# Differentially Expressed Cellular Gene Profiles between Healthy HIV-infected Koreans and AIDS Patients

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**Background:** The global effect of HIV infection on the host cell gene expression profiles in healthy HIV-infected patients, as long-term non-progressors, remains largely unknown. To identify the cellular genes related with HIV infection and delayed disease progression in vivo, the host gene expression profiles between healthy HIV-infected Koreans and AIDS patients were investigated.

**Methods:** Differential expression gene analysis was performed via oligonucleotide microarray with using Magic-oligo 10K chip. Ten HIV-uninfected persons and 10 HIV-infected patients (healthy HIV-infected patients vs. AIDS patients. respectively) were studied.

**Results:** Only 10.8% (1,097 genes) of the total genes, that is, 331 up-regulated genes and 766 down-regulated genes were differentially expressed with more than a two-fold change in the HIV-infected persons as compared to those of the HIV-uninfected persons. Especially, 97 genes (8.8%) among 1,097 genes were commonly up- or down-regulated in both the healthy HIV-infected patients and the AIDS patients. 187 genes were differently expressed on the gene expression analysis between the healthy HIV-infected patients and the AIDS patients. Twenty-eight genes out of them showed very significant differences with a $P$ value $<0.01$. Especially, tripartite motif (TRIM) 14 protein and interferon gamma receptor 2 were dramatically up-regulated in healthy HIV-infected patients, while death-associated protein, DNA directed RNA polymerase II polypeptide A and STAT were over-expressed in AIDS patients.

**Conclusion:** Although this microarray study has some limitations, the above results will be helpful for performing more detailed, future functional studies on the differentially expressed genes related to HIV infection and delayed disease progression in vivo. ***(Korean J Hematol 2007;42:33-42.)***

**Key Words:** Differentially expressed genes (DEGs), Oligonucleotide microarray, Healthy HIV-infected patients, TRIM 14 protein, In vivo

## INTRODUCTION

HIV drives dramatic changes of the host cell's whole-gene expression during HIV infection and AIDS pathogenesis.[1] Recent microarray technology has been applied to investigate the interaction between viruses and host cells. Several studies have described the gene expression profiles in host cellular genes related with the HIV

접수 : 2006년 11월 20일, 수정 : 2006년 12월 19일
승인 : 2007년 1월 17일
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infection and/or the HIV pathogenesis due to acute HIV infection and the expression of HIV proteins, HIV-1 *Nef* and HIV *Tat*.[2,3] Swingler et al.[2] reported that the HIV-1 *Nef* protein induced expression of chemokines such as RANTES, Mip-1 $\alpha$ and Mip-1 $\beta$ in macrophages and Izmailova et al.[3] suggested that HIV *Tat* proteins induced interferon-mediated antiviral responses by the expression of interferon-inducible genes.

Although these reports were valuable, these genes were mainly examined in acute infection status.[2-4] The gene expression profiling data obtained by acute HIV-1 infection have some limitations such as the exclusion of gene expression profiles caused by both non-synchronous HIV-1 infection and large number of defective viral particles generated by every infectious virion. Even if highly active antiretroviral therapy (HAART) have contributed to the dramatic decline in the incidence of AIDS and AIDS-related mortality of HIV-1-infected patients, the persistence of latently HIV-infected reservoirs, resting CD4+ T cells, in HIV-infected patients is the major obstacle to HIV-1 eradication.[5] Recently, Chun et al.[6] investigated gene expression profiles in resting CD4+ T cells in viremic versus aviremic HIV-infected patients to find out some clues for eradicating HIV-1 in vivo. Unfortunately, the global effect of HIV infection on host cell gene expression profiles in healthy HIV-infected patients, long-term non-progressors, remains largely unknown. To fully understand the interaction between HIV infection and host cells, various in vivo studies are required.

Considering these respects, we investigated host gene expression profiles between healthy HIV-infected Koreans and AIDS patients to identify cellular genes related with delayed disease progression in vivo.

## MATERIALS AND METHODS

### 1. Study patients

Ten HIV-uninfected persons and ten HIV-infected patients were recruited with their informed consent. Five healthy HIV-infected patients and five AIDS patients were selected to investigate host genes showing the clear difference on disease progression to AIDS. The healthy HIV-infected patient was defined as the patient who had CD4+ T cell count of $>500$ cells/mm$^3$, no symptoms related to HIV infection, and no history of taking anti-HIV drugs. AIDS patient was defined as the patient who had CD4+ T cell counts of $<100$ cells/mm$^3$. The mean value of age and CD4+ T cell count were 39.8 and 626 cells/mm$^3$ in Healthy HIV-infected patients 37.4 and 74.6 cells/mm$^3$ in AIDS patients.

