THE POLYCOMB PROTEINS RING1B AND EZH2 REPRESS THE TUMORAL PROINFLAMMATORY FUNCTION IN METASTASIZING PRIMARY CUTANEOUS SQUAMOUS CELL CARCINOMA

Eugenia Hernández-Ruiz^{1,2*}, Agustí Toll^{1,3*}, Irene García-Diez¹, Evelyn Andrades³, Carla Ferrandiz-Pulido², Emili Masferrer⁴, Mireia Yébenes⁵, Ane Jaka⁶, Javier Gimeno⁷, Ramón Gimeno⁸, Vicenç García-Patos², Ramón M Pujol^{1,3}, Inmaculada Hernández-Muñoz³

* Both authors contributed equally to this work.

¹ Department of Dermatology, Hospital del Mar. Parc de Salut Mar. Universitat Autònoma de Barcelona, Barcelona, Spain.

² Department of Dermatology, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona. Barcelona, Spain.

³ Group of Inflammatory and Neoplastic Dermatological Diseases, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

⁴ Department of Dermatology. Hospital Universitari Mútua de Terrassa, Barcelona, Spain.

⁵ Department of Dermatology, Corporació Sanitària i Universitària Parc Taulí, Sabadell, Spain

⁶ Department of Dermatology. Hospital Germans Trias i Pujol. Badalona. Spain.

⁷ Department of Pathology. Hospital del Mar. Parc de Salut Mar. Barcelona. Spain.

⁸ Department of Immunology. Hospital del Mar. Parc de Salut Mar. Barcelona. Spain.

Correspondence:

Inmaculada Hernández-Muñoz

IMIM (Hospital de Mar Medical Research Institute)

Doctor Aiguader 88, 08003-Barcelona (Spain)

Phone: +34 93 316 0421

Fax: +34 933160410

mhernandez@imim.es (www.imim.es)

ABSTRACT

Cutaneous squamous cell carcinoma (cSCC) is the second most common malignancy in humans and approximately 5% metastasize, usually to regional lymph nodes. Epigenetic regulation of gene expression may allow tumoral cells to acquire new functions in order to escape from the primary tumor. The aim of this study was to investigate the expression and function of proteins of the Polycomb family of epigenetic regulators in the metastatic process of cSCC. A higher expression of RING1B and EZH2 was detected by immunohistochemistry in a series of primary cSCC tumors that metastasized (MSCC) when compared to non-metastasizing cSCC (non-MSCC). Stable downregulation of RING1B and EZH2 in cSCC cells results in enhanced expression of inflammatory cytokines and activation of the NF- κ B signaling pathway. Accordingly, non-MSCC display higher levels of membranous pS176-IKK and their stroma is enriched in neutrophils and eosinophils when compared to MSCC. In vitro, hematopoietic cells exhibit a substantial migratory response to supernatants from Polycomb-depleted cSCC cells. Altogether these data indicate that RING1B and EZH2 repress the innate inflammatory cSCC function and impair tumor immunosurveillance and suggest that patients with high risk cSCC could benefit from clinical therapies addressed to harness the immune response.

Summary

RING1B and EZH2 are members of the Polycomb family whose expression was found to be increased in metastasizing cutaneous squamous cell carcinoma. They repress the innate inflammatory function and promote metastases through the inhibition of the NF- κ B signaling pathway.

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most common human cancer, preceded by basal cell carcinoma (BCC). cSCC incidence is rising worldwide, being higher in the caucasian ethnic group. cSCC metastases, usually in regional lymph nodes, occurs in approximately 5 percent of patients (1). Prominent factors linked with higher metastatic risk include immunosuppression and certain tumor locations such as ears, lips and areas of chronic injuries. Clinical parameters of the primary tumor associated with poor prognosis are diameter greater than 2 cm, depth greater than 4 mm, poor histological differentiation and perineural invasion. Active research in cSCC is currently focused on the identification of prognostic markers with clinical value that could help clinicians to identify those cancer patients with higher metastatic risk. This would allow early diagnosis, improved follow-up and new and better therapeutic strategies of high-risk patients.

The Polycomb group (PcGs) is a family of proteins that use epigenetic mechanisms to regulate gene expression. Polycomb proteins have been classified in two main complexes: the Polycomb repressive complex 2 and 1 (PRC2 and PRC1, respectively). PRC2 contains EZH2 that catalyzes trimethylation of histone H3 at lysine 27, a transcriptionally repressive mark and docking site for PRC1, although PRC1 can also be recruited in the absence of PRC2. BMI1 belongs to PRC1, which displays ubiquitin ligase activity for histone H2A conferred by RING1B (2).

The expression of different Polycomb proteins has been studied in a wide variety of tumors, where they are often misregulated (3). To date, studies addressed to investigate their

role in cSCC have been mainly restricted to determine the expression of EZH2 and BMI1. However, PRC1 proteins are highly redundant in mammals, and proteomic analysis reported six major groups of PRC1 subcomplexes with specific functions and mutually exclusive PRC1 subunits, in which RING1B is the unique common nexus for all the PRC1 subcomplexes (4). Our group previously reported differential expression of BMI1 and RING1B in the progression of pancreatic adenocarcinoma and ductal breast carcinoma (5,6). In both of them RING1B expression is directly associated with their metastatic stage. The aims of the present study were to investigate the expression and prognostic value of three Polycomb proteins, EZH2, BMI1 and RING1B, in cSCC and to identify their role in the metastatic process.

MATERIALS AND METHODS

Patients

Six tertiary care hospitals of Spain participated in this study. Records at these Centers were searched to identify patients who had developed MSCCs between 2001 and 2011. Fifty-six primary metastasizing cSCCs that had evolved to histologically confirmed lymph node (n=51) or cutaneous in-transit (n=5) metastases and a control group of fifty-one patients with cSCCs who had not developed any metastasis in a 5-year follow-up period were included in the study. Thirty-nine metastases (35 lymph node/4 cutaneous in-transit) from 39 patients were also evaluated. Approval to conduct this study was obtained from the ethics committees in accordance with the guidelines of the Helsinki Declaration (1975), revised in 1983. The following clinical data were recorded for each patient: gender, age, immunosuppression status, year of diagnosis, recurrences, tumor size and location (Table S1). Histopathological evaluation of the samples has already been described (7).

Immunohistochemical and immunofluorescence procedures

Immunofluorescence and immunohistochemistry were performed on 4-mm-thick TMA sections. Antigen retrieval was performed in 10 mM citrate (pH 6) for 15 min in a pressure cooker. The slides were then incubated with primary antibodies for 12 hours. After washing, the Envision+ System-HRP antibody reagent was applied Dako (Agilent Technologies). Immunohistochemical reactions were developed using diaminobenzidine (DAB) as chromogenic substrate. Sections were counterstained with hematoxylin, dehydrated and mounted. Immunofluorescence reactions were developed with the TSATM Plus Cyanine3/Fluorescein System (PerkinElmer). Nuclei were counterstained with Hoesch and examined with a fluorescence microscope (Olympus BX61). The following antibodies were used: RING1B and BMI1 (Millipore, Sigma-Aldrich), EZH2 (Cell Signaling), Ki67 (Novocastra, Leica Biosystems), pSer176-IKK (MyBioSource), C/EBP β and JUN D (Santa Cruz Biotechnology), CD8 (Roche). Immunohistochemical staining was scored by two observers (EH and IHM). The intensity (0, 1, 2, 3) of the immunostainings except for Ki67 were evaluated and scored as follows: 0, negative or trace amounts; 1, low staining; 2, medium staining; 3, strong staining. Correlation between qualitative variables was evaluated using χ^2 test or Fisher exact test when appropriate. Continuous data (Ki67) were compared using Student *t* test. Polycomb expression in metastasis versus primary tumors was evaluated using dichotomous McNemar test. *P* less than 0.05 was considered statistically significant. Analysis was performed with the SPSS software (SPSS 18.0, SPSS Inc).

Cell culture

SCC13 cells were a generous gift from Dr. S. Aznar-Benitah (IRB, Barcelona, Spain) and cultured as previously described (8,9). Independent cell line characterization was performed in September 2017 by qGenomics (Barcelona, Spain) utilizing nine short tandem

repeat (STR) loci (TH01, D21S11, D5S828, D13S317, D7S820, D16S539, CSF1PO, vWA and TPOX), a gender-specific marker (AMEL) to establish the presence of sex chromosomes, and a specific marker to detect the presence of murine sequences. SCC13 cells correspond to a human female, according to their origin, and display unique STR markers, indicating no contamination with other cell lines. The retroviral supernatants from Phoenix cells transfected with shRNA vectors were used to infect the cells, which were selected with 2 µg/ml puromycin (Sigma-Aldrich)(10). Sequences of shRNAs used were shControl (GCTGACCCTGAAGTTCATC), shBMI1 (GTATTGTCCTATTTGTGAT), shRING1B (GAAGAACTTCGAAGCAAA) and shEZH2 (GCCATTCCTCAATGTTTC). Transient expression of short interfering RNAs (siRNA, Dharmacon) was performed by oligofection as described earlier (5). When indicated, cells were treated with 50 ng/ml IL17A or 30 ng/ml TNFα (Immunotools and Peprotech, respectively).

Migration experiments were performed with cells isolated from peripheral blood from healthy donors after standard Ficoll–Paque gradient centrifugation. Polymorphonuclear cells were isolated from erythrocyte sediments (left after mononuclear isolation) using HES (hydroxyethyl starch, Grifols). The mono and polymorphonuclear enriched fractions were washed three times with PBS after isolation and resuspended in high glucose medium until the moment of use. Cell migration was measured with CytoSelect™ 96-well Cell Migration Fluorometric Assay (5 µm, Cell Biolabs), with conditioned medium from SCC13 cells in the bottom and hematopoietic cell suspension in the top compartment for 3h 30min and following manufacturer's instructions.

RNA isolation, qRT-PCR and expression arrays

RNA was isolated with Genelute Total Mammalian RNA Kit (Sigma-Aldrich) and cDNA was obtained by using Transcriptor First Strand cDNA Synthesis Kit (Roche). For expression arrays, samples were processed following user's manuals (Ambion WT Expression PN 4425209; Revised B 05/2009, Thermo Fisher Scientific; Affymetrix WT Terminal Labeling and Hybridization PN 702808 and Expression, Wash, Stain and Scan PN 702731, Affymetrix). The expression platform used was Human Gene 2.0 ST (Affymetrix).

qRT-PCR assays were performed using SYBR Green PCR master mix (Applied Biosystems, Life Technologies). For normalization purposes, we run simultaneously qRT-PCR with primers for GAPDH. The ABI PRISM 7900HT cycler's software calculated a threshold cycle number (Ct) at which each PCR amplification reached a significant threshold level. Figures present the amount of target mRNA/GAPDH mRNA relative copies ratio. Primers used for qRT-PCR were RING1B (CAGACAAACGGAACTCAACCATT; CTGTTATTGCCTCCTGAGGTGTT); IL1A (CTTCTGGGAAACTCACGGCA; AGCACA CCCAGTAGTCTTGTC); IL1B (CTCTTCGAGGCACAAGGCAC; ATCCAGAGGGCAGAG GTCCAG); IL6 (AGCCACTCACCTCTTCAGAAC; GTGCCTCTTTGCTGCTTTCAC); IL8 (TCTCTTGGCAGCCTTCCTGATTTC; ATTTCTGTGTTGGCGCAGTGTG); BMP2 (TCCACCATGAAGAATCTTTG; TAATTCGGTGATGGAAACTG); CSF3 (ATTTAAAC AGCAGTGTTCCC; AGAAGAAAAACGAGATTCCC); CCL20 (TATATTGTGCGTCTCC TCAG; GCTATGTCCAATTCCATTCC); CXCL1 (GTCTCTTCTTCCCTAGGAGCG; GATGCAGGATTGAGGCAAGC); LIF (TCTCTATTACACAGCCCAG; AAGGTACACG ACTATGCG); S100A7 (GCATGATCGACATGTTTCACAAATACAC; TGGTAGTCTGT GGCTATGTCTCCC); S100A8 (AGCCCTGCATGTCTCTTGTC; ACGTCTGCACCCTTTT TCCT); S100A9 (GCTCCTCGGCTTTGACAGAGTGCAAG; GCATTTGTGTCCAGGTCC

TCCATGATGTGT); GAPDH (AGTCAGCCGCATCTTCTTTTG; AAATCCGTTGACTCC GACCTT).

Protein extraction, western blot and immunoprecipitation

These protocols were performed following standard techniques. Polycomb antibodies were the same as those for immunohistochemistry. Antibodies to detect NF- κ B proteins and NIK were from Cell Signaling. Lamin B1 antibody was from Abcam, Actin and α -Tubulin antibodies from Sigma-Aldrich and HRP-conjugated antibodies from Dako (Agilent Technologies). For immunoprecipitation experiments cells were lysed 30 min at 4°C in 300 μ l PBS plus 0.5% Triton X-100, 1mM EDTA, 100 mM Sodium Orthovanadate, 0.25 mM PMSF and complete protease inhibitor cocktail (Roche, Spain). Supernatants were precleared 2 hours with 1% of BSA, 1 μ g IgGs and 50 μ l Protein G Agarose beads (Sigma-Aldrich) and then incubated O/N at 4°C with Protein G Agarose beads together with anti-IKK α (clone 881H3, Millipore, Sigma-Aldrich) antibody. The beads were washed three times with lysis buffer and directly resuspended in sample buffer, separated by SDS-PAGE, transferred to a Nitrocellulose membrane and analyzed by immunoblotting. The antibody used to detect IKK phosphorylated at Ser176 was from MyBioSource.

RESULTS

1. The Polycomb proteins EZH2 and RING1B are overexpressed in metastasizing primary cSCC

To analyze BMI1, RING1B and EZH2 expression by immunohistochemistry we used a retrospective cohort of tumor samples that included 107 primary cSCC, 51 corresponding to primary non-metastasizing cSCC (non-MSCC) and 56 to primary metastasizing cSCC

(MSCC) that had evolved to histologically confirmed lymph node (n = 51) or cutaneous in-transit (n = 5) metastases (Table S1)(7). BMI1 was equally expressed in cSCC tumors regardless their metastasizing abilities ($p=0.244$). In contrast, expression levels of RING1B, the other PRC1 protein analyzed, were enhanced in MSCC *versus* non-MSCC ($p<0.01$)(Figure 1). In respect to PRC2, EZH2 expression was also significantly enhanced in MSCC when compared to non-MSCC tumors ($p<0.01$)(Table S2). BMI1 and RING1B expression in the metastases from 39 patients did not significantly change when compared to their primary tumors, while there is a trend to lower EZH2 levels in metastases (Table S3).

