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Original Article

CCL2-CCL5/CCR4 contributed to radiation-induced epithelial-mesenchymal transition of HPAEpiC cells via the ERK signaling pathways

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Abstract: Radiation-induced lung toxicity, including radiation pneumonitis and pulmonary fibrosis, often occurs in patients receiving radiation therapy. Epithelial-mesenchymal transition (EMT) of alveolar epithelial cells (AECs) plays critical roles in radiation-induced lung toxicity. In the present study, RNA sequencing was applied to examine the whole transcriptomes of human pulmonary AEC cells (HPAEpiC) with or without radiation treatment. We found that cytokine, chemokine and cell adhesion signaling pathways were enriched in radiation-treated cells. CCL2 (C-C Motif Chemokine Ligand 2), CCL5 and CCR4 (C-C Motif Chemokine Receptor 4) were among the top enriched genes in chemokine signaling pathway. The upregulation of CCL2, CCL5 and CCR4 in response to irradiation was confirmed at both mRNA and protein levels by real-time PCR, western blotting and enzyme-linked immunosorbent assay analyses. Ophiopogonin B, a bioactive ingredient of Radix *Ophiopogon japonicas*, was found to attenuate radiation-induced EMT in HPAEpiC cells as demonstrated by the alteration in cell morphology, and the expression of E-cadherin and Vimentin. Ophiopogonin B could also reduce radiation-induced expression of CCL2, CCL5, CCR4 and phosphorylated ERK (p-ERK). Moreover, CCR4 knockdown, U0126 (a MEK/ERK inhibitor) or ophiopogonin B also partially blocked the EMT promoting effects of CCL2 and CCL5. Our data suggested CCL2, CCL5 and CCR4 may be potential therapeutic targets for radiation-induced lung toxicity. Ophiopogonin B, which could down-regulate CCL2, CCL5 and CCR4, may be a useful radioprotective agent.

Keywords: Chemokines, EMT, alveolar epithelial cells, ophiopogonin B

Introduction

The lung is highly sensitive to radiation and represents the major organ targeted for irradiation-induced damage [1]. Radiation-induced lung toxicity, including radiation pneumonitis and pulmonary fibrosis, is common in patients receiving radiotherapy [2]. Radiation pneumonitis usually occurs within a few weeks to several months after the start of radiation therapy, whose symptoms include cough, shortness of breath and fever. Pulmonary fibrosis is a permanent scarring of lung tissue that responds more slowly to initial tissue damage (lasting months to years) [3-5]. The inflammation and fibrosis processes are initiated and maintained by a complex network of cytokines and chemokines [1, 6]. Alveolar epithelial cells (AECs), as a rich cellular source of chemokines, play important roles in radiation-induced lung toxicity. By utilizing a co-culture system, Hong et al. found that irridiation significantly increased the levels of several cytokines (CSF2 [Colony Stimulating Factor 2], CSF3, IL-6 [interleukin-6] and CCL2 [C-C Motif Chemokine Ligand 2]) in a dose-dependent manner [7]. During the processes of radiation-induced lung toxicity, AECs convert into myofibroblasts by epithelial-mesenchymal transition (EMT) [8], in which TGF-β (transforming growth factor-β)/Smad [9] and ERK (extracellular signal-regulated kinase) [10] signaling pathways are involved. The myofibroblasts pro-

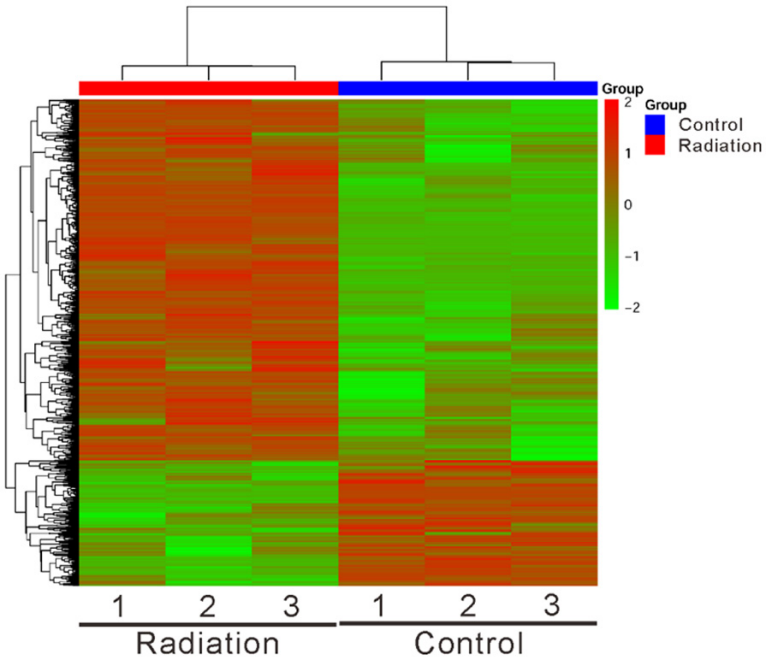

Figure 1. Cluster analysis and heatmap of RNA sequencing data from radiation-treated and control HPAEpic cells. The color bar across the top of the heat map indicates the Radiation group (red) and the Control group (blue). Color from red to green indicates high to low expression.

duce matrix molecules, thus contributing to the radiation-induced lung toxicity [11, 12].

Increasing evidence has been presented that traditional Chinese medicine [13], such as ginseng [14], astragalus [15] and turmeric [16], have potential radioprotective effects. Ophiopogonin B is a bioactive ingredient of Radix *Ophiopogon japonicas*, a traditional Chinese herbal drug which has been reported to exert cardioprotective, antibacterial, anti-cancer, anti-inflammation and radiation protective activities [17, 18]. Ophiopogonin B has been reported to exert anticancer effects in cervical cancer, gastric cancer and lung cancer via regulating JNK (c-Jun N-terminal kinase), ERK or PI3K (phosphatidylinositol 3-kinase)/AKT signaling [19-23]. However, little is known about the role of ophiopogonin B in radiation-induced lung toxicity.

In the present study, whole transcriptomes of human pulmonary AECs (HPAEpiC) in response to radiation was sequenced by next-generation RNA sequencing. Significantly changed genes were identified. Functional analysis suggested that radiation was positively correlated with multiple genes in cytokine, chemokine, cell adhesion signaling pathways. CCL2, CCL5 and CCR4 (C-C Motif Chemokine Receptor 4) were enriched genes in chemokine signaling pathway. Real-time PCR, western blot and ELISA (enzyme-linked immunosorbent assay) analyses confirmed the upregulation of CCL2, CCL5 and CCR4 in response to irradiation. We also investigate the effects of ophiopogonin B on radiation-induced EMT and the expression of CCL2, CCL5, CCR4 and phosphorylated ERK (p-ERK) in HPAEpiC cells.

Materials and methods

Cell culture

Human pulmonary alveolar epithelial cells (HPAEpiC) obtained from ScienCell Research Laboratories (Carlsbad, CA, USA) were maintained in Dulbecco's Modified Eagle Medium (DMEM)/F12 (Hyclone, Logan, UT, USA) supplemented with 10% fetal bovine serum (FBS) in under 5% CO_2 at 37°C.

RNA extraction and RNA sequencing

HPAEpiC cells were exposed to 8 Gray of ^{60}Co γ-rays (Hangzhou Cancer Hospital) and cultured for 24 h. Then, total RNA was extracted from 3 samples with radiation (Radiation group) and 3 samples without radiation (Control group) using a Trizol kit (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocol. The isolated RNA was quantified using a Nanodrop spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA), and the integrity of isolated RNA was checked by denaturing formaldehyde gel electrophoresis. Complementary DNA (cDNA) libraries were constructed with TruSeq® RNA LT Sample Prep Kit v2 (Illumina, San Diego, CA, USA) following the manufacturer's protocol. Sequencing was performed using Illumina Hiseq 2500 instruments (Illumina). RNA sequencing data was analyzed as previously described [24]. Differentially expressed genes (DEG) were chosen according to the p value ≤ 0.05 and the Fold Change (FC) value ≥ 2. Gene set enrichment analysis (GSEA) was performed as describe previously [24] to iden-

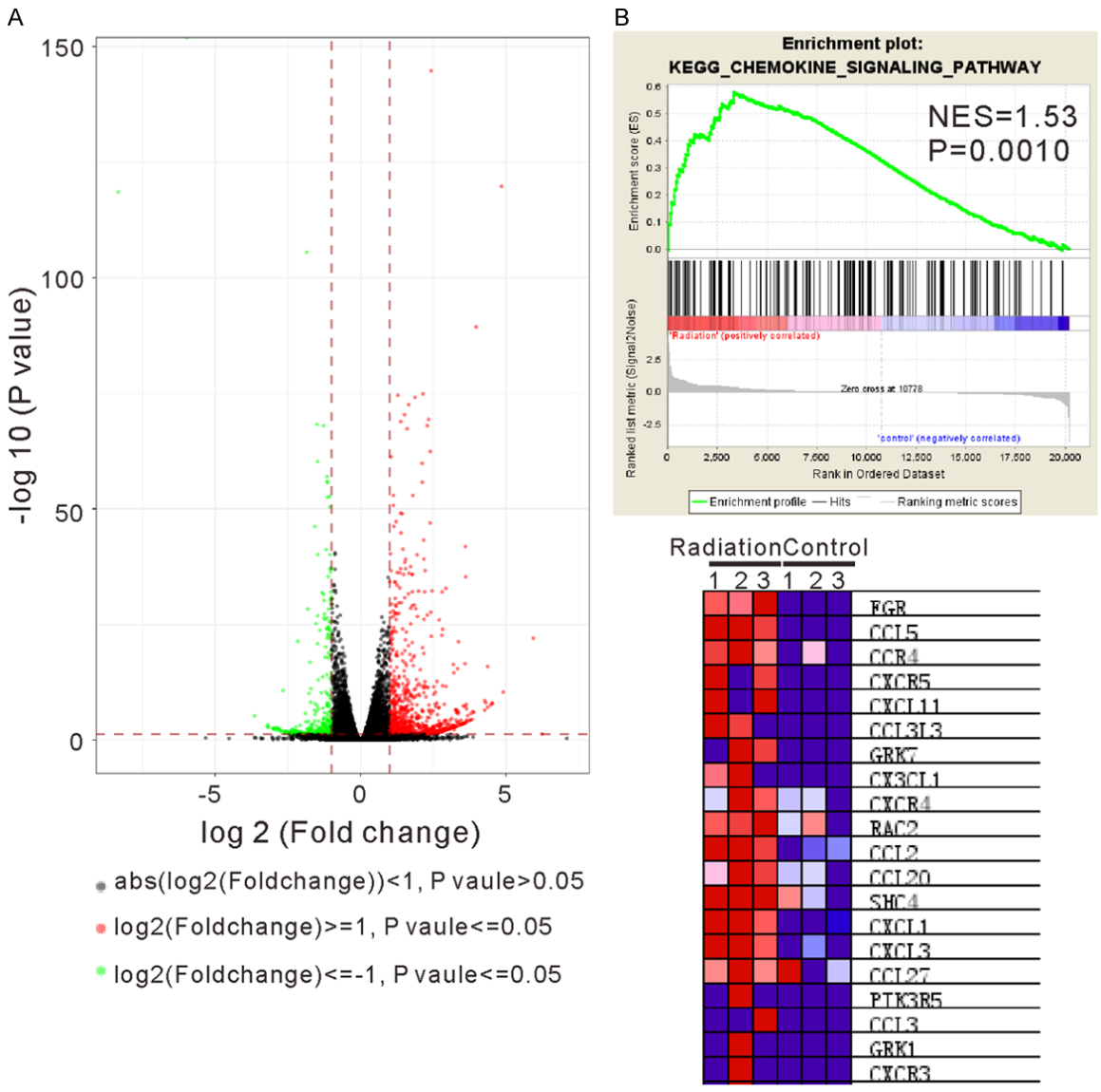

Figure 2. Analysis of significantly changed genes in response to radiation. A. Volcano analysis was performed with a minimum of a 2-fold change and P<0.05 between the Radiation group and the Control group. The log2 (fold change) is plotted on the x-axis and the negative log10 (*P*-value) is plotted on the y-axis. Red and green dots represented up-regulated and down-regulated genes, respectively. B. Gene set enrichment analysis (GSEA) showed that KEGG chemokine signaling pathway was correlated with radiation response. The enrichment plot (upper panel) and the top 20 enriched genes (bottom panel) are shown.

tify KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways enriched in the Radiation group and the Control group.

Quantitative real-time PCR

Total RNA was reversed transcribed into cDNA with the cDNA Reverse Transcription Kit (Thermo fisher, Rockford, IL, USA). SYBR green PCR mix (Thermo fisher) was used for quantitative real-time PCR on an ABI 7300 series PCR machine (Applied Biosystems, Foster City, CA, USA). The mRNA expression levels were quantified using the $^{2-\Delta\Delta}$CT method, with GAPDH as the internal control. The primers for real-time PCR analysis are as follows: CCL2, 5'-AACCGAGAGGCTGAGACTAAC-3' (forward) and 5'-TGCCAACCCAGAGAAGAAATG-3' (reverse); CCL5, 5'-AACCGAGAGGCTGAGACTAAC-3' (forward) and 5'-AGGACAAGAGCAAGCAGAAAC-3' (reverse); CCR4, 5'-CCTTCCTGGCTTTCTGTTC-3' (forward) and 5'-CATCTTCACCGCCTTGTTC-3' (reverse);

Table 1. Statistically significant KEGG classifications of enrichment in radiation-treated HPAEpiC cells

Name	Size	NES	NOM *p*-val	FDR q-val
AUTOIMMUNE_THYROID_DISEASE	27	1.7672	0.0000	0.0092
HEMATOPOIETIC_CELL_LINEAGE	61	1.7366	0.0000	0.0112
GRAFT_VERSUS_HOST_DISEASE	23	1.7120	0.0000	0.0144
CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	186	1.6692	0.0000	0.0211
B_CELL_RECEPTOR_SIGNALING_PATHWAY	68	1.6452	0.0000	0.0223
CHEMOKINE_SIGNALING_PATHWAY	145	1.5332	0.0010	0.0594
CELL_ADHESION_MOLECULES_CAMS	107	1.5561	0.0011	0.0572
TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY	85	1.5568	0.0011	0.0608
DRUG_METABOLISM_OTHER_ENZYMES	39	1.6249	0.0012	0.0251
TYPE_I_DIABETES_MELLITUS	30	1.7054	0.0013	0.0124
NOTCH_SIGNALING_PATHWAY	42	1.6262	0.0024	0.0269
PROXIMAL_TUBULE_BICARBONATE_RECLAMATION	21	1.6600	0.0026	0.0194
ALLOGRAFT_REJECTION	24	1.6688	0.0027	0.0176
LEISHMANIA_INFECTION	56	1.5425	0.0035	0.0621
VIRAL_MYOCARDITIS	56	1.5742	0.0036	0.0514
LEUKOCYTE_TRANSENDOTHELIAL_MIGRATION	100	1.4851	0.0043	0.0798
VASCULAR_SMOOTH_MUSCLE_CONTRACTION	99	1.4880	0.0064	0.0792
CYTOSOLIC_DNA_SENSING_PATHWAY	40	1.5406	0.0073	0.0599
NEUROACTIVE_LIGAND_RECEPTOR_INTERACTION	181	1.3489	0.0082	0.2307
NOD_LIKE_RECEPTOR_SIGNALING_PATHWAY	53	1.5378	0.0091	0.0588
PRION_DISEASES	23	1.5768	0.0115	0.0532
ONE_CARBON_POOL_BY_FOLATE	16	1.5469	0.0139	0.0623
ABC_TRANSPORTERS	41	1.5293	0.0143	0.0596
SYSTEMIC_LUPUS_ERYTHEMATOSUS	38	1.4924	0.0157	0.0784
PANTOTHENATE_AND_COA_BIOSYNTHESIS	15	1.5206	0.0160	0.0641
FOCAL_ADHESION	187	1.3368	0.0164	0.2281
INTESTINAL_IMMUNE_NETWORK_FOR_IGA_PRODUCTION	31	1.5124	0.0172	0.0656
AXON_GUIDANCE	118	1.3750	0.0212	0.1975
ADHERENS_JUNCTION	68	1.4183	0.0245	0.1542
STARCH_AND_SUCROSE_METABOLISM	34	1.5007	0.0245	0.0736
PENTOSE_AND_GLUCURONATE_INTERCONVERSIONS	16	1.5189	0.0259	0.0625
FC_EPSILON_RI_SIGNALING_PATHWAY	66	1.4097	0.0264	0.1587
EPITHELIAL_CELL_SIGNALING_IN_HELICOBACTER_PYLORI_INFECTION	64	1.4159	0.0268	0.1532
LONG_TERM_DEPRESSION	59	1.4194	0.0272	0.1578
JAK_STAT_SIGNALING_PATHWAY	119	1.3342	0.0342	0.2230
NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY	97	1.3437	0.0380	0.2246
ECM_RECEPTOR_INTERACTION	80	1.3443	0.0403	0.2287
OLFACTORY_TRANSDUCTION	26	1.4469	0.0413	0.1238
MELANOMA	62	1.3664	0.0450	0.2083
ASCORBATE_AND_ALDARATE_METABOLISM	15	1.4317	0.0492	0.1431

and GAPDH, 5'-AATCCCATCACCATCTTC-3' (forward) and 5'-AGGCTGTTGTCATACTTC-3' (reverse).