### 2. Extraction of total RNA from PBMCs

The total RNAs from isolated PBMCs were extracted using acid phenol extraction (Trizol LS, Gibco BRL, USA) as the procedure recommended by the manufacturer. The purity of RNA was confirmed by measuring the optical density at 260 and 280nm. High purity RNA showed over 1.8 of the ratio (260/280nm) and the quality of purified RNA was confirmed by 1% agarose gel electrophoresis.

### 3. Oligonucleotide chip microarray using T7-promoter amplification protocol

Oligonucleotide chip microarray was performed using 10K oligo microarray amplification kit (Macrogen. co., Korea) as the procedure recommended by the manufacturer. Magic-oligo 10K chip (Macrogen. co., Korea) was consisted of 10,375 genes: 4,270 molecular function genes, 2,073 biological process genes, 1,689 cellular group component genes, 2,083 unknown genes and 260 control genes. Briefly, First strand cDNA was synthesized using RNA-primer mixture containing 5$\sim$20 $\mu$g of total RNA, 1 $\mu$L of oligo [(dT)24 T7 promoter] $_{65}$ primer, and filled nuclease free water up to 21 $\mu$L and incubated for 10 min at 70$^{o}$C on thermocycler. Reverse transcription (RT) reaction mixture contained 8 $\mu$L of 5X RT buffer, 2 $\mu$L of 0.1M DTT, 1ul of AMV reverse tran-

scriptase (25U/ $\mu$L), 0.5 $\mu$L of RNase inhibitor (25U/ul), 2 $\mu$L of dNTP mix (10mM, each nucleotide), 5.5 $\mu$L of nuclease free water, and RNA-primer mixture. The reaction mixture was incubated for 1 h at 42°C after vortexing and second strand DNA was synthesized using 20 $\mu$L of 5X 2nd strand-buffer, 0.75 $\mu$L of dNTP mix (10 mM, each nucleotide), 3.25 $\mu$L of 2nd strand enzyme mix, 36 $\mu$L of nuclease free water, and 40 $\mu$L of 1st strand cDNA reaction mixture in 100 $\mu$L of total volume. The reaction mixture was incubated 2 h at 16°C and then incubated with T4 DNA polymerase 10U for 5 min at 16°C. This reaction was stopped with 6.8 $\mu$L of EDTA (0.5M pH 8.0) and 0.75 $\mu$L of RNase I (7.5U) for 30 min at 37°C. Finally, second strand cDNA synthesis was finished by incubation with 2.5 $\mu$L of protease K (1.5U) for 30 min at 37°C. Double strand DNA (ds DNA) was purified by using QIAGEN RNase kit (Qiagen co., USA). 40 $\mu$L of ds DNA was eluted at 14,000rpm for 2 min and dried in speed-vac for 1 h. T7 transcription and cRNA labeling were performed mixing dried dsDNA with 2 $\mu$L of 10X reaction buffer, 3 $\mu$L of ATP/CTP/GTP-mix stock solution (25mM each), 1 $\mu$L of U-nucleotide stock solution (50 mM), 10 $\mu$L of nuclease free water, 1.5 $\mu$L of T7 RNA polymerase, and 2.5 $\mu$L of cy3-UTP for control or cy5-UTP for target (5mM) for at least 16 hrs at 37°C. After cRNA purification, fragmentation was performed with 20 $\mu$L of 5X fragmentation buffer for 15 min at 94°C, cooled on ice, dried using speed vacuum, and then eluted with hybridization mixture. The labeled cRNA to the microarray was hybridized at 42°C for overnight and washed with 2x SSC, 0.1% SDS for 5 min,