The role of Polycomb proteins in regulating tumor growth is frequently associated with their ability to repress the *INK4A/ARF* locus, a negative regulator of cell cycle progression (11). However, immunohistochemical detection of the proliferative Ki67 nuclear antigen showed that Ki67 expression was similar in non-MSCC and MSCC (Figure 1 and data not shown).

2. EZH2 and RING1B downregulation in cSCC cells enhances the production of proinflammatory cytokines

Polycomb proteins are involved in the regulation of multiple programs such as cell cycle, DNA damage repair and cell death (11–13). Whereas many of these biological activities can be shared by a variety of tumors, other Polycomb functions seem to be cell-type specific (12). To investigate their role in cSCC we chose the SCC13 cell line, initially originated from a human SCC of the facial epidermis (8), since mice orthotopically transplanted with these cells developed cSCC tumors that invaginate and extensively migrate into the stroma and that are histologically similar to those of patients (S. Mejjeta, Master's

thesis, UPF, 2013; <http://hdl.handle.net/10803/283482>). To identify Polycomb-regulated genes, SCC13 cells were stably depleted from BMI1, RING1B or EZH2 expression by short hairpin RNA (shRNA) technology followed by puromycin selection (Figure 2a). Gene expression analysis (GEA) performed with duplicated samples identified 1919, 3263 and 1761 annotated sequences differentially regulated by BMI1, RING1B and EZH2, respectively (Figure S1a). Unsupervised hierarchical clustering of the most variably expressed genes stratified the cells into one main group formed by shControl and shBMI1 and segregated the other two conditions, shRING1B and shEZH2, as separate entities (Figure S1b). Venn diagram representation of differentially regulated sequences revealed that only few of them were co-regulated by the three Polycomb proteins, while most of the sequences were specifically regulated by each Polycomb protein in SCC13 cells (Figure 2b). Sequence classification according to their canonical functions with the Ingenuity Pathways Analysis (IPA) software further substantiated that BMI1, RING1B and EZH2 deficiency impinged in a variety of functions specific for each condition (Figure 2c).

Enhanced RING1B and EZH2, but not BMI1, expression levels were found to associate with cSCC metastatic behavior (see above). IPA of the sequences differentially co-regulated by these two proteins revealed that RING1B and EZH2 downregulation affected the expression of genes functionally involved in inflammatory response and immune regulation (Figures 2c, 2d, S2). Indeed, depletion of each of these two Polycomb proteins resulted in increased expression of cytokines, chemokines and other inflammatory mediators such as CSF3, IL1, IL8 and LIF (Figures 2d, 3a). In addition, RING1B deficient cells displayed enhanced mRNA levels of the calcium-binding proteins S100A7 (PSORIASIN), S100A8 (MRP-8) and S100A9 (MRP-14)(Figure 3a). These proteins are highly expressed at sites of acute and chronic inflammation (14), including psoriasis (15,16).

To further validate the inverse relationship between Polycomb and the tumoral inflammatory/immune signaling we investigated the molecular profile of a subgroup of 45 metastasis-prone aggressive lung tumors within a cohort of 293 lung tumors, which included 85 adenocarcinomas and 61 SCC and other histologic lung tumors (GSE30219)(17). EZH2 was among the upregulated genes in metastasis-prone lung tumors (3.7 fold change), whereas 43% of the downregulated genes were identified as involved in the development or functioning of the immune system or in cell defense responses by Gene Set Enrichment Analysis (GSEA) from the Broad Institute Database. EZH2 expression inversely correlated with 80% of the immune/inflammatory genes in the five metastasis-prone SCC lung tumors (correlation coefficient ≤ -0.5 in 45% of them; Table S4). Importantly, this inverse correlation was also observed in 95% (60% with $p < 0.05$) of the immune/inflammatory genes in the whole group of metastasis-prone lung tumors ($n=45$). Furthermore, the expression of many of the upregulated targets upon RING1B and EZH2 downregulation in SCC13 cells (i.e. CCL20, IL1B, CXCL3, S100A8, S100A9) inversely correlated with EZH2 expression in metastasis-prone lung tumors (Table S4).

3. RING1B and EZH2 downregulation results in the activation of the non-canonical NF- κ B pathway in cSCC cells

Accordingly to the inflammatory gene expression profile, IPA software identified NF- κ B as the most significantly altered node in RING1B and EZH2 deficient cells (Figure 3b). The NF- κ B family is composed of five members (Rel A, Rel B, Rel C, NF- κ B1, and NF- κ B2) that form dimeric complexes able to transactivate numerous target genes. NF- κ B1 and NF- κ B2 are translated as precursor proteins, p105 and p100 respectively, and processing of these precursors produces the mature p50/NF- κ B1 and p52/NF- κ B2 proteins (18). NF- κ B2 was

among the upregulated targets upon RING1B and EZH2 downregulation (Figure S2) and p100/NF- κ B2 expression was enhanced in these conditions, as detected by western blot, while no significant changes were observed in the other family members (Figure 4a). To better characterize the NF- κ B pathway in Polycomb-depleted SCC13 cells, cytoplasmic and nuclear fractions were prepared. Both shRING1B and shEZH2 cells displayed enhanced nuclear p100/NF- κ B2 and p52/NF- κ B2 levels when compared to shControl and shBMI1 cells (Figure 4b). In addition, p50/NF- κ B1 nuclear levels also increased in shRING1B and shEZH2 cells (Figure 4b).

While canonical p105/NF- κ B1 processing is constitutive and can be further induced by most physiological NF- κ B stimuli such as TNF and IL1, p100/NF- κ B2 is barely converted to p52/NF- κ B2 and its processing requires NIK, the NF- κ B-inducing kinase (19), which predominantly phosphorylates IKK α on Serine 176 (18,20–23). Western blot analysis of protein extracts from shRING1B, shEZH2 and shRING1B/siEZH2 (shRING1B cells transiently depleted from EZH2 with short interfering RNA) showed that these cells displayed enhanced NIK protein levels (Figure 4c). To further characterize NF- κ B2 activation, we performed immunoprecipitation with an antibody for IKK α followed by western blot to specifically determine S176 phosphorylation of IKK α . We also tested IL17A ability to phosphorylate S176-IKK α in parental SCC13 cells since IPA annotation pointed to IL17A signaling. Immunodetection of total IKK α allowed the identification of two bands, one of them corresponding to the full length 85 kDa protein and the other to the previously identified 45 kDa truncated-IKK α (24). S176 phosphorylation was only detected in the truncated IKK α , and both IL17A treated cells as well as shRING1B and shEZH2 cells displayed enhanced phosphorylated S176-IKK α levels (Figure 4d). Accordingly, IL17A increased p52/NF- κ B2 levels, that raised as early as one hour after the start of treatment, reaching maximal levels at

8h that were maintained 24h later (Figure 4e). IL17A treatment also enhanced p50/NF- κ B1 levels and induced IKK α / β phosphorylation (Figure 4e), in line with the reported IL17-induced activation of canonical NF- κ B1 in different tumor cell lines (25). Therefore, IL17A is able to activate both the canonical and non-canonical NF- κ B pathways in SCC13 cells.

4. RING1B and EZH2 deficient SCC13 cells display enhanced IL17A and TNF α responses

RING1B and EZH2 deficient SCC13 cells constitutively display NF- κ B2 activation and enhanced expression of inflammatory mediators under basal conditions. Next we investigated their response to TNF α and IL17A stimulation, as these two cytokines are present in the skin milieu of various cutaneous diseases (26). IL17A treatment enhanced p50/NF- κ B1 levels to a similar extent in all the conditions. In contrast, p52/NF- κ B2 induction was only observed in shControl and shBMI1 cells upon IL17A treatment, while untreated shRING1B and shEZH2 cells already displayed high p52/NF- κ B2 levels (Figure 5a). TNF α treatment barely affected NF- κ B levels in any condition at this time point, except for shRING1B cells, in which TNF α was able to further increase p50/NF- κ B1 and p52/NF- κ B2 levels (Figure 5a). To test the functional relevance of this differential NF- κ B activation we analyzed mRNA levels of IL1, IL6 and IL8 in response to IL17A and TNF α . IL17A treatment of shControl, shBMI1 and shEZH2 cells did not affect cytokine levels, while TNF α effectively induced them. In contrast, both IL17A and TNF α stimulation of shRING1B cells resulted in enhanced cytokine expression to different extents (Figure 5b).

5. Non-metastasizing cSCC displayed increased expression of inflammation-associated transcription factors and enhanced presence of inflammatory cells

Our data suggested that non-canonical NF- κ B would be repressed by RING1B and EZH2 in metastasis-prone cSCC. To test the activation of this pathway in non-MSCC and MSCC tumor samples we evaluated plasma membrane levels of phosphorylated IKK, since IKK relocation from cytosol to membrane has been reported to be associated with its activation (27). Levels of pS176-IKK α/β at the cytoplasmic membrane detected by immunofluorescence were higher in non-MSCC than in MSCC tumors ($p=0.05$)(Figure 6a; Table S5), supporting the notion that metastatic behavior is associated with defective activation of non-canonical NF- κ B in the tumoral cells.

NF- κ B-dependent transcription of inflammatory mediators is not only tightly controlled by regulatory mechanisms of this pathway but is also closely coordinated with other signaling molecules such as Sp1, AP-1, STAT3 and C/EBP β (28). Careful inspection of differentially expressed sequences in the GEA revealed that JUN D (member of the AP-1 family) and C/EBP β were among the sequences overrepresented in shRING1B and shEZH2 cells. Immunohistochemical detection of JUN D and C/EBP β revealed that non-MSCC tumors expressed higher levels of both proteins than MSCC tumors (JUN D $p=0.041$; C/EBP β $p=0.001$)(Figure 6b).

These data suggested that non-metastasizing cSCC tumor cells are engineered to secrete immunomodulatory factors. Identification and quantification of inflammatory cells in the primary cSCC tumors by conventional H&E staining revealed that non-MSCC displayed an enrichment in neutrophils and eosinophils when compared to MSCC ($p<0.02$ and $p<0.05$ respectively; Figure 6c and 6d). It has been reported that tumor-homing eosinophils are critical accessory cells that guide CD8 $^{+}$ T cells into the tumor, which results in tumor

eradication and survival (29). Immunohistochemical evaluation of the CD8⁺ population revealed that coordinated presence of both eosinophils and high numbers of CD8⁺ cells were more frequently found in non-MSCC tumors, according to the direct effect of the eosinophils in the regulation of tumoral adaptive immunity (29).

Non-MSCC tumors display low Polycomb levels, increased expression of factors that regulate the transcription of inflammatory cytokines and enhanced inflammatory responses. Since Polycomb-depleted SCC13 cells expressed higher levels of pro-inflammatory cytokines and chemokines we wondered whether these factors could be responsible for the recruitment of inflammatory cells. Chemotactic assays revealed that hematopoietic cells displayed higher chemotactic activity towards conditioned media from cultures of Polycomb-depleted SCC13 cells than from shControl cells (Figure 6e), which indicated that low Polycomb levels allow the expression of tumoral chemokines that are indeed responsible for attracting hematopoietic cells. Of note, BMI1 depleted cells also displayed chemotactic abilities to recruit PMN cells despite their transcriptome profile did not reveal overall changes in cytokine expression. This effect could be explained by the expression of a particular cytokine such as CXCL3, identified as an upregulated gene in the GEA of shBMI1 cells and with a potent chemotactic ability for neutrophils (30), or by the expression of low levels of other chemoattractant proteins.

DISCUSSION

Tumorigenesis is a multistage process characterized by uncontrolled proliferation of the tumoral cell. However, neoplastic cells often require additional factors in order to metastasize. Many Polycomb proteins have been reported to be upregulated in solid tumors

and their expression generally associates with poor prognosis. In cutaneous malignancies EZH2 is absent in nevi but its expression increased along malignant transformation of melanocytes (31). In non-melanoma skin cancer a sequential increase in EZH2 expression from normal skin to actinic keratosis (AK) and then to cSCC has been observed (32,33). In contrast, BMI expression seems to be highly tumor-specific, likely due to cell-context modulation of different signaling pathways and cell cycle regulators and by yet-to-discover functions of each Polycomb protein in a particular cell type. For instance RING1B is involved in melanoma genesis and progression acting, at least, by two different mechanisms: on one side, RING1B is able to activate TGF β signaling by repressing repressors of this pathway and on the other is able to directly activate cyclin D2 expression (34).

Besides the impact on cell cycle progression, EZH2 and other Polycomb proteins have been shown to display immunomodulatory functions. Most of these functions have been reported to occur in immune and inflammatory cells, where Polycomb proteins regulate cytokine repertoires as part of their differentiation programs (35). However, innate immune responses in non-immune cells are also essential in order to maintain tissue homeostasis and to response to different insults and some authors have already reported Polycomb involvement in these functions. For instance, EZH2 downregulation in hepatocytes exacerbates inflammation (36), while depletion of SUZ12, another PRC2 protein, in intestinal epithelial cells specifically increased basal and IL1-dependent inflammatory responses, including the expression of transcription factors such as C/EBP β . Importantly, this positive effect on inflammatory gene expression was revealed in the absence of the cyclin-dependent kinase inhibitor p16 (37).

Skin keratinocytes have a significant immunologic activity in addition to serving as structural components. They secrete proinflammatory cytokines and mediators, including

interleukin IL1, IL6, IL10, TNF α and GM-CSF, in response to ultraviolet radiation or other cell insults (38). The immunomodulatory function of the keratinocyte is best exemplified in psoriasis, a chronic inflammatory skin disorder. Although the pathogenesis of psoriasis remains unclear, accumulating evidence suggests that immune-mediated inflammatory cytokine overproduction and amplified inflammation by keratinocytes are key abnormalities (39,40). Within the psoriatic lesions, keratinocytes respond to inflammatory cytokines produced by the immune cells by releasing chemokines and cytokines, actively maintaining inflammatory microenvironments and sustaining psoriatic plaque development (26,40). In addition, TNF α , highly expressed in psoriatic skin, amplifies the IL17A effects on keratinocyte (41). Similarly, the skin in BCC and cSCC is infiltrated with a high number of IL17(+) T lymphocytes, and IL17 induced proliferation and migration of BCC and SCC cell lines, IL6 and IL8 production and NF- κ B upregulation (42). Our data show that non-MSCCs display low RING1B and EZH2 levels, phosphorylated S176-IKK α/β at the cytoplasmic membrane, high expression of C/EBP β and JUN D and enhanced inflammatory infiltrate, suggesting an increased expression of proinflammatory cytokines, whereas high RING1B and EZH2 levels in MSCC would impair NF- κ B activation and the expression of transcription factors involved in the inflammatory response. Rosseaux and colleagues reported that the functions depleted in 45 histologically different metastatic-prone lung tumors were related to the immune response, suggesting a reduced number of infiltrating immune cells within the tumors and/or in their environment (17). Accordingly we here report that non-MSCC display enhanced numbers of eosinophils and neutrophils. Tumor-homing eosinophils secrete chemoattractants that guide T cells into the tumor and initiate substantial changes in the tumor microenvironment, including macrophage polarization and normalization of the tumor vasculature, which are known to promote tumor rejection (29). Our *in vitro* studies support the notion that Polycomb represses the innate immune response by silencing the expression of

chemotactic factors in the tumoral cell and favoring the escape from immune surveillance systems in very aggressive and metastasis-prone cancer cells. More importantly, our results suggest that patients with high risk cSCC could benefit from clinical therapies addressed to harness the immune response.