Western blotting analysis

The cells were washed twice with PBS and lysed in ice-cold radioimmunoprecipitation buffer (Solarbio, Beijing, China) following the manufacturer's protocols. Equal amount of protein from each sample was separated by electrophoresis and transferred onto nitrocellulose membranes (Millipore, Bredford, USA). The membranes were blocked and incubation with the primary antibodies at 4°C overnight. Following incubation with horseradish

Table 2. Statistically significant KEGG classifications of enrichment in control cells

Name	Size	NES	NOM *p*-val	FDR q-val
SPLICEOSOME	116	-1.741	0.0000	0.108
DNA_REPLICATION	36	-1.519	0.0109	0.285
RNA_DEGRADATION	54	-1.464	0.0175	0.272
AMINOACYL_TRNA_BIOSYNTHESIS	41	-1.404	0.0444	0.300
CELL_CYCLE	124	-1.261	0.0196	0.395
PARKINSONS_DISEASE	108	-1.252	0.0492	0.364

peroxidase (HRP)-labeled secondary antibody (Beyotime, Shanghai, China; dilution 1:1000) at room temperature for 1 h, protein expression was detected with an enhanced chemiluminescence kit (Millipore). The sources of primary antibodies were as follows: anti-CCL2 (dilution 1:2000), anti-CCL5 (dilution 1:500), anti-CCR4 (dilution 1:500) were from Abcam (Cambridge, MA, USA), while anti-phosphor-ERK (dilution 1:1000) anti-ERK (dilution 1:1000), anti-Vimentin (dilution 1:1000), anti-E-cadherin(dilution 1:1000) and anti-GAPDH (dilution 1:2000) were obtained from Cell Signaling Technology (Danvers, MA, USA). Experiments were repeated at least for three times and representative blots are shown.

Enzyme-linked immunosorbent assay (ELISA)

The concentrations of CCL2 and CCL5 in the culture medium were measured with ELISA kits (R&D Systems, Minneapolis, MN, USA) following the manufacturer's instructions.

Statistical analysis

All data were analyzed with Graphpad Prism 6.0 program (GraphPad, San Diego, CA, USA) and presented as the mean ± standard deviation (SD). The comparison among different groups was made by one-way analysis of variance (ANOVA). Values of $P<0.05$ were considered statistically significant.

Results

Whole transcriptional profile of the response to radiation in HPAEpic cells by RNA sequencing analysis

We examined the changes of the whole transcriptional profile of HPAEpic cells in response to radiation by using RNA-seq method. The heat map (**Figure 1**) clearly showed a noteworthy difference in gene expression pattern between the Radiation group and the Control group. The volcano analysis was conducted with a minimum of a 2-fold change and $P \leq 0.05$ and showed more up-regulated genes than down-regulated genes in response to radiation (**Figure 2A**). A total of 1,385 genes was found significantly changed after radiation treatment, of which 1,028 genes were up-regulated (Supplementary Table 1) and 357 genes were down-regulated (Supplementary Table 2). Base on GSEA analysis, 40 and 6 pathways were enriched in radiation-treated cells (**Table 1**) and control cells (**Table 2**), respectively. It is worth noting that radiation exposure was positively correlated with cytokine, chemokine (**Figure 2B**) and cell adhesion signaling pathways (**Table 1**), while negatively correlated with DNA replication and cell cycle processes (**Table 2**).

Radiation induced CCL2, CCL5 and CCR4 in HPAEpic cells

CCL5, CCR4 and CCL2, which were among the top 20 enriched genes in chemokine signaling pathway (**Figure 2B**), were selected for further study. As shown in **Figure 3A**, radiation time-dependently increased the mRNA expression of CCL2, CCL5 and CCR4 comparing with Control cells. Furthermore, a significant increase in protein level of CCL2, CCL5 and CCR4 were observed in radiation-treated cells as measured by western blot (**Figures 3B**, S1). ELISA assay confirmed the elevated release of CCL2 and CCL5 to the medium in response to radiation at a time-dependent manner (**Figure 3C**).

Ophiopogonin B attenuated radiation-induced EMT of HPAEpic cells

Upon radiation, AECs undergo EMT, which plays a critical role in the pathogenesis of radiation-induced lung toxicity. To study the radioprotective effects of ophiopogonin B, HPAEpic cells were pre-treated with ophiopogonin B (OP-B) and then subjected to radiation. As illustrated in **Figure 4A**, Control cells without radiation treatment displayed classical epithelial morphology, while radiation-treated cells had elon-

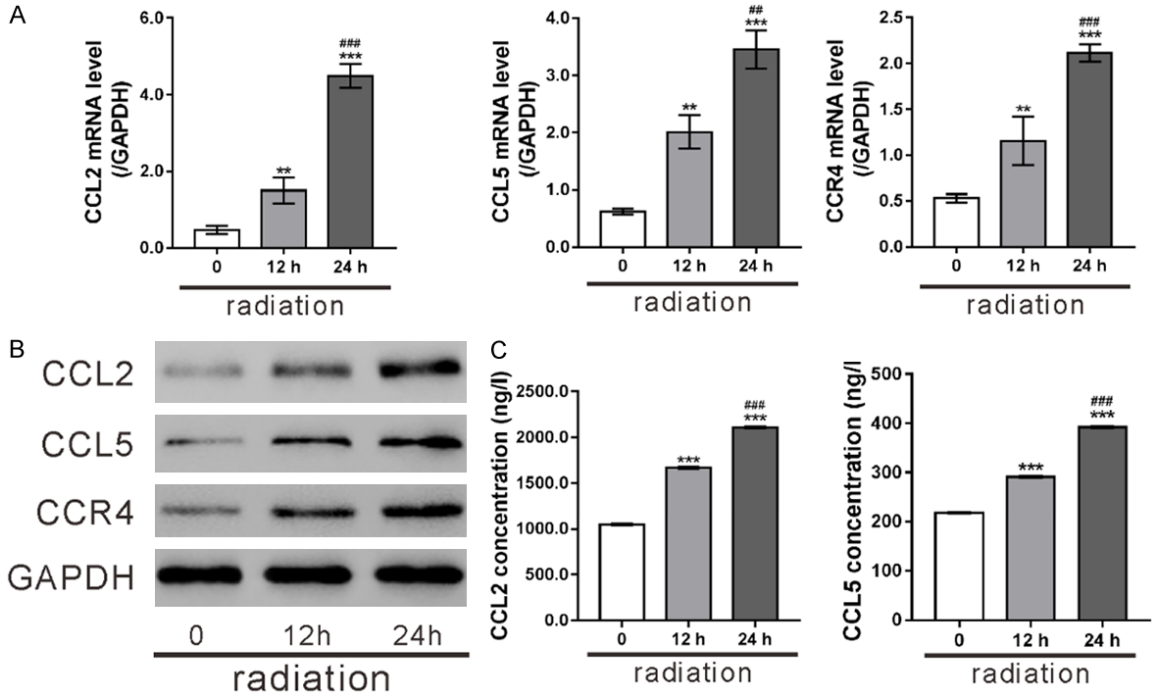

Figure 3. Radiation induced CCL2, CCL5 and CCR4 in HPAEpic cells. HPAEpic cells subjected to radiation (8 Gray) and then cultured for 0, 12 and 24 h. (A, B) The mRNA and protein expression of CCL2, CCL5 and CCR4 was assessed by real-time PCR analysis (A) and western blotting (B), respectively. (C) The release of CCL2 and CCL5 in the culture medium was detected by ELISA assays. **P<0.01, ***P<0.001 versus 0 h; ##P<0.01, ###P<0.001 versus 12 h.

gated spindle-like shape. Pre-treatment with ophiopogonin B improved the morphological alteration caused by radiation.

The reduced expression of epithelial molecular markers (such as E-cadherin) and elevated expression of mesenchymal molecular markers (such as Vimentin) are main characteristics of EMT [8]. Western blot analysis showed that radiation increased Vimentin expression and decreased E-cadherin expression, which was partially reversed by ophiopogonin B treatment (**Figures 4B**, S2). Additionally, the ERK signaling pathway is an important regulatory factor in radiation-induced EMT [10, 25]. Ophiopogonin B treatment obviously decreased radiation-elevated ERK phosphorylation (p-ERK) (**Figure 4B**). These data suggested that ophiopogonin B attenuated radiation-induced EMT of HPAEpic cells.

Ophiopogonin B inhibited CCL2, CCL5 and CCR4 in radiation-exposed HPAEpic cells

The effects of ophiopogonin B on the expression of CCL2, CCL5 and CCR4 were also studied. As shown in **Figures 5A**, **5B** and S3, ophiopogonin B dose-dependently suppressed the expression of CCL2, CCL5 and CCR4 in radiation-treated HPAEpic cells at both mRNA and protein levels. Moreover, ophiopogonin B treatment reduced the release of CCL2 and CCL5 in radiation-exposed HPAEpic cells at a dose-dependent fashion (**Figure 5C**). The above findings strongly indicated that ophiopogonin B regulated CCL2, CCL5 and CCR4 expression in AECs cells.

CCR4 knockdown and ophiopogonin B affected the levels of EMT-related proteins in CCL2 or CCL5 treated HPAEpic cells

To explore whether CCR4 mediated the functions of CC2 or CCL5, CCR4 expression was knocked down in HPAEpic cells. HPAEpic cells were transduced with CCR4 shRNAs (sh#1, sh#2 and sh#3) or control shRNA (shCon). Real-time PCR (**Figure 6A**) and western blotting analysis (**Figures 6B**, S4A) showed that CCR4 was efficiently knocked down by all CCR4 shRNAs, of which sh#3 displayed the best knock-down efficiency. Next, HPAEpic cells were transduced

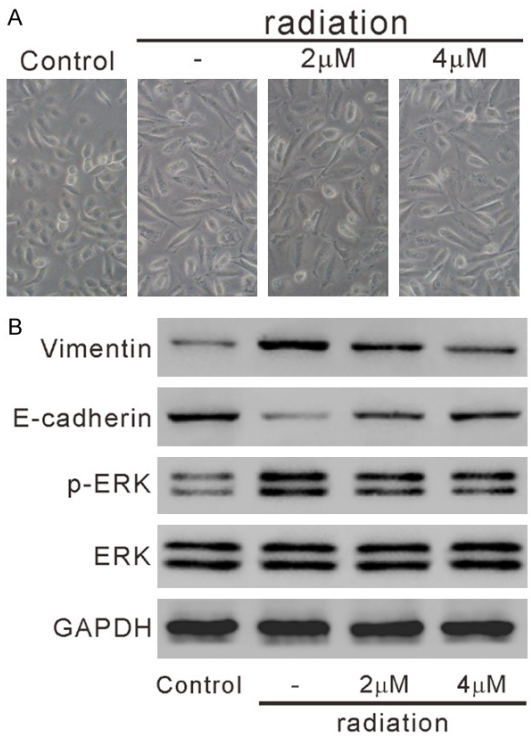

Figure 4. Ophiopogonin B (OP-B) affected the morphology changes and the levels of EMT-related proteins in radiation-treated HPAEpic cells. HPAEpic cells were pre-treated with 0, 2 or 4 mM OP-B for 2 h, then subjected to radiation (8 Gray) and cultured for another 24 h. Cells without any treatment were served as negative control. A. Cell morphology was observed under a microscope. The representative phase contrast images from three independent experiments are shown (magnification 200×). B. The levels of E-cadherin, Vimentin, p-ERK and ERK was detected by western blotting.

with sh#3 or shCon in the present of CCL2 or CCL5. Western blot analysis (**Figures 6C**, S4B) showed that CCL2 and CCL5 increased p-ERK and Vimentin, but decreased E-cadherin. CCR4 knockdown partially blocked the effects of CCL2 and CCL5. These data suggested that the effect of CCL2 and CCL5 on the EMT-related proteins was dependent on CCR4.

Further, HPAEpic cells were treated with 4 mM ophiopogonin B in the present of CCL2 or CCL5. Ophiopogonin B also partially blocked the effects of CCL2 and CCL5 on the EMT-related proteins.

U0126 suppressed CCL2 or CCL5-induced EMT

To investigate the involvement of ERK in CCL2 or CCL5-induced EMT, HPAEpic cells were pre-treated with a MEK/ERK inhibitor U0126 and then with CCL2/CCL5. As illustrated in **Figure 7A**, cells treated with CCL2 or CCL5 had elongated spindle-like shape, which was improved by the treatment with U0126. Western blot analysis showed that CCL2/CCL5 increased the levels of Vimentin and p-ERK, and decreased E-cadherin expression, which was partially reversed by U0126 treatment (**Figures 7B**, S5).

Discussion

RNA sequencing has been applied to assess the global radiation responses at whole transcriptome level in non-small cell lung cancer (NSCLC) A549 cells [26]. In this study, we conducted RNA sequencing on normal alveolar epithelial cells (HPAEpic) with or without radiation treatment. We identified 1,385 significant changed genes (DEGs) in response to radiation (Supplementary Tables 1 and 2). Radiation-induced inflammation and fibrosis processes are initiated and maintained by a complex network of cytokines and chemokines [1, 6]. It is not surprising that multiple genes in cytokine and chemokine signaling pathways were positively correlated with radiation treatment (**Table 1**).

Chemokines are a large family of small chemotactic cytokines and more than 40 members have been identified. The chemokines exert their biological functions by binding with the G protein-linked transmembrane receptors [27]. Here, CCL2 (also known as MCP1), CCL5 (also known as RANTES) and CCR4 were identified as up-regulated genes in response to radiation and enriched in chemokine signaling pathway (**Figure 2B**). It has been reported that metaplastic epithelial cells of idiopathic pulmonary fibrosis produce more CCL2 and the increased CCL2 was associated with disease activity [28]. CCL2 secretion was found significantly increased by radiation in type II AECs [7]. CCL2/CCL5 was upregulated in radiation-treated NSCLC cells [29]. CCR4, an important receptor for CCL2 and CCL5, can promote metastasis of lung cancer and colon cancer [30]. Thus, we then chose these three DEGs for subsequent experiments. The mRNA and protein expression of the above three DEGs were time-dependently increased by radiation exposure. In addition, the release of CCL2 and CCL5 was also elevated with time following