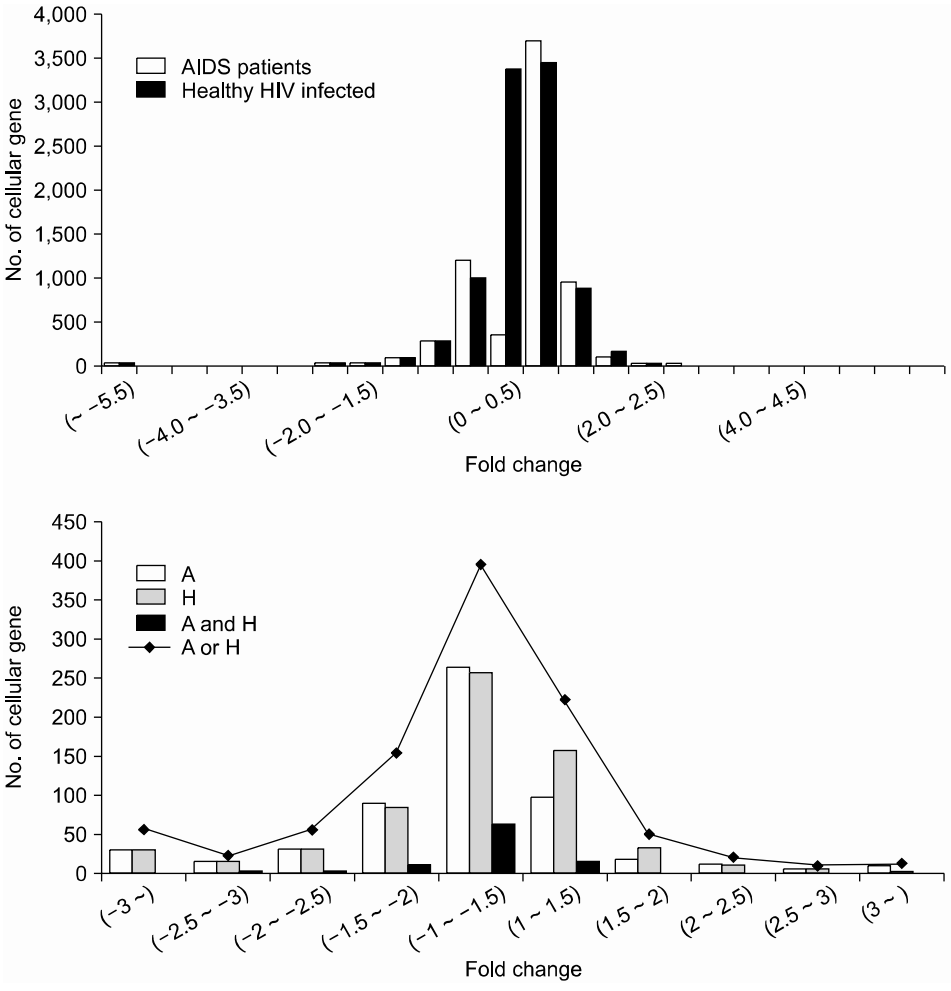


**Fig. 1.** Distribution of the changes of gene expression profiles in healthy HIV-infected and AIDS patients compared to those of HIV-uninfected persons. The upper and lower show whole gene expression profiles and the distribution of differentially expressed genes (DEGs) with > two-fold change between healthy HIV-infected and AIDS patients, respectively. A and H represent AIDS patients and Healthy HIV-infected persons. (A and H) means DEGs that were commonly expressed in two groups and (A or H) means the total number of differentially expressed genes with > two fold change in two groups. Each value of fold change was presented in log 2.

1x SSC for 5 min, and 0.5x SSC for 5 min. The slides were dried by centrifugation at 1,000rpm for 5 min.

### 4. Data analysis

After the microarray slide was scanned using scanner with Imagene Software, microarray images were analyzed with Gene Cluster, Tree View, and Array-Tools software (Stanford Univ., USA). Ten microarray data sets from five healthy HIV-infected persons and five AIDS patients were analyzed with these softwares to investigate host gene expression profiles.

## RESULTS

### 1. The differentially expressed genes between HIV-uninfected and HIV-infected patients in vivo

Most cellular genes didn't show any difference in gene expression profiles of HIV-infected persons compared to those of HIV-uninfected person (the upper of Fig. 1). Only 10.8% (1,097 genes) of total 10,115 genes were differentially expressed with more than two-fold change in HIV-infected persons (the lower of Fig. 1). 331 out of 1,097 differentially expressed genes (DEGs) were up-regulated and 766 genes were down-regulated in HIV-infected persons. Most DEGs showed two- or three-fold change in the gene expression profile and the number of DEGs with more than four-fold change was 254 genes of total 1,097 DEGs. Especially, ninety-seven genes (8.8%) among 1,097 DEGs, 17 up-regulated genes and 80 down-regulated genes, were commonly up- or down-regulated in both healthy HIV-infected and AIDS patients. The representative over-expressed genes in both groups were zinc finger protein, translation initiation factor 2, interferon-induced protein, serine/threonine kinase 4, keratin 9, kinesin-like 5 and so on (Table 1). Also, the representative commonly down-regulated genes with more than three-fold change in both two groups were eukaryotic translation elongation factor 1, T cell activator, chemokine (c-x-c motif) ligand 16, TNF receptor-associated factor 5, G-protein-coupled receptor 64, troponin t1, and so on (Table 2).

