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Th17 common genes in CD4 T-cells of HIV-1-infected naïve patients and elite controllers

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ABSTRACT:

— ***Introduction:*** Th17 cells are a recent characterized subtype of CD4+ T cells that respond to viral, bacterial and fungal antigens and are important in mucosal immunology. HIV infection results in loss of CD4+ T cells as well as in changes of the gastrointestinal tract permeability that causes microbial translocation and immune activation. It is believed that Th17 cells potentially interpret an important role in HIV progression. Here we examine the Th17 cells gene expression ofCD4+ T cells of HIV patients.

— ***Materials and Methods:*** We interrogated two microarray datasets obtained from the NCBI Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) under accession number GSE18233 and GSE54627 in order to define the th17 gene profile characterizing HIV+ naive patients and Elite Controllers (EC) CD4 T cells. The Th17 cells gene pathway obtained after CD4 T cell differentiation from TH0 to Th17 was used as a control.

— ***Results****:* Microarray analysis showed that 402, 405 and 443 TH17 genes were significantly upregulated in HIV, EC and Th17 respectively, while 380, 376 and 378 were significantly downregulated in HIV, EC and Th17 respectively, as compared to healthy and Th0. A total of 375 were common between HIV and EC and 11 common between HIV, EC and Th17. There were 30 genes characteristic of EC, 27 characteristic of HIV and 432 characteristic of Th17. Among the downregulated genes, 373 were common to HIV and EC and 2 were common between HIV, EC and Th17. There were 3 genes characteristic of EC, 7 were characteristic of HIV and 376 characteristic of Th17.We focused on 11 (upregulated) and 2 (downregulated) genes common between HIV, EC and Th17.

— ***Conclusions****:* Understanding the mechanisms of HIV-associated to Th17 is critical to strategically plan focused interventions.

— ***Key words:*** CD4+, HIV, EC, HLA.

— ***Abbreviations:*** Th17, T helper 17; CD4, cluster of differentiation 4; HIV, HIV+ naïve patients; EC, elite controller; HLA, human leukocyte antigen.

INTRODUCTION

Th17 cells are the most recent subset of T helper (Th) family, defined by the secretion of IL-17, and IL-10 family cytokine (IL21, IL22 and IL26)[1]. The polarizing cytokines TGF-β along with IL-6, IL-21 and IL-23 are responsible for differentiation, amplification and stabilization of the Th17 cells respectively[1-3]. Th17 development is independent of both IFNγ and IL-4, cytokines required for Th1 and Th2 maturation, respectively. TGFβ and IL-6 work in synergy to induce the maturation of Th17 cells, and the addition of TNFα and IL-1 further increases this effect[4]. IL-23, which shares its p40 subunit with IL-12, was the first cytokine to be shown to selectively regulate IL-17A expression[5]. It has now been established that while TGFβ and IL-6 direct initial maturation of Th17 cells, IL-23 regulates

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their expansion as they acquire expression of the IL-23 receptor. Functionally, Th17 cells play a role in host defense against extracellular pathogens by mediating the recruitment of neutrophils and macrophages to infected tissues. Moreover, it is becoming evident that aberrant regulation of Th17 cells may play a significant role in the pathogenesis of multiple inflammatory and autoimmune disorders[6-9]. Through the potent induction of cytokines, Th17 cells can bridge innate and adaptive immunity and attract other proinflammatory cytokines, chemokines, metalloproteinases from various tissues and Th cells to the sites of infection[10]. Although there are ample evidences regarding their involvement in both protective and harmful immune responses in various disease models, their function in HIV infection is not yet fully characterized. HIV specific Th17 cells were recently demonstrated in peripheral blood by few groups, proposing a possible role of these cells in host defense against HIV[10,11]. It was shown that HIV infection is associated with a significant increase in IL-17 production in both CD4+ and CD4− T cells in peripheral blood[11]. Moreover, lower frequencies of Th17 and Th1 cells were reported in the peripheral blood of aviremic HIV+ subjects on antiretroviral therapy (ART), but those of ART-naive patients were comparable with uninfected healthy subjects[12]. The Elite Controllers (EC) mare a group of HIV-infected patients who are able to spontaneously control viral infection in the absence of antiretroviral therapy. To date, these patients have an immunological profile which remains uncharacterized. Based exclusively on the serological criteria, the EC have a low viral load, a higher number of CD4 compared to the HIV patient, and show increased survival. Since these patients have a higher survival and fail to control the virus, they represent the best candidates for comparative studies with HIV patients. With the progressive loss of CD4+ T cells during HIV infection, the dysfunction in the T cell compartments is reflected by cytokine expression levels[13,14]. HIV infection disrupts cytokine production and function of the CD4+ T helper and CD8+ cytotoxic T cells with disease progression mainly associated with a Th2 cytokine profile despite some contradictory references[15-17]. The cytokines mainly expressed during HIV infection are IL1b, IL6, Tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ) and IL-10. Measuring these cytokines gives an indication of the degree of immune activation (elevated levels of TNF-α, IL-6 and IL-1), the extent of the immune response and disease progression.