The expression of PRC1 and PRC2 proteins is integrated through a network of regulatory microRNAs (miRNA) wherein epigenetic repression of PRC1-targeting miRNAs by PRC2 establishes a positive feedback loop, ensuring coexpression and cooperation of these two major Polycomb complexes (43). Therefore altered silencing or deletion of miRNA targeting Polycomb proteins could account for their aberrant expression in metastasizing cSCCs. In addition, the translational control of RING1B, with a highly active IRES in the 5'-UTR, is a complex multi-layered process that likely affects protein levels without significant changes at the mRNA levels (44). Since many tumoral gene expression databases rely on mRNA detection, RING1B protein abundance could be underestimated in a number of solid tumors. Identification of the mechanisms that result in Polycomb overexpression will be essential to understand and prevent tumor dissemination.

CONCLUSIONS

Polycomb represses the innate immune response by silencing the expression of chemotactic factors in the tumoral cell and favoring the escape from immune surveillance systems in very aggressive and metastasis-prone cancer cells.

LIST OF ABBREVIATIONS

cSCC, Cutaneous squamous cell carcinoma; BCC, basal cell carcinoma; PRC2 and PRC1, Polycomb repressive complex 2 and 1; MSCC, metastasizing primary cSCC; shRNA,

short hairpin RNA; siRNA, short interfering RNA; GEA, Gene Expression Analysis; IPA, Ingenuity Pathways Analysis; miRNA, microRNA.

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Figure 1. RING1B and EZH2 are overexpressed in primary metastasizing cSCC.

Expression of BMI1, RING1B and EZH2 in non-metastasizing (left column) and metastasizing (right column) cSCC, detected by immunohistochemistry. Insets: Higher magnification of the same lesions. Lower panel, proliferative rate detected by Ki67 staining. Scale bar, 100 μ m.

Figure 2. Effects of BMI1, RING1B and EZH2 downregulation in SCC13 cells. (a) Efficiency of stable downregulation of the three Polycomb proteins, determined by western blot analysis. (b) Venn diagram of differentially expressed sequences in each experimental condition, identified by gene expression array (GEA). (c) Ingenuity Pathway Analysis (IPA) identification of molecular and cellular functions affected by Polycomb downregulation in SCC13 cells. (d) Heat map depicting the first 24 annotated and upregulated genes in shRING1B and shEZH2 cells. Array data deposited at the Gene Expression Omnibus (GEO, National Center for Biotechnology Information) with accession number GSE108682.

Figure 3. Identification of gene expression changes upon Polycomb modulation in SCC13 cells. (a) Independent validation of some genes identified in the GEA of RING1B and EZH2 cells. Mean $\pm$ SD of triplicate samples from three independent experiments. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.005$. (b) In silico identification of the top-scoring multigene network associated to the inflammatory gene expression profile in shRING1B and shEZH2 cells. Red, overexpressed genes; green, downregulated genes.

Figure 4. RING1B and EZH2 downregulation results in activation of non-canonical NF- κ B signaling. (a) Total extracts of SCC13 cells stably depleted from BMI1, RING1B and EZH2 were subjected to western blot analysis to detect the indicated NF- κ B proteins. Lower

panel, quantification of the intensity of normalized bands corresponding to the indicated proteins and referred to control conditions. Graph display results from five independent experiments. **(b)** NF- κ B1 and NF- κ B2 levels in cytoplasmic and nuclear extracts from Polycomb depleted cells. Nuclear protein Lamin B and cytosolic protein α -Tubulin were detected as protein loading controls. **(c)** NIK levels in total extracts from Polycomb-depleted SCC13 cells. Signal intensity was normalized to Actin signal, as measure of protein relative abundance in the different samples and referred to control conditions, using Image J densitometry software. **(d)** Cytoplasmic extracts from SCC13 cells treated 24 h with IL17A (50 ng/ml) or from cells with downregulated Polycomb proteins were immunoprecipitated with an antibody specific for IKK α and western blot was performed to specifically detect pS176-IKK α . Intensity of pS176-IKK α signal was normalized to Actin signal. **(e)** Total extracts from SCC13 treated with IL17A (50 ng/ml) for the indicated time points, and subjected to western blot.

Figure 5. Effect of IL17A and TNF α on NF- κ B signaling and cytokine expression in Polycomb downregulated SCC13 cells. Cells were treated with IL17A (50 ng/ml; left) or TNF α (30 ng/ml; right). Twenty four hours later, total extracts and total RNA were subjected to western blot (**a**) or qRT-PCR analysis (**b**), respectively. Mean $\pm$ SD of triplicate samples from three independent experiments. *, $p < 0.05$.

Figure 6. Expression of pS176-IKK, C/EBP β and JUN D in non-MSCC and MSCC. (a)

Immunolocalization of pS176-IKK, detected by immunofluorescence. Observe cell membrane localization of the signal in two representative non-MSCC. Inset pictures, pS176-IKK in red and nuclei counterstained with Hoesch in blue. **(b)** C/EBP β and JUN D expression, detected by immunohistochemistry. Scale bar, 100 μ m. **(c)** Neutrophils and eosinophils detected by H&E staining and CD8+ cells detected by immunohistochemistry in metastasis-prone and

non-metastasizing primary cutaneous squamous cell carcinomas. **(d)** Neutrophils and eosinophils in a representative H/E stained section of a primary cSCC. **(e)** Chemotactic migration of peripheral blood mononuclear or polymorphonuclear (PMN) cells to 2-days conditioned media from SCC13 cell cultures. Mean $\pm$ SD of triplicate samples from three independent experiments. *, $p < 0.05$; **, $p < 0.01$.

	Metastasizing SCC (%)	Non-metastasizing SCC (%)	<i>p</i> -Value
Gender			NS (0.518)
Males	38/52 (73.1)	32/49 (65.3)	
Area			NS (0.074)
Head	43 (79.6)	40 (81.6)	
Trunk	5 (9.3)	0 (0)	
Extremities	6 (11.1)	9 (18.4)	
Ear			NS (0.369)
Yes	8/54 (14.8)	4/48 (8.3)	
Lip			NS (0.219)
Yes	0/54 (0)	2/48 (4.2)	
Horizontal size			NS (0.559)
>20 mm	27/54 (50)	22/51 (43)	
Sun exposed			NS (0.495)
Yes	47 /49 (95.9)	46/46 (100)	
Immunosuppression			NS (0.878)
Yes	6/51 (11.8)	6/53 (11.3)	

Table S1. Univariate analysis of clinical information of the patients included in the study.

	Signal Intensity	Metastasizing SCC	Non-metastasizing SCC	p-Value
RING1B	0	11/54 (20.4%)	13/51 (25.5%)	<0.01
	1	10/54 (18.5%)	24/51 (47.1%)	
	2	16/54 (29.6%)	13/51 (25.5%)	
	3	17/54 (31.5%)	1/51 (2.0%)	
EZH2	0	5/48 (10.4%)	17/49 (34.7%)	<0.01
	1	19/48 (39.6%)	18/49 (36.7%)	
	2	17/48 (35.4%)	14/49 (28.6%)	
	3	7/48 (14.6%)	0/49 (0%)	
BMI1	0	12/54 (22.2%)	10/48 (20.8%)	0.244
	1	24/54 (44.4%)	16/48 (33.3%)	
	2	18/54 (33.3%)	22/48 (45.8%)	

Table S2. Immunohistochemical expression of Polycomb markers in primary metastasizing and non-metastasizing cutaneous squamous cell carcinomas. Initial cohorts: 56 MSCC and 51 non-MSCC. In some cases, signal could not be evaluated due to technical limitations.

	Primary MSCC	Metastasis		
	Signal Intensity	0-1	2-3	p-Value
RING1B	0-1	5	8	0.791
	2-3	6	16	
EZH2	0-1	13	4	0.077
	2-3	12	3	
BMI1	0-1	7	12	0.238
	2	6	9	

Table S3. Immunohistochemical expression of Polycomb markers in thirty nine primary MSCC and their corresponding metastasis. In some cases, signal could not be evaluated due to technical limitations.

Figure S1. (a) Primary heat map of sequences differentially expressed in each of the four experimental conditions in SCC13. (b) Unsupervised cluster dendrogram derived from array expression data of the four different experimental conditions performed in duplicate.

Figure S2. Heat map of the most deregulated genes involved in inflammatory and vascular functions, identified by IPA network analysis in shRING1B and shEZH2 SCC13 cells.

	SCC.P3.Spearman's.Rho (N=5)	SCC.P3.Spearman's.p.value (N=5)	SCC.P3.Pearson's.cor (N=5)	SCC.P3.Pearson's.p.value (N=5)	All.P3.Spearman's.Rho (N=45)	All.P3.Spearman's.p.value (N=45)	All.P3.Pearson's.cor (N=45)	All.P3.Pearson's.p.value (N=45)
ITGAL	-1	0.02	-1.0	0.01	-0.3	0.04	-0.4	0.01
ITGB2	-1	0.02	-1.0	0.01	-0.5	0.00	-0.5	0.00
EGFR	-1	0.02	-0.9	0.04	0.2	0.23	0.2	0.12
TIMP3	-1	0.02	-0.9	0.02	-0.4	0.00	-0.5	0.00
IFITM2	-1	0.02	-0.9	0.02	-0.7	0.00	-0.7	0.00
LIPA	-1	0.02	-0.9	0.02	-0.3	0.03	-0.3	0.02
GBP1	-1	0.02	-1.0	0.01	-0.1	0.38	-0.2	0.10
ITGAV	-1	0.02	-1.0	0.01	-0.5	0.00	-0.5	0.00
IFI27	-1	0.02	-1.0	0.01	-0.3	0.07	-0.2	0.16
ICAM1	-1	0.02	-1.0	0.01	-0.5	0.00	-0.5	0.00
WIPF1	-1	0.02	-1.0	0.00	-0.4	0.01	-0.4	0.01
CD4	-1	0.02	-1.0	0.01	-0.4	0.01	-0.4	0.00
FSTL3	-1	0.02	-1.0	0.00	-0.5	0.00	-0.5	0.00
EDNRA	-1	0.02	-0.9	0.02	-0.4	0.00	-0.4	0.00
ESR1	-1	0.02	-1.0	0.01	-0.4	0.01	-0.3	0.03
C4BPA	-1	0.02	-0.9	0.06	-0.2	0.22	-0.3	0.08
CD86	-1	0.02	-0.7	0.15	-0.4	0.00	-0.5	0.00
LY86	-1	0.02	-1.0	0.01	-0.3	0.04	-0.3	0.04
CD84	-1	0.02	-0.9	0.05	-0.4	0.01	-0.4	0.00
LCP1	-1	0.02	-0.9	0.04	-0.5	0.00	-0.5	0.00
RGN	-1	0.02	-0.9	0.03	-0.2	0.13	-0.2	0.14
IFITM3	-1	0.02	-0.9	0.03	-0.6	0.00	-0.6	0.00
NACC2	-1	0.02	-0.9	0.07	-0.2	0.25	-0.2	0.29
SFTPD	-1	0.02	-0.8	0.12	-0.3	0.09	-0.3	0.06
SIGLEC1	-1	0.02	-1.0	0.01	-0.3	0.03	-0.4	0.01
TREM2	-1	0.02	-0.9	0.04	-0.4	0.00	-0.4	0.01
COLEC12	-1	0.02	-0.9	0.02	-0.4	0.00	-0.5	0.00
TNFSF15	-1	0.02	-0.9	0.05	-0.4	0.02	-0.4	0.01
SH2D3C	-0.9	0.08	-0.8	0.08	-0.2	0.15	-0.3	0.07
CSF3R	-0.9	0.08	-0.8	0.09	-0.3	0.02	-0.4	0.02
C1S	-0.9	0.08	-0.8	0.10	-0.6	0.00	-0.6	0.00
ADAM9	-0.9	0.08	-0.9	0.02	-0.5	0.00	-0.4	0.00
AP1S3	-0.9	0.08	-0.7	0.18	0.1	0.72	0.0	0.78
BANK1	-0.9	0.08	-0.9	0.04	-0.4	0.01	-0.5	0.00
LTB	-0.9	0.08	-0.8	0.08	-0.1	0.40	-0.1	0.53
HOPX	-0.9	0.08	-0.8	0.09	0.0	0.90	0.0	0.99
CX3CR1	-0.9	0.08	-0.7	0.22	-0.1	0.33	-0.1	0.48
INPP5D	-0.9	0.08	-0.5	0.37	-0.3	0.09	-0.3	0.05
SLC1A3	-0.9	0.08	-0.8	0.11	-0.2	0.22	-0.1	0.40
SPARC	-0.9	0.08	-0.9	0.04	-0.4	0.00	-0.4	0.01
CTSD	-0.9	0.08	-0.8	0.09	-0.4	0.00	-0.4	0.00
STAT1	-0.9	0.08	-0.8	0.13	-0.2	0.12	-0.3	0.03
SERPING1	-0.9	0.08	-0.9	0.06	-0.6	0.00	-0.6	0.00
HLA-DPB1	-0.9	0.08	-0.9	0.05	-0.3	0.06	-0.3	0.05
ZFP36L2	-0.9	0.08	-0.9	0.04	-0.4	0.02	-0.4	0.00
BST2	-0.9	0.08	-1.0	0.01	-0.4	0.00	-0.4	0.00
CD14	-0.9	0.08	-0.8	0.07	-0.5	0.00	-0.5	0.00
DCN	-0.9	0.08	-0.9	0.05	-0.6	0.00	-0.6	0.00
MX1	-0.9	0.08	-0.8	0.09	-0.3	0.07	-0.3	0.02