**Table 1.** The representative genes that were commonly up-regulated in Healthy HIV-infected and AIDS groups compared to those of HIV-uninfected group

| Functional group | Gene symbol | Gene description | ACC. No | Fold change |
|---|---|---|---|---|
| Gene/protein expression | ZDHHC2 | Zinc finger, DHHC domain containing 2 | NM_016353.1 | 1.07 |
| | KIAA0741 | Translation initiation factor IF2 | AB018284.1 | 1.25 |
| Immune response | IFIT4 | Interferon-induced protein with tetratricopeptide repeats 4 | NM_001549.1 | 1.56 |
| | SSA2 | RO/SSA autoantigen | NM_004600.1 | 1.22 |
| Signaling/communication | EGR4 | Early growth response 4 | NM_001965.1 | 2.08 |
| | STK4 | Serine/threonine kinase 4 | NM_006282.1 | 1.53 |
| | PRKG2 | Protein kinase, cGMP-dependent, type ii | NM_006259.1 | 1.26 |
| | TTK | TTK protein kinase | NM_003318.1 | 1.10 |
| | BKS | Brk kinase substrate | AJ245719.1 | 1.04 |
| | PCDH13 | Protocadherin 13 | AF169693.1 | 1.41 |
| Structure/mobility | SNX7 | Sorting nexin 7 | AF121857.1 | 1.63 |
| | TMEPAI | Transmembrane, prostate androgen induced RNA | NM_020182.1 | 1.05 |
| | KRT9 | Keratin 9 | NM_000226.1 | 1.99 |
| | HIP1 | Huntingtin interacting protein 1 | NM_005338.1 | 1.54 |
| | KNSL5 | Kinesin-like 5 | NM_004856.1 | 1.06 |

In healthy HIV-infected patients, 208 genes were up-regulated above two fold and 418 genes were down-regulated more than those of HIV-uninfected persons. The major changes among 626 genes were genes related with gene/protein expression class, signaling/communication class, and metabolism class. The distribution of the genes by ontology didn't show any difference between up-regulated and down-regulated genes (Fig. 2). Genes involved in signaling and communication, kinase, ligand, and phosphates were stimulated and genes related with cell division, transcription, and translation factors including eukaryotic translational elongation factor 1 alpha 1, dead/h (asp-glu-ala-asp/his) box polypeptide 1 were down-regulated. Many signal transducers, receptors and kinase such as G-protein coupled receptor, chemokine (c-c motif) receptor-like 2, FAS-activated serine/threonine kinase, serine/threonine kinase 4, and early growth response 4 were up-regulated.

**Table 2.** The representative genes that were simultaneously down-regulated in Healthy HIV-infected and AIDS groups compared to those of HIV-uninfected group

| Functional group | Gene symbol | Gene description | ACC. No | Fold change |
|---|---|---|---|---|
| Gene/protein expression | EIF4G1 | Eukaryotic translation initiation factor 4 gamma, 1 | NM_004953.1 | −2.12 |
| | RENT1 | Regulator of nonsense transcripts 1 | NM_002911.1 | −1.74 |
| | ZFS5 | Zinc-finger protein | D70835.1 | −1.72 |
| | PRPF8 | U5 snRNP-specific protein | NM_006445.1 | −1.61 |
| | EEF1A1 | Eukaryotic translation elongation factor 1 alpha 1 | NM_001402.1 | −1.56 |
| Immune response | FCER1A | Fc fragment of IgE, high affinity i, receptor for; alpha polypeptide | NM_002001.1 | −2.65 |
| | C1QR1 | Complement component c1q receptor | NM_012072.1 | −2.51 |
| | TACTILE | T cell activation, increased late expression | NM_005816.1 | −2.11 |
| | CXCL16 | Chemokine (c-x-c motif) ligand 16 | NM_022059.1 | −1.70 |
| | PPBP | Pro-platelet basic protein | NM_002704.1 | −1.53 |
| Oncogene | GAS41 | Glioma-amplified sequence-41 | NM_006530.1 | −2.43 |
| | MYC | V-myc myelocytomatosis viral oncogene homolog (avian) | NM_002467.1 | −2.32 |
| | MYCL2 | V-myc myelocytomatosis viral oncogene homolog 2 (avian) | NM_005377.1 | −1.99 |
| | GCYS20 | Gastric cancer-related protein gcys-20 | AF219140.1 | −1.87 |
| | TRAF5 | TNF receptor-associated factor 5 | NM_004619.1 | −1.55 |
| Cell division | REC14 | Meiotic recombination protein | AF309553.1 | −1.65 |
| Signaling/communication | KCND3 | Potassium voltage-gated channel, shal-related subfamily, member 3 | NM_004980.1 | −5.61 |
| | PRKDC | Protein kinase, DNA-activated, catalytic polypeptide | NM_006904.1 | −2.16 |
| | GABRB3 | Gamma-aminobutyric acid (gaba) a receptor, beta 3, isoform1 precursor | NM_000814.1 | −2.08 |
| | FGFR2 | Fibroblast growth factor receptor 2, isoform 3 precursor | NM_022970.1 | −1.89 |
| | GPR64 | G protein-coupled receptor 64 | XM_013056.1 | −1.83 |
| | EBI2 | EBV-induced g protein-coupled receptor 2 | NM_004951.1 | −1.61 |
| Structure/mobility | TNNT1 | Troponin t1, skeletal, slow | XM_048167.1 | −2.90 |
| | CLC | Charot-leyden crystal protein | NM_001828.1 | −2.30 |