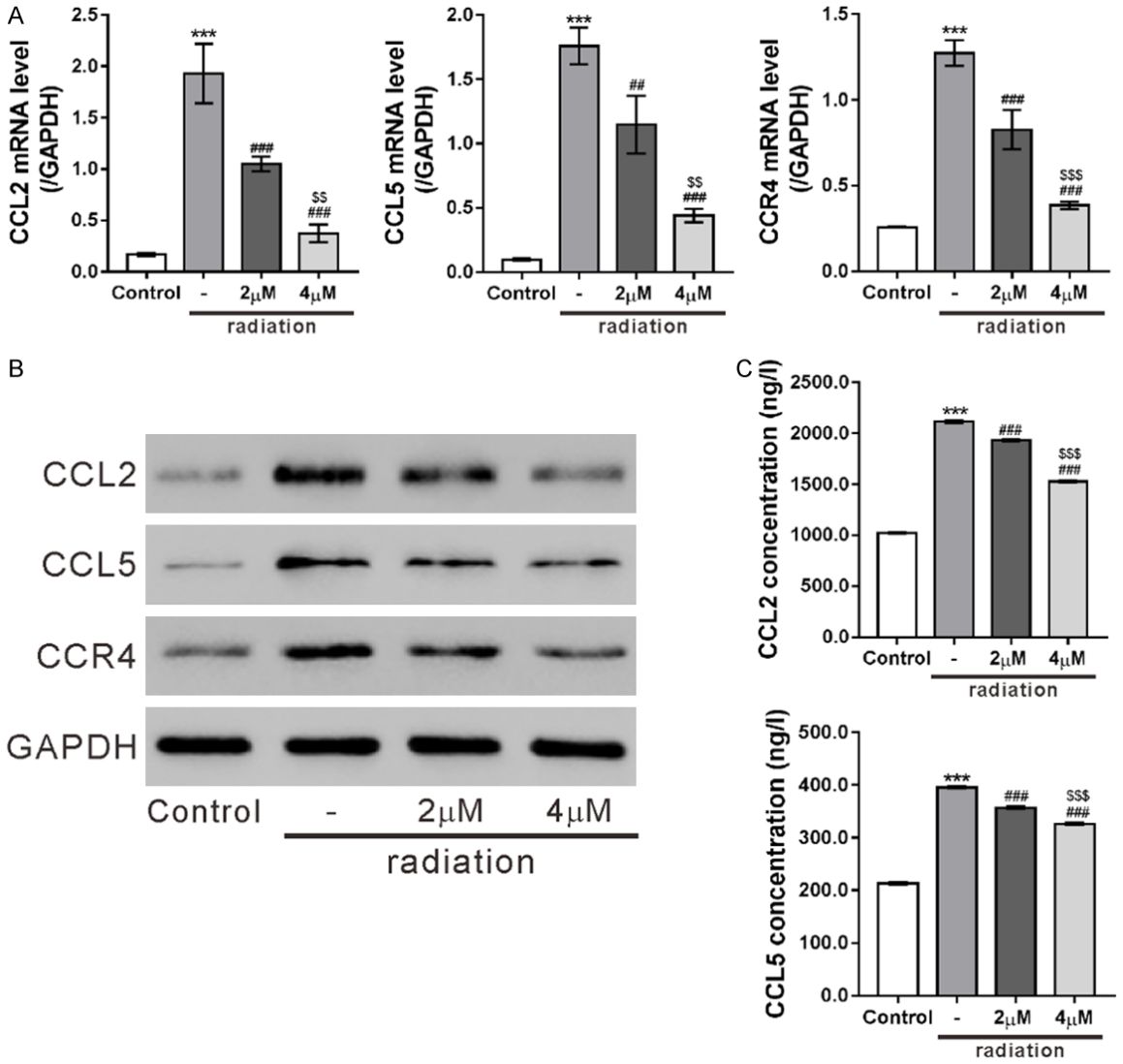

Figure 5. Ophiopogonin B (OP-B) inhibited CCL2, CCL5 and CCR4 in HPAEpic cells. HPAEpic cells were pre-treated with 0, 2 or 4 mM OP-B for 2 h, then subjected to radiation (8 Gray) and cultured for another 24 h. Cells without any treatment were served as negative control. The mRNA and protein expression of CCL2, CCL5 and CCR4 was assessed by real-time PCR analysis (A) and western blotting (B), respectively. (C) The release of CCL2 and CCL5 in the culture medium was detected by ELISA assays. ***P<0.001 versus Control; ##P<0.01, ###P<0.001 versus radiation; $$P<0.01, $$$P<0.001 versus 2 mM OP-B + radiation.

radiation treatment (**Figure 3**). Further, CCL2 and CCL5 treatment could decrease E-cadherin expression and increased Vimentin expression, suggested the direct promotion effect of CCL2 and CCL5 on the EMT in HPAEpic cells (**Figure 6C**). Such effect was weakened by CCR4 knockdown, which suggesting that CCR4 mediated the EMT promoting effect of CCL2 and CCL5.

Ophiopogon decoction can prevent radiation pulmonary injury in rats [18], which prompted us to study the effects of ophiopogonin B, a bioactive ingredient of ophiopogon on irradiation-treated HPAEpic cells. In this study, ophiopogonin B attenuated radiation-induced EMT of HPAEpic cells as indicated by the changes of morphology and the levels of EMT-related proteins (**Figure 4**). More importantly, ophiopogonin B could reduce irradiation-induced expression of CCL2, CCL5 and CCR4, and attenuated the EMT promoting effect of CCL2 and CCL5. These data suggested that ophiopogonin B could protect alveolar epithelial cells from irra-

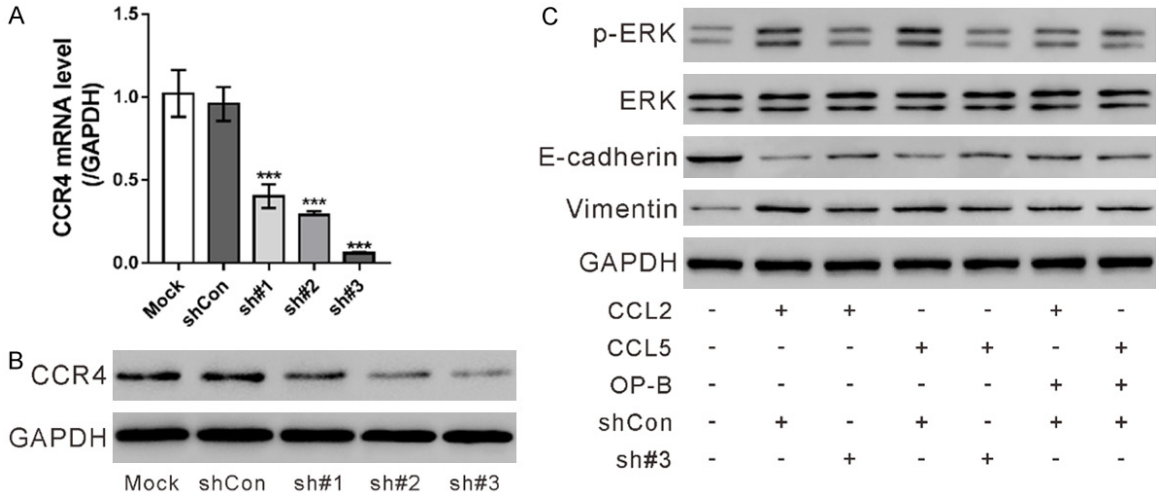

Figure 6. CCR4 knockdown and ophiopogonin B (OP-B) affected the levels of EMT-related proteins in CCL2 or CCL5 treated HPAEpic cells. (A, B) HPAEpic cells were transduced with CCR4 shRNAs (sh#1, sh#2 and sh#3) or control shRNA (shCon). The mRNA and protein expression of CCR4 was assessed by real-time PCR (A) and western blotting analysis (B), respectively, at 48 h post transduction. Cells without any treatment (Mock) were used as negative control. ***P<0.001 versus shCon. (C) HPAEpic cells were divided into 7 groups and pre-treated with shCon or sh#3 for 24 h, or with 4 mM OP-B for 2 h, and then exposed to 100 ng/ml CCL2 (R&D Systems, Minneapolis, MN, USA) or CCL5 (R&D Systems) or not as indicated for 24 h. The levels of E-cadherin, Vimentin, p-ERK and ERK was detected by western blotting.

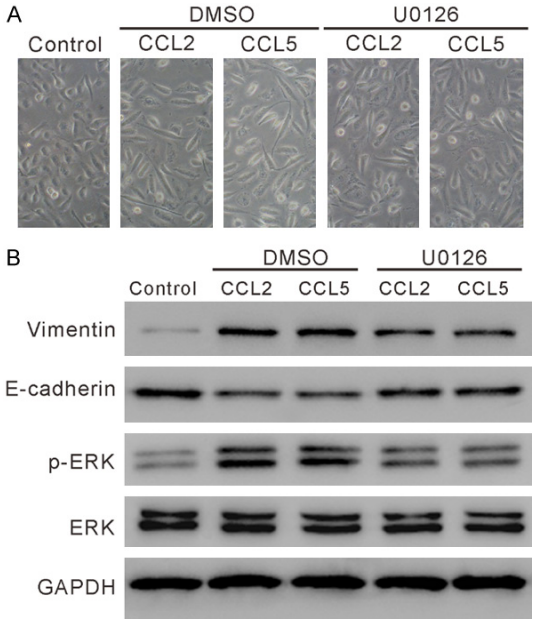

Figure 7. U0126 suppressed CCL2 or CCL5-induced EMT. HPAEpic cells were pre-treated with 10 mM U0126 (Selleck Chemicals, Houston, TX, USA) or DMSO for 2 h and then exposed to 100 ng/ml CCL2 (R&D Systems, Minneapolis, MN, USA) or CCL5 (R&D Systems) as indicated for 24 h. Cells without any treatment were served as negative control. A. Cell morphology was observed under a microscope. The representative phase contrast images from three independent experiments are shown (magnification 200×). B. The levels of E-cadherin, Vimentin, p-ERK and ERK was detected by western blotting.

diation-induced EMT. Ophiopogonin B may be an effective radioprotective agent via downregulating CCL2 and CCL5, although further experiments with animal models are required.

The ERK signaling pathway is an important regulatory factor in radiation-induced EMT [10, 25]. Here, Ophiopogonin B decreased radiation-induced phosphorylation of ERK (**Figure 4B**), which was in line was previous findings in human gastric cancer cells [22]. Evidence has been presented for the involvement of CCL2, CCL5 and CCR4 in the ERK signaling pathway. CCL2 [31] and CCL5 [32] could enhance the migration of chondrosarcoma and osteosarcoma cells respectively by activating the ERK signaling. CCR4 facilitated colon cancer cells metastasis via ERK/NF-κB/MMP13 pathway [33] and hepatocellular carcinoma cell metastases via ERK/AKT/MMP2 pathway [34]. Consistently with the previous findings, CCL2 and CCL5 treatment increased the phosphorylation of ERK, which was dependent on the expression of CCR4 (**Figure 6C**). U0126, a MEK/ERK inhibitor, attenuated the EMT promoting effect of CCL2 and CCL5 (**Figure 7**). Moreover, ophiopogonin B could also attenuate the promoting effect of CCL2 and CCL5 on ERK phosphorylation. Thus, we speculated that ophiopogonin B effectively improved radiation-

induced EMT through CCL2-CCL5/CCR4/ERK signaling.

Collectively, we reported the expression profile of AECs in response to irradiation. We found that CCL2-CCL5/CCR4 was involved in radiation-induced AECs EMT via the ERK signaling. Our data suggested CCL2, CCL5 and CCR4 may be potential therapeutic targets for radiation-induced lung toxicity. Ophiopogonin B, which could down-regulate CCL2, CCL5 and CCR4, may be a useful radioprotective agent.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Identification of significantly up-regulated genes in irradiated HPAEpiC cells using RNA-seq

Gene_ID	Symbol	log2 Fold Change	*P* value
ENSG00000283515	CTD-3138B18.4	6.241	0.0477
ENSG00000162692	VCAM1	5.934	8.72E-23
ENSG00000213886	UBD	4.904	4.32E-11
ENSG00000271503	CCL5	4.850	1.65E-120
ENSG00000134321	RSAD2	4.535	1.30E-08
ENSG00000131203	IDO1	4.520	1.03E-08
ENSG00000152463	OLAH	4.473	2.66E-08
ENSG00000257529	RPL36A-HNRNPH2	4.370	1.22E-16
ENSG00000160188	RSPH1	4.365	8.53E-08
ENSG00000162490	DRAXIN	4.303	8.53E-09
ENSG00000224294	RP3-326I13.1	4.271	2.95E-09
ENSG00000090512	FETUB	4.270	3.31E-07
ENSG00000135114	OASL	3.978	4.35E-90
ENSG00000143632	ACTA1	3.892	9.86E-07
ENSG00000174343	CHRNA9	3.861	7.32E-07
ENSG00000198203	SULT1C2	3.830	3.36E-05
ENSG00000136999	NOV	3.795	1.87E-06
ENSG00000189058	APOD	3.786	4.72E-05
ENSG00000078081	LAMP3	3.746	5.82E-05
ENSG00000125735	TNFSF14	3.685	5.69E-06
ENSG00000107187	LHX3	3.681	9.64E-05
ENSG00000251095	RP11-115D19.1	3.647	1.89E-07
ENSG00000231574	KCCAT211	3.642	4.81E-05
ENSG00000258590	NBEAP1	3.632	2.04E-08
ENSG00000186847	KRT14	3.617	0.0001
ENSG00000144452	ABCA12	3.610	5.04E-36
ENSG00000111335	OAS2	3.603	1.37E-42
ENSG00000255398	HCAR3	3.603	0.0002
ENSG00000261150	EPPK1	3.592	5.62E-08
ENSG00000162654	GBP4	3.590	3.02E-17
ENSG00000168314	MOBP	3.570	0.0002
ENSG00000234754	C1orf140	3.559	0.0002
ENSG00000117707	PROX1	3.543	0.0003
ENSG00000246145	RRS1-AS1	3.535	0.0003
ENSG00000227028	SLC8A1-AS1	3.532	3.92E-08
ENSG00000260704	LINC00543	3.500	0.0004
ENSG00000182676	PPP1R27	3.491	0.0003
ENSG00000198573	SPANXC	3.475	0.0004
ENSG00000115461	IGFBP5	3.463	0.0004
ENSG00000237512	UNC5B-AS1	3.461	5.52E-05
ENSG00000120675	DNAJC15	3.456	0.0004
ENSG00000262445	CTD-2545H1.2	3.441	0.0005
ENSG00000249396	RP11-1C1.4	3.398	0.0006
ENSG00000113494	PRLR	3.390	0.0001
ENSG00000125538	IL1B	3.374	9.73E-07
ENSG00000019186	CYP24A1	3.366	5.12E-22
ENSG00000263155	MYZAP	3.345	1.93E-06

ENSG00000134042	MRO	3.342	0.0009
ENSG00000213626	LBH	3.337	3.38E-16
ENSG00000183072	NKX2-5	3.335	0.0002
ENSG00000128422	KRT17	3.331	0.0002
ENSG00000176532	PRR15	3.322	3.62E-07
ENSG00000113140	SPARC	3.315	8.07E-07
ENSG00000278626	RP11-467L19.16	3.300	0.0011
ENSG00000189275	LINC01164	3.296	1.10E-06
ENSG00000150551	LYPD1	3.280	4.46E-05
ENSG00000133106	EPSTI1	3.273	3.04E-07
ENSG00000065320	NTN1	3.267	2.49E-07
ENSG00000278919	AP006285.2	3.257	0.0013
ENSG00000047936	ROS1	3.245	0.0014
ENSG00000144488	ESPNL	3.237	0.0014
ENSG00000259783	RP11-1006G14.2	3.234	0.0015
ENSG00000228010	AC073343.13	3.229	0.0016
ENSG00000182759	MAFA	3.225	0.0009
ENSG00000256612	CYP2B7P	3.221	0.0008
ENSG00000168878	SFTPB	3.220	0.0058
ENSG00000168685	IL7R	3.207	2.90E-15
ENSG00000260807	RP11-161M6.2	3.201	0.0018
ENSG00000154451	GBP5	3.200	0.0019
ENSG00000163554	SPTA1	3.193	0.0019
ENSG00000108342	CSF3	3.190	0.0007
ENSG00000234465	PINLYP	3.189	0.0019
ENSG00000162511	LAPTM5	3.188	4.39E-17
ENSG00000175426	PCSK1	3.181	0.0020
ENSG00000178573	MAF	3.180	0.0020
ENSG00000100234	TIMP3	3.177	0.0016
ENSG00000229056	AC020571.3	3.175	0.0011
ENSG00000101203	COL20A1	3.144	0.0007
ENSG00000265096	C1QTNF1-AS1	3.132	2.28E-05
ENSG00000166257	SCN3B	3.126	0.0027
ENSG00000173947	PIFO	3.105	0.0029
ENSG00000176040	TMPRSS7	3.102	0.0029
ENSG00000189350	FAM179A	3.101	0.0028
ENSG00000136531	SCN2A	3.080	0.0011
ENSG00000093072	CECR1	3.079	4.80E-05
ENSG00000274570	SPDYE10P	3.069	0.0031
ENSG00000248587	GDNF-AS1	3.066	0.0035
ENSG00000026751	SLAMF7	3.059	0.0031
ENSG00000282851	BISPR	3.054	0.0038
ENSG00000176746	MAGEB6	3.049	0.0039
ENSG00000138622	HCN4	3.048	0.0039
ENSG00000135423	GLS2	3.047	0.0004
ENSG00000144837	PLA1A	3.044	0.0027
ENSG00000254973	RP11-429J17.7	3.024	0.0038
ENSG00000165025	SYK	3.014	0.0043
ENSG00000170523	KRT83	3.014	0.0043
ENSG00000272168	CASC15	2.997	0.0005