	SCC.P3.Spearman's.Rho (N=5)	SCC.P3.Spearman's.p.value (N=5)	SCC.P3.Pearson's.cor (N=5)	SCC.P3.Pearson's.p.value (N=5)	All.P3.Spearman's.Rho (N=45)	All.P3.Spearman's.p.value (N=45)	All.P3.Pearson's.cor (N=45)	All.P3.Pearson's.p.value (N=45)
ST5	-0.9	0.08	-0.6	0.26	-0.1	0.37	-0.1	0.42
IRF1	-0.9	0.08	-1.0	0.00	-0.1	0.36	-0.2	0.11
AXL	-0.9	0.08	-0.8	0.09	-0.4	0.01	-0.4	0.01
GBP2	-0.9	0.08	-0.9	0.06	-0.3	0.03	-0.4	0.01
SERPINA1	-0.9	0.08	-0.9	0.06	-0.6	0.00	-0.6	0.00
SP100	-0.9	0.08	-0.9	0.02	-0.5	0.00	-0.6	0.00
CTSS	-0.9	0.08	-0.8	0.09	-0.4	0.00	-0.4	0.01
IL1R1	-0.9	0.08	-0.9	0.06	-0.6	0.00	-0.6	0.00
C7	-0.9	0.08	-0.7	0.22	-0.4	0.00	-0.5	0.00
TIMP2	-0.9	0.08	-0.9	0.06	-0.3	0.07	-0.3	0.06
RASSF2	-0.9	0.08	-0.8	0.10	-0.3	0.03	-0.2	0.13
S100A4	-0.9	0.08	-0.7	0.18	-0.6	0.00	-0.6	0.00
LGALS9	-0.9	0.08	-0.8	0.08	-0.4	0.01	-0.4	0.00
ZEB2	-0.9	0.08	-0.8	0.07	-0.4	0.01	-0.4	0.02
IL32	-0.9	0.08	-0.9	0.05	-0.5	0.00	-0.6	0.00
VCAM1	-0.9	0.08	-1.0	0.01	-0.6	0.00	-0.6	0.00
PIK3CD	-0.9	0.08	-0.9	0.04	-0.4	0.02	-0.3	0.02
HLA-DMB	-0.9	0.08	-0.9	0.04	-0.3	0.06	-0.3	0.03
KDELR3	-0.9	0.08	-0.7	0.16	-0.5	0.00	-0.5	0.00
CD48	-0.9	0.08	-0.9	0.03	-0.3	0.02	-0.4	0.02
TYROBP	-0.9	0.08	-0.9	0.03	-0.3	0.07	-0.3	0.05
GEM	-0.9	0.08	-0.9	0.04	-0.5	0.00	-0.4	0.00
CCL21	-0.9	0.08	-0.6	0.26	-0.6	0.00	-0.6	0.00
IFIT3	-0.9	0.08	-0.9	0.02	-0.2	0.23	-0.2	0.13
FAS	-0.9	0.08	-0.9	0.02	-0.4	0.00	-0.5	0.00
TYMP	-0.9	0.08	-0.9	0.03	-0.6	0.00	-0.6	0.00
AOC3	-0.9	0.08	-0.8	0.10	-0.6	0.00	-0.5	0.00
TCF21	-0.9	0.08	-0.8	0.09	-0.4	0.01	-0.3	0.03
IL1B	-0.9	0.08	-0.9	0.03	-0.5	0.00	-0.4	0.01
ATP2B4	-0.9	0.08	-0.8	0.08	0.1	0.71	0.0	0.82
SLC22A3	-0.9	0.08	-0.8	0.11	-0.2	0.11	-0.2	0.19
CCL20	-0.9	0.08	-1.0	0.01	-0.6	0.00	-0.6	0.00
C5	-0.9	0.08	-0.8	0.07	-0.1	0.44	-0.1	0.33
BTK	-0.9	0.08	-0.8	0.12	-0.4	0.00	-0.5	0.00
ASPH	-0.9	0.08	-0.6	0.30	-0.4	0.01	-0.4	0.01
CTSE	-0.9	0.08	-0.8	0.14	-0.2	0.19	-0.3	0.09
CD1C	-0.9	0.08	-0.6	0.28	-0.3	0.07	-0.3	0.04
PRRX1	-0.9	0.08	-0.8	0.08	-0.6	0.00	-0.6	0.00
PTPN22	-0.9	0.08	-0.8	0.13	-0.4	0.01	-0.4	0.00
XAF1	-0.9	0.08	-0.9	0.05	-0.4	0.01	-0.4	0.01
PTAFR	-0.9	0.08	-0.8	0.10	-0.5	0.00	-0.5	0.00
HLA-DOA	-0.9	0.08	-0.9	0.06	-0.1	0.33	-0.2	0.19
CCR7	-0.9	0.08	-0.9	0.04	-0.4	0.01	-0.5	0.00
IGSF6	-0.9	0.08	-0.8	0.08	-0.3	0.06	-0.3	0.10
PLXNC1	-0.9	0.08	-0.8	0.10	0.0	0.98	0.0	0.93
CCR6	-0.9	0.08	-0.9	0.02	-0.4	0.01	-0.4	0.00
CCR5	-0.9	0.08	-0.9	0.04	-0.3	0.07	-0.4	0.01
JAK3	-0.9	0.08	-0.9	0.03	-0.1	0.48	-0.1	0.47
TGFBR2	-0.9	0.08	-1.0	0.01	-0.5	0.00	-0.4	0.01

	SCC.P3.Spearman's.Rho (N=5)	SCC.P3.Spearman's.p.value (N=5)	SCC.P3.Pearson's.cor (N=5)	SCC.P3.Pearson's.p.value (N=5)	All.P3.Spearman's.Rho (N=45)	All.P3.Spearman's.p.value (N=45)	All.P3.Pearson's.cor (N=45)	All.P3.Pearson's.p.value (N=45)
AQP1	-0.9	0.08	-0.7	0.17	-0.2	0.17	-0.2	0.11
GPR171	-0.9	0.08	-0.6	0.27	-0.3	0.03	-0.4	0.02
CAPN2	-0.9	0.08	-0.7	0.15	-0.4	0.01	-0.4	0.01
ENPP2	-0.9	0.08	-0.8	0.08	-0.4	0.00	-0.4	0.00
RARRES2	-0.9	0.08	-0.9	0.05	-0.5	0.00	-0.5	0.00
IGF1	-0.9	0.08	-0.9	0.06	-0.6	0.00	-0.6	0.00
NCKAP1L	-0.9	0.08	-0.8	0.09	-0.4	0.01	-0.4	0.01
HGF	-0.9	0.08	-0.7	0.15	-0.6	0.00	-0.5	0.00
OLR1	-0.9	0.08	-0.9	0.06	-0.4	0.01	-0.4	0.01
AQP4	-0.9	0.08	-0.9	0.04	-0.2	0.23	-0.3	0.09
MS4A1	-0.9	0.08	-0.9	0.05	-0.3	0.03	-0.5	0.00
LY9	-0.9	0.08	-0.9	0.06	-0.3	0.04	-0.4	0.01
BIRC3	-0.9	0.08	-1.0	0.01	-0.6	0.00	-0.4	0.00
TRIM5	-0.9	0.08	-0.9	0.04	-0.5	0.00	-0.5	0.00
PLAUR	-0.9	0.08	-0.9	0.06	-0.4	0.00	-0.4	0.00
CAPN3	-0.9	0.08	-0.8	0.09	-0.3	0.07	-0.2	0.17
ITK	-0.9	0.08	-0.7	0.16	-0.3	0.10	-0.4	0.02
CCRL2	-0.9	0.08	-0.9	0.02	-0.4	0.01	-0.4	0.01
C1R	-0.9	0.08	-0.9	0.05	-0.7	0.00	-0.7	0.00
RRAS	-0.9	0.08	-0.9	0.03	-0.6	0.00	-0.6	0.00
CREB3L1	-0.9	0.08	-1.0	0.00	-0.6	0.00	-0.5	0.00
TRIM22	-0.9	0.08	-0.9	0.05	-0.4	0.00	-0.5	0.00
G0S2	-0.9	0.08	-0.9	0.03	-0.4	0.01	-0.4	0.01
GPR65	-0.9	0.08	-0.9	0.04	-0.3	0.04	-0.3	0.04
LPXN	-0.9	0.08	-0.8	0.07	-0.5	0.00	-0.5	0.00
CCL2	-0.9	0.08	-0.9	0.04	-0.5	0.00	-0.5	0.00
TNFRSF12A	-0.9	0.08	-0.9	0.03	-0.4	0.00	-0.5	0.00
DNAJC15	-0.9	0.08	-0.9	0.04	-0.2	0.13	-0.3	0.07
C8orf4	-0.9	0.08	-0.9	0.03	-0.6	0.00	-0.6	0.00
PDGFC	-0.9	0.08	-0.9	0.02	-0.5	0.00	-0.5	0.00
PID1	-0.9	0.08	-0.9	0.05	-0.3	0.05	-0.2	0.17
TREM1	-0.9	0.08	-0.8	0.11	-0.6	0.00	-0.6	0.00
CLEC5A	-0.9	0.08	-0.9	0.01	-0.5	0.00	-0.4	0.00
C5AR1	-0.9	0.08	-0.9	0.05	-0.5	0.00	-0.5	0.00
CLEC2D	-0.9	0.08	-0.8	0.14	-0.2	0.11	-0.3	0.06
TLR7	-0.9	0.08	-0.9	0.07	-0.3	0.07	-0.3	0.07
CISH	-0.9	0.08	-0.9	0.07	-0.5	0.00	-0.5	0.00
SLC40A1	-0.9	0.08	-0.7	0.14	-0.4	0.01	-0.4	0.02
NEK6	-0.9	0.08	-0.7	0.17	0.0	0.91	0.0	0.86
PARP9	-0.9	0.08	-0.8	0.08	-0.2	0.17	-0.3	0.05
TNFSF13B	-0.9	0.08	-0.9	0.06	-0.3	0.07	-0.3	0.03
SLC46A2	-0.9	0.08	-0.7	0.16	-0.2	0.10	-0.3	0.03
C10orf54	-0.9	0.08	-0.7	0.21	-0.4	0.00	-0.4	0.01
SLC27A1	-0.9	0.08	-0.9	0.03	-0.4	0.01	-0.4	0.01
SPRED1	-0.9	0.08	-1.0	0.00	-0.6	0.00	-0.6	0.00
AMICA1	-0.9	0.08	-0.3	0.58	-0.3	0.03	-0.3	0.03
CCL5	-0.8	0.13	-0.9	0.06	-0.2	0.22	-0.2	0.17
SMPDL3B	-0.8	0.13	-0.7	0.23	-0.3	0.02	-0.4	0.01
STAP1	-0.8	0.13	-0.7	0.15	-0.4	0.01	-0.4	0.00
APBB1IP	-0.8	0.13	-0.4	0.54	-0.3	0.03	-0.3	0.03

	SCC.P3.Spearman's.Rho (N=5)	SCC.P3.Spearman's.p.value (N=5)	SCC.P3.Pearson's.cor (N=5)	SCC.P3.Pearson's.p.value (N=5)	All.P3.Spearman's.Rho (N=45)	All.P3.Spearman's.p.value (N=45)	All.P3.Pearson's.cor (N=45)	All.P3.Pearson's.p.value (N=45)
PDGFRA	-0.8	0.13	-0.9	0.05	-0.3	0.04	-0.3	0.07
PTGS2	-0.8	0.13	-0.8	0.12	-0.6	0.00	-0.6	0.00
KLHL6	-0.8	0.13	-0.8	0.08	-0.2	0.18	-0.3	0.09
CFI	-0.8	0.13	-0.8	0.08	-0.6	0.00	-0.6	0.00
SAMSN1	-0.8	0.13	-0.7	0.16	-0.3	0.03	-0.4	0.01
CD79A	-0.8	0.13	-0.7	0.19	-0.4	0.00	-0.5	0.00
CLEC2B	-0.8	0.13	-0.8	0.11	-0.3	0.06	-0.4	0.01
PECAM1	-0.8	0.13	-0.5	0.38	-0.5	0.00	-0.4	0.01
GAS6	-0.8	0.13	-0.7	0.19	-0.2	0.16	-0.2	0.26
GPX1	-0.8	0.13	-0.7	0.19	-0.1	0.55	-0.1	0.54
ARL6IP5	-0.8	0.13	-0.7	0.18	-0.5	0.00	-0.5	0.00
FLNA	-0.8	0.13	-0.9	0.06	-0.3	0.08	-0.3	0.03
TXNIP	-0.8	0.13	-0.7	0.21	-0.1	0.44	-0.1	0.33
CYR61	-0.8	0.13	-0.8	0.09	-0.5	0.00	-0.5	0.00
TNC	-0.8	0.13	-0.8	0.10	-0.3	0.02	-0.4	0.02
LYN	-0.8	0.13	-0.7	0.20	-0.5	0.00	-0.5	0.00
CD93	-0.8	0.13	-0.6	0.31	-0.4	0.02	-0.3	0.03
CSF1R	-0.8	0.13	-0.8	0.08	-0.5	0.00	-0.4	0.00
IL2RG	-0.8	0.13	-0.8	0.11	-0.5	0.00	-0.5	0.00
FLI1	-0.8	0.13	-0.7	0.15	-0.1	0.33	-0.2	0.29
MMP7	-0.8	0.13	-0.8	0.09	-0.4	0.01	-0.4	0.00
KYNU	-0.8	0.13	-0.7	0.16	-0.3	0.03	-0.2	0.21
FOLR1	-0.8	0.13	-0.8	0.12	-0.5	0.00	-0.5	0.00
IRF4	-0.8	0.13	-0.7	0.18	-0.3	0.02	-0.5	0.00
SELL	-0.8	0.13	-0.8	0.07	-0.4	0.00	-0.5	0.00
SLC7A7	-0.8	0.13	-0.9	0.04	-0.4	0.01	-0.4	0.00
CDH5	-0.8	0.13	-0.6	0.24	-0.3	0.04	-0.3	0.03
LTBP2	-0.8	0.13	-0.8	0.12	-0.6	0.00	-0.6	0.00
FOLR2	-0.8	0.13	-0.6	0.28	-0.3	0.04	-0.3	0.03
IL10RA	-0.8	0.13	-0.9	0.06	-0.5	0.00	-0.5	0.00
SASH3	-0.8	0.13	-0.9	0.06	-0.4	0.01	-0.4	0.01
TLR2	-0.8	0.13	-0.9	0.03	-0.5	0.00	-0.5	0.00
ICAM3	-0.8	0.13	-0.8	0.14	-0.6	0.00	-0.6	0.00
ORM1	-0.8	0.13	-0.8	0.09	-0.6	0.00	-0.6	0.00
CIITA	-0.8	0.13	-0.6	0.31	-0.2	0.32	-0.1	0.43
LAMA2	-0.8	0.13	-0.8	0.07	-0.6	0.00	-0.6	0.00
NCF4	-0.8	0.13	-0.7	0.23	-0.4	0.01	-0.4	0.01
NR3C2	-0.8	0.13	-0.8	0.10	-0.3	0.04	-0.2	0.22
LCP2	-0.8	0.13	-0.8	0.10	-0.4	0.00	-0.4	0.01
FYB	-0.8	0.13	-0.9	0.05	-0.3	0.07	-0.3	0.03
IL2RB	-0.8	0.13	-0.7	0.16	-0.3	0.09	-0.3	0.04
AGTR1	-0.8	0.13	-0.7	0.22	-0.3	0.07	-0.2	0.12
FMO1	-0.8	0.13	-0.7	0.19	-0.4	0.01	-0.3	0.02
ITGAM	-0.8	0.13	-0.9	0.03	-0.5	0.00	-0.5	0.00
MARCO	-0.8	0.13	-0.9	0.06	-0.3	0.08	-0.3	0.07
CD2	-0.8	0.13	-0.8	0.12	-0.3	0.05	-0.3	0.04
CD27	-0.8	0.13	-0.7	0.19	-0.3	0.02	-0.4	0.00
ADRB2	-0.8	0.13	-0.9	0.06	-0.5	0.00	-0.5	0.00
PRKCE	-0.8	0.13	-0.8	0.09	-0.2	0.18	-0.2	0.15
CALCRL	-0.8	0.13	-0.7	0.18	-0.4	0.01	-0.4	0.01

