 50 | GO:0030638 | polyketide metabolic process | 0.000909 | 0.279 | 43.49 |
| 51 | GO:0044598 | doxorubicin metabolic process | 0.000909 | 0.274 | 43.49 |
| 52 | GO:0044597 | daunorubicin metabolic process | 0.000909 | 0.269 | 43.49 |
| 53 | GO:0045935 | positive regulation of nucleobase-containing compound metabolic process | 0.000919 | 0.267 | 2.12 |
| 54 | GO:1901653 | cellular response to peptide | 0.000977 | 0.278 | 5.29 |

Table S3. Psoriatic patients' information and experimental techniques were applied to their samples. #PSO1: psoriatic patient code 1; RNA-seq, RNA-sequencing; IF, immunofluorescence staining.

| <i>Psoriatic patients' information and experiments applied to their samples</i> | | | | | | | |
|---|--------|-----|---|------------------------------------|-----------------------------|---|--|
| Patient's Code | Gender | Age | PASI score before initiating systemic therapy | PASI score at the time of sampling | Therapy | Punch biopsies body origin | Samples used for |
| #PSO1 | Male | 48 | 17.2 | 0 | Ustekinumab | Never-lesional: Buttocks Resolved: Thigh | RNA-seq, IF staining, and Real-Time RT-PCR |
| #PSO2 | Male | 35 | 18.4 | 18.4 | Methotrexate | Never-lesional: Thigh Resolved: Thigh | IF staining |
| #PSO3 | Male | 30 | 24.4 | 13.6 | Methotrexate | Never-lesional: Abdomen Resolved: Abdomen | IF staining |
| #PSO4 | Male | 65 | 15.6 | 2 | Infliximab+ Methotrexate | Never-lesional: Trunk Resolved: Upper arm | IF staining |
| #PSO5 | Female | 39 | 17.1 | 0 | Ustekinumab | Never-lesional: Lower back Resolved: arm | RNA-seq and Real-Time RT-PCR |
| #PSO6 | Male | 38 | 17 | 0 | Ustekinumab | Never-lesional: Buttocks Resolved: Right leg | RNA-seq and Real-Time RT-PCR |
| #PSO7 | Male | 26 | 18 | 0 | Ustekinumab | Never-lesional: Thigh Resolved: Thigh | RNA-seq |

Table S4. Real-Time RT-PCR TaqMan assay Probes.

| Number | Gene Symbol | Catalog No | Assay ID |
|--------|-------------|------------|---------------|
| 1 | TET1 | 4331182 | Hs04189344_g1 |
| 2 | TET2 | 4331182 | Hs00325999_m1 |
| 3 | TET3 | 4331182 | Hs00896441_m1 |
| 4 | 18s rRNA | 4331182 | Hs99999901_s1 |