ENSG00000268089	GABRQ	2.981	0.0046
ENSG00000130487	KLHDC7B	2.976	0.0043
ENSG00000148204	CRB2	2.965	0.0055
ENSG00000279296	RP11-609D21.3	2.965	0.0056
ENSG00000163017	ACTG2	2.964	0.0051
ENSG00000133665	DYDC2	2.964	0.0023
ENSG00000276633	AJ011931.1	2.954	0.0053
ENSG00000168621	GDNF	2.953	9.52E-05
ENSG00000164116	GUCY1A3	2.949	0.0049
ENSG00000144671	SLC22A14	2.944	0.0054
ENSG00000172738	TMEM217	2.938	0.0047
ENSG00000243232	PCDHAC2	2.936	0.0004
ENSG00000164849	GPR146	2.934	2.63E-12
ENSG00000100867	DHRS2	2.934	1.60E-33
ENSG00000146038	DCDC2	2.922	4.82E-05
ENSG00000160588	MPZL3	2.909	0.0070
ENSG00000170477	KRT4	2.909	0.0071
ENSG00000261730	RP4-668J24.2	2.906	0.0027
ENSG00000279608	RP11-182N22.9	2.904	0.0031
ENSG00000142149	HUNK	2.902	0.0063
ENSG00000197046	SIGLEC15	2.894	0.0044
ENSG00000137033	IL33	2.889	0.0035
ENSG00000188404	SELL	2.884	1.91E-08
ENSG00000154864	PIEZO2	2.877	0.0037
ENSG00000136514	RTP4	2.877	7.79E-05
ENSG00000127252	HRASLS	2.871	0.0073
ENSG00000132164	SLC6A11	2.860	0.0086
ENSG00000120949	TNFRSF8	2.857	0.0137
ENSG00000231453	LINC01305	2.847	0.0079
ENSG00000102935	ZNF423	2.838	0.0039
ENSG00000007908	SELE	2.832	0.0076
ENSG00000138829	FBN2	2.829	0.0002
ENSG00000267890	CTD-2126E3.4	2.824	0.0095
ENSG00000143217	NECTIN4	2.819	1.12E-24
ENSG00000271553	RP11-274B21.10	2.817	0.0052
ENSG00000110042	DTX4	2.813	1.79E-12
ENSG00000228882	CICP9	2.811	0.0090
ENSG00000073282	TP63	2.809	0.0172
ENSG00000090339	ICAM1	2.804	9.80E-33
ENSG00000161544	CYGB	2.795	2.11E-23
ENSG00000082074	FYB	2.783	0.0027
ENSG00000166407	LMO1	2.775	0.0215
ENSG00000245468	RP11-367J11.3	2.774	0.0005
ENSG00000133107	TRPC4	2.771	0.0118
ENSG00000143631	FLG	2.768	0.0205
ENSG00000223511	RP13-297E16.4	2.765	0.0067
ENSG00000187479	C11orf96	2.760	0.0006
ENSG00000147689	FAM83A	2.746	0.0105
ENSG00000271977	AC226119.4	2.740	0.0064

ENSG00000106123	EPHB6	2.739	0.0137
ENSG00000267251	AC139100.3	2.738	0.0077
ENSG00000226965	AC003088.1	2.736	0.0003
ENSG00000267454	ZNF582-AS1	2.729	0.0004
ENSG00000122641	INHBA	2.723	0.0040
ENSG00000282308	DPRXP3	2.723	0.0142
ENSG00000130768	SMPDL3B	2.721	0.0004
ENSG00000115155	OTOF	2.720	0.0109
ENSG00000274322	RP11-314N13.10	2.716	0.0010
ENSG00000105246	EBI3	2.703	1.06E-26
ENSG00000015520	NPC1L1	2.695	0.0142
ENSG00000128594	LRRC4	2.695	0.0276
ENSG00000137673	MMP7	2.695	9.88E-08
ENSG00000253295	RP11-779O18.1	2.694	0.0144
ENSG00000136274	NACAD	2.693	0.0009
ENSG00000158301	GPRASP2	2.693	8.01E-05
ENSG00000189157	FAM47E	2.690	0.0010
ENSG00000042832	TG	2.689	0.0161
ENSG00000095713	CRTAC1	2.683	1.08E-07
ENSG00000223382	RP5-1125N11.2	2.672	0.0156
ENSG00000163293	NIPAL1	2.659	0.0007
ENSG00000139364	TMEM132B	2.656	0.0332
ENSG00000177098	SCN4B	2.653	0.0180
ENSG00000167617	CDC42EP5	2.653	0.0255
ENSG00000124749	COL21A1	2.647	3.41E-06
ENSG00000147614	ATP6V0D2	2.645	0.0169
ENSG00000267629	AC138430.4	2.636	0.0006
ENSG00000271810	RP11-426L16.10	2.635	0.0108
ENSG00000169439	SDC2	2.630	0.0088
ENSG00000214381	LINC00488	2.626	1.01E-08
ENSG00000173432	SAA1	2.625	2.22E-13
ENSG00000260012	RP11-329J18.4	2.621	0.0183
ENSG00000224936	SUCLA2P1	2.617	0.0167
ENSG00000280326	RP11-642A1.1	2.612	0.0195
ENSG00000170961	HAS2	2.608	0.0122
ENSG00000268423	AC011551.3	2.605	0.0195
ENSG00000283293	RN7SK	2.602	0.0127
ENSG00000184867	ARMCX2	2.599	0.0128
ENSG00000161643	SIGLEC16	2.599	0.0201
ENSG00000166183	ASPG	2.599	0.0206
ENSG00000147889	CDKN2A	2.597	0.0124
ENSG00000183813	CCR4	2.590	0.0138
ENSG00000277406	CH17-385C13.2	2.590	0.0222
ENSG00000162438	CTRC	2.586	0.0189
ENSG00000186310	NAP1L3	2.586	6.49E-08
ENSG00000166707	ZCCHC18	2.585	0.0152
ENSG00000230408	AC007163.6	2.585	0.0332
ENSG00000184809	B3GALT5-AS1	2.583	0.0206
ENSG00000250234	CTD-2024P10.1	2.581	0.0226

ENSG00000136928	GABBR2	2.581	0.0226
ENSG00000226673	LINC01108	2.579	0.0213
ENSG00000136275	C7orf69	2.575	0.0009
ENSG00000095932	SMIM24	2.572	0.0256
ENSG00000161896	IP6K3	2.570	4.56E-11
ENSG00000095585	BLNK	2.562	0.0137
ENSG00000161958	FGF11	2.561	1.91E-08
ENSG00000279455	RP11-495K9.10	2.538	0.0185
ENSG00000235770	LINC00607	2.536	0.0026
ENSG00000224721	AC007182.6	2.533	0.0319
ENSG00000010319	SEMA3G	2.533	0.0243
ENSG00000142449	FBN3	2.533	0.0243
ENSG00000204335	SP5	2.529	0.0273
ENSG00000007062	PROM1	2.529	0.0253
ENSG00000103313	MEFV	2.525	0.0031
ENSG00000164400	CSF2	2.524	2.97E-12
ENSG00000273079	GRIN2B	2.521	0.0202
ENSG00000261121	RP11-496D24.2	2.519	0.0152
ENSG00000184156	KCNQ3	2.518	1.40E-10
ENSG00000260604	RP1-140K8.5	2.510	0.0019
ENSG00000277502	uc_338	2.509	0.0010
ENSG00000187017	ESPN	2.509	0.0095
ENSG00000081277	PKP1	2.507	0.0229
ENSG00000153012	LGI2	2.506	5.49E-07
ENSG00000183128	CALHM3	2.502	0.0040
ENSG00000161270	NPHS1	2.498	0.0030
ENSG00000154258	ABCA9	2.496	0.0175
ENSG00000276953	TRBV12-4	2.495	0.0265
ENSG00000154589	LY96	2.494	0.0217
ENSG00000107954	NEURL1	2.491	0.0184
ENSG00000283265	RP11-95M15.3	2.491	0.0297
ENSG00000272908	RP11-121A8.1	2.489	0.0222
ENSG00000258593	CTD-3051D23.4	2.486	0.0181
ENSG00000116132	PRRX1	2.484	0.0295
ENSG00000227938	AC104695.4	2.481	0.0268
ENSG00000127325	BEST3	2.480	0.0013
ENSG00000181378	CFAP65	2.478	0.0168
ENSG00000152049	KCNE4	2.473	0.0305
ENSG00000261644	RP11-327F22.1	2.470	0.0307
ENSG00000186047	DLEU7	2.469	0.0203
ENSG00000273294	C1QTNF3-AMACR	2.466	0.0204
ENSG00000137965	IFI44	2.457	5.23E-33
ENSG00000128683	GAD1	2.456	0.0041
ENSG00000257925	RP11-493L12.3	2.454	0.0060
ENSG00000144908	ALDH1L1	2.447	0.0306
ENSG00000243478	AOX2P	2.446	0.0191
ENSG00000225899	FRG2B	2.443	0.0297
ENSG00000272459	RP11-1277A3.3	2.442	0.0188
ENSG00000152779	SLC16A12	2.439	0.0032

ENSG00000171234	UGT2B7	2.438	0.0328
ENSG00000235244	DANT2	2.436	0.0305
ENSG00000169126	ARMC4	2.436	0.0220
ENSG00000109625	CPZ	2.430	4.24E-07
ENSG00000130477	UNC13A	2.430	3.75E-23
ENSG00000125730	C3	2.428	1.68E-145
ENSG00000188897	CTD-3088G3.8	2.425	2.05E-06
ENSG00000266913	CTC-548K16.2	2.425	0.0213
ENSG00000183831	ANKRD45	2.417	0.0307
ENSG00000229278	RP11-483F11.7	2.417	0.0327
ENSG00000012779	ALOX5	2.417	0.0451
ENSG00000152229	PSTPIP2	2.415	2.20E-28
ENSG00000137975	CLCA2	2.414	0.0247
ENSG00000223638	RFPL4A	2.412	0.0331
ENSG00000272273	XXbac-BPG252P9.10	2.411	0.0336
ENSG00000185640	KRT79	2.407	0.0375
ENSG00000158473	CD1D	2.406	0.0377
ENSG00000187608	ISG15	2.399	3.77E-63
ENSG00000134853	PDGFRA	2.395	0.0121
ENSG00000223949	ROR1-AS1	2.394	0.0327
ENSG00000178462	TUBAL3	2.393	0.0329
ENSG00000196562	SULF2	2.392	1.04E-47
ENSG00000158258	CLSTN2	2.391	0.0043
ENSG00000272159	RP11-350N15.6	2.389	0.0197
ENSG00000251665	RP11-700H6.2	2.388	0.0379
ENSG00000272551	RP11-324L17.1	2.387	0.0263
ENSG00000257767	RP11-162P23.2	2.387	0.0256
ENSG00000222000	AC092675.3	2.385	0.0388
ENSG00000183067	IGSF5	2.385	0.0388
ENSG00000263823	RP11-326K13.4	2.383	0.0063
ENSG00000197915	HRNR	2.374	0.0145
ENSG00000138615	CILP	2.370	0.0050
ENSG00000187288	CIDEC	2.366	0.0247
ENSG00000205978	NYNRIN	2.365	7.86E-07
ENSG00000174611	KY	2.360	0.0375
ENSG00000170703	TTLL6	2.359	1.51E-05
ENSG00000011590	ZBTB32	2.357	0.0122
ENSG00000258952	SALRNA1	2.357	0.0438
ENSG00000144481	TRPM8	2.356	0.0081
ENSG00000259627	RP11-244F12.2	2.355	0.0445
ENSG00000187848	P2RX2	2.353	0.0394
ENSG00000120278	PLEKHG1	2.351	2.65E-08
ENSG00000260777	CTD-2008P7.1	2.344	3.04E-07
ENSG00000253347	CTD-2026D20.2	2.344	0.0396
ENSG00000250893	RP11-588L15.2	2.342	0.0403
ENSG00000266978	CTD-2369P2.5	2.340	0.0420
ENSG00000180644	PRF1	2.339	0.0447
ENSG00000121858	TNFSF10	2.338	0.0057
ENSG00000169429	CXCL8	2.335	4.67E-70

ENSG00000162676	GFI1	2.334	0.0060
ENSG00000077522	ACTN2	2.333	0.0463
ENSG00000007350	TKTL1	2.333	0.0463
ENSG00000254980	RP11-794P6.6	2.322	0.0473
ENSG00000273139	XXbac-B444P24.14	2.320	0.0329
ENSG00000187994	RINL	2.320	4.57E-12
ENSG00000133256	PDE6B	2.319	0.0474
ENSG00000136918	WDR38	2.318	0.0356
ENSG00000134627	PIWIL4	2.317	0.0435
ENSG00000237975	FLG-AS1	2.314	0.0260
ENSG00000113212	PCDHB7	2.314	0.0356
ENSG00000253102	RP1-117B12.4	2.313	0.0328
ENSG00000169432	SCN9A	2.305	0.0441
ENSG00000224897	POT1-AS1	2.305	0.0358
ENSG00000132915	PDE6A	2.302	1.40E-05
ENSG00000270000	RP3-449M8.9	2.299	0.0448
ENSG00000260643	RP11-303E16.8	2.299	0.0017
ENSG00000119283	TRIM67	2.295	8.67E-28
ENSG00000268738	HSFX2	2.295	0.0323
ENSG00000119917	IFIT3	2.294	1.03E-68
ENSG00000154262	ABCA6	2.285	0.0471
ENSG00000241489	AF011889.5	2.280	3.49E-12
ENSG00000120156	TEK	2.280	0.0100
ENSG00000116183	PAPPA2	2.279	0.0076
ENSG00000101276	SLC52A3	2.275	0.0489
ENSG00000175229	GAL3ST3	2.274	0.0497
ENSG00000198576	ARC	2.272	8.38E-05
ENSG00000221381	SNORD88B	2.266	0.0034
ENSG00000147485	PXDNL	2.260	0.0131
ENSG00000233198	RNF224	2.259	0.0154
ENSG00000179362	HMGN2P46	2.259	0.0077
ENSG00000185933	CALHM1	2.258	0.0363
ENSG00000137959	IFI44L	2.257	0.0007
ENSG00000204967	PCDHA4	2.250	4.58E-10
ENSG00000198788	MUC2	2.247	0.0014
ENSG00000145708	CRHBP	2.246	0.0383
ENSG00000232709	MARK2P9	2.245	0.0099
ENSG00000257894	RP1-78O14.1	2.241	0.0179
ENSG00000233554	B4GALT1-AS1	2.240	0.0097
ENSG00000021645	NRXN3	2.240	0.0011
ENSG00000254143	RP11-470M17.2	2.238	0.0457
ENSG00000120324	PCDHB10	2.238	0.0154
ENSG00000185338	SOCS1	2.233	0.0279
ENSG00000260454	RP11-367F23.2	2.222	0.0407
ENSG00000260784	AC026150.6	2.219	0.0079
ENSG00000163739	CXCL1	2.215	2.17E-37
ENSG00000066056	TIE1	2.212	0.0285
ENSG00000164342	TLR3	2.209	2.43E-13
ENSG00000185924	RTN4RL1	2.204	8.71E-33

ENSG00000138271	GPR87	2.203	0.0454
ENSG00000189431	RASSF10	2.202	1.44E-12
ENSG00000151067	CACNA1C	2.200	0.0418
ENSG00000130303	BST2	2.197	0.0214
ENSG00000116701	NCF2	2.197	4.01E-12
ENSG00000232471	RP11-241F15.7	2.189	0.0129
ENSG00000147606	SLC26A7	2.188	0.0237
ENSG00000283201	RP11-15H20.8	2.188	0.0010
ENSG00000132274	TRIM22	2.185	7.37E-40
ENSG00000277586	NEFL	2.185	7.45E-27
ENSG00000228021	RP11-383C5.3	2.182	0.0031
ENSG00000079385	CEACAM1	2.181	5.42E-11
ENSG00000165376	CLDN2	2.180	1.81E-19
ENSG00000123342	MMP19	2.174	5.74E-12
ENSG00000183690	EFHC2	2.173	0.0195
ENSG00000171345	KRT19	2.172	0.0491
ENSG00000185742	C11orf87	2.171	0.0207
ENSG00000263050	RP11-667K14.3	2.170	0.0392
ENSG00000019169	MARCO	2.169	0.0008
ENSG00000136378	ADAMTS7	2.168	5.42E-44
ENSG00000042062	FAM65C	2.162	0.0144
ENSG00000259342	RP11-519G16.5	2.148	0.0223
ENSG00000128510	CPA4	2.146	1.33E-75
ENSG00000158270	COLEC12	2.144	7.31E-07
ENSG00000107731	UNC5B	2.138	0.0038
ENSG00000234444	ZNF736	2.137	0.0199
ENSG00000104848	KCNA7	2.130	0.0312
ENSG00000049249	TNFRSF9	2.128	1.04E-20
ENSG00000272896	RP11-216L13.17	2.124	0.0499
ENSG00000271447	MMP28	2.123	0.0003
ENSG00000173557	C2orf70	2.122	0.0208
ENSG00000085117	CD82	2.120	1.72E-56
ENSG00000273983	HIST1H3G	2.117	0.0009
ENSG00000064300	NGFR	2.113	5.77E-07
ENSG00000240219	RP11-430C7.5	2.111	2.92E-07
ENSG00000119922	IFIT2	2.110	1.39E-60
ENSG00000259828	RP11-63E9.1	2.108	0.0221
ENSG00000248360	LINC00504	2.102	0.0224
ENSG00000135373	EHF	2.096	0.0167
ENSG00000228146	CASP16P	2.090	0.0239
ENSG00000162643	WDR63	2.084	1.79E-12
ENSG00000144852	NR1I2	2.077	0.0241
ENSG00000261744	RP11-21B21.4	2.074	0.0254
ENSG00000109072	VTN	2.067	1.17E-05
ENSG00000108691	CCL2	2.057	6.42E-16
ENSG00000226472	RP11-551L14.4	2.056	0.0026
ENSG00000135517	MIP	2.052	0.0340
ENSG00000134339	SAA2	2.047	0.0250
ENSG00000244649	CTD-2377D24.6	2.042	0.0326