In this study, we have performed a comparative analysis of the TH17 immunological profile of CD4+ T cells from Healthy individuals, HIV patients with a high viral set point and EC.

MATERIALS AND METHODS

Bioinformatic analysis

We interrogated two microarray datasets obtained from the NCBI Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) under accession number GSE18233[18] and GSE54627[19] in order to define the th17 gene profile characterizing HIV+ naive patients and Elite Controllers (EC) CD4 T cells and healthy individuals. The Th17 cells gene pathway obtained after CD4 T cell differentiation from TH0 to Th17 was used as a control (GSE54627).

For the present analysis, ART-naïve patients were selected and stratified using the viral set point as parameter. HIV patients from the upper quartile were considered in this study as HIV group, which included 27 subjects. The EC group, defined in Rotger et al, corresponded to the subjects in the 25th percentile and included 16 patients. Eight samples from 3 healthy controls served as control population. Transcriptiomic profile of Th17 cells was obtained using the GSE5427 dataset, which included data from 4 human naïve T cells differentiated in vitro in Th17 cells, and used as a control. Complete experimental details can be retrieved in the publication by Touzot et al. The MultiExperiment Viewer (MeV) software was used to identify differentially expressed genes and to generate expression heatmaps. In cases where multiple probes insisted on the same NCBI GeneID, we used those with the highest variance. In order to identify genes commonly modulated in HIV patients, Elite Controllers and Th17 cells, Venn Diagrams were drawn using the web-based utility Venn Diagram Generator (http://www.bioinformatics.lu). Weighted Gene Networks were built for the commonly modulated genes using String DB software (http://string-db.org/). String DB reports a global view of interactions between genes, based on functional interconnection among genes derived from published experimental data and bioinformatic predictions. For each genes, weight is calculated using linear regression, therefore, the more the genes are interconnected, the shorter the edge linking them.

RESULTS

The top 10 upregulated and downregulated genes in TH17 *in vitro* differentiated cells and CD4+ T cell of HIV, EC and Healthy

Microarray analysis showed the characteristic gene expression pattern for the CD4+ T cells from HIV+ patients (HIV), Elite Controllers (EC) and healthy subjects, as well as for *in vitro* differentiated Th17 cells (Figure 1 A,B). Our results show that the top 10 upregulated genes in Th17 were the following: DNAJC12 (DnaJ (Hsp40) homolog, subfamily C, member 12); PRG4 (proteoglycan 4); IL26 (interleukin 26); RAB13 (member RAS oncogene family); IL23R (interleukin 23 receptor); TSHZ2 (teashirt zinc finger homeobox 2); KNOP1 (chromosome 16 open reading frame 88); ZBED2 (zinc finger, BED-type containing 2); ELL2 (elongation factor, RNA polymerase II, 2); LTA [lymphotoxin alpha (TNF superfamily, member 1)]. Surprisingly, only IL26 (third position) and IL17F (56 position), two typical markers for Th17, were among of the top 100 most upregulated. Moreover, the top 10 downregulated genes in the Th17 were the following: LRRN3 (leucine rich repeat neuronal 3); IPCEF1 (interaction protein for cytohesin exchange

