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Antiviral gene expression in psoriasis

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Abstract

Background—Psoriasis patients have relatively infrequent cutaneous viral infections compared to atopic dermatitis patients. Increased expression of four antiviral proteins (MX1, BST2, ISG15, and OAS2) has been reported in psoriatic skin and genetic studies of psoriasis have identified susceptibility genes in antiviral pathways.

Objective—To determine if psoriasis is associated with pervasive expression of antiviral genes in skin and blood.

Methods—We performed RNA-sequencing on skin samples of 18 subjects with chronic plaque psoriasis and 16 healthy controls. We examined the expression of a pre-defined set of 42 antiviral genes, each of which has been shown in previous studies to inhibit viral replication. In parallel, we examined antiviral gene expression in atopic dermatitis, non-lesional psoriatic skin, and psoriatic blood. We performed HIV-1 infectivity assays in CD4+ peripheral blood T cells from psoriatic and healthy individuals.

Results—We observed significant overexpression of 16 antiviral genes in lesional psoriatic skin, with a greater than two-fold increase in ISG15, RSAD2, IRF7, MX2, and TRIM22 ($p<1E-07$). None of these genes was overexpressed in atopic dermatitis skin ($p<0.0001$) or non-lesional psoriatic skin. In contrast to the skin compartment, no differences in antiviral gene expression were detected in the peripheral blood of psoriasis cases compared to healthy controls. CD4+ T cells from both psoriatic and healthy patients supported HIV-1 infection at a similar rate.

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Conclusion—Our findings highlight psoriasis as an inflammatory disease with cutaneous but not systemic immune activation against viral pathogens.

Introduction

Autoimmune and immune-mediated diseases arise from aberrant activation of host immune pathways. However, whether particular autoimmune diseases activate pathways specific for certain classes of pathogens remains unclear. Psoriasis, an immune-mediated inflammatory disease of the skin, has been recently associated with increased cutaneous expression of select antiviral proteins,[1] which may explain the relative infrequency of cutaneous viral infections observed in these patients. Genetic studies performed by our group have shown that certain psoriasis susceptibility alleles such as HLA-B*57 are also associated with host control of HIV-1 infection.[2] Moreover, a number of psoriasis susceptibility variants identified by genome-wide association studies (GWAS) map to genes associated with the innate antiviral response.[3] Such genes include *IFIH1* (MDA5) and *DDX58* (RIG-I), which code for innate antiviral receptors recognizing cytosolic viral RNA, and *RNF114*, which regulates MDA5/RIG-I signaling.[4] Therefore, it is of interest to determine whether psoriasis is associated with a systemic antiviral phenotype.

"Restriction factors" are innate antiviral proteins that are produced in the host and oppose or "restrict" viral replication. Our current knowledge of restriction factors stems from the large body of studies performed in HIV virology.[5] The discovery of restriction factors and their antiviral nature is relatively recent, but has already been implicated in many host mechanisms of antiviral defense. Examples include BST2/Tetherin,[6, 7] which blocks the release of enveloped viruses; SAMHD1,[8] which is thought to inhibit viral replication by reducing the cellular levels of dNTP and mediating pro-inflammatory responses to TNF-alpha signaling; and TRIM5,[9] which blocks the uncoating of viral capsid. The different expression levels of restriction factors between cell types may explain the varying levels of permissiveness of different cell types to HIV-1 infection.

We have recently developed a custom-made quantitative real-time PCR array to characterize the expression of different restriction factors in primary human cells[10, 11] and have also correlated their expression with HIV-1 infectivity.[12] A comprehensive table of host antiviral genes and their functions is depicted in Table 1.

In this report, we investigated the expression of a large panel of antiviral genes in psoriatic skin and blood. To determine whether psoriasis is associated with systemic antiviral immunity against HIV-1, we performed *ex vivo* HIV-1 replication assays in purified CD4+ T cells from individuals with psoriasis and healthy controls.