ENSG00000246228	CASC8	2.042	0.0372
ENSG00000283233	AL034550.1	2.038	0.0019
ENSG00000237945	LINC00649	2.036	0.0449
ENSG00000157782	CABP1	2.030	0.0260
ENSG00000100346	CACNA1I	2.027	0.0310
ENSG00000260136	CTD-2270L9.4	2.024	2.43E-10
ENSG00000228363	AC015971.2	2.021	0.0009
ENSG00000141338	ABCA8	2.014	0.0449
ENSG00000255974	CYP2A6	2.012	0.0034
ENSG00000137699	TRIM29	2.008	0.0322
ENSG00000132517	SLC52A1	2.007	6.84E-13
ENSG00000178947	SMIM10L2A	2.003	1.40E-10
ENSG00000140279	DUOX2	2.002	0.0380
ENSG00000230495	RP11-462D18.2	1.998	0.0389
ENSG00000254783	RP11-320L11.2	1.990	0.0420
ENSG00000138449	SLC40A1	1.988	6.11E-33
ENSG00000145029	NICN1	1.988	5.41E-06
ENSG00000150687	PRSS23	1.987	0.0006
ENSG00000215481	BCRP3	1.985	0.0011
ENSG00000105509	HAS1	1.981	1.46E-05
ENSG00000251615	RP11-77403.3	1.980	0.0004
ENSG00000110169	HPX	1.975	6.27E-06
ENSG00000239670	RP4-803A2.2	1.972	0.0364
ENSG00000128340	RAC2	1.970	0.0381
ENSG00000178033	FAM26E	1.970	2.12E-05
ENSG00000131737	KRT34	1.963	0.0347
ENSG00000164379	FOXQ1	1.959	0.0358
ENSG00000100100	PIK3IP1	1.958	1.97E-27
ENSG00000159450	TCHH	1.957	0.0003
ENSG00000182175	RGMA	1.953	0.0421
ENSG00000204947	ZNF425	1.950	1.60E-12
ENSG00000091583	APOH	1.949	1.68E-05
ENSG00000100033	PRODH	1.949	0.0007
ENSG00000248671	ALG1L9P	1.948	0.0123
ENSG00000182704	TSKU	1.946	0.0428
ENSG00000205426	KRT81	1.942	8.78E-41
ENSG00000237961	RP11-1281K21.1	1.942	2.49E-08
ENSG00000182329	KIAA2012	1.939	0.0459
ENSG00000145002	FAM86B2	1.937	0.0472
ENSG00000161328	LRRC56	1.929	2.74E-05
ENSG00000236098	RP11-148B18.4	1.920	0.0403
ENSG00000197191	CYSRT1	1.918	7.70E-14
ENSG00000133321	RARRES3	1.915	2.29E-10
ENSG00000169085	C8orf46	1.914	1.14E-05
ENSG00000168824	NSG1	1.899	1.46E-06
ENSG00000167703	SLC43A2	1.895	3.93E-29
ENSG00000169435	RASSF6	1.895	0.0356
ENSG00000119630	PGF	1.885	7.95E-12
ENSG00000185904	LINC00839	1.882	0.0386

ENSG00000225950	NTF4	1.878	0.0106
ENSG00000173918	C1QTNF1	1.870	7.32E-75
ENSG00000123610	TNFAIP6	1.857	0.0499
ENSG00000166145	SPINT1	1.855	6.32E-10
ENSG00000117228	GBP1	1.850	6.05E-19
ENSG00000183114	FAM43B	1.848	0.0011
ENSG00000167100	SAMD14	1.845	0.0003
ENSG00000176907	C8orf4	1.842	6.32E-30
ENSG00000144182	LIPT1	1.840	1.31E-11
ENSG00000267469	AC005944.2	1.839	0.0068
ENSG00000272597	RP11-446H18.6	1.834	0.0177
ENSG00000283020	DUX4L37	1.833	0.0335
ENSG00000113211	PCDHB6	1.832	0.0002
ENSG00000240970	RPL23AP64	1.826	0.0142
ENSG00000180155	LYNX1	1.816	1.42E-18
ENSG00000171444	MCC	1.814	7.84E-17
ENSG00000100302	RASD2	1.805	6.90E-10
ENSG00000182568	SATB1	1.798	0.0026
ENSG00000136114	THSD1	1.797	1.21E-53
ENSG00000134762	DSC3	1.780	8.84E-33
ENSG00000163453	IGFBP7	1.779	1.41E-36
ENSG00000279718	SNX18P12	1.778	7.78E-22
ENSG00000134326	CMPK2	1.777	0.0001
ENSG00000026103	FAS	1.772	1.60E-07
ENSG00000153294	ADGRF4	1.772	1.55E-36
ENSG00000187944	C2orf66	1.770	1.27E-05
ENSG00000170369	CST2	1.768	1.87E-08
ENSG00000137460	FHDC1	1.766	2.54E-10
ENSG00000163071	SPATA18	1.766	8.80E-30
ENSG00000168918	INPP5D	1.765	2.49E-07
ENSG00000067445	TRO	1.764	5.06E-06
ENSG00000107282	APBA1	1.755	0.0010
ENSG00000120057	SFRP5	1.752	0.0094
ENSG00000172748	ZNF596	1.746	9.43E-05
ENSG00000127129	EDN2	1.744	0.0030
ENSG00000138131	LOXL4	1.744	6.32E-18
ENSG00000168490	PHYHIP	1.741	0.0013
ENSG00000158023	WDR66	1.741	3.13E-10
ENSG00000183778	B3GALT5	1.741	0.0103
ENSG00000057704	TMCC3	1.733	0.0009
ENSG00000162415	ZSWIM5	1.732	1.38E-05
ENSG00000235142	RP1-60019.1	1.728	0.0002
ENSG00000100985	MMP9	1.727	0.0010
ENSG00000006283	CACNA1G	1.725	3.11E-29
ENSG00000107485	GATA3	1.722	1.14E-10
ENSG00000164938	TP53INP1	1.721	3.17E-38
ENSG00000101335	MYL9	1.720	7.72E-26
ENSG00000279204	RP11-175K6.2	1.716	0.0008
ENSG00000158683	PKD1L1	1.712	0.0009

ENSG00000167992	VWCE	1.706	4.28E-09
ENSG00000226674	TEX41	1.706	7.55E-05
ENSG00000279208	bP-21264C1.1	1.705	3.07E-19
ENSG00000104951	IL4I1	1.703	0.0314
ENSG00000177076	ACER2	1.700	2.10E-10
ENSG00000147573	TRIM55	1.700	0.0117
ENSG00000140839	CLEC18B	1.697	0.0072
ENSG00000160161	CILP2	1.688	0.0035
ENSG00000121552	CSTA	1.687	0.0019
ENSG00000183160	TMEM119	1.687	0.0068
ENSG00000169247	SH3TC2	1.684	8.86E-05
ENSG00000179292	TMEM151A	1.683	0.0002
ENSG00000215018	COL28A1	1.681	9.41E-05
ENSG00000130700	GATA5	1.681	0.0007
ENSG00000174125	TLR1	1.680	4.60E-11
ENSG00000128262	POM121L9P	1.676	0.0002
ENSG00000278590	RN7SL113P	1.675	0.0233
ENSG00000079931	MOXD1	1.674	3.89E-07
ENSG00000109846	CRYAB	1.671	0.0031
ENSG00000187699	C2orf88	1.666	0.0102
ENSG00000226535	RP11-417L14.1	1.664	0.0120
ENSG00000155629	PIK3AP1	1.662	0.0009
ENSG00000185728	YTHDF3	1.661	8.20E-37
ENSG00000230280	HNRNPA1P59	1.657	0.0067
ENSG00000115129	TP53I3	1.654	2.90E-73
ENSG00000157601	MX1	1.650	3.46E-13
ENSG00000100767	PAPLN	1.644	3.85E-21
ENSG00000275294	RP11-428O18.6	1.640	0.0307
ENSG00000065325	GLP2R	1.639	2.24E-32
ENSG00000150510	FAM124A	1.631	2.94E-08
ENSG00000248583	RP11-241F15.1	1.629	1.39E-11
ENSG00000106025	TSPAN12	1.629	0.0173
ENSG00000007264	MATK	1.628	5.61E-07
ENSG00000100298	APOBEC3H	1.624	8.91E-10
ENSG00000136367	ZFHX2	1.620	2.47E-11
ENSG00000249962	RP11-80H5.5	1.618	0.0475
ENSG00000165917	RAPSN	1.616	0.0116
ENSG00000164112	TMEM155	1.613	0.0078
ENSG00000128284	APOL3	1.612	2.79E-09
ENSG00000173805	HAP1	1.609	9.85E-07
ENSG00000250753	RP11-241F15.10	1.607	0.0119
ENSG00000244122	UGT1A7	1.607	9.05E-05
ENSG00000137868	STRA6	1.606	1.14E-12
ENSG00000152433	ZNF547	1.604	0.0100
ENSG00000149212	SESN3	1.602	0.0018
ENSG00000256124	LINC01152	1.602	0.0016
ENSG00000244694	PTCHD4	1.601	1.53E-05
ENSG00000165029	ABCA1	1.600	4.87E-68
ENSG00000073756	PTGS2	1.600	8.35E-14

ENSG00000135929	CYP27A1	1.591	0.0063
ENSG00000168874	ATOH8	1.588	3.88E-07
ENSG00000260912	RP11-363E7.4	1.585	1.02E-11
ENSG00000135525	MAP7	1.583	1.90E-12
ENSG00000144596	GRIP2	1.583	0.0244
ENSG00000187372	PCDHB13	1.580	0.0094
ENSG00000134668	SPOCD1	1.578	7.64E-17
ENSG00000280138	RP11-463O12.5	1.578	5.74E-11
ENSG00000132970	WASF3	1.574	0.0041
ENSG00000100557	C14orf105	1.571	0.0025
ENSG00000174567	GOLT1A	1.571	0.0001
ENSG00000222009	BTBD19	1.570	0.0041
ENSG00000185745	IFIT1	1.567	4.34E-24
ENSG00000151892	GFRA1	1.566	6.78E-08
ENSG00000183423	LRIT3	1.566	0.0214
ENSG00000099994	SUSD2	1.559	6.84E-08
ENSG00000150540	HNMT	1.558	1.74E-06
ENSG00000111344	RASAL1	1.555	0.0092
ENSG00000164695	CHMP4C	1.554	4.03E-06
ENSG00000140557	ST8SIA2	1.553	0.0141
ENSG00000215009	ACSM4	1.553	0.0270
ENSG00000197852	FAM212B	1.552	2.66E-11
ENSG00000163734	CXCL3	1.551	1.16E-10
ENSG00000137968	SLC44A5	1.549	0.0003
ENSG00000115008	IL1A	1.549	0.0036
ENSG00000198719	DLL1	1.548	0.0002
ENSG00000140465	CYP1A1	1.547	0.0025
ENSG00000107796	ACTA2	1.546	8.93E-38
ENSG00000056558	TRAF1	1.546	7.87E-40
ENSG00000008056	SYN1	1.544	0.0050
ENSG00000234537	RP11-100G15.7	1.544	0.0008
ENSG00000241962	RP11-111H13.1	1.544	0.0024
ENSG00000235618	FAM21EP	1.542	0.0063
ENSG00000008517	IL32	1.539	2.19E-22
ENSG00000175600	SUGCT	1.539	6.00E-11
ENSG00000237452	BHMG1	1.534	0.0176
ENSG00000272674	PCDHB16	1.532	0.0434
ENSG00000169896	ITGAM	1.532	1.76E-07
ENSG00000250337	LINC01021	1.532	2.12E-17
ENSG00000087085	ACHE	1.531	5.31E-10
ENSG00000112299	VNN1	1.529	9.99E-08
ENSG00000136383	ALPK3	1.529	0.0001
ENSG00000129910	CDH15	1.520	0.0046
ENSG00000188993	LRRC66	1.520	5.10E-05
ENSG00000111261	MANSC1	1.519	1.47E-09
ENSG00000259207	ITGB3	1.515	3.62E-39
ENSG00000095752	IL11	1.514	4.52E-20
ENSG00000271943	RP11-222K16.1	1.514	0.0478
ENSG00000214447	FAM187A	1.513	1.72E-31

ENSG00000230965	SNX18P13	1.512	0.0170
ENSG00000266680	RP5-1148A21.3	1.511	0.0003
ENSG00000171509	RXFP1	1.509	0.0014
ENSG00000213931	HBE1	1.509	0.0069
ENSG00000135679	MDM2	1.508	4.21E-71
ENSG00000186197	EDARADD	1.507	0.0004
ENSG00000278385	RP11-89H19.2	1.505	0.0249
ENSG00000021300	PLEKHB1	1.503	0.0030
ENSG00000169583	CLIC3	1.500	1.77E-14
ENSG00000157873	TNFRSF14	1.500	2.54E-07
ENSG00000225339	RP11-513I15.6	1.500	0.0042
ENSG00000103740	ACSBG1	1.499	2.88E-07
ENSG00000175040	CHST2	1.496	1.09E-15
ENSG00000165072	MAMDC2	1.494	5.37E-12
ENSG00000162738	VANGL2	1.493	0.0022
ENSG00000173013	CCDC96	1.493	2.94E-05
ENSG00000137393	RNF144B	1.487	1.03E-06
ENSG00000198108	CHSY3	1.487	0.0251
ENSG00000136244	IL6	1.484	1.54E-36
ENSG00000198520	C1orf228	1.483	1.13E-10
ENSG00000204131	NHSL2	1.481	9.12E-05
ENSG00000180422	LINC00304	1.480	0.0174
ENSG00000149633	KIAA1755	1.479	0.0137
ENSG00000116833	NR5A2	1.479	2.28E-11
ENSG00000140379	BCL2A1	1.478	8.67E-06
ENSG00000120327	PCDHB14	1.477	0.0002
ENSG00000167614	TTYH1	1.474	0.0080
ENSG00000197580	BCO2	1.472	0.0020
ENSG00000158825	CDA	1.471	5.49E-06
ENSG00000248596	RP11-844P9.5	1.467	0.0212
ENSG00000275445	CTD-2649C14.3	1.467	0.0409
ENSG00000145911	N4BP3	1.465	0.0019
ENSG00000050628	PTGER3	1.464	0.0025
ENSG00000175463	TBC1D10C	1.463	0.0472
ENSG00000253522	MIR3142HG	1.460	0.0306
ENSG00000166920	C15orf48	1.459	5.19E-42
ENSG00000179023	KLHDC7A	1.457	4.78E-09
ENSG00000251630	RP11-241F15.9	1.453	0.0472
ENSG00000151617	EDNRA	1.452	0.0162
ENSG00000164736	SOX17	1.452	0.0046
ENSG00000157064	NMNAT2	1.451	0.0003
ENSG00000163661	PTX3	1.444	7.23E-13
ENSG00000154822	PLCL2	1.444	7.11E-18
ENSG00000120322	PCDHB8	1.442	0.0079
ENSG00000186594	MIR22HG	1.440	9.77E-25
ENSG00000134548	SPX	1.439	2.69E-07
ENSG00000135636	DYSF	1.437	0.0015
ENSG00000164850	GPER1	1.435	0.0384
ENSG00000228412	RP4-625H18.2	1.434	0.0347