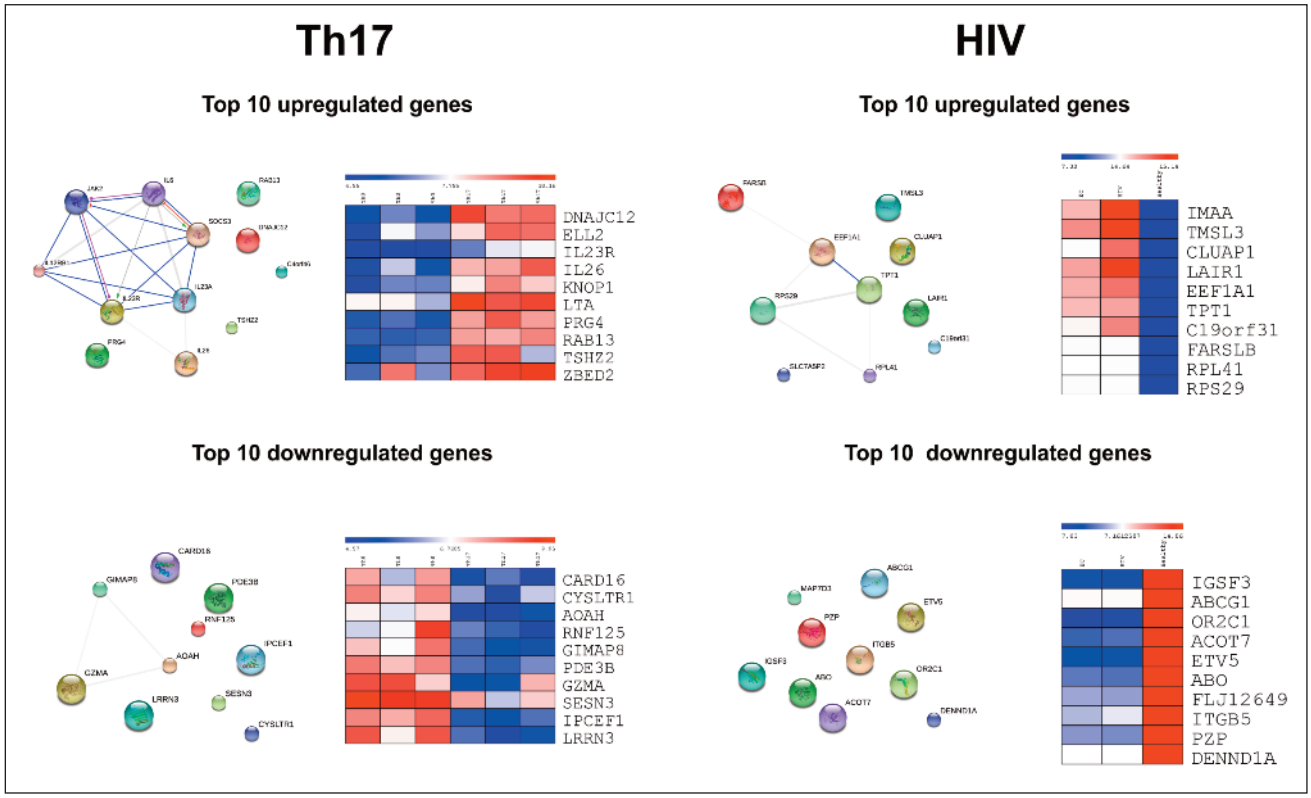


Figure 1. The top 10 upregulated and downregulated TH17 genes in *in vitro* differentiated TH17 cells and CD4+T cells from HIV, EC and Healthy subjects. Genes more expressed in CD4+ T cells from Healthy donors, HIV+ patients (HIV), Elite Controllers (EC) and T helper 17; Hierarchical clustering of the repertoire of Cytokine expressed in CD4+ T cells from Healthy donors, HIV+ patients (HIV) and Elite Controllers (EC). Unsupervised hierarchical clustering and Euclidean distance were used for similarity measurement. Gene expression values are colour coded from bright red (most upregulated) to dark blue (most downregulated).

factors 1); SESN3 (sestrin 3); GZMA [granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3)]; PDE3B (phosphodiesterase 3B, cGMP-inhibited); GIMAP8 (GTPase, IMAP family member 8); AOAH (acyloxyacyl hydrolase (neutrophil); RNF125 (ring finger protein 125, E3 ubiquitin protein ligase); CYSLTR1 (cysteinyl leukotriene receptor 1); CARD16 (caspase recruitment domain family, member 16).

We also analyzed the top 10 genes upregulated in HIV CD4+ T cells (HIV, EC vs healthy individuals) and the following were identified: IMAA [solute carrier family 7 (amino acid transporter light chain, L system)]; TMSL3 (thymosin beta 4, X-linked pseudogene 8); CLUAP1 (clusterin associated protein 1); LAIR1 (leukocyte-associated immunoglobulin-like receptor 1); EEF1A1 (eukaryotic translation elongation factor 1 alpha 1); TPT1 (tumor protein, translationally-controlled 1); C19orf31 (putative uncharacterized protein); FARSLB (phenylalanyl-tRNAsynthetase, beta subunit); RPL41 (ribosomal protein L41); RPS29 (ribosomal protein S29).

Additional evidence comes from the top 10 downregulated genes in HIV CD4+ T cells, which were represented by: IGSF3 (immunoglobulin superfamily, member 3); ABCG1 (ATP-binding cassette, sub-family G (WHITE), member 1); OR2C1 [olfactory receptor, family 2, subfamily C, member 1; Odorant receptor (Potential)]; ACOT7 (acyl-CoA thioesterase 7); ETV5 (ets variant 5); ABO (transferase A, alpha 1-3-N-acetylgalactosaminyltransferase); FLJ12649 alias MAP7 (MAP7 domain containing 3); ITGB5 (integrin, beta 5); PZP (pregnancy-zone protein); DENND1A (DENN/MADD domain containing 1A).

Common genes in CD4+ T cells from HIV, EC and *in vitro* differentiated Th17 cells

The gene expression analysis showed that 402, 405 and 443 genes were significantly upregulated in HIV, EC and Th17 cells, respectively, while 380, 376 and 378 were significantly downregulated in HIV, EC and Th17 cells respectively (Figure 2). Among the upregulated genes, 375 were common between HIV and EC, while 11 were in common between HIV, EC and in vitro differentiated Th17 cells. There were 30 genes characteristic of EC, 27 characteristic of HIV and 432 characteristic of Th17 (Supplementary material 1). Among the downregulated genes, 371 were common to HIV and EC and 2 common genes between HIV, EC and Th17 cells. There were 3 genes characteristic of EC, 7 were characteristic of HIV and 376 characteristic of Th17 (Supplementary material 1).