Fifty-six of 626 genes were related with cancer or oncogenesis (data not shown).

In AIDS patients, 568 genes showed the different expression profiles above two-fold compared to those of HIV-uninfected persons. One hundred forty genes showed more than two-fold induction and 428 genes showed above two-fold suppression compared to those of HIV-uninfected persons. These genes were involved in gene/protein expression class, cell division class, metabolism class, signal/communication class, structure/mobility class, immune response class, and apoptosis class (Fig. 2). Twenty percent among these genes was also unknown genes. Approximately 60% among 568 genes was genes related with signal/communication, gene/protein expression, and metabolisms.

### 2. Cellular gene expression profiles between healthy HIV-infected patients and AIDS patients in vivo

ArrayTool and SAM (Significant Array Method) were used to investigate the difference in host gene expression between healthy HIV-infected person and AIDS patient and $P<0.05$ was considered statistically significant. One hundred eighty seven genes showed the significant difference between healthy HIV-infected group and AIDS group (data not shown). 74 out of 187 genes were up-regulated in healthy HIV-infected person whereas the rest genes were up-regulated in AIDS patient.

Especially, twenty-eight genes showed very significant difference with $P<0.01$ in host gene ex-

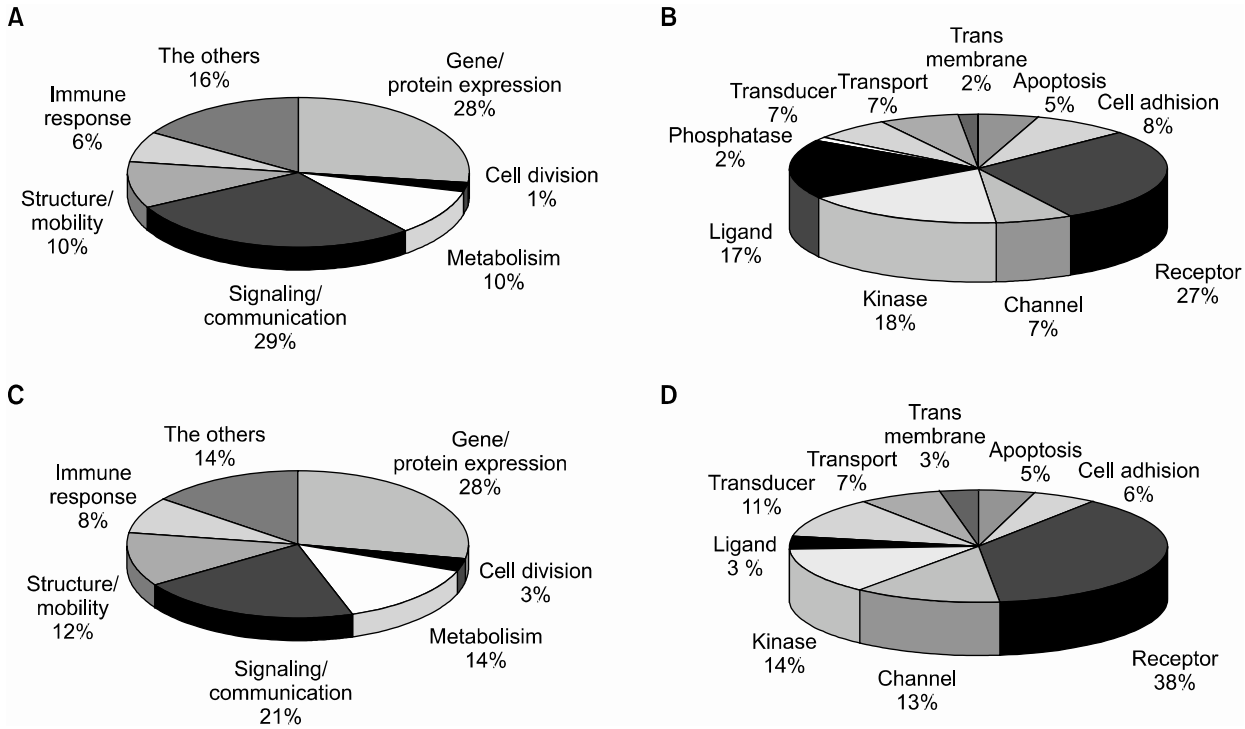


**Fig. 2.** The functional distribution of differentially expressed genes in HIV-infected patients. DEGs were divided into 7 categories based on their function. Numbers mean the percentages of genes in each category compared to total number of genes regulated. (A) The distribution of 331 up-regulated genes based on their cellular function. Genes that involved in signaling/communication were mostly up-regulated. (B) The distribution of overexpressed signaling/communication related genes in HIV-infected patients according to sub-categories. Signaling/communication genes were further divided into 10 classes. Receptors, ligands, and kinases genes were mostly up-regulated. (C) The distribution of 766 down-regulated genes based on their cellular function. (D) Distribution of down-regulated signaling/communication related genes in HIV-infected patients according to sub-categories. Signaling/communication genes were further divided into 10 classes. Receptors related genes were mostly down-regulated.

pression between healthy HIV-infected person and AIDS patient (Table 3). Eleven of these genes were highly expressed in healthy HIV-infected group than in AIDS patient group. On the other hand, the rest genes were highly expressed in AIDS patient and most of these genes were transcription-related genes. Especially, DNA directed RNA polymerase II (GB Access No.NM_000937) was up-regulated above 10-fold in AIDS patients than in healthy HIV-infected persons. On the other hand, interferon gamma receptor 2 (GB Access No.NM_005534) was down-regulated more than 10-fold in healthy HIV-infected persons.

## DISCUSSION

HIV infection into host cells causes the abnormal immune activation that can lead to active viral replication. The presence of HIV-1 viremia may create directly or indirectly a vigorous cycle that has an important impact on the pathogenesis of HIV.[7] As shown in Fig. 1, ninety-seven genes that were differentially expressed in both healthy HIV-infected and AIDS patients might be associated with HIV infection and HIV pathogenesis. The main functions of these genes were gene/protein expression, signaling/communication, immune response, and structure/mobility (Table 1, 2). Several studies have reported that some genes

**Table 3.** Gene lists showing the significant difference with $P<0.01$ in gene expression profiles between healthy HIV-infected and AIDS patients by the univariate test