Materials and Methods

Samples

Eighteen adult subjects with chronic, plaque psoriasis with affected body surface area > 10% and not on systemic medications were recruited from the University of California San Francisco Dermatology Department by a board-certified dermatologist. Five millimeter

punch biopsies were taken from the edge of a psoriatic plaque. Sixteen normal skin samples were obtained from healthy control surgical discard specimens. All subjects provided written, informed consent for study participation under the approval of local Institutional Review Boards. Skin samples were stored in RNALater at −80°C, mechanically homogenized using a Bio-Gen Pro 200 homogenizer, and total RNA was extracted using the Qiagen RNeasy mini kit. The quality of the RNA was assessed using an Agilent 2100 Bioanalyzer. Ribosomal RNA was depleted using Ribo-Zero Gold rRNA removal kit, followed by cDNA synthesis and library preparation using ScriptSeq Complete kits (Human/Mouse/Rat) from Epicentre. The quality and quantity of library was assessed by Agilent 2100 Bioanalyzer.

Human primary peripheral blood mononuclear cells (PBMC) were isolated by the use of a Ficoll gradient from collected blood obtained from psoriasis patients (N=32) and healthy control individuals (N=25). After processing, PBMC were stored and frozen in 10% DMSO-FCS prior to subsequent analysis. Based on cell numbers and patient availability, a subset of samples was destined for ex vivo HIV-1 infectivity assays and CD4+ T cells were enriched from PBMCs using the EasySep Human CD4+ T cell enrichment magnetic kit (Stem Cell Technologies), according to manufacturer's instructions.

RNA-sequencing gene expression in psoriatic skin and healthy control skin

RNA-seq on blinded samples was performed on an Illumina HiSeq 2500. We obtained an average of 52.3 million 101 bp paired end reads per sample. Quality was validated using FastQC. Quality and adapter trimming was performed with Trimmomatic (version 0.3). Reads were aligned to the human genome (hg19) using Tophat2 (version 2.0.9). An average of 34.8 million paired end reads were aligned for each library (minimum of 25.3 million, maximum of 61.4 million). For differential gene expression, the RefSeq gene set (UCSC genome browser, January 2013) was used as the genome annotation. Differential gene expression was calculated using EdgeR[13], with counts per gene measured using htseq-count and analyzed as described.

Microarray gene expression analysis in lesional and non-lesional psoriatic skin, control skin, and atopic dermatitis skin

We validated top hits using a publically available, independent dataset (Gene Expression Omnibus dataset GSE13355) consisting of 58 lesional psoriasis skin samples, 58 non-lesional psoriasis skin samples, and 64 healthy control samples profiled using the Affymetrix HU133 Plus 2.0 Microarray containing >54,000 gene probes. The raw microarray data were processed using the Robust Multichip Average (RMA) method. Differential gene expression was calculated using the limma (Linear Models for Microarray Analysis) R package, which applies multiple-testing corrections on p-values to help correct for the occurrence of false positives.

We also examined the same set of antiviral genes in Affymetrix HU133A microarray data from atopic dermatitis skin (N=10) and healthy control skin (N=10) (Gene Expression Omnibus dataset GSE6012). Differential gene expression was calculated as above for psoriatic skin.

Real-time quantitative PCR from PBMCs

PBMC samples were quickly thawed and total RNA was extracted using Qiazol reagent from miRNeasy Mini kit (Qiagen) with the on-column DNAase treatment option using Qiagen RNase-Free DNase Set. DNase-treated clean RNA was transcribed into cDNA using random primers and the SuperScript VILO™ cDNA Synthesis Kit (Invitrogen) according to manufacturer's instructions. Quantitative real-time PCR on blinded samples utilized custom made TaqMan Low Density Array (TLDA) from Applied Biosystems and followed the manufacturer's instructions. Thermal cycling was performed using an ABI ViiA7 Real-Time PCR System. Up to 350ng cDNA in 200μl of Applied Biosystems TaqMan Universal PCR Master Mix, with UNG was loaded onto the designated ports of the TLDA plates. Data was analyzed using ABI ViiA7 software. A panel of 6 housekeeping genes was included in the TLDA plates (GAPDH, 18S, ACTB, PPIA, RPLP0, and UBC). RPLP0 was identified as the most stably expressed gene from those 6 housekeeping genes among the whole samples using the GeNorm algorithm.[14] Therefore, raw cycle threshold numbers of amplified gene products were normalized to the housekeeping gene, RPLP0, (Ribosomal protein, large, P0) to control for cDNA input amounts. Fold induction was determined using the comparative Ct method.