ENSG00000165556	CDX2	1.433	0.0230
ENSG00000159388	BTG2	1.430	1.16E-49
ENSG00000156510	HKDC1	1.427	1.44E-07
ENSG00000165887	ANKRD2	1.427	3.87E-05
ENSG00000105499	PLA2G4C	1.426	2.30E-19
ENSG00000275708	MIR3648-1	1.424	0.0080
ENSG00000172602	RND1	1.424	7.58E-08
ENSG00000173868	PHOSPHO1	1.420	1.12E-05
ENSG00000196872	KIAA1211L	1.416	2.40E-06
ENSG00000258376	RP4-647C14.2	1.416	1.98E-07
ENSG00000140519	RHCG	1.414	0.0005
ENSG00000253540	FAM86HP	1.410	0.0005
ENSG00000251455	RP11-164P12.3	1.409	0.0202
ENSG00000168481	LGI3	1.405	0.0049
ENSG00000139626	ITGB7	1.401	0.0066
ENSG00000254560	BBOX1-AS1	1.401	0.0149
ENSG00000264044	RP11-192H23.7	1.400	0.0265
ENSG00000144843	ADPRH	1.399	6.06E-05
ENSG00000153029	MR1	1.398	2.09E-30
ENSG00000170373	CST1	1.398	1.00E-07
ENSG00000270681	RP11-372K14.2	1.396	0.0230
ENSG00000226053	RP5-1070A16.1	1.395	0.0378
ENSG00000225969	ABHD11-AS1	1.395	0.0036
ENSG00000256540	RP11-598F7.6	1.392	0.0136
ENSG00000184347	SLIT3	1.391	1.47E-45
ENSG00000138311	ZNF365	1.391	0.0002
ENSG00000213760	ATP6V1G2	1.389	0.0339
ENSG00000171219	CDC42BPG	1.388	2.34E-07
ENSG00000068615	REEP1	1.384	0.0026
ENSG00000248751	RP1-130H16.18	1.384	0.0309
ENSG00000133687	TMTC1	1.384	0.0001
ENSG00000235609	AF127936.9	1.382	7.84E-05
ENSG00000055163	CYFIP2	1.381	1.36E-69
ENSG00000173678	SPDYE2B	1.381	0.0251
ENSG00000260328	RP11-416I2.1	1.378	4.06E-09
ENSG00000078237	TIGAR	1.377	8.09E-50
ENSG00000166446	CDYL2	1.377	0.0019
ENSG00000139567	ACVRL1	1.377	0.0041
ENSG00000162552	WNT4	1.376	0.0141
ENSG00000265190	ANXA8	1.374	8.45E-38
ENSG00000197385	ZNF860	1.373	0.0170
ENSG00000166592	RRAD	1.371	0.0018
ENSG00000205861	C1QTNF9B-AS1	1.371	0.0291
ENSG00000113578	FGF1	1.367	0.0077
ENSG00000132965	ALOX5AP	1.366	0.0034
ENSG00000267106	ZNF561-AS1	1.363	5.18E-08
ENSG00000157570	TSPAN18	1.362	0.0415
ENSG00000241935	HOGA1	1.358	2.33E-10
ENSG00000182612	TSPAN10	1.354	3.78E-07

ENSG00000185296	CTD-2139B15.1	1.354	0.0331
ENSG00000277639	RP11-467J12.4	1.354	1.42E-06
ENSG00000138356	AOX1	1.353	6.95E-37
ENSG00000129009	ISLR	1.353	0.0001
ENSG00000170099	SERPINA6	1.352	0.0173
ENSG00000115009	CCL20	1.352	0.0035
ENSG00000273706	LHX1	1.351	1.14E-05
ENSG00000156453	PCDH1	1.348	0.0022
ENSG00000169116	PARM1	1.347	9.71E-07
ENSG00000136603	SKIL	1.346	1.24E-33
ENSG00000249673	NOP14-AS1	1.344	1.14E-09
ENSG00000124762	CDKN1A	1.342	0.0404
ENSG00000169903	TM4SF4	1.339	0.0066
ENSG00000116106	EPHA4	1.339	2.23E-05
ENSG00000174521	TTC9B	1.334	0.0299
ENSG00000116661	FBXO2	1.329	2.01E-09
ENSG00000277693	AP003900.6	1.328	0.0467
ENSG00000182782	HCAR2	1.327	0.0394
ENSG00000228824	MIR4500HG	1.327	0.0485
ENSG00000146374	RSPO3	1.327	5.79E-06
ENSG00000152763	WDR78	1.326	0.0028
ENSG00000245105	A2M-AS1	1.326	0.0026
ENSG00000181804	SLC9A9	1.326	0.0046
ENSG00000282057	RP4-621F18.2	1.325	0.0219
ENSG00000167895	TMC8	1.324	0.0145
ENSG00000264462	MIR3648-2	1.323	0.0187
ENSG00000132357	CARD6	1.323	3.72E-14
ENSG00000196502	SULT1A1	1.321	1.40E-09
ENSG00000092421	SEMA6A	1.320	0.0262
ENSG00000106078	COBL	1.319	0.0068
ENSG00000262655	SPON1	1.318	0.0144
ENSG00000103196	CRISPLD2	1.316	4.06E-28
ENSG00000251257	CTD-2263F21.1	1.315	0.0234
ENSG00000275395	FCGBP	1.315	1.65E-14
ENSG00000135144	DTX1	1.313	0.0145
ENSG00000124257	NEURL2	1.312	0.0136
ENSG00000236567	TCF3P1	1.310	0.0477
ENSG00000280152	RP11-331F4.5	1.309	0.0021
ENSG00000118503	TNFAIP3	1.309	2.24E-30
ENSG00000253731	PCDHGA6	1.308	0.0006
ENSG00000215246	RP11-43F13.3	1.308	0.0004
ENSG00000229851	ARSD-AS1	1.308	0.0377
ENSG00000205710	C17orf107	1.306	0.0075
ENSG00000185015	CA13	1.303	0.0331
ENSG00000091592	NLRP1	1.303	2.91E-12
ENSG00000237161	RP11-32B5.1	1.302	0.0160
ENSG00000184925	LCN12	1.302	0.0010
ENSG00000185101	ANO9	1.299	0.0121
ENSG00000171931	FBXW10	1.297	1.13E-12

ENSG00000109472	CPE	1.294	0.0204
ENSG00000224321	RPL12P14	1.291	0.0200
ENSG00000148357	HMCN2	1.287	0.0163
ENSG00000010030	ETV7	1.287	0.0033
ENSG00000264717	CH17-360D5.1	1.285	7.53E-13
ENSG00000264175	MIR3189	1.283	0.0168
ENSG00000118257	NRP2	1.282	2.64E-75
ENSG00000049192	ADAMTS6	1.280	0.0002
ENSG00000197142	ACSL5	1.280	0.0069
ENSG00000144847	IGSF11	1.279	0.0216
ENSG00000260401	RP11-800A3.4	1.278	1.62E-05
ENSG00000163803	PLB1	1.276	0.0005
ENSG00000204174	NPY4R	1.276	6.23E-19
ENSG00000229891	LINC01315	1.275	0.0103
ENSG00000260193	RP11-83N9.5	1.275	0.0003
ENSG00000103742	IGDCC4	1.272	3.75E-09
ENSG00000101098	RIMS4	1.270	0.0019
ENSG00000178404	CEP295NL	1.270	0.0134
ENSG00000138623	SEMA7A	1.270	0.0003
ENSG00000279699	RP1-102K2.9	1.268	0.0290
ENSG00000232070	TMEM253	1.265	0.0036
ENSG00000182752	PAPPA	1.264	6.43E-37
ENSG00000271334	CTD-2078B5.2	1.263	0.0128
ENSG00000174899	PQLC2L	1.261	0.0003
ENSG00000279806	RP11-580I9.2	1.261	3.33E-34
ENSG00000168487	BMP1	1.261	5.36E-28
ENSG00000281991	TMEM265	1.260	0.0023
ENSG00000158887	MPZ	1.259	0.0003
ENSG00000166448	TMEM130	1.258	1.35E-06
ENSG00000126970	ZC4H2	1.258	3.04E-10
ENSG00000125966	MMP24	1.256	9.05E-13
ENSG00000186994	KANK3	1.256	9.34E-09
ENSG00000160207	HSF2BP	1.251	0.0026
ENSG00000076604	TRAF4	1.249	8.41E-20
ENSG00000111181	SLC6A12	1.248	0.0008
ENSG00000169403	PTAFR	1.247	0.0040
ENSG00000008735	MAPK8IP2	1.247	1.79E-16
ENSG00000269486	CTC-360G5.9	1.247	2.43E-05
ENSG00000275793	RIMBP3	1.247	1.29E-05
ENSG00000135477	KRT87P	1.245	0.0006
ENSG00000139132	FGD4	1.243	0.0008
ENSG00000170545	SMAGP	1.242	9.43E-07
ENSG00000148735	PLEKHS1	1.241	1.84E-08
ENSG00000082126	MPP4	1.241	0.0004
ENSG00000211448	DIO2	1.239	0.0013
ENSG00000103888	CEMIP	1.238	7.07E-05
ENSG00000198133	TMEM229B	1.237	0.0345
ENSG00000238005	RP11-443B7.1	1.237	0.0001
ENSG00000183134	PTGDR2	1.236	0.0339

ENSG00000170647	TMEM133	1.235	0.0153
ENSG00000141469	SLC14A1	1.234	0.0116
ENSG00000170006	TMEM154	1.231	0.0103
ENSG00000172667	ZMAT3	1.231	0.0030
ENSG00000134198	TSPAN2	1.231	0.0311
ENSG00000177106	EPS8L2	1.230	5.08E-19
ENSG00000158125	XDH	1.230	2.25E-10
ENSG00000135919	SERPINE2	1.228	1.14E-29
ENSG00000114779	ABHD14B	1.227	4.16E-24
ENSG00000197646	PDCD1LG2	1.227	0.0002
ENSG00000183729	NPBWR1	1.226	0.0256
ENSG00000249867	RP11-115J23.1	1.226	0.0023
ENSG00000261456	TUBB8	1.225	0.0246
ENSG00000139899	CBLN3	1.224	2.14E-10
ENSG00000173705	SUSD5	1.223	3.41E-19
ENSG00000179772	FOXS1	1.222	0.0009
ENSG00000106366	SERPINE1	1.221	5.88E-48
ENSG00000170381	SEMA3E	1.220	2.66E-05
ENSG00000100604	CHGA	1.220	2.22E-05
ENSG00000106772	PRUNE2	1.219	9.13E-05
ENSG00000028137	TNFRSF1B	1.218	0.0002
ENSG00000272070	AC005618.6	1.218	0.0070
ENSG00000038427	VCAN	1.218	8.24E-27
ENSG00000107104	KANK1	1.218	0.0068
ENSG00000279821	RP11-1334A24.5	1.217	9.90E-06
ENSG00000143355	LHX9	1.216	0.0187
ENSG00000145022	TCTA	1.216	0.0048
ENSG00000198794	SCAMP5	1.212	1.10E-13
ENSG00000197380	DACT3	1.211	0.0438
ENSG00000267681	CTD-3199J23.6	1.211	0.0081
ENSG00000161249	DMKN	1.211	4.55E-09
ENSG00000223403	MEG9	1.205	0.0223
ENSG00000160326	SLC2A6	1.205	6.76E-30
ENSG00000128849	CGNL1	1.204	2.75E-05
ENSG00000166394	CYB5R2	1.203	7.52E-09
ENSG00000006606	CCL26	1.203	1.01E-06
ENSG00000130513	GDF15	1.202	3.72E-28
ENSG00000262678	RP5-1050D4.4	1.201	0.0119
ENSG00000271380	RP11-307C12.12	1.199	0.0006
ENSG00000198774	RASSF9	1.199	0.0006
ENSG00000125347	IRF1	1.197	7.68E-35
ENSG00000163520	FBLN2	1.196	0.0216
ENSG00000267475	CTD-2538C1.2	1.195	0.0215
ENSG00000182578	CSF1R	1.195	0.0130
ENSG00000091262	ABCC6	1.194	6.58E-05
ENSG00000099889	ARVCF	1.192	2.35E-07
ENSG00000175591	P2RY2	1.190	1.28E-06
ENSG00000130635	COL5A1	1.189	2.36E-31
ENSG00000279692	RP11-1055B8.1	1.187	0.0037

ENSG00000183044	ABAT	1.185	3.59E-06
ENSG00000102109	PCSK1N	1.184	2.82E-11
ENSG00000115414	FN1	1.184	3.24E-28
ENSG00000064205	WISP2	1.183	3.94E-13
ENSG00000280587	LINC01348	1.182	0.0002
ENSG00000105699	LSR	1.182	2.99E-05
ENSG00000180787	ZFP3	1.182	0.0198
ENSG00000258461	RP11-164J13.1	1.181	0.0045
ENSG00000173546	CSPG4	1.179	0.0001
ENSG00000129993	CBFA2T3	1.178	0.0239
ENSG00000276851	RP5-875H18.9	1.177	1.85E-08
ENSG00000281490	CICP14	1.175	2.08E-08
ENSG00000232692	AP001596.6	1.175	0.0309
ENSG00000107742	SPOCK2	1.173	7.38E-05
ENSG00000149506	ZP1	1.173	0.0047
ENSG00000069667	RORA	1.173	0.0001
ENSG00000183171	RP11-49C9.2	1.173	0.0155
ENSG00000177409	SAMD9L	1.173	1.98E-12
ENSG00000274214	RP11-757O6.6	1.172	0.0136
ENSG00000152137	HSPB8	1.171	1.60E-11
ENSG00000238228	OR7E7P	1.169	0.0090
ENSG00000100292	HMOX1	1.169	6.56E-35
ENSG00000145287	PLAC8	1.169	0.0360
ENSG00000062038	CDH3	1.168	3.53E-05
ENSG00000117461	PIK3R3	1.167	3.62E-13
ENSG00000198934	MAGEE1	1.163	4.12E-06
ENSG00000184985	SORCS2	1.162	2.85E-08
ENSG00000198440	ZNF583	1.161	3.02E-06
ENSG00000184584	TMEM173	1.161	1.31E-05
ENSG00000162772	ATF3	1.160	9.35E-10
ENSG00000132386	SERPINF1	1.159	0.0012
ENSG00000258777	HIF1A-AS1	1.158	0.0035
ENSG00000135127	BICDL1	1.158	8.82E-08
ENSG00000105559	PLEKHA4	1.158	2.89E-05
ENSG00000019505	SYT13	1.157	1.29E-07
ENSG00000164674	SYTL3	1.157	0.0286
ENSG00000095739	BAMBI	1.156	1.83E-14
ENSG00000164051	CCDC51	1.156	0.0358
ENSG00000108947	EFNB3	1.156	0.0255
ENSG00000083812	ZNF324	1.156	6.86E-06
ENSG00000227496	RP11-145A3.1	1.156	0.0029
ENSG00000135678	CPM	1.155	2.11E-24
ENSG00000248187	RP11-184M15.1	1.155	7.00E-11
ENSG00000168016	TRANK1	1.152	1.24E-15
ENSG00000228492	RAB11FIP1P1	1.151	9.84E-06
ENSG00000260944	FOXC2-AS1	1.150	0.0010
ENSG00000158315	RHBDL2	1.149	3.65E-05
ENSG00000033100	CHPF2	1.148	5.81E-47
ENSG00000131378	RFTN1	1.147	1.44E-27

ENSG00000256628	ZBTB11-AS1	1.147	2.43E-09
ENSG00000135604	STX11	1.147	0.0001
ENSG00000269951	RP11-797A18.6	1.145	0.0198
ENSG00000254607	RP11-115C10.1	1.142	0.0385
ENSG00000260633	RP11-375I20.6	1.142	0.0239
ENSG00000221890	NPTXR	1.141	4.38E-25
ENSG00000215559	ANKRD20A11P	1.140	0.0043
ENSG00000167600	CYP2S1	1.137	2.31E-12
ENSG00000123700	KCNJ2	1.137	1.70E-09
ENSG00000228314	CYP4F29P	1.137	7.25E-07
ENSG00000058085	LAMC2	1.136	1.21E-53
ENSG00000092529	CAPN3	1.134	0.0297
ENSG00000198959	TGM2	1.134	1.67E-51
ENSG00000177675	CD163L1	1.133	2.37E-08
ENSG00000138646	HERC5	1.132	1.01E-13
ENSG00000142156	COL6A1	1.132	1.09E-28
ENSG00000272933	RP11-47A8.5	1.131	4.81E-09
ENSG00000183346	C10orf107	1.130	0.0006
ENSG00000183287	CCBE1	1.130	3.48E-11
ENSG00000166833	NAV2	1.128	0.0009
ENSG00000228570	NUTM2E	1.123	0.0114
ENSG00000049089	COL9A2	1.120	0.0186
ENSG00000272695	GAS6-AS2	1.119	3.73E-06
ENSG00000101842	VSIG1	1.118	0.0204
ENSG00000140678	ITGAX	1.114	2.92E-06
ENSG00000197757	HOXC6	1.113	0.0086
ENSG00000165434	PGM2L1	1.113	1.97E-20
ENSG00000187957	DNER	1.112	0.0001
ENSG00000187860	CCDC157	1.109	0.0145
ENSG00000140416	TPM1	1.105	1.20E-22
ENSG00000266993	RP4-657D16.3	1.105	0.0154
ENSG00000269994	RP11-276H19.2	1.103	0.0414
ENSG00000234546	RP3-510D11.2	1.102	0.0019
ENSG00000111348	ARHGDIB	1.100	7.02E-07
ENSG00000182492	BGN	1.100	0.0161
ENSG00000148677	ANKRD1	1.099	9.48E-09
ENSG00000184368	MAP7D2	1.099	0.0032
ENSG00000227268	KLLN	1.099	1.56E-05
ENSG00000100647	SUSD6	1.098	4.83E-24
ENSG00000155792	DEPTOR	1.098	0.0001
ENSG00000069020	MAST4	1.097	2.33E-06
ENSG00000121270	ABCC11	1.097	0.0365
ENSG00000123095	BHLHE41	1.096	4.39E-12
ENSG00000185909	KLHDC8B	1.095	0.0037
ENSG00000166847	DCTN5	1.095	0.0230
ENSG00000238271	IFNWP19	1.094	4.34E-06
ENSG00000099139	PCSK5	1.093	0.0395
ENSG00000111885	MAN1A1	1.092	2.60E-05
ENSG00000070614	NDST1	1.092	0.0027