The 11 common upregulated genes between HIV, EC and in vitro differentiated Th17 cells were the following: BTG1 (B-cell translocation gene 1, anti-proliferative), C6orf48 (chromosome 6 open reading frame 48), CD81 (CD81 molecule), FTL (ferritin, light polypeptide), JUN (jun proto-oncogene), NFKBIA (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor,

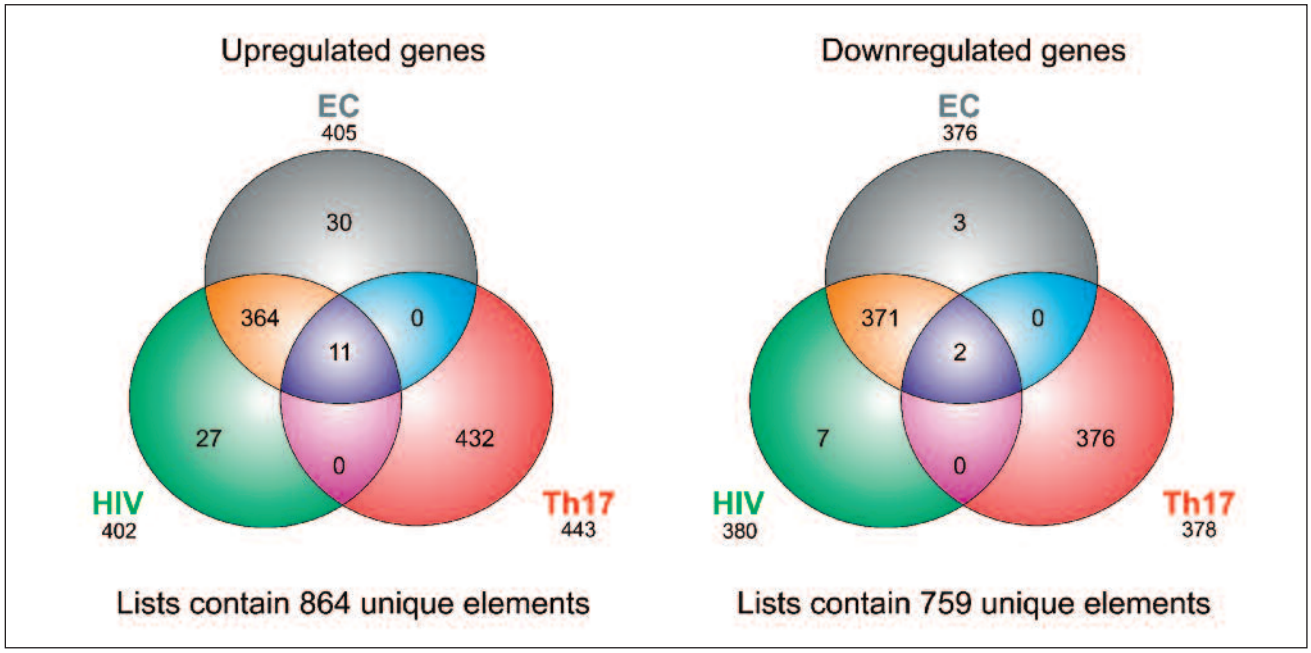


Figure 2. Venn diagram analysis for common upregulated and downregulated genes in HIV, EC and *in vitro* differentiated TH17 cells. The Venn diagram show the common upregulated and downregulated genes in HIV, EC and *in vitro* differentiated TH17 cells. The analysis showed that 402, 405 and 443 genes were significantly upregulated in HIV, EC and Th17 respectively, while 380, 376 and 378 were significantly downregulated in HIV, EC and Th17 respectively, as compared to healthy and Th0, respectively.

alpha), PSMD12 (proteasome, prosome, macropain) 26S subunit, non-ATPase), RGS2 (regulator of G-protein signaling 2, 24kDa), S100A10 (S100 calcium binding protein A10), TNFAIP3 (tumor necrosis factor, alpha-induced protein 3) and S100A6 (S100 calcium binding protein A6) (Figures 3 and 4). The BTG1 is a member of an anti-proliferative gene family that regulates cell growth and differentiation. The encoded protein interacts with several nuclear receptors, and functions as a coactivator of cell differentiation.