| Gene | Gene description | Fold change* | ACC. No |
|---|---|---|---|
| LOC51174 | Delta-tubulin | 0.042 | NM 016261.1 |
| RBPJK | Recombination signal binding protein | 0.067 | L07875.1 |
| TRIM14 | Tripartite motif protein trim14 isoform alpha; trim14 | 0.079 | NM_033220 |
| IFNGR2 | Interferon gamma receptor 2 (interferon gamma transducer 1) | 0.093 | NM_005534.1 |
| C18ORF1 | Chromosome 18 open reading frame 1 | 0.099 | NM_004338.1 |
| | Potassium large conductance calcium-activated channel | 0.105 | NM_014407.1 |
| CNTN3 | Contactin 3 (plasmacytoma associated) | 0.128 | XM_039627.1 |
| MAP-1 | Map-1 protein | 0.314 | NM_022151.1 |
| | Complement c1r-like proteinase precursor loc51279 | 0.438 | XM_043329.1 |
| | cAMP response element-binding protein cre-bpa | 0.442 | NM_004904.1 |
| PRX2 | Paired related homeobox protein | 2.121 | NM_016307.1 |
| FZD10 | Frizzled homolog 10 (drosophila) | 2.212 | NM_007197.1 |
| TRIP11 | Thyroid hormone receptor interactor 11 | 2.223 | NM_004239.1 |
| STAT2 | Signal transducer and activator of transcription 2 | 2.312 | NM_005419.1 |
| SNAPC2 | Small nuclear RNA activating complex, polypeptide 2 | 2.348 | NM_003083.1 |
| AFAP | Actin filament associated protein | 2.581 | XM_052622.1 |
| IFNA6 | Interferon, alpha 6 | 3.495 | NM_021002.1 |
| ZNFL69 | Krueppel-type zinc finger protein | 3.644 | U28251.1 |
| ARPC4 | Actin related protein 2/3 complex, subunit 4 | 4.565 | NM_005718.1 |
| DAPK3 | Death-associated protein kinase 3 | 5.174 | XM_031906.1 |
| DMRT1 | Doublesex and mab-3 related transcription factor 1 | 8.164 | NM_021951.1 |
| POLR2A | DNA directed RNA polymerase ii polypeptide A | 11.344 | NM_000937.1 |
| | Mip-t3 | 14.744 | AF230877.1 |
| H2BFH | H2b histone family, member h | 20.468 | NM_003523.1 |
| MEF2A | Mads box transcription enhancer factor 2 | 29.941 | NM_005587.1 |
| KIAA0925 | Kiaa0925 protein | 37.106 | AB023142.1 |

*Fold change means the fold difference of geometric mean values in AIDS patients versus Healthy HIV-infected patients.

among the commonly over-expressed genes in two groups, translation initiation factor 2 (IF2), serine/threonine protein kinase 4 (PKR), and ttk protein kinase, interact with HIV viral proteins. Wilson et al.[8] suggested HIV matrix protein inhibited general translation for human genes by blocking IF2 function and Endo-Munoz et al.[9] reported that HIV-1 Tat might escape the anti-viral IFN response through the competitive binding with eIF2 alpha by acting as a substrate homologue for eIF2 alpha enzyme. Among HIV-repressed cellular genes in this study, eukaryotic translation initiation factor 4 gamma (eIF4G), eukaryotic translation elongation factor 1 alpha (eEF1 alpha), complement component c1q receptor (gC1q-R), and TNF receptor-associated factor 5 (TRAF5) were associated with the regulation of HIV viral proteins in the previous literatures.[10-13] Especially, Szabo et al. reported that complement component c1q receptor (gC1q-R) was a strong inhibitor of HIV-1 infection by blocking the interaction between CD4 molecule and gp 120 viral protein.