Ex vivo HIV-1 infectivity assay

pNL-LucR.T2A-Bal.ecto was a kind gift from Dr. Christina Ochsenbauer (University of Alabama at Birmingham). The plasmid encodes an infectious molecular clone that has Tat-regulated Renilla luciferase (rLuc is between Env and Nef) and it contains the entire ectodomain and a portion of the transmembrane region of Bal.[15] Briefly, viral stocks were generated by transfecting proviral DNA into 293T cells using FuGENE6 according to manufacturer's instructions. Viral supernatants were harvested 60h post-transfection, span and filtered through a 0.45μm pore size, before being frozen at −80°C.

On the day before infection, CD4+ T cells were enriched from frozen PBMCs, as described above and placed over-night in complete media (RPMI1640, 10% FCS, Pen/Strep and L-glutamine). The next day, a viable cell count was performed and 100,000 CD4+ T cells were infected in duplicate for 7 days in the presence of 50 U/ml IL-2 in a total volume of 200μl in U-bottom 96-well plates. Mock infections were also performed. After 7 days of infection, cells were lysed in 1x Renilla Luciferase assay lysis buffer and 50μl of each cell lysate was transferred to a solid-white flat bottom 96-well plate and analysed for LucR activity. Samples were analysed using a Veritas luminiometer (Promega) programed to inject 100μl of LucR assay reagent per well with an integration time of 2.5s/well and reporting relative light units (RLU).

Results

Elevated antiviral gene expression in psoriatic but not atopic dermatitis skin

We selected a panel of 42 antiviral genes for investigation in this study; the function and activity of these genes have been documented in the literature (Table 1).

To evaluate the expression of these genes in psoriasis, we obtained punch biopsies from the edge of a psoriatic plaque in subjects (N=18) with chronic psoriasis not on systemic medications. In parallel, normal skin samples (N=16) were obtained from healthy control surgical discard specimens. RNA-seq was performed using an Illumina HiSeq 2500 resulting in an average of 52 million paired-end reads per sample.

We observed statistically significant up-regulation of 16 of 42 antiviral genes (Table 2), including ISG15 (9.93 fold increase, p=1.05E-25), RSAD2/Viperin (9.95 fold increase, p = 2.11E-20), TRIM21 (2.21 fold increase, p = 8.68E-17), IRF7 (3.40-fold increase, p = 3.60E-14) and MX2 (3.52-fold increase, p = 9.25E-12). In contrast, SLFN11 (0.64-fold decrease, p=2.44E-04), TRIM32 (0.75-fold decrease, p = 9.97E-04), SUN2 (0.76-fold decrease, p=0.001), and BRD4 (0.72-fold decrease, p = 0.020) were among the genes that were down-regulated in psoriatic skin. Several members of the APOBEC3-family (A3A, A3B, A3D, A3G and A3H) were not differentially expressed between psoriatic and healthy skin.

To confirm our RNA-seq results, we validated top hits using an independent dataset of 58 lesional psoriasis skin samples and 64 healthy control samples profiled using the Affymetrix HU133 Plus 2.0 Microarray containing over 54,000 gene probes. We found that 18 out of our 20 most significant hits were replicated (Table 2).

To determine whether the differential antiviral gene expression observed in psoriatic skin was due to generalized skin inflammation, we examined the same set of antiviral genes in atopic dermatitis skin (N=10) and healthy control skin (N=10) profiled on the Affymetrix HU133A microarray data. Atopic dermatitis is an inflammatory skin disorder characterized clinically by erythema and itch and histologically by a lymphocytic infiltrate and the presence of intercellular edema. Among the 36 target genes for which data were available in the atopic dermatitis dataset, only 6 genes were differentially expressed ($p < 0.05$) between atopic dermatitis skin and healthy control skin (APOBEC3A, CH25H, IFITM1, IRF7, ISG15 and LGALS3BP). All six genes showed significant under-expression in atopic dermatitis skin (Supplementary Table 1). This contrasted with psoriasis in which a significant number of antiviral genes were elevated compared to control skin (16 of 42 in psoriasis vs 0 of 36 in atopic dermatitis, $p < 0.0001$, Fisher's exact test). Furthermore, we examined antiviral gene expression in non-lesional psoriatic skin and found none to be significantly elevated (Supplementary Table 1). These data suggest that lesional psoriatic skin exhibits a selective overexpression of antiviral genes that is not a general feature of inflammatory skin disease or of non-lesional psoriatic skin.