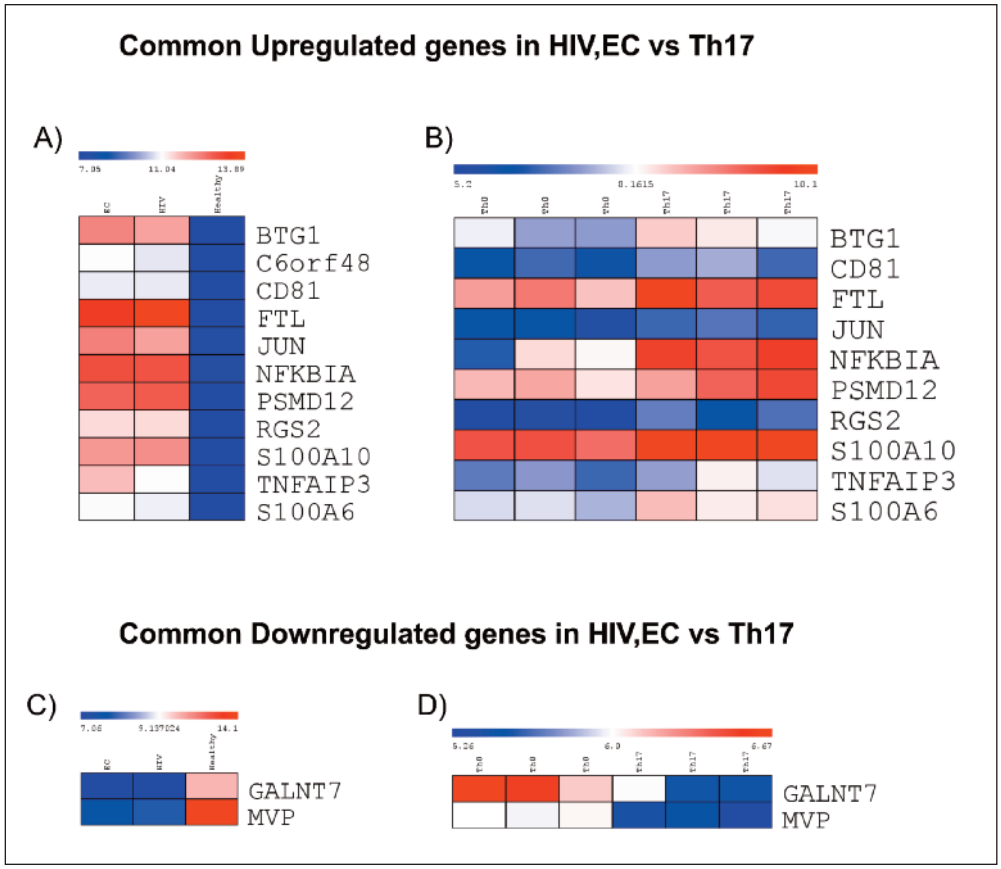


Figure 3. Heat map of common upregulated and downregulate genes in HIV, EC, Healthy and *in vitro* differentiated TH17 cells. *A-B,* The Heat map show the 11 significant common upregulated genes in HIV, EC, Healthy and Th17 vs TH0 cells. *C-D,* The two significant common downregulated genes in HIV, EC, Healthy and Th17 vs TH0 cells. Gene expression values are colour coded from bright red (most upregulated) to dark blue (most downregulated).

As for CD81, this gene is a member of the transmembrane 4 superfamily, also known as the tetraspanin family. Most of these members are cell-surface proteins that are characterized by the presence of four hydrophobic domains. The proteins mediate signal transduction events that play a role in the regulation of cell development, activation, growth and motility. This encoded protein is a cell surface glycoprotein that is known to complex with integrins. This protein appears to promote muscle cell fusion and support myotube maintenance. Also it may be involved in signal transduction. This gene is localized in the tumor-suppressor gene region and thus it is a candidate gene for malignancies.

Connected to intracellular iron storage protein in prokaryotes and eukaryotes, FTL is one of the most prominent element. A major function of ferritin is the storage of iron in a soluble and non toxic state. Defects in this light chain ferritin gene are associated with several neurodegenerative diseases and hyperferritinemia-cataract syndrome.

Among the transcription factors we identified JUN. This gene is the putative transforming gene of avian sarcoma virus 17. It encodes a protein which is highly similar to the viral protein, and which interacts directly with specific target DNA sequences to regulate gene expression.

NFKBIA gene encodes a member of the NF-kappa-B inhibitor family, which contains multiple ankrin repeat domains. The encoded protein interacts with REL dimers to inhibit NF-kappa-B/REL complexes which are involved in inflammatory responses. The encoded protein moves between the cytoplasm and the nucleus via a nuclear localization signal and CRM1-mediated nuclear export. Mutations in this gene have been found in ectodermal dysplasia anhidrotic with T-cell immunodeficiency autosomal dominant disease.

The 26S proteasome (PSMD12) is a multicatalytic proteinase complex with a highly ordered structure composed of 2 complexes, a 20S core and a 19S regulator. The 20S core is composed of 4 rings of 28 non-identical subunits; 2 rings are composed of 7 alpha subunits and 2 rings are composed of 7 beta subunits. The 19S regulator is composed of a base, which contains 6 ATPase subunits and 2 non-ATPase subunits, and a lid, which contains up to 10 non-ATPase subunits. Proteasomes are distributed throughout eukaryotic cells at a high concentration and cleave peptides in an ATP/ubiquitin-dependent process in a non-lysosomal pathway. An essential function of a modified proteasome, the immunoproteasome, is the processing of class I MHC peptides. This gene encodes a non-ATPase subunit of the 19S regulator.

Among the molecules strictly regulating the GTPase, we found G Regulator of G protein signaling (RGS) belonging family members regulatory molecules that act as GTPase activating proteins (GAPs) for G alpha subunits of heterotrimeric G proteins. RGS proteins are able to deactivate G protein subunits of the Gi alpha, Go alpha and Gq alpha subtypes. They drive G proteins into their inactive GDP-bound forms. Regulator of G protein signaling 2 belongs to this family.