	SCC.P3.Spearman's.Rho (N=5)	SCC.P3.Spearman's.p.value (N=5)	SCC.P3.Pearson's.cor (N=5)	SCC.P3.Pearson's.p.value (N=5)	All.P3.Spearman's.Rho (N=45)	All.P3.Spearman's.p.value (N=45)	All.P3.Pearson's.cor (N=45)	All.P3.Pearson's.p.value (N=45)
TSC22D3	-0.8	0.13	-0.4	0.51	-0.3	0.04	-0.3	0.02
CSF2RA	-0.8	0.13	-0.6	0.25	-0.3	0.06	-0.2	0.20
PTGES	-0.8	0.13	-0.9	0.06	-0.5	0.00	-0.5	0.00
RAC2	-0.8	0.13	-0.8	0.09	-0.5	0.00	-0.6	0.00
TNFRSF1A	-0.8	0.13	-0.9	0.06	-0.6	0.00	-0.6	0.00
LAX1	-0.8	0.13	-0.6	0.24	-0.5	0.00	-0.5	0.00
SP140	-0.8	0.13	-0.8	0.10	-0.4	0.01	-0.4	0.00
CXCL3	-0.8	0.13	-0.8	0.13	-0.4	0.00	-0.4	0.01
MEF2C	-0.8	0.13	-0.8	0.13	-0.2	0.20	-0.2	0.12
AKAP13	-0.8	0.13	-0.8	0.09	-0.4	0.01	-0.4	0.00
CFLAR	-0.8	0.13	-0.7	0.17	-0.5	0.00	-0.4	0.01
HLA-DRA	-0.8	0.13	-0.8	0.08	-0.3	0.04	-0.3	0.02
TNFRSF14	-0.8	0.13	-0.6	0.25	-0.4	0.00	-0.4	0.01
ECM1	-0.8	0.13	-0.9	0.05	-0.6	0.00	-0.6	0.00
CHI3L1	-0.8	0.13	-0.7	0.15	-0.5	0.00	-0.5	0.00
TRAC	-0.8	0.13	-0.8	0.11	-0.4	0.02	-0.4	0.01
SERPINB9	-0.8	0.13	-0.6	0.33	-0.2	0.16	0.0	0.99
SELPLG	-0.8	0.13	-0.8	0.12	-0.5	0.00	-0.5	0.00
C3AR1	-0.8	0.13	-0.8	0.11	-0.4	0.01	-0.4	0.01
IDO1	-0.8	0.13	-0.7	0.16	-0.2	0.28	-0.2	0.13
SH2D1A	-0.8	0.13	-0.8	0.10	-0.2	0.14	-0.2	0.11
CST7	-0.8	0.13	-0.7	0.18	-0.4	0.01	-0.4	0.00
GZMH	-0.8	0.13	-0.8	0.13	-0.1	0.43	-0.1	0.53
ZEB1	-0.8	0.13	-0.8	0.11	-0.2	0.11	-0.1	0.35
FCGR2C	-0.8	0.13	-0.7	0.15	-0.4	0.00	-0.4	0.00
COL6A1	-0.8	0.13	-0.8	0.09	-0.5	0.00	-0.4	0.01
PIK3R1	-0.8	0.13	-0.9	0.02	-0.1	0.33	-0.2	0.15
CD3D	-0.8	0.13	-0.7	0.15	-0.2	0.17	-0.2	0.13
KLRB1	-0.8	0.13	-0.5	0.36	-0.4	0.01	-0.4	0.01
HLA-DMA	-0.8	0.13	-0.8	0.08	-0.4	0.01	-0.4	0.01
C3	-0.8	0.13	-0.8	0.11	-0.6	0.00	-0.5	0.00
RBM47	-0.8	0.13	-0.7	0.22	-0.4	0.01	-0.5	0.00
ZC3H12A	-0.8	0.13	-0.8	0.11	-0.4	0.01	-0.4	0.01
ASPN	-0.8	0.13	-0.5	0.38	-0.5	0.00	-0.4	0.00
SLAMF7	-0.8	0.13	-0.8	0.14	-0.3	0.08	-0.4	0.02
BIN2	-0.8	0.13	-0.8	0.11	-0.4	0.00	-0.4	0.00
KLF2	-0.8	0.13	-0.9	0.05	-0.5	0.00	-0.6	0.00
P2RY13	-0.8	0.13	-0.6	0.34	-0.3	0.05	-0.3	0.05
TAOK3	-0.8	0.13	-0.9	0.03	-0.6	0.00	-0.6	0.00
TRIM8	-0.8	0.13	-0.8	0.09	-0.6	0.00	-0.5	0.00
GUCY1A3	-0.8	0.13	-0.9	0.06	-0.4	0.00	-0.4	0.01
CXXC5	-0.8	0.13	-0.7	0.19	0.0	0.98	0.0	0.93
ERRF1	-0.8	0.13	-0.9	0.03	-0.4	0.01	-0.4	0.01
ESAM	-0.8	0.13	-0.8	0.09	-0.3	0.03	-0.3	0.05
DOCK8	-0.8	0.13	-0.9	0.06	-0.4	0.01	-0.4	0.01
PAG1	-0.8	0.13	-0.9	0.04	-0.5	0.00	-0.5	0.00
PODN	-0.8	0.13	-0.6	0.32	-0.5	0.00	-0.5	0.00
MYO1G	-0.8	0.13	-0.7	0.16	-0.3	0.02	-0.3	0.02
TBC1D10C	-0.8	0.13	-0.8	0.12	-0.3	0.09	-0.3	0.02
NLRC3	-0.8	0.13	-0.8	0.12	-0.3	0.04	-0.4	0.01

	SCC.P3.Spearman's.Rho (N=5)	SCC.P3.Spearman's.p.value (N=5)	SCC.P3.Pearson's.cor (N=5)	SCC.P3.Pearson's.p.value (N=5)	All.P3.Spearman's.Rho (N=45)	All.P3.Spearman's.p.value (N=45)	All.P3.Pearson's.cor (N=45)	All.P3.Pearson's.p.value (N=45)
HAVCR2	-0.7	0.23	-0.6	0.24	-0.1	0.42	-0.2	0.18
FCER1G	-0.7	0.23	-0.7	0.17	-0.3	0.06	-0.3	0.04
IFIH1	-0.7	0.23	-0.8	0.08	-0.4	0.02	-0.4	0.01
LYZ	-0.7	0.23	-0.7	0.22	-0.5	0.00	-0.4	0.00
TNFRSF10E	-0.7	0.23	-0.9	0.05	-0.2	0.32	-0.2	0.32
RBPMS	-0.7	0.23	-0.6	0.31	-0.4	0.00	-0.3	0.04
MAP3K13	-0.7	0.23	-0.4	0.54	0.3	0.05	0.3	0.06
MSN	-0.7	0.23	-0.9	0.05	-0.3	0.03	-0.3	0.02
LGALS3BP	-0.7	0.23	-0.4	0.56	-0.5	0.00	-0.5	0.00
ITGB5	-0.7	0.23	-0.6	0.32	-0.6	0.00	-0.7	0.00
ATP1B1	-0.7	0.23	-0.6	0.32	-0.3	0.07	-0.3	0.03
VAMP3	-0.7	0.23	-1.0	0.01	-0.3	0.05	-0.3	0.06
NBL1	-0.7	0.23	-0.9	0.05	-0.5	0.00	-0.5	0.00
OPTN	-0.7	0.23	-0.6	0.32	-0.3	0.08	-0.3	0.07
SERPINF1	-0.7	0.23	-0.6	0.29	-0.7	0.00	-0.6	0.00
TNFSF10	-0.7	0.23	-0.5	0.35	-0.4	0.01	-0.4	0.00
FOXO1	-0.7	0.23	-0.6	0.31	-0.5	0.00	-0.5	0.00
DAPK1	-0.7	0.23	-0.3	0.59	-0.1	0.64	-0.1	0.41
PLEK	-0.7	0.23	-0.6	0.24	-0.2	0.10	-0.2	0.14
LOXL1	-0.7	0.23	-0.8	0.14	-0.3	0.08	-0.3	0.04
SEMA3C	-0.7	0.23	-0.9	0.07	-0.2	0.13	-0.2	0.14
IRF9	-0.7	0.23	-0.8	0.08	-0.2	0.16	-0.3	0.06
HPGD	-0.7	0.23	-0.6	0.30	-0.3	0.02	-0.4	0.01
SFRP4	-0.7	0.23	-0.7	0.23	-0.5	0.00	-0.5	0.00
MRC1	-0.7	0.23	-0.5	0.44	-0.4	0.00	-0.4	0.00
GAS1	-0.7	0.23	-0.8	0.14	-0.3	0.07	-0.2	0.18
COL17A1	-0.7	0.23	-0.7	0.17	0.0	0.91	-0.2	0.21
MNDA	-0.7	0.23	-0.8	0.09	-0.4	0.02	-0.4	0.02
MAP3K8	-0.7	0.23	-0.6	0.34	-0.6	0.00	-0.5	0.00
IL1RAP	-0.7	0.23	-0.9	0.04	-0.4	0.01	-0.4	0.00
PLAU	-0.7	0.23	-0.8	0.10	-0.5	0.00	-0.5	0.00
TNFSF12	-0.7	0.23	-0.6	0.24	-0.5	0.00	-0.4	0.00
IL7R	-0.7	0.23	-0.5	0.37	-0.5	0.00	-0.5	0.00
FCN3	-0.7	0.23	-0.3	0.61	-0.1	0.57	-0.1	0.39
MMP13	-0.7	0.23	-0.9	0.02	-0.5	0.00	-0.5	0.00
P2RY14	-0.7	0.23	-0.4	0.46	-0.2	0.26	-0.1	0.51
CPB2	-0.7	0.23	-0.9	0.07	-0.4	0.01	-0.2	0.11
LILRB1	-0.7	0.23	-0.8	0.10	-0.2	0.14	-0.2	0.11
ICAM4	-0.7	0.23	-0.7	0.18	-0.1	0.69	0.0	0.85
RNF125	-0.7	0.23	-0.6	0.32	-0.6	0.00	-0.6	0.00
CITED2	-0.7	0.23	-0.7	0.23	-0.1	0.69	-0.1	0.50
CHIT1	-0.7	0.23	-0.7	0.20	-0.2	0.25	-0.2	0.28
PLXNB2	-0.7	0.23	-0.8	0.12	-0.2	0.16	-0.2	0.10
CTGF	-0.7	0.23	-0.8	0.08	-0.5	0.00	-0.5	0.00
NFKB1	-0.7	0.23	-0.7	0.20	-0.6	0.00	-0.7	0.00
CA2	-0.7	0.23	-0.5	0.42	0.0	0.91	0.0	0.85
IKKB	-0.7	0.23	-0.7	0.21	-0.3	0.08	-0.2	0.11
AGER	-0.7	0.23	-0.6	0.32	-0.1	0.33	-0.2	0.16
MGLL	-0.7	0.23	-0.5	0.39	-0.2	0.23	-0.2	0.24
ZFP36L1	-0.7	0.23	-0.5	0.35	-0.3	0.04	-0.3	0.02