ENSG00000169894	MUC3A	1.091	0.0028
ENSG00000176125	UFSP1	1.091	0.0042
ENSG00000147003	TMEM27	1.088	0.0412
ENSG00000113070	HBEGF	1.088	4.27E-20
ENSG00000244242	IFITM10	1.084	0.0002
ENSG00000124225	PMEPA1	1.084	7.41E-24
ENSG00000089199	CHGB	1.084	6.97E-09
ENSG00000118515	SGK1	1.082	2.42E-24
ENSG00000140092	FBLN5	1.082	0.0009
ENSG00000211455	STK38L	1.082	7.96E-09
ENSG00000156804	FBXO32	1.082	1.21E-13
ENSG00000173928	SWSAP1	1.080	0.0136
ENSG00000170801	HTRA3	1.080	0.0002
ENSG00000198125	MB	1.077	0.0302
ENSG00000267452	RP11-1018N14.5	1.077	0.0475
ENSG00000159713	TPPP3	1.077	0.0023
ENSG00000213654	GPSM3	1.077	0.0057
ENSG00000235423	RP11-282O18.3	1.075	0.0022
ENSG00000185483	ROR1	1.074	2.15E-21
ENSG00000183876	ARSI	1.073	2.11E-12
ENSG00000203499	FAM83H-AS1	1.073	0.0007
ENSG00000174137	FAM53A	1.072	0.0075
ENSG00000126882	FAM78A	1.071	0.0001
ENSG00000137752	CASP1	1.071	1.34E-10
ENSG00000167080	B4GALNT2	1.068	7.08E-13
ENSG00000172508	CARNS1	1.068	0.0302
ENSG00000213468	FIRRE	1.067	0.0227
ENSG00000184492	FOXD4L1	1.066	0.0260
ENSG00000267104	TBC1D3P1-DHX40P1	1.064	0.0070
ENSG00000280002	RP11-76C10.6	1.063	0.0362
ENSG00000167772	ANGPTL4	1.062	2.92E-27
ENSG00000177694	NAALADL2	1.061	0.0070
ENSG00000164220	F2RL2	1.060	3.95E-12
ENSG00000100906	NFKBIA	1.059	3.69E-30
ENSG00000143341	HMCN1	1.058	8.32E-05
ENSG00000184497	TMEM255B	1.058	0.0007
ENSG00000204514	ZNF814	1.056	4.13E-05
ENSG00000230438	SERPINB9P1	1.056	0.0251
ENSG00000129946	SHC2	1.053	0.0001
ENSG00000110092	CCND1	1.051	5.55E-62
ENSG00000196793	ZNF239	1.051	0.0003
ENSG00000161513	FDXR	1.049	2.28E-22
ENSG00000171533	MAP6	1.049	2.48E-11
ENSG00000138207	RBP4	1.049	0.0346
ENSG00000154760	SLFN13	1.048	0.0108
ENSG00000259370	RP11-1069G10.1	1.047	0.0104
ENSG00000154114	TBCEL	1.046	3.97E-07
ENSG00000174514	MFSD4A	1.046	0.0187
ENSG00000081041	CXCL2	1.045	5.15E-15

ENSG00000267254	ZNF790-AS1	1.044	0.0063
ENSG00000140022	STON2	1.044	0.0145
ENSG00000233695	GAS6-AS1	1.044	1.08E-11
ENSG00000080573	COL5A3	1.043	2.41E-06
ENSG00000261342	AC006538.1	1.043	0.0155
ENSG00000273382	RP5-1065J22.8	1.043	0.0011
ENSG00000139278	GLIPR1	1.042	2.37E-37
ENSG00000171428	NAT1	1.042	0.0230
ENSG00000174808	BTC	1.041	4.26E-09
ENSG00000067715	SYT1	1.041	4.59E-05
ENSG00000140931	CMTM3	1.038	1.17E-21
ENSG00000166016	ABTB2	1.037	3.00E-23
ENSG00000121068	TBX2	1.037	6.75E-18
ENSG00000258130	RP11-347C12.3	1.036	0.0062
ENSG00000185669	SNAI3	1.035	0.0010
ENSG00000143786	CNIH3	1.034	0.0031
ENSG00000283294	RP11-681B3.4	1.032	0.0003
ENSG00000185055	EFCAB10	1.030	2.83E-05
ENSG00000227953	LINC01341	1.028	0.0139
ENSG00000236022	RP11-160E2.16	1.028	0.0387
ENSG00000115226	FNDC4	1.026	0.0009
ENSG00000114270	COL7A1	1.026	5.23E-41
ENSG00000116962	NID1	1.026	0.0079
ENSG00000187837	HIST1H1C	1.026	3.45E-22
ENSG00000242732	RGAG4	1.024	3.19E-11
ENSG00000170962	PDGFD	1.023	1.47E-16
ENSG00000126561	STAT5A	1.023	7.96E-09
ENSG00000225614	ZNF469	1.023	2.17E-19
ENSG00000166147	FBN1	1.021	7.48E-24
ENSG00000165804	ZNF219	1.021	2.75E-28
ENSG00000250091	DNAH10OS	1.020	0.0195
ENSG00000188015	S100A3	1.017	6.49E-15
ENSG00000181458	TMEM45A	1.017	5.33E-06
ENSG00000187796	CARD9	1.017	0.0136
ENSG00000189001	SBSN	1.016	0.0020
ENSG00000126947	ARMCX1	1.016	6.83E-07
ENSG00000185112	FAM43A	1.015	0.0030
ENSG00000264230	ANXA8L1	1.015	2.82E-25
ENSG00000100626	GALNT16	1.014	2.66E-09
ENSG00000164308	ERAP2	1.010	2.74E-06
ENSG00000136235	GPNMB	1.010	0.0196
ENSG00000174307	PHLDA3	1.010	6.59E-35
ENSG00000184988	TMEM106A	1.008	0.0005
ENSG00000170629	DPY19L2P2	1.006	0.0079
ENSG00000256235	SMIM3	1.005	0.0001
ENSG00000269937	RP11-20I23.8	1.003	0.0270
ENSG00000234869	RP3-439F8.1	1.002	0.0323
ENSG00000261613	RP11-20I23.13	1.000	0.0016
ENSG00000183578	TNFAIP8L3	1.000	2.36E-06

Supplementary Table 2. Identification of significantly down-regulated genes in irradiated HPAEpiC cells using RNA-seq

Gene_ID	Symbol	log2 Fold Change	*P* value
ENSG00000125931	CITED1	-1.055	0.0497
ENSG00000174236	REP15	-1.08	0.0496
ENSG00000235748	SEPT14P12	-1.93	0.0488
ENSG00000272905	RP11-265E18.1	-2.131	0.048
ENSG00000257803	RP11-575G13.2	-2.225	0.0476
ENSG00000263080	RP11-485G7.5	-1.129	0.0475
ENSG00000251013	GAPDHP62	-1.007	0.0475
ENSG00000268649	MIR296	-1.134	0.0466
ENSG00000185303	SFTPA2	-2.273	0.0465
ENSG00000259155	RP11-831F12.3	-1.382	0.0464
ENSG00000017483	SLC38A5	-1.09	0.0461
ENSG00000271937	RP11-424N24.2	-1.874	0.046
ENSG00000244462	RBM12	-1.065	0.0459
ENSG00000129317	PUS7L	-1.703	0.0457
ENSG00000232855	AF131217.1	-2.025	0.0454
ENSG00000168454	TXNDC2	-1.888	0.0453
ENSG00000273287	CTA-268H5.14	-1.864	0.0452
ENSG00000250021	C15orf38-AP3S2	-1.77	0.0445
ENSG00000233246	RP11-415J8.5	-1.978	0.0436
ENSG00000268750	CTD-2583A14.10	-1.128	0.0436
ENSG00000272141	RP11-465B22.8	-1.945	0.0436
ENSG00000276203	ANKRD20A3	-1.404	0.0435
ENSG00000278419	RP11-298E9.7	-2.588	0.0433
ENSG00000134962	KLB	-1.39	0.0432
ENSG00000272576	RP11-365H22.2	-1.582	0.0426
ENSG00000139187	KLRG1	-1.21	0.0423
ENSG00000228663	PSMD10P1	-2.292	0.0413
ENSG00000187122	SLIT1	-1.168	0.0405
ENSG00000156097	GPR61	-1.246	0.0405
ENSG00000258186	SLC7A5P2	-1.419	0.0394
ENSG00000243675	RP11-379F4.1	-2.213	0.0394
ENSG00000262222	RP11-876N24.4	-1.253	0.0392
ENSG00000253476	RP11-395I14.2	-1.28	0.0389
ENSG00000258725	PRC1-AS1	-1.135	0.0388
ENSG00000226520	KIRREL-IT1	-1.415	0.0381
ENSG00000277151	RP11-380B4.3	-2.33	0.0381
ENSG00000237248	LINC00987	-1.386	0.0376
ENSG00000086570	FAT2	-2.251	0.0374
ENSG00000263786	RP11-649A18.4	-1.006	0.0373
ENSG00000267125	CTB-31O20.6	-2.21	0.0372
ENSG00000155087	ODF1	-2.231	0.0364
ENSG00000197406	DIO3	-2.112	0.0363
ENSG00000240006	RP11-200A1.1	-2.218	0.0361
ENSG00000279758	RP11-752G15.10	-1.076	0.0359
ENSG00000232977	LINC00327	-2.364	0.0358
ENSG00000267030	CTB-50L17.7	-1.681	0.0356

ENSG00000120341	SEC16B	-1.81	0.0356
ENSG00000273076	RP3-508I15.22	-1.977	0.0349
ENSG00000249363	CTB-78021.1	-2.301	0.0348
ENSG00000124215	CDH26	-1.276	0.0346
ENSG00000276712	MIR7111	-1.108	0.0344
ENSG00000186105	LRRC70	-2.276	0.0338
ENSG00000271009	RP11-346C20.3	-1.994	0.0338
ENSG00000225806	RP1-309F20.3	-1.981	0.0337
ENSG00000272017	RP1-199J3.7	-1.322	0.0335
ENSG00000181856	SLC2A4	-1.364	0.0332
ENSG00000230333	AC004538.3	-1.001	0.0331
ENSG00000229447	RP11-490K7.4	-1.342	0.0329
ENSG00000272843	RP11-313P13.5	-1.982	0.0328
ENSG00000267430	RP11-635N19.2	-2.426	0.0327
ENSG00000269559	RP11-629B11.5	-1.355	0.0327
ENSG00000140009	ESR2	-1.042	0.0319
ENSG00000273000	KB-1572G7.2	-1.596	0.0318
ENSG00000232531	AC027612.1	-1.103	0.0316
ENSG00000265912	RP11-583F2.2	-1.978	0.0314
ENSG00000173838	10-Mar	-2.013	0.0313
ENSG00000278852	NPPA-AS1_2	-1.75	0.0312
ENSG00000160352	ZNF714	-1.256	0.0311
ENSG00000213939	RP11-314A20.1	-1.113	0.0309
ENSG00000275383	RP11-615I2.6	-2.392	0.0306
ENSG00000130649	CYP2E1	-1.219	0.0304
ENSG00000214132	RP11-420O16.2	-2.398	0.0304
ENSG00000196628	TCF4	-1.402	0.0302
ENSG00000278931	bP-218909.2	-1.04	0.0295
ENSG00000226318	RP11-474D14.2	-1.801	0.0294
ENSG00000237343	RP11-763B22.4	-2.458	0.0292
ENSG00000260526	RP11-73K9.2	-1.002	0.0289
ENSG00000281808	SNORA17	-1.37	0.0285
ENSG00000235852	AC005540.3	-1.566	0.0281
ENSG00000237852	RP4-630A11.3	-1.948	0.0279
ENSG00000126217	MCF2L	-1.334	0.0269
ENSG00000057468	MSH4	-2.377	0.0264
ENSG00000244556	ODCP	-1.297	0.0264
ENSG00000270179	RP11-159N11.4	-1.01	0.0262
ENSG00000214946	TBC1D26	-2.409	0.0261
ENSG00000213397	HAUS7	-1.032	0.0257
ENSG00000260100	RP11-220I1.5	-2.364	0.0254
ENSG00000248235	AC037459.4	-1.898	0.0252
ENSG00000276524	RP11-323F24.3	-2.052	0.0248
ENSG00000274341	RP11-227G15.10	-1.544	0.0243
ENSG00000259396	RP11-1609.2	-2.535	0.0242
ENSG00000228828	RP11-162G10.1	-2.479	0.0239
ENSG00000268041	CTD-2575K13.6	-1.077	0.0235
ENSG00000262155	RP11-266L9.5	-1.108	0.0235
ENSG00000234491	HNRNPA1P51	-1.805	0.0232

ENSG00000251441	RTEL1P1	-2.065	0.0231
ENSG00000235351	AC114730.11	-1.542	0.0228
ENSG00000231028	LINC00271	-2.042	0.0228
ENSG00000231473	LINC00441	-2.041	0.0221
ENSG00000275401	RP4-564F22.7	-2.629	0.0215
ENSG00000222014	RAB6C	-2.599	0.0215
ENSG00000232613	AC007386.4	-2.492	0.0214
ENSG00000213070	HMGB3P6	-1.212	0.0214
ENSG00000283078	RP11-11M20.4	-2.423	0.0213
ENSG00000227001	NBPF2P	-1.407	0.0211
ENSG00000280423	RP11-299J5.1	-2.564	0.0208
ENSG00000256167	ATF4P4	-1.631	0.0204
ENSG00000274015	CTD-2302E22.6	-2.202	0.0198
ENSG00000261757	AC005592.3	-2.093	0.0196
ENSG00000254862	RP11-159H22.2	-2.128	0.019
ENSG00000272008	RP11-393I2.4	-1.48	0.019
ENSG00000277232	GTSE1-AS1	-1.107	0.0186
ENSG00000259488	RP11-154J22.1	-1.066	0.0185
ENSG00000091137	SLC26A4	-1.092	0.0183
ENSG00000151135	TMEM263	-1.256	0.0183
ENSG00000232987	LINC01219	-2.13	0.0176
ENSG00000260907	AC008088.4	-1.379	0.0174
ENSG00000198040	ZNF84	-1.343	0.0174
ENSG00000157600	TMEM164	-1.471	0.0172
ENSG00000236581	STARD13-AS	-1.399	0.0172
ENSG00000108551	RASD1	-2.09	0.017
ENSG00000270720	RP11-84C13.2	-2.425	0.0169
ENSG00000260423	RP13-735L24.1	-2.24	0.0166
ENSG00000198221	AFDN-AS1	-1.297	0.0166
ENSG00000235489	DBF4P1	-1.506	0.0165
ENSG00000233296	AC092159.2	-2.116	0.0163
ENSG00000228393	LINC01004	-1.293	0.0163
ENSG00000213539	YBX1P6	-2.412	0.016
ENSG00000243055	GK-AS1	-2.562	0.0155
ENSG00000251350	LVCAT1	-1.422	0.0154
ENSG00000243181	RP11-734J24.1	-1.393	0.0154
ENSG00000247151	CSTF3-AS1	-1.455	0.015
ENSG00000104722	NEFM	-2.674	0.0149
ENSG00000224992	RP11-295G24.5	-1.177	0.014
ENSG00000261997	RP11-212I21.4	-1.357	0.0137
ENSG00000279982	RP11-45A17.3	-1.472	0.0131
ENSG00000259010	RP11-973N13.2	-2.549	0.0124
ENSG00000273925	RP11-227D13.5	-2.586	0.0123
ENSG00000232713	AC010733.5	-1.363	0.0122
ENSG00000227014	AC007285.6	-1.321	0.0121
ENSG00000237594	AP000251.3	-2.235	0.012
ENSG00000214289	RPL39P5	-1.452	0.0116
ENSG00000137960	GIPC2	-2.761	0.0111
ENSG00000186897	C1QL4	-1.012	0.0107