No antiviral signature in PBMC from psoriatic patients

Since psoriatic skin was enriched for antiviral genes, we investigated whether peripheral blood mononuclear cells (PBMC) from psoriatic patients might also possess increased expression of host restriction factors. We obtained PBMC from psoriatic patients (N=32) and healthy control individuals (N=25) and quantified the expression of 42 different antiviral genes using quantitative real-time PCR.

In contrast with the increased gene expression levels detected in the skin of psoriatic patients, PBMC from psoriatic patients did not exhibit statistically significant increase in the expression of antiviral genes compared to healthy controls (Supplementary Table 2). These data suggest a compartmentalization of the antiviral gene signature in psoriasis whereby expression of antiviral genes is up-regulated in skin but not in peripheral blood.

Ex vivo HIV infectivity assay

We then investigated whether peripheral blood CD4+ T cells from psoriatic patients would support HIV-1 replication at the same rate as control CD4+ T cells. Based on cell availability, we infected CD4+ T cells from psoriatic patients (N=7) and healthy control individuals (N=10) with HIV-1_{BaL} encoding Renilla Luciferase (LucR) reporter gene. After 7 days of infection we quantified LucR activity using a luminometer and detected no statistically significant differences in HIV-1 infectivity in CD4+ T cells from psoriatic and healthy individuals ($p > 0.05$, Mann-Whitney) (Supplementary Figure 2).

Discussion

Here we have examined a large panel of antiviral genes in psoriasis and identified overexpression of innate antiviral genes in psoriatic skin. Our findings were determined using two independent cohorts and two technical approaches: RNA sequencing and microarrays.

Our findings build on a previous observation that four antiviral proteins, MX1, BST2, ISG15, and OAS2, are increased in psoriatic skin and induced by IL-29.[1] The type I interferon signaling pathway is activated in psoriatic lesional skin[16] and the blocking of IFN-alpha signaling or blocking the ability of plasmacytoid dendritic cells to produce IFN-alpha prevented the development of disease in a xenograft model of human psoriasis.[17] The significant up-regulation of antiviral genes in psoriatic skin is in agreement with the role of interferon-alpha in inducing antiviral gene expression. Moreover, the two most up-regulated genes in our study, ISG15 and RSAD2/Viperin, are strongly induced by exogenous interferon-alpha *in vivo*.[18]

We did not observe the same differential expression of antiviral genes in atopic dermatitis skin. Psoriasis, a Th1 and Th17 driven disease, activates distinct immune pathways compared to atopic dermatitis, a Th2 driven disease. Furthermore, psoriasis more than atopic dermatitis is associated with expansion of keratinocytes and it is possible that antiviral genes are expressed robustly in keratinocytes. However, prior studies in HIV (Table 1) have shown innate antiviral genes to be highly expressed in immune cells; thus our results may reflect a combination of antiviral activity in both immunocytes and keratinocytes.

In chronic HIV-1 infection, CD4+ T cell activation is elevated in viremic non-controller patients and it gradually decreases from ART-suppressed to elite controllers; it is low in HIV-1 seronegative individuals.[19] We have previously reported a strong correlation between the levels of CD4+ T cell activation and the expression of antiviral genes.[10, 20] Curiously, we did not observe elevated antiviral gene expression in psoriatic peripheral blood, despite the increased activation levels previously shown in psoriatic PBMCs.[21] It is possible that

psoriatic autoantigens are expressed primarily in the skin and thus the observed antiviral immune responses localize preferentially in skin.

An important clinical question is whether psoriasis patients have enhanced immunity to systemic viral infections. Here, we specifically examined the effect of psoriasis on infection by HIV-1. Addition of HIV-1 reporter virus to psoriatic and non-psoriatic peripheral CD4+ T cells did not reveal any differences in viral replication. This suggests the antiviral phenotype of psoriatic skin does not impact viral replication within the blood. In agreement, we observed no significant difference in the viral loads of HIV positive patients with psoriasis and without psoriasis (see companion manuscript, Wu et al).