	SCC.P3.Spearman's.Rho (N=5)	SCC.P3.Spearman's.p.value (N=5)	SCC.P3.Pearson's.cor (N=5)	SCC.P3.Pearson's.p.value (N=5)	All.P3.Spearman's.Rho (N=45)	All.P3.Spearman's.p.value (N=45)	All.P3.Pearson's.cor (N=45)	All.P3.Pearson's.p.value (N=45)
HLA-DPA1	-0.7	0.23	-0.7	0.21	-0.3	0.04	-0.3	0.09
IFITM1	-0.7	0.23	-0.9	0.06	-0.6	0.00	-0.6	0.00
ITGA8	-0.7	0.23	-0.5	0.36	-0.3	0.03	-0.4	0.01
FCGR1B	-0.7	0.23	-0.7	0.22	-0.3	0.04	-0.4	0.02
FPR3	-0.7	0.23	-0.7	0.19	-0.1	0.35	-0.2	0.20
TRIM56	-0.7	0.23	-0.7	0.18	-0.1	0.53	-0.1	0.43
IFIT2	-0.7	0.23	-0.8	0.11	-0.2	0.15	-0.2	0.15
RAB31	-0.7	0.23	-0.9	0.01	-0.5	0.00	-0.5	0.00
FLRT3	-0.7	0.23	-0.8	0.11	-0.4	0.00	-0.4	0.00
CHIA	-0.7	0.23	-0.8	0.11	-0.2	0.15	-0.2	0.16
SHISA5	-0.7	0.23	-0.5	0.41	-0.6	0.00	-0.6	0.00
CAMK2D	-0.7	0.23	-0.9	0.02	-0.3	0.04	-0.4	0.01
SUSD2	-0.7	0.23	-0.7	0.18	-0.4	0.02	-0.3	0.03
GBP5	-0.7	0.23	-0.7	0.16	-0.2	0.25	-0.2	0.12
GAPT	-0.6	0.35	-0.9	0.02	-0.5	0.00	-0.4	0.00
IL16	-0.6	0.35	-0.6	0.26	0.0	0.83	0.0	0.83
PGC	-0.6	0.35	-0.6	0.33	-0.4	0.00	-0.3	0.02
KLF6	-0.6	0.35	-0.5	0.35	-0.5	0.00	-0.4	0.00
LGALS3	-0.6	0.35	-0.6	0.25	-0.2	0.27	-0.1	0.36
SAMHD1	-0.6	0.35	-0.5	0.40	-0.1	0.41	-0.1	0.33
MDFIC	-0.6	0.35	-0.4	0.54	-0.3	0.05	-0.1	0.34
JAK2	-0.6	0.35	-0.5	0.41	-0.1	0.53	-0.1	0.57
GSN	-0.6	0.35	-0.1	0.81	-0.1	0.44	-0.1	0.34
DUOX1	-0.6	0.35	-0.6	0.31	-0.2	0.18	-0.2	0.27
CXCL2	-0.6	0.35	-0.5	0.35	-0.5	0.00	-0.3	0.03
GLI3	-0.6	0.35	-0.6	0.26	-0.2	0.29	-0.2	0.28
CD81	-0.6	0.35	-0.7	0.18	-0.5	0.00	-0.4	0.01
MCL1	-0.6	0.35	-0.8	0.14	-0.2	0.19	-0.3	0.08
CTSB	-0.6	0.35	-0.7	0.22	-0.5	0.00	-0.5	0.00
EPAS1	-0.6	0.35	-0.6	0.33	-0.7	0.00	-0.6	0.00
DUSP1	-0.6	0.35	-0.4	0.54	-0.5	0.00	-0.5	0.00
STOM	-0.6	0.35	-0.5	0.39	-0.4	0.01	-0.4	0.01
BTG2	-0.6	0.35	-0.5	0.43	-0.3	0.07	-0.3	0.02
IGFBP4	-0.6	0.35	-0.5	0.34	-0.6	0.00	-0.6	0.00
ST6GAL1	-0.6	0.35	-0.6	0.24	-0.3	0.02	-0.4	0.01
PARP4	-0.6	0.35	-0.5	0.35	-0.4	0.01	-0.4	0.01
CYP1B1	-0.6	0.35	-0.9	0.03	-0.3	0.03	-0.2	0.20
NOTCH2	-0.6	0.35	-0.7	0.19	-0.3	0.05	-0.4	0.01
CTSK	-0.6	0.35	-0.7	0.15	-0.7	0.00	-0.6	0.00
IFNGR1	-0.6	0.35	-0.7	0.20	-0.5	0.00	-0.5	0.00
AHR	-0.6	0.35	-0.8	0.14	-0.5	0.00	-0.5	0.00
IL4R	-0.6	0.35	-0.8	0.14	-0.5	0.00	-0.6	0.00
EDEM1	-0.6	0.35	-0.7	0.17	-0.7	0.00	-0.7	0.00
CXCL12	-0.6	0.35	-0.6	0.25	-0.4	0.01	-0.3	0.02
DPP4	-0.6	0.35	-0.6	0.24	-0.5	0.00	-0.5	0.00
MAP3K5	-0.6	0.35	-0.8	0.14	-0.3	0.07	-0.3	0.03
KAT2B	-0.6	0.35	-0.4	0.55	-0.3	0.08	-0.3	0.08
CYBB	-0.6	0.35	-0.7	0.20	-0.4	0.01	-0.4	0.02
PIM2	-0.6	0.35	-0.5	0.39	-0.4	0.00	-0.5	0.00
PSMB9	-0.6	0.35	-0.7	0.23	-0.1	0.35	-0.2	0.16

	SCC.P3.Spearman's.Rho (N=5)	SCC.P3.Spearman's.p.value (N=5)	SCC.P3.Pearson's.cor (N=5)	SCC.P3.Pearson's.p.value (N=5)	All.P3.Spearman's.Rho (N=45)	All.P3.Spearman's.p.value (N=45)	All.P3.Pearson's.cor (N=45)	All.P3.Pearson's.p.value (N=45)
ALOX5	-0.6	0.35	-0.6	0.24	-0.1	0.60	0.0	0.78
CXCL1	-0.6	0.35	-0.6	0.25	-0.3	0.05	-0.3	0.06
IL6ST	-0.6	0.35	-0.6	0.25	-0.3	0.05	-0.3	0.06
OAS2	-0.6	0.35	-0.8	0.09	-0.3	0.04	-0.5	0.00
FCN1	-0.6	0.35	-0.7	0.16	-0.4	0.00	-0.4	0.00
GPR183	-0.6	0.35	-0.6	0.24	-0.5	0.00	-0.4	0.01
LY75	-0.6	0.35	-0.6	0.25	-0.5	0.00	-0.5	0.00
ZBTB16	-0.6	0.35	-0.4	0.45	-0.2	0.27	-0.1	0.45
IL27RA	-0.6	0.35	-0.7	0.17	0.0	0.93	-0.1	0.60
FOXF1	-0.6	0.35	-0.5	0.39	-0.6	0.00	-0.6	0.00
IL6R	-0.6	0.35	-0.7	0.18	-0.4	0.01	-0.4	0.01
IL15	-0.6	0.35	-0.8	0.13	-0.4	0.00	-0.4	0.00
CASP1	-0.6	0.35	-0.8	0.13	-0.4	0.00	-0.4	0.00
TNFRSF10C	-0.6	0.35	-0.5	0.40	-0.5	0.00	-0.5	0.00
RORC	-0.6	0.35	-0.8	0.08	-0.3	0.03	-0.3	0.05
AIM2	-0.6	0.35	-0.6	0.32	-0.2	0.26	-0.3	0.08
TNFRSF17	-0.6	0.35	-0.6	0.31	-0.5	0.00	-0.5	0.00
IL7	-0.6	0.35	-0.8	0.14	-0.3	0.02	-0.4	0.01
TEK	-0.6	0.35	-0.6	0.32	-0.5	0.00	-0.5	0.00
GNG7	-0.6	0.35	-0.6	0.28	-0.2	0.17	-0.3	0.05
CXCR6	-0.6	0.35	-0.6	0.31	-0.2	0.11	-0.3	0.05
CCR2	-0.6	0.35	-0.6	0.27	-0.3	0.03	-0.4	0.01
SMAD6	-0.6	0.35	-0.7	0.18	-0.2	0.10	-0.3	0.06
PLA2G10	-0.6	0.35	-0.4	0.46	-0.3	0.03	-0.2	0.15
IL15RA	-0.6	0.35	-0.7	0.23	-0.5	0.00	-0.5	0.00
MS4A2	-0.6	0.35	-0.4	0.49	-0.3	0.07	-0.3	0.06
GADD45B	-0.6	0.35	-0.5	0.36	-0.6	0.00	-0.6	0.00
AGR2	-0.6	0.35	-0.6	0.29	-0.5	0.00	-0.5	0.00
IGHM	-0.6	0.35	-0.7	0.23	-0.4	0.00	-0.4	0.00
CCL19	-0.6	0.35	-0.4	0.51	-0.4	0.01	-0.4	0.01
IGFBP3	-0.6	0.35	-0.7	0.15	-0.5	0.00	-0.5	0.00
PLA2G4A	-0.6	0.35	-0.8	0.10	-0.5	0.00	-0.5	0.00
LST1	-0.6	0.35	-0.7	0.19	-0.3	0.06	-0.3	0.03
AGPAT2	-0.6	0.35	-0.3	0.58	-0.3	0.10	-0.2	0.11
FCGR2B	-0.6	0.35	-0.6	0.32	-0.4	0.00	-0.5	0.00
CYLD	-0.6	0.35	-0.8	0.13	-0.7	0.00	-0.6	0.00
CLIC5	-0.6	0.35	-0.7	0.19	-0.1	0.65	-0.1	0.68
SECTM1	-0.6	0.35	-0.5	0.36	-0.5	0.00	-0.5	0.00
RSAD2	-0.6	0.35	-0.8	0.11	-0.2	0.26	-0.3	0.07
CFH	-0.6	0.35	-0.8	0.13	-0.7	0.00	-0.6	0.00
HLA-A	-0.6	0.35	-0.8	0.13	-0.4	0.01	-0.5	0.00
IFI44	-0.6	0.35	-0.9	0.05	-0.1	0.50	-0.1	0.62
CTSW	-0.6	0.35	-0.8	0.07	-0.2	0.15	-0.3	0.07
PRDM1	-0.6	0.35	-0.7	0.19	-0.5	0.00	-0.6	0.00
PLSCR4	-0.6	0.35	-0.4	0.50	-0.5	0.00	-0.4	0.00
C1RL	-0.6	0.35	-0.6	0.33	-0.5	0.00	-0.4	0.00
JAM2	-0.6	0.35	-0.8	0.14	-0.4	0.00	-0.4	0.01
MMP28	-0.6	0.35	-0.6	0.26	-0.3	0.05	-0.3	0.09
CLEC4A	-0.6	0.35	-0.7	0.18	-0.1	0.64	0.0	0.76
TLR8	-0.6	0.35	-0.6	0.33	-0.2	0.12	-0.3	0.09

	SCC.P3.Spearman's.Rho (N=5)	SCC.P3.Spearman's.p.value (N=5)	SCC.P3.Pearson's.cor (N=5)	SCC.P3.Pearson's.p.value (N=5)	All.P3.Spearman's.Rho (N=45)	All.P3.Spearman's.p.value (N=45)	All.P3.Pearson's.cor (N=45)	All.P3.Pearson's.p.value (N=45)
APOL3	-0.6	0.35	-0.8	0.11	-0.2	0.11	-0.3	0.07
PYCARD	-0.6	0.35	-0.7	0.19	-0.4	0.01	-0.4	0.01
LDLRAP1	-0.6	0.35	-0.8	0.09	0.0	0.89	0.0	0.92
GBP3	-0.6	0.35	-0.6	0.30	-0.1	0.39	-0.2	0.29
TRIM6	-0.6	0.35	-0.6	0.29	-0.4	0.02	-0.4	0.02
TMEM173	-0.6	0.35	-0.9	0.07	-0.4	0.01	-0.5	0.00
TP53INP1	-0.6	0.35	-0.6	0.33	-0.3	0.06	-0.3	0.05
FAM20C	-0.6	0.35	-0.8	0.14	-0.2	0.21	-0.1	0.43
LRRK2	-0.6	0.35	-0.5	0.40	-0.3	0.05	-0.3	0.03
LRRK15	-0.5	0.45	-0.4	0.54	-0.2	0.27	-0.2	0.13
DNAJB9	-0.5	0.45	-0.6	0.33	-0.2	0.11	-0.3	0.06
ALOX15B	-0.5	0.45	-0.4	0.46	-0.4	0.00	-0.5	0.00
C19orf66	-0.5	0.45	-0.5	0.38	-0.3	0.02	-0.3	0.03
TAPBP	-0.5	0.45	-0.5	0.37	-0.5	0.00	-0.5	0.00
RPS6KA2	-0.5	0.45	-0.5	0.44	-0.1	0.45	-0.1	0.46
PARVA	-0.5	0.45	-0.5	0.41	-0.3	0.07	-0.3	0.08
MYLK	-0.5	0.45	-0.5	0.38	-0.3	0.08	-0.3	0.08
TPP1	-0.5	0.45	-0.5	0.40	-0.7	0.00	-0.6	0.00
FTTH1	-0.5	0.45	-0.6	0.30	-0.3	0.03	-0.3	0.03
HLA-E	-0.5	0.45	-0.5	0.40	-0.4	0.01	-0.5	0.00
TRIB1	-0.5	0.45	-0.6	0.31	-0.4	0.01	-0.4	0.00
CAV1	-0.5	0.45	-0.3	0.64	-0.3	0.04	-0.3	0.03
IRF2	-0.5	0.45	-0.4	0.46	-0.3	0.03	-0.4	0.01
CDO1	-0.5	0.45	-0.4	0.46	-0.2	0.15	0.0	0.77
EDNRB	-0.5	0.45	-0.5	0.38	-0.1	0.60	0.0	0.80
FGFR3	-0.5	0.45	-0.6	0.26	0.0	0.96	0.0	0.93
HLA-F	-0.5	0.45	-0.7	0.17	-0.5	0.00	-0.5	0.00
BTN3A3	-0.5	0.45	-0.6	0.27	-0.5	0.00	-0.5	0.00
BCL3	-0.5	0.45	-0.6	0.32	-0.4	0.00	-0.5	0.00
CSF2RB	-0.5	0.45	-0.8	0.13	-0.4	0.00	-0.4	0.01
PDGFA	-0.5	0.45	-0.6	0.26	-0.5	0.00	-0.4	0.01
HRH1	-0.5	0.45	-0.6	0.34	-0.4	0.00	-0.4	0.00
TLR3	-0.5	0.45	-0.5	0.35	-0.3	0.03	-0.3	0.02
CLEC10A	-0.5	0.45	-0.1	0.93	-0.2	0.15	-0.2	0.19
BTN3A1	-0.5	0.45	-0.7	0.18	-0.5	0.00	-0.5	0.00
IL1A	-0.5	0.45	-0.5	0.44	0.2	0.25	0.1	0.38
HLA-B	-0.5	0.45	-0.6	0.28	-0.4	0.01	-0.4	0.00
HLA-C	-0.5	0.45	-0.6	0.26	-0.4	0.00	-0.5	0.00
DUSP6	-0.5	0.45	-0.2	0.71	-0.6	0.00	-0.6	0.00
RAB27A	-0.5	0.45	-0.7	0.19	-0.3	0.04	-0.3	0.03
GATA3	-0.5	0.45	-0.6	0.25	-0.2	0.13	-0.4	0.01
NCF2	-0.5	0.45	-0.7	0.22	-0.5	0.00	-0.5	0.00
CD1A	-0.5	0.45	-0.4	0.46	-0.1	0.47	-0.1	0.34
HLA-G	-0.5	0.45	-0.6	0.29	-0.5	0.00	-0.5	0.00
IL1RN	-0.5	0.45	-0.4	0.51	-0.5	0.00	-0.5	0.00
MYO1C	-0.5	0.45	-0.7	0.19	-0.4	0.01	-0.4	0.01
OGN	-0.5	0.45	-0.3	0.60	-0.5	0.00	-0.5	0.00
TAPBPL	-0.5	0.45	-0.6	0.29	-0.6	0.00	-0.5	0.00
ADAMTS1	-0.5	0.45	-0.5	0.42	-0.4	0.01	-0.4	0.01
NFKBIZ	-0.5	0.45	-0.5	0.35	-0.3	0.02	-0.4	0.01