ENSG00000170509	HSD17B13	-2.211	0.0105
ENSG00000257474	RP11-359M6.1	-2.761	0.0102
ENSG00000181350	LRRC75A	-1.16	0.0102
ENSG00000257108	NHLRC4	-1.543	0.0099
ENSG00000168813	ZNF507	-1.134	0.0098
ENSG00000279081	AL356585.1	-1.522	0.0097
ENSG00000183148	ANKRD20A2	-1.316	0.0097
ENSG00000144827	ABHD10	-1.194	0.0093
ENSG00000203546	RP11-176H8.1	-1.375	0.0091
ENSG00000254911	SCARNA9	-1.807	0.009
ENSG00000161180	CCDC116	-2.333	0.009
ENSG00000215283	HMGB3P24	-1.095	0.0087
ENSG00000100138	SNU13	-1.109	0.0083
ENSG00000127578	WFIKKN1	-1.434	0.0082
ENSG00000253404	AC034243.1	-1.29	0.0082
ENSG00000250326	RP11-284M14.1	-2.263	0.0082
ENSG00000125046	SSUH2	-1.436	0.0081
ENSG00000278202	RP11-152F13.8	-1.396	0.0081
ENSG00000135702	CHST5	-2.28	0.0077
ENSG00000259845	HERC2P10	-2.879	0.0075
ENSG00000271590	RP11-181E10.3	-1.357	0.0072
ENSG00000261560	RP11-166B2.3	-1.114	0.0069
ENSG00000229525	AC053503.4	-1.727	0.0067
ENSG00000276259	RP11-481J2.4	-1.354	0.0066
ENSG00000232177	MTND4P24	-2.354	0.0065
ENSG00000130943	PKDREJ	-1.151	0.0063
ENSG00000283245	SCHIP1	-1.72	0.0062
ENSG00000266896	RP1-266L20.9	-1.434	0.0061
ENSG00000278238	RP11-245D16.4	-1.035	0.006
ENSG00000215417	MIR17HG	-1.031	0.0056
ENSG00000220875	HIST1H3PS1	-2.785	0.0055
ENSG00000137878	GCOM1	-1.333	0.0054
ENSG00000272892	RP11-57G10.8	-1.679	0.0051
ENSG00000162669	HFM1	-1.78	0.005
ENSG00000263164	RP11-333E1.2	-2.958	0.0049
ENSG00000224126	UBE2SP2	-1.116	0.0049
ENSG00000256566	RP4-734P14.4	-2.359	0.0048
ENSG00000271105	SCML2P2	-1.645	0.0048
ENSG00000233230	AC079807.2	-1.041	0.0047
ENSG00000006047	YBX2	-1.104	0.0047
ENSG00000273007	RP11-170N16.3	-1.084	0.0045
ENSG00000231154	MORF4L2-AS1	-1.104	0.0045
ENSG00000261008	LINC01572	-1.159	0.0044
ENSG00000167945	PRR25	-1.853	0.0042
ENSG00000103184	SEC14L5	-1.419	0.0041
ENSG00000273759	RP4-563E14.1	-1.024	0.004
ENSG00000186453	FAM228A	-3.008	0.0039
ENSG00000265185	SNORD3B-1	-1.448	0.0038
ENSG00000230251	PHBP4	-3.01	0.0037

ENSG00000197561	ELANE	-1.295	0.0036
ENSG00000267892	CTD-2540F13.2	-1.122	0.0035
ENSG00000273473	LL09NC01-139C3.1	-2.85	0.0034
ENSG00000261159	RP11-723O4.9	-1.052	0.0032
ENSG00000230530	LIMD1-AS1	-3.014	0.0032
ENSG00000269026	AC003006.7	-2.811	0.0031
ENSG00000261215	RP11-195F19.30	-1.792	0.0031
ENSG00000180481	GLIPR1L2	-1.433	0.003
ENSG00000186907	RTN4RL2	-1.172	0.0029
ENSG00000141449	GREB1L	-1.066	0.0027
ENSG00000155189	AGPAT5	-1.37	0.0027
ENSG00000166763	STRCP1	-2.884	0.0025
ENSG00000251259	AC004069.2	-1.143	0.0025
ENSG00000213062	RP1-206D15.6	-1.729	0.0024
ENSG00000138398	PPIG	-1.233	0.0021
ENSG00000226321	CROCC2	-2.936	0.0021
ENSG00000167550	RHEBL1	-1.013	0.002
ENSG00000011347	SYT7	-1.028	0.002
ENSG00000222881	Y_RNA	-1.721	0.0019
ENSG00000065361	ERBB3	-1.021	0.0017
ENSG00000231256	C17orf105	-3.169	0.0017
ENSG00000236194	AC003104.1	-2.228	0.0015
ENSG00000234129	RP11-120D5.1	-1.217	0.0015
ENSG00000227963	RP5-1074L1.1	-3.21	0.0014
ENSG00000272734	ADIRF-AS1	-1.063	0.0014
ENSG00000102385	DRP2	-1.012	0.0014
ENSG00000171827	ZNF570	-1.37	0.0013
ENSG00000241549	GUSBP2	-1.12	0.0013
ENSG00000259790	ANP32BP1	-1.231	0.0011
ENSG00000204623	ZNRD1ASP	-1.258	0.0009
ENSG00000230667	SETSIP	-1.054	0.0009
ENSG00000264743	DPRXP4	-1.659	0.0009
ENSG00000250033	SLC7A11-AS1	-1.512	0.0008
ENSG00000226833	AC097724.3	-1.248	0.0007
ENSG00000272524	RP11-254F7.4	-2.085	0.0007
ENSG00000277846	SNORD30	-1.307	0.0007
ENSG00000273002	RP11-336K24.12	-1.01	0.0006
ENSG00000225173	XXbac-BPG308K3.5	-3.185	0.0005
ENSG00000213772	EIF1P7	-1.696	0.0005
ENSG00000139354	GAS2L3	-1.241	0.0005
ENSG00000271888	RP11-560J1.2	-1.255	0.0004
ENSG00000150672	DLG2	-1.162	0.0004
ENSG00000260924	LINC01311	-1.173	0.0004
ENSG00000141314	RHBDL3	-1.003	0.0003
ENSG00000105479	CCDC114	-1.64	0.0003
ENSG00000167011	NAT16	-1.296	0.0002
ENSG00000241749	RPSAP52	-1.059	0.0002
ENSG00000156509	FBXO43	-1.23	0.0002
ENSG00000106336	FBXO24	-1.324	0.0002

ENSG00000024526	DEPDC1	-1.02	0.0001
ENSG00000278743	RP11-707G18.1	-1.881	0.0001
ENSG00000004838	ZMYND10	-1.792	0.0001
ENSG00000222898	RN7SKP97	-1.439	7.74E-05
ENSG00000272501	XXbac-BPG299F13.17	-1.015	7.47E-05
ENSG00000164362	TERT	-1.582	7.36E-05
ENSG00000274925	CTD-2547G23.4	-1.087	6.91E-05
ENSG00000167525	PROCA1	-1.081	6.52E-05
ENSG00000226416	MRPL23-AS1	-1.136	6.13E-05
ENSG00000228218	ATF4P3	-1.128	5.93E-05
ENSG00000181544	FANCB	-1.147	4.88E-05
ENSG00000197587	DMBX1	-1.052	4.13E-05
ENSG00000225872	LINC01529	-1.277	3.60E-05
ENSG00000143882	ATP6V1C2	-1.128	3.56E-05
ENSG00000214776	RP11-726G1.1	-1.279	2.48E-05
ENSG00000276672	RP11-142E9.1	-1.236	1.39E-05
ENSG00000267698	AC002116.7	-1.014	7.08E-06
ENSG00000224934	RP11-441O15.3	-1.111	6.54E-06
ENSG00000258984	UBE2F-SCLY	-3.651	6.08E-06
ENSG00000066279	ASPM	-1.565	3.48E-06
ENSG00000230002	ALMS1-IT1	-1.147	1.84E-06
ENSG00000233589	RP4-694A7.2	-1.893	1.79E-06
ENSG00000126500	FLRT1	-1.244	1.33E-06
ENSG00000257167	TMPO-AS1	-1.075	8.47E-07
ENSG00000133739	LRRCC1	-1.021	7.53E-07
ENSG00000176244	ACBD7	-1.518	7.09E-07
ENSG00000138587	MNS1	-1.019	5.06E-07
ENSG00000198417	MT1F	-1.585	3.78E-07
ENSG00000148773	MKI67	-1.459	1.75E-07
ENSG00000215158	RP11-1023L17.1	-1.297	1.33E-07
ENSG00000103995	CEP152	-1.071	6.13E-08
ENSG00000122483	CCDC18	-1.15	4.29E-08
ENSG00000166762	CATSPER2	-1.503	3.64E-08
ENSG00000111981	ULBP1	-1.152	3.64E-08
ENSG00000255152	MSH5-SAPCD1	-1.142	1.60E-08
ENSG00000100206	DMC1	-1.077	1.42E-08
ENSG00000128965	CHAC1	-1.562	1.40E-08
ENSG00000188610	FAM72B	-1.158	9.17E-09
ENSG00000163009	C2orf48	-1.719	6.38E-09
ENSG00000235823	OLMALINC	-1.022	1.46E-09
ENSG00000265415	CTD-2510F5.4	-1.053	5.04E-10
ENSG00000174799	CEP135	-1.103	1.63E-10
ENSG00000111247	RAD51AP1	-1.144	1.10E-10
ENSG00000228727	SAPCD1	-1.768	8.73E-11
ENSG00000264207	RP11-196G18.23	-1.346	5.50E-11
ENSG00000129007	CALML4	-1.196	3.86E-11
ENSG00000196415	PRTN3	-2.674	1.95E-11
ENSG00000205362	MT1A	-1.011	1.03E-11
ENSG00000267374	RP11-244M2.1	-1.71	7.47E-12

ENSG00000166845	C18orf54	-1.46	1.06E-13
ENSG00000176225	RTTN	-1.004	6.10E-14
ENSG00000154920	EME1	-1.054	4.46E-14
ENSG00000121211	MND1	-1.304	2.46E-14
ENSG00000158402	CDC25C	-1.16	7.91E-15
ENSG00000006634	DBF4	-1.009	2.74E-15
ENSG00000238227	C9orf69	-1.742	1.32E-17
ENSG00000136108	CKAP2	-1.121	1.69E-18
ENSG00000140451	PIF1	-1.212	1.20E-18
ENSG00000102384	CENPI	-1.053	6.47E-19
ENSG00000142731	PLK4	-1.108	1.45E-19
ENSG00000112029	FBXO5	-1.003	4.84E-20
ENSG00000121621	KIF18A	-1.187	7.20E-21
ENSG00000129173	E2F8	-1.485	1.54E-21
ENSG00000167131	CCDC103	-2.16	4.21E-22
ENSG00000113810	SMC4	-1.066	9.80E-23
ENSG00000178999	AURKB	-1.158	8.98E-23
ENSG00000129534	MIS18BP1	-1.015	6.15E-23
ENSG00000164611	PTTG1	-1.091	2.11E-23
ENSG00000196550	FAM72A	-1.128	1.37E-23
ENSG00000080986	NDC80	-1.027	2.56E-24
ENSG00000164118	CEP44	-1.397	1.73E-24
ENSG00000119397	CNTRL	-1.074	1.59E-24
ENSG00000153044	CENPH	-1.148	9.72E-25
ENSG00000184445	KNTC1	-1.174	8.75E-25
ENSG00000137804	NUSAP1	-1.078	4.19E-25
ENSG00000115163	CENPA	-1.119	3.70E-25
ENSG00000176208	ATAD5	-1.534	6.90E-26
ENSG00000213390	ARHGAP19	-1.036	2.96E-26
ENSG00000164104	HMGB2	-1.067	2.70E-26
ENSG00000144554	FANCD2	-1.213	8.06E-27
ENSG00000004777	ARHGAP33	-1.263	3.97E-27
ENSG00000112742	TTK	-1.153	3.78E-27
ENSG00000118193	KIF14	-1.475	1.35E-27
ENSG00000137812	KNL1	-1.24	5.46E-28
ENSG00000122966	CIT	-1.098	4.80E-29
ENSG00000138778	CENPE	-1.811	4.63E-29
ENSG00000068489	PRR11	-1.033	3.73E-30
ENSG00000138182	KIF20B	-1.26	6.17E-31
ENSG00000186185	KIF18B	-1.031	5.93E-31
ENSG00000169607	CKAP2L	-1.036	3.26E-31
ENSG00000237649	KIFC1	-1.003	1.26E-31
ENSG00000163535	SGO2	-1.274	3.03E-32
ENSG00000163808	KIF15	-1.322	1.40E-32
ENSG00000109674	NEIL3	-1.019	1.07E-32
ENSG00000142945	KIF2C	-1.113	4.94E-36
ENSG00000076382	SPAG5	-1.034	4.67E-37
ENSG00000114346	ECT2	-1.048	1.03E-37
ENSG00000011426	ANLN	-1.003	9.56E-38

ENSG00000145386	CCNA2	-1.03	6.11E-38
ENSG00000138160	KIF11	-1.048	7.84E-41
ENSG00000185480	PARPBP	-1.469	7.64E-41
ENSG00000143228	NUF2	-1.182	6.20E-42
ENSG00000117724	CENPF	-1.564	6.19E-47
ENSG00000131747	TOP2A	-1.051	3.73E-51
ENSG00000238266	LINC00707	-1.138	3.08E-53
ENSG00000072571	HMMR	-1.064	2.04E-53
ENSG00000169679	BUB1	-1.139	2.22E-56
ENSG00000126787	DLGAP5	-1.155	9.54E-57
ENSG00000112984	KIF20A	-1.156	1.07E-57
ENSG00000215784	FAM72D	-1.482	5.57E-61
ENSG00000117650	NEK2	-1.277	1.07E-68
ENSG00000263513	FAM72C	-1.5	5.31E-69
ENSG00000169756	LIMS1	-1.855	3.06E-106
ENSG00000260772	RP11-311C24.1	-8.337	3.01E-119
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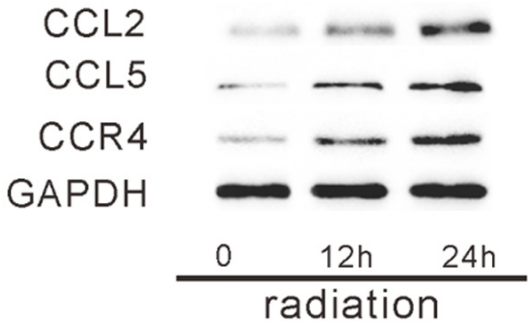
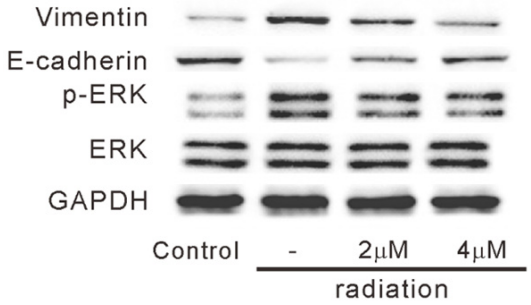
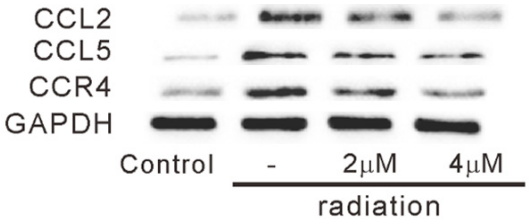


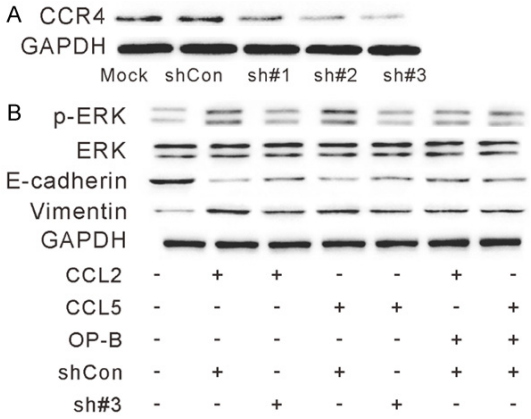
Supplementary Figure 1. Original western blot data of **Figure 3B**.



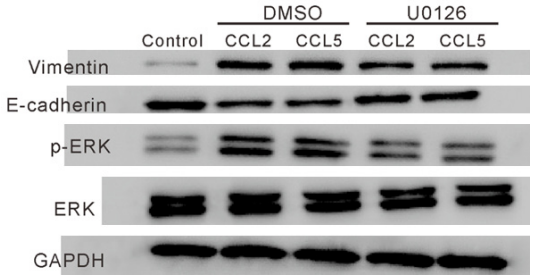
Supplementary Figure 2. Original western blot data of **Figure 4B**.



Supplementary Figure 3. Original western blot data of **Figure 5B**.



Supplementary Figure 4. Original western blot data of **Figure 6B** (A) and **6C** (B).



Supplementary Figure 5. Original western blot data of **Figure 7B**.