A limitation of the present study is that psoriasis is a genetically heterogeneous disease and with our sample size we were not able to stratify psoriasis patients by genetic subtype. For example, only about 25% of psoriasis patients in the North American population are positive for the psoriasis susceptibility allele *HLA-B*57*, which is also associated with control of both HIV-1[22] and hepatitis C virus.[23] We have previously shown that the presence of the *HLA-B*57* allele is associated with increased expression of antiviral restriction factors in the PBMCs of healthy individuals.[11] A second limitation to this study is that we did not perform HIV-1 infectivity assays on CD4+ T cells derived from psoriatic skin, as it is technically difficult to obtain a requisite numbers of cells from skin. Thus, we were not able to directly ascertain whether the high antiviral gene expression in psoriatic skin could impact HIV-1 replication. However, it has been clinically observed that psoriasis patients have decreased occurrence of cutaneous bacterial and viral skin infections compared to atopic dermatitis patients[24] and have significant overproduction of antimicrobial peptides with both antibacterial and antiviral activity.[25]

Our findings highlight psoriasis as an immune-mediated, inflammatory disease with compartmentalized immune activation against viral pathogens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Host antiviral genes and their functions.

NAME	GENE DESCRIPTION	KEY ANTI-HIV-1 ROLE(S)	REFS
APOBEC3 (A,B,C,D,F,G,H)	Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like3	Hypermutation; lethal mutations in viral DNA Inhibition of reverse transcription Inhibition of integration	26–34
BRD4	Bromodomain-containing protein 4	Transcriptional repression of HIV-1	35
BST-2/Tetherin	Bone marrow stromal cell antigen 2	Blocks release of enveloped viruses	6, 7
CD74	HLA-DR antigens-associated invariant chain or CD74 (Cluster of Differentiation 74)	Inhibits viral replication in a cellular overexpression assay	36
CDKN1A (P21)	Cyclin-dependent kinase inhibitor 1A (p21, Cip1)	Blocks reverse transcription Blocks RNA transcription by reducing activity of CDK9	37, 38
CH25H	Cholesterol 25-hydroxylase	Inhibits viral entry.	39
CNP	2′,3′-Cyclic Nucleotide 3′ Phosphodiesterase	Blocks HIV-1 particle assembly.	40
CTR9	Ctr9, Paf1/RNA polymerase II complex component	Inhibits early events of viral life cycle from reverse transcription to integration	41
EIF2AK2 (PKR)	Eukaryotic translation initiation factor 2-alpha kinase 2	Inhibits viral protein translation by protein phosphorylation; promotes innate immune signaling	42
HERC5	HECT domain and RLD 5	Blocks early stage of retroviral particle assembly	43
IFITM Family (3 members)	Interferon induced transmembrane protein	Inhibition of cytosolic entry	43
IRF1	Interferon regulatory factor 1	Inhibits viral replication in a cellular overexpression assay	36
IRF7	Interferon regulatory factor 7	Inhibits viral replication in a cellular overexpression assay	36
ISG15	ISG15 ubiquitin-like modifier	Blocks interaction between HIV-1 Gag and Tsg101 (ESCRT-I) required for efficient budding of HIV-1	44
LGALS3BP	lectin, galactoside-binding, soluble, 3 binding protein	Interferes with the maturation and incorporation of HIV-1 Env molecules into virions.	45
MOV10	Mov10, Moloney leukemia virus 10, homolog	Inhibits proteolytic processing of Gag and reverse transcription	46
MX2	Myxovirus resistance 2	Inhibits capsid-dependent nuclear import of subviral complexes.	47–49
PAF1	Paf1, RNA polymerase II associated factor	Inhibits early events of viral life cycle from reverse transcription to integration	41
RNASEL	Ribonuclease L (2′,5′-oligoisoadenylate synthetase-dependent)	Cleave single-stranded RNA in U-rich sequences; activate antiviral innate immunity	50
RSAD2 (Viperin)	Radical S-adenosyl methionine domain containing 2	Inhibits viral production	51
RTF1	Rtf1, Paf1/RNA polymerase II complex component	Inhibits early events of viral life cycle from reverse transcription to integration	41
SAMHD1	SAM domain and HD domain 1	Inhibits HIV replication in myeloid cells, probably by regulating cellular dNTP supply	8
SLFN11	Schlafen family member 11	Inhibits viral protein synthesis	52
SUN2	Sad1 and UNC84 domain containing 2	Inhibits viral replication in a cellular overexpression assay	36

NAME	GENE DESCRIPTION	KEY ANTI-HIV-1 ROLE(S)	REFS
TNFRSF10A	Tumor necrosis factor receptor superfamily, member 10a	Inhibits viral replication in a cellular overexpression assay	36
TRIM family (9 members)	Tripartite motif family	Targeting of viral capsid Inhibition of viral transcription	9, 53–55

Table 2

Antiviral restriction factor expression in psoriatic versus healthy skin

The expression levels of antiviral restriction factors were measured in psoriatic (N=18) and healthy skin (N=16) using RNA-seq. Differentially expressed genes ($p < 0.05$) were confirmed using independent microarray data. Fold change refers expression level in psoriatic skin relative to control skin.