	SCC.P3.Spearman's.Rho (N=5)	SCC.P3.Spearman's.p.value (N=5)	SCC.P3.Pearson's.cor (N=5)	SCC.P3.Pearson's.p.value (N=5)	All.P3.Spearman's.Rho (N=45)	All.P3.Spearman's.p.value (N=45)	All.P3.Pearson's.cor (N=45)	All.P3.Pearson's.p.value (N=45)
CXCL16	-0.5	0.45	-0.8	0.07	-0.6	0.00	-0.6	0.00
MUC20	-0.5	0.45	-0.6	0.32	-0.2	0.10	-0.2	0.28
GGT1	-0.5	0.45	-0.3	0.56	0.0	0.81	0.1	0.62
IRF6	-0.4	0.52	-0.2	0.76	0.0	0.88	-0.1	0.68
DNAJC3	-0.4	0.52	-0.4	0.56	-0.4	0.01	-0.4	0.01
PRNP	-0.4	0.52	-0.1	0.82	-0.4	0.00	-0.4	0.01
SH3BGRL	-0.4	0.52	-0.8	0.09	-0.3	0.05	-0.4	0.00
PTGS1	-0.4	0.52	-0.3	0.62	-0.3	0.06	-0.3	0.07
ARHGAP6	-0.4	0.52	-0.3	0.62	-0.4	0.01	-0.4	0.02
MYD88	-0.4	0.52	-0.7	0.21	-0.4	0.00	-0.5	0.00
HLA-DQB2	-0.4	0.52	-0.4	0.53	-0.2	0.19	-0.2	0.19
P2RY12	-0.4	0.52	-0.3	0.57	-0.3	0.08	-0.3	0.08
HLA-DOB	-0.3	0.68	-0.1	0.92	-0.2	0.25	-0.2	0.23
SLAMF1	-0.3	0.68	-0.3	0.65	-0.5	0.00	-0.5	0.00
PRKCA	-0.3	0.68	0.0	0.99	0.2	0.19	0.2	0.24
NRP1	-0.3	0.68	-0.1	0.84	-0.2	0.11	-0.1	0.49
NPC2	-0.3	0.68	-0.3	0.62	-0.5	0.00	-0.5	0.00
BHLHE40	-0.3	0.68	-0.6	0.31	-0.5	0.00	-0.5	0.00
CST3	-0.3	0.68	-0.4	0.51	-0.4	0.00	-0.5	0.00
CAT	-0.3	0.68	0.1	0.85	-0.2	0.25	-0.1	0.33
ZFP36	-0.3	0.68	-0.3	0.68	-0.4	0.00	-0.5	0.00
CTSH	-0.3	0.68	-0.5	0.39	-0.5	0.00	-0.5	0.00
PRKCD	-0.3	0.68	0.0	0.95	-0.5	0.00	-0.5	0.00
OAS1	-0.3	0.68	-0.8	0.13	-0.3	0.02	-0.4	0.01
SIRPA	-0.3	0.68	-0.3	0.68	-0.2	0.21	-0.3	0.09
S100A8	-0.3	0.68	-0.5	0.36	-0.5	0.00	-0.5	0.00
HCLS1	-0.3	0.68	-0.3	0.66	-0.5	0.00	-0.5	0.00
IFIT1	-0.3	0.68	-0.8	0.10	-0.2	0.10	-0.3	0.04
S100A9	-0.3	0.68	-0.6	0.29	-0.5	0.00	-0.5	0.00
IFIT5	-0.3	0.68	-0.6	0.27	-0.4	0.01	-0.4	0.02
CD151	-0.3	0.68	-0.3	0.57	-0.5	0.00	-0.5	0.00
IFI44L	-0.3	0.68	-0.7	0.15	-0.3	0.07	-0.3	0.03
APOH	-0.3	0.68	-0.2	0.79	-0.2	0.13	-0.2	0.32
CASP10	-0.3	0.68	-0.3	0.67	-0.5	0.00	-0.5	0.00
LAMP3	-0.3	0.68	-0.3	0.64	-0.2	0.12	-0.3	0.04
ADORA2B	-0.3	0.68	-0.5	0.41	-0.3	0.08	-0.3	0.05
IL13RA2	-0.3	0.68	-0.4	0.45	-0.4	0.01	-0.3	0.06
PLA2G1B	-0.3	0.68	-0.2	0.75	-0.4	0.01	-0.3	0.02
CEACAM1	-0.3	0.68	-0.7	0.22	-0.3	0.10	-0.4	0.02
LY96	-0.3	0.68	-0.5	0.41	-0.6	0.00	-0.5	0.00
CD1E	-0.3	0.68	-0.3	0.65	-0.1	0.60	-0.2	0.30
FOS	-0.3	0.68	-0.2	0.71	-0.3	0.06	-0.4	0.02
TLR5	-0.3	0.68	-0.5	0.38	-0.4	0.01	-0.4	0.01
XDH	-0.3	0.68	-0.2	0.75	-0.4	0.01	-0.3	0.02
IGHD	-0.3	0.68	-0.5	0.38	-0.5	0.00	-0.4	0.00
LAMB2	-0.3	0.68	-0.5	0.43	-0.6	0.00	-0.6	0.00
LXN	-0.3	0.68	-0.3	0.65	-0.5	0.00	-0.5	0.00
DDX60	-0.3	0.68	-0.5	0.41	-0.3	0.06	-0.3	0.04
UNC93B1	-0.3	0.68	-0.5	0.38	-0.5	0.00	-0.5	0.00
RNASEL	-0.3	0.68	-0.2	0.76	-0.2	0.18	-0.3	0.08

	SCC.P3.Spearman's.Rho (N=5)	SCC.P3.Spearman's.p.value (N=5)	SCC.P3.Pearson's.cor (N=5)	SCC.P3.Pearson's.p.value (N=5)	All.P3.Spearman's.Rho (N=45)	All.P3.Spearman's.p.value (N=45)	All.P3.Pearson's.cor (N=45)	All.P3.Pearson's.p.value (N=45)
TMEM27	-0.3	0.68	-0.3	0.57	0.2	0.20	0.3	0.10
DERL3	-0.3	0.68	-0.3	0.59	-0.3	0.04	-0.4	0.01
MYOCD	-0.3	0.68	0.0	0.94	-0.4	0.01	-0.3	0.06
RASGRF1	-0.2	0.78	-0.4	0.48	-0.1	0.58	-0.1	0.39
FCRL5	-0.2	0.78	-0.4	0.52	0.0	0.78	0.1	0.41
CP	-0.2	0.78	-0.5	0.42	-0.3	0.06	-0.3	0.06
CTNNA1	-0.2	0.78	-0.5	0.35	-0.1	0.35	-0.3	0.08
CFB	-0.2	0.78	-0.3	0.58	-0.6	0.00	-0.5	0.00
FEZ1	-0.2	0.78	-0.1	0.88	-0.4	0.01	-0.4	0.02
THBD	-0.2	0.78	-0.1	0.90	-0.6	0.00	-0.5	0.00
KDR	-0.2	0.78	-0.5	0.44	-0.3	0.04	-0.3	0.06
VDR	-0.2	0.78	-0.7	0.18	-0.3	0.02	-0.5	0.00
ADCY9	-0.2	0.78	-0.1	0.81	-0.3	0.05	-0.3	0.04
ADAM8	-0.2	0.78	-0.2	0.69	-0.2	0.17	-0.3	0.02
NPAS2	-0.2	0.78	-0.5	0.40	-0.3	0.02	-0.4	0.01
GNLY	-0.2	0.78	-0.1	0.92	-0.1	0.45	-0.1	0.40
CPA3	-0.2	0.78	-0.3	0.57	-0.4	0.00	-0.5	0.00
CYP24A1	-0.2	0.78	-0.3	0.64	-0.3	0.05	-0.3	0.03
MR1	-0.2	0.78	-0.2	0.71	-0.4	0.01	-0.4	0.01
BLNK	-0.2	0.78	-0.5	0.42	-0.3	0.05	-0.3	0.04
DMBT1	-0.2	0.78	-0.2	0.76	-0.4	0.02	-0.4	0.00
IFI35	-0.2	0.78	-0.2	0.75	-0.5	0.00	-0.5	0.00
HLA-DQB1	-0.2	0.78	0.0	0.99	-0.3	0.04	-0.2	0.13
IL33	-0.2	0.78	-0.4	0.55	-0.4	0.01	-0.3	0.02
ERBB2	-0.2	0.78	-0.2	0.78	-0.3	0.09	-0.2	0.11
CRY2	-0.2	0.78	0.3	0.66	-0.1	0.47	-0.2	0.25
TMF1	-0.2	0.78	-0.1	0.87	-0.4	0.02	-0.4	0.01
ARRB1	-0.2	0.78	-0.5	0.44	-0.3	0.08	-0.2	0.16
NTN4	-0.2	0.78	-0.3	0.58	-0.4	0.00	-0.5	0.00
CPEB4	-0.2	0.78	-0.5	0.44	-0.3	0.03	-0.4	0.01
CMPK2	-0.2	0.78	-0.7	0.17	0.1	0.58	0.0	0.88
PXK	-0.1	0.95	-0.1	0.85	-0.4	0.01	-0.3	0.02
SIAE	-0.1	0.95	0.0	0.94	0.1	0.56	0.1	0.45
CLEC7A	-0.1	0.95	-0.7	0.19	-0.4	0.01	-0.5	0.00
GNG12	-0.1	0.95	-0.4	0.48	-0.2	0.23	-0.2	0.15
A2M	-0.1	0.95	-0.2	0.70	-0.1	0.70	-0.1	0.62
DAB2	-0.1	0.95	0.2	0.72	-0.1	0.65	0.0	0.85
HERC6	-0.1	0.95	0.3	0.68	0.0	0.78	0.0	0.88
RFTN1	-0.1	0.95	-0.3	0.66	-0.1	0.69	0.0	0.82
CD59	-0.1	0.95	-0.4	0.54	-0.5	0.00	-0.5	0.00
SQSTM1	-0.1	0.95	-0.1	0.85	-0.4	0.00	-0.6	0.00
JUNB	-0.1	0.95	-0.1	0.86	-0.4	0.01	-0.4	0.00
VAMP8	-0.1	0.95	0.4	0.49	-0.3	0.02	-0.4	0.01
CAV2	-0.1	0.95	0.2	0.78	-0.4	0.01	-0.4	0.01
KLF9	-0.1	0.95	-0.1	0.89	0.0	0.87	-0.1	0.72
CX3CL1	-0.1	0.95	0.3	0.67	-0.2	0.15	-0.3	0.05
LPAR1	-0.1	0.95	0.0	0.95	-0.4	0.01	-0.4	0.00
F3	-0.1	0.95	0.1	0.87	-0.2	0.10	-0.3	0.08
IRS1	-0.1	0.95	-0.4	0.46	-0.4	0.01	-0.3	0.02
HPN	-0.1	0.95	0.5	0.44	-0.5	0.00	-0.5	0.00

	SCC.P3.Spearman's.Rho (N=5)	SCC.P3.Spearman's.p.value (N=5)	SCC.P3.Pearson's.cor (N=5)	SCC.P3.Pearson's.p.value (N=5)	All.P3.Spearman's.Rho (N=45)	All.P3.Spearman's.p.value (N=45)	All.P3.Pearson's.cor (N=45)	All.P3.Pearson's.p.value (N=45)
SRPX	-0.1	0.95	0.0	1.00	-0.4	0.01	-0.5	0.00
CFTR	-0.1	0.95	0.0	0.99	-0.3	0.04	-0.3	0.08
MECOM	-0.1	0.95	-0.1	0.87	0.0	0.83	0.0	0.86
EZR	-0.1	0.95	-0.5	0.39	-0.1	0.72	-0.1	0.51
APOL1	-0.1	0.95	-0.4	0.50	-0.3	0.03	-0.4	0.02
CARD10	-0.1	0.95	-0.3	0.62	-0.3	0.02	-0.3	0.07
ALAD	-0.1	0.95	0.3	0.66	-0.2	0.23	-0.3	0.05
SEMA4A	-0.1	0.95	0.0	0.94	-0.3	0.02	-0.4	0.01
DUOX2	-0.1	0.95	0.0	0.99	-0.1	0.66	-0.2	0.22
NOD2	-0.1	0.95	-0.1	0.88	-0.4	0.01	-0.4	0.01
WLS	-0.1	0.95	0.2	0.79	-0.3	0.04	-0.3	0.04
LATS2	-0.1	0.95	-0.2	0.77	0.0	0.89	-0.1	0.72
NLR5	-0.1	0.95	-0.3	0.59	-0.3	0.05	-0.3	0.03
GAB1	0	1.00	0.5	0.42	0.2	0.20	0.2	0.32
VNN1	0	1.00	0.2	0.71	-0.3	0.03	-0.3	0.03
EDN1	0	1.00	0.2	0.78	-0.1	0.51	0.0	0.79
ABCA1	0	1.00	0.4	0.50	-0.3	0.05	-0.2	0.27
CTSC	0	1.00	-0.2	0.72	-0.3	0.09	-0.3	0.03
ENG	0	1.00	-0.2	0.76	-0.2	0.16	-0.1	0.35
CIB1	0	1.00	-0.5	0.38	-0.5	0.00	-0.6	0.00
PLSCR1	0	1.00	-0.3	0.67	-0.1	0.64	-0.2	0.21
TGFB1	0	1.00	-0.1	0.83	0.0	0.80	-0.1	0.54
EPHA2	0	1.00	-0.3	0.63	-0.4	0.00	-0.4	0.01
CEACAM6	0	1.00	-0.2	0.74	-0.4	0.00	-0.4	0.00
ACVR1	0	1.00	0.2	0.69	-0.5	0.00	-0.6	0.00
VIPR1	0	1.00	0.5	0.40	-0.1	0.47	-0.1	0.40
CFD	0	1.00	-0.2	0.74	-0.4	0.01	-0.4	0.02
SELP	0	1.00	-0.3	0.58	-0.5	0.00	-0.5	0.00
ZBTB7A	0	1.00	0.1	0.87	-0.1	0.57	-0.1	0.61
BPIFA1	0	1.00	-0.1	0.85	-0.4	0.01	-0.3	0.04
CXCL17	0	1.00	-0.1	0.91	-0.4	0.01	-0.4	0.00
LRG1	0	1.00	-0.3	0.59	-0.3	0.03	-0.4	0.02
DENND1B	0.1	0.95	0.2	0.79	0.2	0.28	0.2	0.25
DOCK2	0.1	0.95	0.4	0.54	0.0	1.00	0.1	0.74
CD55	0.1	0.95	0.2	0.76	-0.6	0.00	-0.5	0.00
CALCOCO2	0.1	0.95	0.1	0.84	-0.1	0.34	-0.1	0.37
FCGR2A	0.1	0.95	-0.1	0.82	-0.1	0.43	-0.1	0.35
IKZF1	0.1	0.95	-0.2	0.71	0.1	0.66	0.1	0.62
MMP2	0.1	0.95	-0.3	0.67	0.3	0.06	0.1	0.33
CD74	0.1	0.95	0.1	0.81	-0.1	0.58	-0.1	0.52
TRADD	0.1	0.95	0.1	0.86	-0.6	0.00	-0.6	0.00
EGR1	0.1	0.95	0.1	0.82	-0.4	0.01	-0.4	0.01
FGFR2	0.1	0.95	0.1	0.88	-0.1	0.48	-0.1	0.36
AQP3	0.1	0.95	-0.4	0.51	-0.4	0.00	-0.5	0.00
PIGR	0.1	0.95	-0.1	0.93	-0.3	0.08	-0.2	0.27
EGR3	0.1	0.95	-0.1	0.92	-0.3	0.03	-0.3	0.07
LY6D	0.1	0.95	-0.2	0.77	-0.5	0.00	-0.3	0.03
ASS1	0.1	0.95	0.0	0.95	-0.2	0.21	-0.1	0.34
CD46	0.1	0.95	0.3	0.63	-0.4	0.01	-0.4	0.02
AIF1	0.1	0.95	0.2	0.75	-0.1	0.45	0.0	0.82