[13] But, the distribution of differentially expressed genes in HIV-infected patients didn't show any difference with ontology between up-regulated genes and down-regulated genes. Overall, signaling and communication-related genes and many kinases including serine/threonine kinase 4, cGMP-dependent type II protein kinase and vascular endothelial growth factor were up-regulated. While cell division-related genes (positive cell cycle regulators such as cell division cycle 2-like 5 and cyclin G1) and most receptor genes (chemokine receptor, G protein coupled receptor, and interleukin 5 receptor) were down-regulated. As reported in other studies,[14,15] our data showed that genes involved in the transcription and translation processes (many transcription factors, DNA helicases, and splice factors) in HIV-infected patients were mostly down-regulated compared to those of HIV-uninfected patients. Our results were consistent with the report that the viral protein Vpr induced $G_2$ arrest[16] but showed some difference with van't Wout et al.[14] reported that many receptors including CD69, LDLR, T-cell receptors were up-regulated by HIV-1 infection. The discrepancy in the expression of receptor genes maybe comes from multi-function of these cellular proteins in the complicated biological network.

In large-scale analysis of host gene expression profiles between healthy HIV-infected persons and AIDS patients, twenty-eight cellular genes showed very significant difference with $P<0.01$. As you showed in Table 4, they were mainly transcription regulatory genes and cellular metabolic pathway-related genes. For example, Actin filament associated protein, Death-associated protein, DNA directed RNA polymerase II polypeptide A, and STAT was over-expressed in AIDS patients. Actin filament associated protein may be involved in the assembly and budding of retroviruses.[17] Death-associated protein kinase 3 was reported to induce apoptosis in mammalian cells when over-expressed.[18] DNA directed RNA polymerase II polypeptide A promotes transcriptional elongation and stimulate nascent viral RNA capping.[19] Chun et al.[6] also reported that the heterogeneous nuclear ribonucleoproteins, some protein-vesicle transports, and endo-exocytosis related proteins were up-regulated in the resting CD4+ T cells from viremic patients compared to those of aviremic patients. He suggests that these results may provide a favorable environment for active HIV-1 replication and release of cell-free virions through facilitation of protein trafficking and vesicle transport. As STAT have the dual function of signal transduction and activation of transcription as part of a phosphorylation cascade, HIV-1 infection lead to activation of the STAT1 signaling pathway in thymus which may contribute to HIV-1 pathogenesis in thymus.[20] Hottiger and Nabel[21] reported that HIV transcription could be regulated by competitive binding of specific cytokine-induced transcription factors to a discrete domain of a transcriptional coactivator.