	RNA-Seq		Microarray			
Gene	**Fold change**	**P-Value**	**Fold change**	**P-Value**	**Confirm**	**Description**
ISG15	9.93	1.05E-25	5.43	6.10E-30	**Yes**	ubiquitin-like protein ISG15
RSAD2	9.95	2.11E-20	5.28	1.10E-24	**Yes***	radical S-adenosyl methionine domain-containing protein 2
TRIM21	2.21	8.68E-17	1.38	6.73E-15	**Yes**	tripartite motif containing 21
IRF7	3.40	3.60E-14	4.56	8.16E-47	**Yes**	interferon regulatory factor 7
MX2	3.52	9.25E-12	2.25	6.24E-16	**Yes**	interferon-induced GTP-binding protein Mx2
CDKN1A	0.43	9.72E-10	1.04	3.72E-02	No*	cyclin-dependent kinase inhibitor 1
TRIM22	2.10	5.69E-08	2.30	3.36E-29	**Yes**	tripartite motif containing 22
BST2	2.09	9.38E-08	1.58	1.64E-08	**Yes**	bone marrow stromal cell antigen 2
EIF2AK2	1.63	1.72E-07	1.19	6.84E-07	**Yes***	eukaryotic translation initiation factor 2-alpha kinase 2
TRIM14	1.78	3.11E-07	2.95	4.32E-48	**Yes***	tripartite motif-containing protein 14
HERC5	1.84	3.75E-07	1.47	5.34E-10	**Yes**	E3 ISG15--protein ligase HERC5
CH25H	0.38	5.26E-07	2.16	6.61E-25	No	cholesterol 25-hydroxylase
SAMHD1	1.58	7.08E-06	1.49	8.01E-10	**Yes***	SAM domain and HD domain 1
PAF1	1.54	2.31E-05	1.15	3.58E-10	**Yes**	Paf1, RNA Polymerase II Associated Factor, Homolog
IFITM1	1.53	9.27E-05	1.55	8.92E-22	**Yes***	interferon-induced transmembrane protein 1 (9–27) isoform 1
TRIM5	1.46	1.87E-04	1.38	7.61E-09	**Yes***	tripartite motif-containing protein 5
IFITM3	1.61	2.05E-04	1.35	3.48E-18	**Yes**	interferon induced transmembrane protein 3
SLFN11	0.64	2.44E-04	0.84	2.60E-03	**Yes**	schlafen family member 11
TRIM32	0.75	9.97E-04	0.82	6.00E-07	**Yes***	E3 ubiquitin-protein ligase TRIM32
SUN2	0.76	0.001	0.87	1.38E-09	**Yes**	SAD1/UNC-84 domain-containing protein 2
IRF1	0.68	0.002	1.91	2.91E-27	No*	interferon regulatory factor 1
APOBEC3C	0.75	0.015	1.17	1.18E-05	No	probable DNA dC->dU-editing enzyme APOBEC-3C

	RNA-Seq		Microarray			
Gene	**Fold change**	**P-Value**	**Fold change**	**P-Value**	**Confirm**	**Description**
BRD4	0.72	0.020	0.79	4.67E-19	**Yes***	bromodomain-containing protein 4
APOBEC3F	0.76	0.023	1.18	1.73E-05	No*	DNA dC->dU-editing enzyme APOBEC-3F
TRIM26	1.20	0.033	1.04	1.25E-01	No	tripartite motif-containing protein 26

* Indicates more than one microarray probe present per gene. Data are from most significant probe displayed.

Genes not differentially expressed (p > 0.05) by RNA-Seq: APOBEC3A, APOBEC3B, APOBEC3D, APOBEC3G, APOBEC3H, CD74, CNP, CTR9, IFITM2, LGALS3BP, MOV10, PML, RNASEL, RTF1, TNFRSF10A, TRIM11, TRIM28