	SCC.P3.Spearman's.Rho (N=5)	SCC.P3.Spearman's.p.value (N=5)	SCC.P3.Pearson's.cor (N=5)	SCC.P3.Pearson's.p.value (N=5)	All.P3.Spearman's.Rho (N=45)	All.P3.Spearman's.p.value (N=45)	All.P3.Pearson's.cor (N=45)	All.P3.Pearson's.p.value (N=45)
MSR1	0.1	0.95	0.6	0.31	0.0	0.78	0.0	0.77
ERAP1	0.1	0.95	0.1	0.85	0.1	0.71	0.1	0.42
LCN2	0.1	0.95	0.0	0.97	-0.5	0.00	-0.4	0.01
APOBEC3F	0.1	0.95	0.0	0.95	-0.5	0.00	-0.4	0.00
CYSLTR1	0.1	0.95	-0.4	0.52	-0.1	0.71	-0.2	0.29
PRDM16	0.1	0.95	0.5	0.44	0.0	0.91	0.0	0.94
BPIFB1	0.1	0.95	0.0	0.94	-0.4	0.01	-0.3	0.04
CPEB2	0.1	0.95	0.0	0.98	-0.6	0.00	-0.6	0.00
SEMA4B	0.1	0.95	-0.2	0.75	-0.5	0.00	-0.5	0.00
IRAK2	0.2	0.78	0.4	0.50	-0.1	0.50	-0.1	0.58
S100B	0.2	0.78	0.0	0.99	-0.1	0.39	-0.1	0.49
MPP7	0.2	0.78	0.5	0.43	-0.3	0.03	-0.3	0.07
IRAK3	0.2	0.78	0.0	0.95	-0.1	0.67	0.0	0.76
HTRA1	0.2	0.78	-0.1	0.83	-0.5	0.00	-0.5	0.00
APOD	0.2	0.78	0.2	0.74	-0.5	0.00	-0.4	0.00
TRIM14	0.2	0.78	0.0	0.99	-0.1	0.34	-0.2	0.20
MET	0.2	0.78	0.5	0.40	-0.2	0.23	-0.2	0.31
MMP1	0.2	0.78	-0.4	0.55	-0.4	0.00	-0.5	0.00
ANG	0.2	0.78	0.2	0.79	-0.5	0.00	-0.4	0.00
GHR	0.2	0.78	0.0	0.99	-0.5	0.00	-0.4	0.01
CDS1	0.2	0.78	0.4	0.49	-0.1	0.67	-0.1	0.33
REL	0.2	0.78	0.3	0.57	-0.1	0.59	-0.1	0.35
HCP5	0.2	0.78	0.1	0.92	-0.2	0.23	-0.2	0.22
PRKCH	0.2	0.78	0.3	0.62	-0.3	0.08	-0.3	0.05
IFI16	0.2	0.78	0.2	0.70	-0.4	0.02	-0.4	0.02
ALPK1	0.2	0.78	0.3	0.61	0.2	0.17	0.3	0.08
GAS2L1	0.2	0.78	0.3	0.66	-0.3	0.06	-0.3	0.06
CASP4	0.2	0.78	0.1	0.83	-0.5	0.00	-0.5	0.00
ELF1	0.2	0.78	-0.1	0.84	-0.4	0.02	-0.4	0.00
PTPRC	0.3	0.68	0.5	0.34	0.2	0.20	0.2	0.20
PTK6	0.3	0.68	0.2	0.71	-0.4	0.01	-0.4	0.02
PDE4D	0.3	0.68	0.3	0.60	-0.4	0.01	-0.3	0.03
ADCY7	0.3	0.68	0.6	0.30	0.0	0.91	0.1	0.68
MITF	0.3	0.68	-0.1	0.90	0.3	0.05	0.3	0.03
ERBB3	0.3	0.68	0.2	0.78	0.2	0.15	0.2	0.12
IQGAP1	0.3	0.68	0.0	0.95	-0.5	0.00	-0.4	0.00
ITGA3	0.3	0.68	0.1	0.87	-0.2	0.26	-0.2	0.11
SGK1	0.3	0.68	0.3	0.60	-0.3	0.02	-0.4	0.02
SLPI	0.3	0.68	0.1	0.84	-0.4	0.02	-0.4	0.01
HBEGF	0.3	0.68	0.4	0.55	-0.2	0.16	-0.2	0.26
RAP1GAP	0.3	0.68	0.6	0.31	-0.1	0.46	-0.1	0.54
ITGA2	0.3	0.68	0.2	0.70	-0.5	0.00	-0.4	0.00
SMAD3	0.3	0.68	0.2	0.81	-0.2	0.14	-0.3	0.07
RASGRP1	0.3	0.68	0.0	0.98	-0.2	0.21	-0.1	0.36
CCL13	0.3	0.68	-0.1	0.88	-0.2	0.15	-0.2	0.11
DUSP5	0.3	0.68	-0.3	0.63	-0.5	0.00	-0.5	0.00
LAT2	0.3	0.68	0.7	0.19	-0.1	0.65	-0.1	0.72
YAP1	0.3	0.68	0.3	0.57	-0.4	0.00	-0.5	0.00
TRPM4	0.3	0.68	0.0	0.98	-0.4	0.01	-0.3	0.04
FAM110C	0.3	0.68	0.5	0.41	-0.3	0.10	-0.3	0.09
SDR16C5	0.3	0.68	-0.1	0.88	-0.4	0.01	-0.4	0.01
LMNA	0.4	0.52	0.4	0.52	-0.3	0.03	-0.4	0.01
STAT6	0.4	0.52	0.2	0.77	-0.5	0.00	-0.5	0.00
NR3C1	0.4	0.52	0.3	0.57	-0.3	0.04	-0.3	0.02
EMP2	0.4	0.52	0.2	0.78	-0.2	0.19	-0.2	0.18
IL18	0.4	0.52	0.2	0.69	-0.3	0.06	-0.3	0.08
PROS1	0.4	0.52	0.7	0.15	-0.5	0.00	-0.5	0.00
CXCL5	0.4	0.52	0.1	0.86	-0.1	0.55	-0.2	0.25
LNPEP	0.4	0.52	0.2	0.76	-0.1	0.45	-0.2	0.30
SPRED2	0.4	0.52	0.6	0.29	-0.2	0.29	-0.1	0.61
OSMR	0.5	0.45	0.5	0.43	-0.4	0.00	-0.4	0.00
ANXA1	0.5	0.45	0.3	0.60	-0.2	0.11	-0.2	0.20
DUSP3	0.5	0.45	0.5	0.44	-0.6	0.00	-0.6	0.00
RXRA	0.5	0.45	0.5	0.42	-0.2	0.11	-0.2	0.22
SPINK5	0.5	0.45	0.2	0.73	-0.2	0.11	-0.3	0.07
P2RY2	0.5	0.45	0.4	0.48	-0.2	0.10	-0.3	0.06
PPP2R3A	0.5	0.45	0.5	0.44	-0.1	0.59	-0.1	0.35
GPR68	0.5	0.45	0.2	0.71	-0.2	0.17	-0.2	0.27
PPP1R13B	0.5	0.45	0.5	0.43	0.0	0.94	0.0	0.80
MKNK2	0.5	0.45	0.4	0.48	-0.2	0.10	-0.3	0.09
AVPI1	0.5	0.45	0.4	0.47	-0.5	0.00	-0.5	0.00
SUSD4	0.5	0.45	0.5	0.40	0.1	0.52	0.1	0.60
GCNT3	0.5	0.45	0.6	0.30	-0.5	0.00	-0.5	0.00
CD207	0.5	0.45	0.4	0.52	-0.1	0.33	-0.1	0.48
XPR1	0.5	0.45	0.6	0.29	-0.3	0.05	-0.4	0.01
CASP8	0.6	0.35	0.9	0.02	-0.1	0.33	-0.2	0.29
RAB7B	0.6	0.35	0.5	0.38	-0.3	0.04	-0.2	0.12
CD44	0.6	0.35	0.7	0.22	-0.4	0.00	-0.4	0.00
MAOB	0.6	0.35	0.7	0.21	0.1	0.61	0.1	0.73
CDH1	0.6	0.35	0.5	0.40	-0.3	0.02	-0.3	0.02
B4GALT1	0.6	0.35	0.6	0.26	-0.2	0.29	-0.2	0.24
MAPKAPK3	0.6	0.35	0.7	0.15	-0.2	0.10	-0.3	0.07
BCL6	0.6	0.35	0.5	0.37	-0.3	0.09	-0.3	0.05
UPP1	0.6	0.35	0.7	0.19	-0.4	0.01	-0.4	0.01
GALNT3	0.6	0.35	0.6	0.33	-0.3	0.06	-0.3	0.08
CEBPA	0.6	0.35	0.6	0.33	-0.1	0.40	-0.1	0.45
F2RL1	0.6	0.35	0.7	0.17	-0.1	0.58	-0.1	0.35
ANXA3	0.6	0.35	0.7	0.17	-0.1	0.48	-0.1	0.42
HIST1H2BC	0.6	0.35	0.7	0.23	-0.2	0.17	-0.2	0.25
S100A14	0.6	0.35	0.3	0.57	-0.3	0.03	-0.4	0.02
DDX58	0.6	0.35	0.5	0.37	0.0	0.94	0.0	0.86
RNF135	0.6	0.35	0.1	0.86	-0.1	0.36	-0.2	0.21
NPNT	0.6	0.35	0.7	0.15	-0.2	0.15	-0.2	0.31
FCER1A	0.7	0.23	0.4	0.50	0.2	0.27	0.2	0.32
ATP6V0E1	0.7	0.23	0.5	0.37	-0.5	0.00	-0.5	0.00
SDC1	0.7	0.23	0.9	0.06	-0.4	0.01	-0.4	0.01
TSPO	0.7	0.23	0.3	0.64	-0.4	0.02	-0.4	0.01
PTGER4	0.7	0.23	0.4	0.52	-0.3	0.05	-0.3	0.08
CD9	0.8	0.13	0.7	0.23	-0.2	0.17	-0.2	0.14
SLC9A3R1	0.8	0.13	0.9	0.02	-0.3	0.05	-0.2	0.13

	SCC. P3. Spearman's.Rho (N=5)		SCC. P3. Spearman's.p.value (N=5)		SCC. P3. Pearson's.cor (N=5)		SCC. P3. Pearson's.p.value (N=5)		All. P3. Spearman's.Rho (N=45)		All. P3. Spearman's.p.value (N=45)		All. P3. Pearson's.cor (N=45)		All. P3. Pearson's.p.value (N=45)	
ACSL1	0.8	0.13	0.7	0.17	-0.4	0.01	-0.3	0.02								
SLC7A8	0.8	0.13	0.9	0.02	-0.4	0.00	-0.4	0.00								
RPS6KA3	0.8	0.13	0.9	0.03	-0.4	0.00	-0.4	0.00								
RAB38	0.8	0.13	0.8	0.14	0.0	0.84	0.0	0.80								
CGN	0.8	0.13	0.8	0.13	-0.3	0.08	-0.3	0.06								
PLA2G4C	0.9	0.08	0.8	0.07	0.3	0.04	0.3	0.03								
PTPRE	0.9	0.08	0.7	0.23	-0.2	0.12	-0.3	0.08								
CLU	0.9	0.08	0.9	0.06	-0.1	0.56	-0.1	0.50								
MICA	0.9	0.08	0.8	0.09	-0.3	0.04	-0.3	0.03								
ANK3	0.9	0.08	0.9	0.06	0.1	0.71	0.1	0.58								
HYAL1	0.9	0.08	0.9	0.05	-0.4	0.00	-0.3	0.02								
MUC5B	0.9	0.08	0.5	0.35	-0.3	0.05	-0.3	0.08								
EFNA1	1	0.02	1.0	0.01	-0.2	0.13	-0.3	0.05								
BAIAP2	1	0.02	0.9	0.03	-0.3	0.05	-0.3	0.05								
MID2	1	0.02	1.0	0.00	-0.3	0.05	-0.2	0.23								

Table S4. List of the 713 genes that are differentially downregulated in poor prognostic group of lung tumors (P3; Rousseaux et al, 2013) and identified by GSEA from the Broad Institute Database as involved in the development or functioning of the immune system or in cell defense responses, and their correlation with EZH2 expression in each of the 5 metastatic-prone SCC lung tumors and in the 45 histologically-different metastatic-prone lung tumors (All, P3 group). In red, inflammatory genes deregulated upon EZH2 and RING1B downregulation in SCC13 cells, as listed in Figure S2.

	Signal Intensity	Metastasizing SCC	Non-metastasizing SCC	p
pS176-IKKα/β	0	34/49 (69.4%)	24/49 (49.0%)	0.05
	1	1/49 (2.0%)	3/49 (6.1%)	
	2	7/49 (14.3%)	17/49 (34.7%)	
	3	7/49 (14.3%)	5/49 (10.2%)	

Table S5. pS176-IKK α / β cytoplasmic membrane expression by immunofluorescence in metastasizing and non-metastasizing primary cutaneous squamous cell carcinomas.