Among the molecules closely related to cancer, we have found S100A10 and S100A6. The protein encoded by this gene is a member of the S100 family of proteins containing 2 EF-hand calcium-binding motifs. S100 proteins are localized in the cytoplasm and/or nucleus of a wide range of cells, and involved in the regulation of a number of cellular processes such as cell cycle progression and differentiation. This protein may function in exocytosis and endocytosis.

Belonging to the TNF family there was TNFAIP3. This gene was identified as a gene whose expression is rapidly induced by the tumor necrosis factor (TNF). The protein encoded by this gene is a zinc finger protein and ubiqitin-editing enzyme, and has been shown to inhibit NF-kappa B activation as well as TNF-mediated apoptosis. The encoded protein, which has both ubiquitin ligase and deubiquitinase activities, is involved in the cytokine-mediated immune and inflammatory responses. Several transcript variants encoding the same protein have been found for this gene.

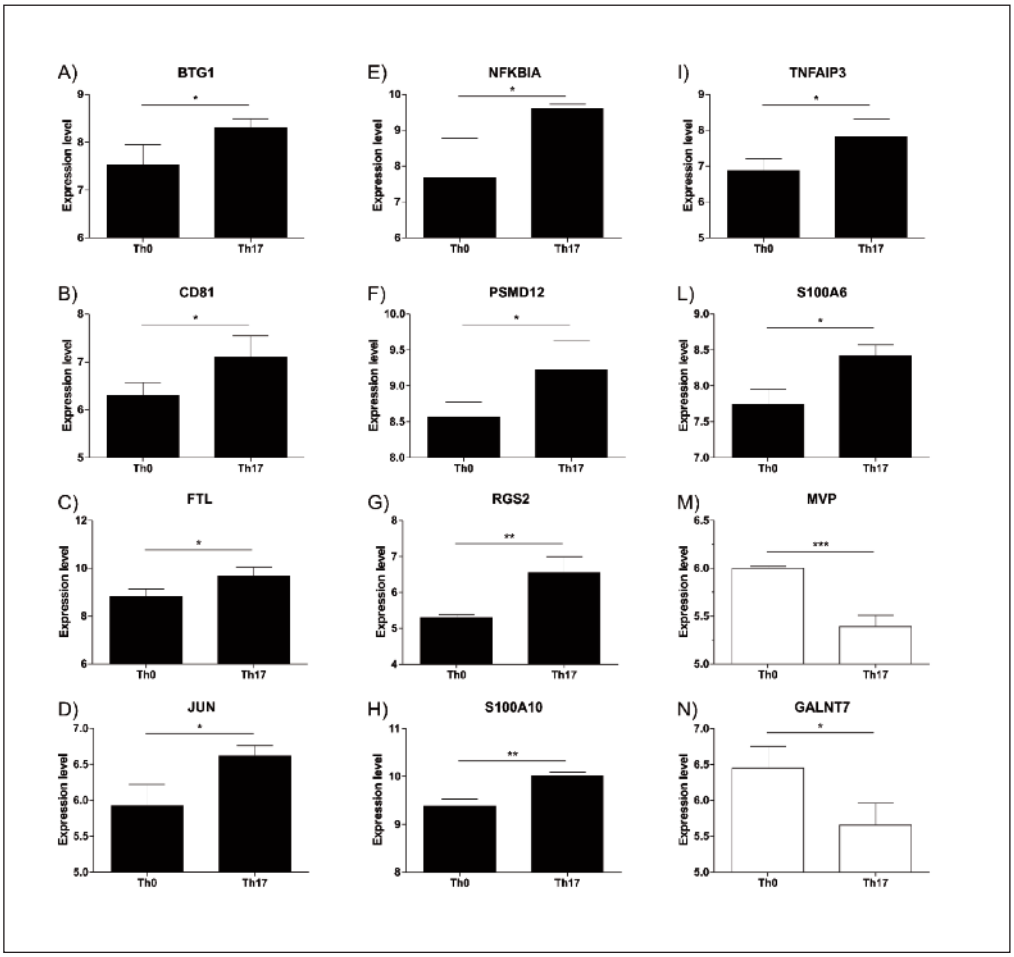
The 2 common downregulated genes between HIV, EC and Th17 were the following: GALNT7 (UDP-N-acetyl-alpha-D-galactosamine) and MVP (major vault protein).