Especially, healthy HIV-infected patients sho-

wed the significant over-expression of the tripartite motif (TRIM) protein and interferon gamma receptor 2 (IFNGR2) relative to those of AIDS patients in this study (Table 3). Recent studies have reported that the new retroviral restriction factor TRIM5$\alpha$ blocks the incoming retroviral capsid soon after entry.[22,23] As TRIM family is proteins that contain RING, B-box, and coiled-coil domains, many TRIM proteins self-associate to form homo-oligomers and hetero-oligomers. Unfortunately, the mechanism by which TRIM5$\alpha$ restricts retroviral infection remains mostly unknown. In our result, TRIM 14 protein in healthy HIV-infected patients was significantly up-regulated compared to those of AIDS patients. It is the first report that TRIM 14 protein may be related with HIV resistance and HIV pathogenesis in vivo. In the near future, we have to investigate whether TRIM 14 confers the delayed HIV disease progression and/or the resistance of HIV infection. Also, IFNGR2 encoded on human chromosome 21 is required for the antiviral activity via the interaction of human interferon gamma (IFN-$\gamma$).[24] IFN-$\gamma$ is produced by CD8 cytotoxic T cells and NK cells and is vital for the control of viral pathogens. Therefore, over-expression of IFNGR2 in healthy HIV-infected persons may be suggested the delayed disease progression via the strong interaction between IFNGR2 and IFN-$\gamma$ relative to those of AIDS patients. Although this study has some limitations such as small sample size and the lack of proteomics approach in these genes, the above results will be provided for making a framework for the detailed functional studies on the long-term non-progression-related genes in vivo.

## ACKNOWLEDGEMENT

Jang-Hoon Choi and Byeong-Sun Choi equally contributed to this study. This project was supported by Intramural Human Genome Project Grant from the National Institute of Health, Korea.

## 요 약

**배경**: 장기 무증상 생존자와 같은 건강한 HIV 감염자에 대한 HIV 감염으로 인한 숙주 세포 유전자 발현 양상 변화는 아직까지 잘 밝혀져 있지 않다. 본 연구에서는 in vivo상에서 건강한 HIV 감염자와 AIDS환자를 대상으로 숙주 유전자 발현 양상을 조사하여 HIV 감염과 질병 진전에 관여하는 숙주 유전자를 규명하고자 하였다.

**방법**: HIV 비감염자 10명, 건강한 HIV 감염자 5명, AIDS 환자 5명을 대상으로 Magic-oligo 10K Chip을 사용하여 숙주 세포 유전자 발현 양상을 비교 분석하였다.

**결과**: HIV 비감염자와 감염자 간의 숙주 유전자 발현 양상을 분석한 결과 전체 유전자의 10.8%에 해당되는 1,097 숙주 유전자가 두 배 이상의 발현 차이를 보였으며, 이들 중 331개 유전자는 HIV 감염으로 인하여 발현이 증가한 반면 나머지 766개 유전자는 발현이 억제되었다. 건강 HIV 감염자와 AIDS 환자 모두에서 HIV 비감염자에 비해 두 배 이상의 발현량 차이를 보이는 유전자 수는 97개였다. 건강 HIV 감염자와 AIDS 환자 간 숙주 세포 유전자 발현 양상을 비교 분석한 결과 187개 유전자가 발현 차이를 보였으며, 이들 중 28개 유전자는 *P*값이 0.01 이하로 두 군 간 매우 유의한 발현 차이를 나타내었다. 대표적으로 tripartite motif (TRIM) 14와 interferon gamma receptor 2는 건강 HIV 감염자에서 유전자 발현이 증가한 반면, death-associated protein, DNA directed RNA polymerase II polypeptide A, STAT 등은 AIDS 환자에서 현저하게 과발현되었다.

**결론**: 상기 결과는 in vivo상에서 장기 무증상 HIV 감염과 관련된 숙주 유전자의 기능 연구에 기초 자료로 활용될 것이다.

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