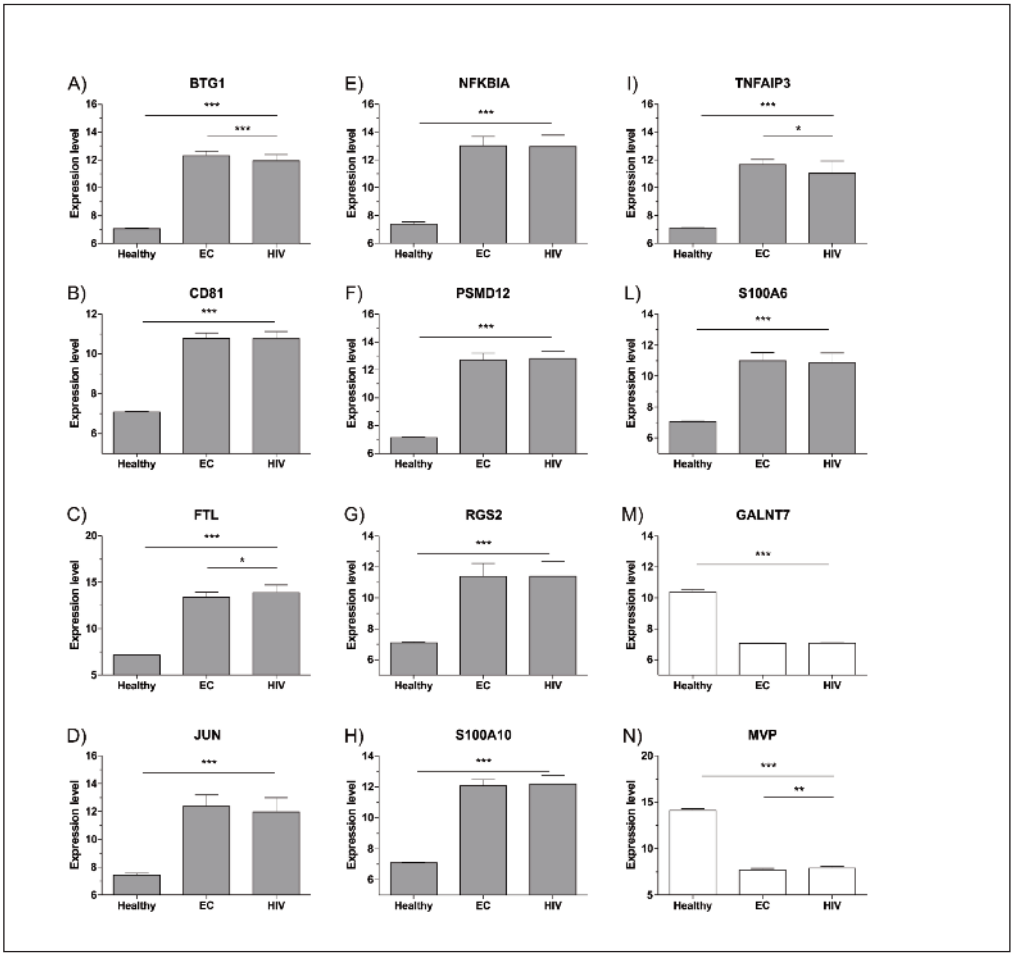
GALNT7 encodes GalNAc transferase 7, a member of the GalNAc-transferase family. The enzyme encoded by this gene controls the initiation step of mucin-type O-linked protein glycosylation and transfer of N-acetyl-galactosamine to serine and threonine amino acid residues. This enzyme is a type II transmembrane protein and shares common sequence motifs with other family members. Unlike other family members, this enzyme shows exclusive specificity for partially GalNAc-glycosylated acceptor substrates and shows no activity with non-glycosylated peptides. This protein may function as a follow-up enzyme in the initiation step of O-glycosylation.

The other downregulated gene common to HIV, EC and Th17 was MVP. This gene encodes the major component of the vault complex. Vaults are multi-subunit ribonucleoprotein structures that may be involved in nucleo-cytoplasmic transport. The encoded protein may play a role in multiple cellular processes by regulating the MAP kinase, JAK/STAT and phosphoinositide 3-kinase/Akt signaling pathways. The encoded protein also plays a role in multidrug resistance, and expression of this gene may be a prognostic marker for several types of cancer. Alternatively spliced transcript variants have been observed for this gene.

Expression levels of 13 common significant regulated genes in HIV, EC and Healthy individuals

The Figure 5 shows the expression trend of the 11 upregulated and the two downregulated genes in CD4+ T cells of HIV, EC compared to the healthy. BTG1, FTL, TNFAIP were significantly more upregulated in EC compared to HIV+ ART naïve patients. MVP was significantly lower in EC as compared to HIV+ ART naïve patients.





Figures 4-5. Expression levels of 13 common significant regulated genes in HIV, EC, Healthy *in vitro* differentiated TH17 cells. The figure shows the expression trend of the 11 upregulated and the two downregulated genes in Th17 compared to Th0 (Figure 4) and CD4+ T cells of HIV, EC compared to the healthy. Unpaired two-tailed Student *t*-test was used to determine statistical significance.

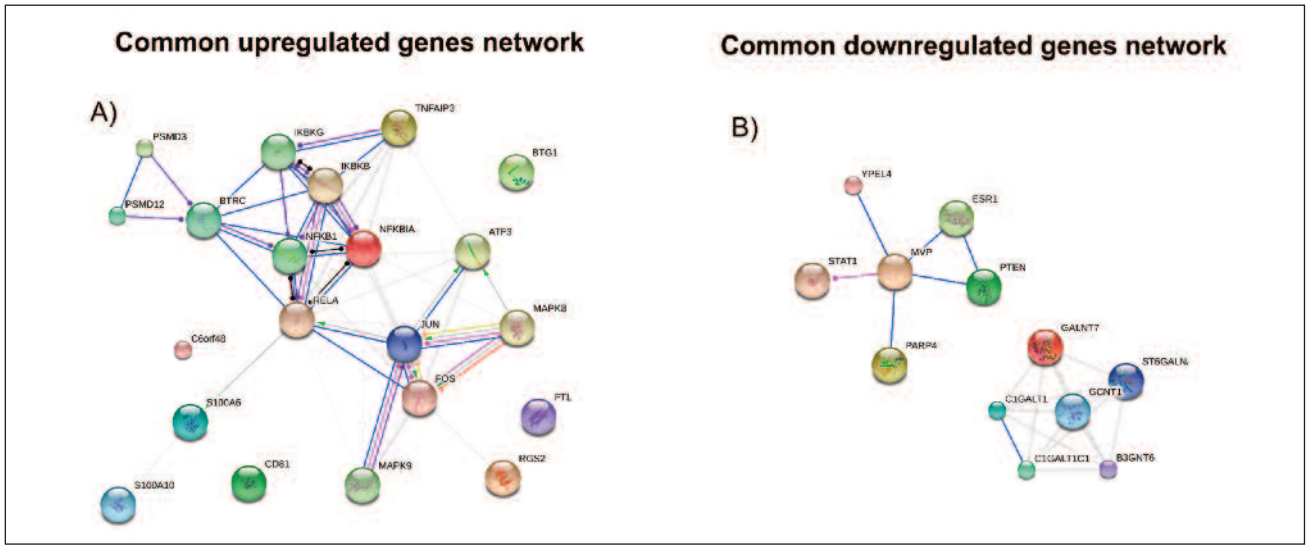


Figure 6. String network of common upregulated and downregulated genes in HIV, EC, Healthy and Th17. Differentially expressed genes are depicted: links have been predicted using STRING (http://string.embl.de/). Predicted interactions are depicted according to the type of available evidence. The interactions (see color labels) include direct (physical) and indirect (functional) associations; they are derived from four sources: genomic context, high-throughput experiments, conserved co-expression, and previous knowledge from literature. doi: 10.1371/journal.ppat.1000781.g002.

Network analysis of common upregulated and downregulated genein HIV, EC and Th17

Genes Networks were constructed for the 11 upregulated genes and the two downregulated genes common in HIV, EC and Th17 (Figure 6). This type of analysis has provided us with new information about the genes closely and significantly related to the 11 and 2 candidates found by the above analysis. We showed that BTG1, FTL and CD81 did not show connections between the genes examined. Conversely, JUN, NFKBIA, PSMD12, RGS2, S100A10, TNFAIP3 and S100A6 presents numerous functional connections.

DISCUSSION

In this paper we have focused to the TH17 genes commonly modulated in CD4+ T cells from HIV patients, using *in vitro* differentiated Th17 cells gene profile as a control, in order to identify signature molecules related to the disease. Surprisingly, the analysis of the data showed an almost complete overlap between the HIV-infected and EC patients, which cannot easily explain the different responses to HIV infection of these two group of patients. Only 27 genes characterized the HIV patients. These 27 genes belonged to immunological response and membrane protein (supplementary table).The EC were characterized by 30 genes, belonging to cell proliferation. The Th17 in vitro differentiated cells showed to be characterized by 432 genes not in common with HIV and EC. By looking at the downregulatedgenes, only 7 genes were found in the CD4 from the HIV patients, 3 genes in the CD4 from EC patients and 376 in the Th17 cells. The common downregulated genes among these three groups were only 2 (GALNT7 and MVP).

The analysis of the 11 upregulated genes common to the three groups showed that most of them are co-expressed in the human central nervous system (CNS)[20] and modulated in response to bacterial infection[21]. The co-expression of these genes in bacterial infections could be justified by the immune activation of CD4 cells to the virus. It is known that 5 of the 11 genes present a genetic interaction[22]. These interactions partly explain their co-expression in the HIV, EC and Th17.

The analysis of the 2 downregulated genes common to the HIV, EC and Th17 showed no direct network interaction. As for MVP, it was shown that this molecule interacts with PARP4 (linked to the hepatocellular carcinoma[23], in turn connected to GALNT12. Roth RB et al[24] showed the co-expression of these molecule in the CNS[20]. There are no relations between GALT7 and HIV or viral infections. This molecule is only closely related to tumor growth.

CONCLUSIONS

A T-cell repertoire dysfunction characterizes HIV infection, but the pathogenic processes underlying it remain unclear. Disease progression is probably due to a profound dysregulation of Th1, Th2, Th17 and Treg patterns, however the superimposable features between high viremic individual and EC do not allow for the precise characterization of the mechanisms of viral replication, immune evasion and immune system viral control.

Conflict of interest

The Authors declare that they have no conflict of interests.

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