Which One of the Human Immune Genes are more Involved in Against HTLV-1 Infection?

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Research

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Abstract

Background: Human T-lymphotropic virus type 1 (HTLV-1) is a main member of type C retrovirus. This virus was first isolated from cutaneous T-cell lymphoma cases. Among all infected individuals, only 5% of cases progress to acute form, and 4% of them to chronic form. Nevertheless, about 90% of patients remain asymptomatic. Adult T cell leukaemia/lymphoma (ATLL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) are accounted as acute and chronic forms of disease respectively.

Methods: The gene expression profile of CD4+ T cells in four groups, healthy donors, asymptomatic HTLV-1 carriers (ACs), HAM/TSP (HTLV-1-associated myelopathy/tropical spastic paraparesis), and ATLL (Adult T-cell leukemia/lymphoma) based on GPL9686 platform was evaluated.

Results: According to Gene enrichment analysis, it was determined that hub genes in present study are able effect on various pathways such as apoptosis, proliferation and T cell activation, Ras signaling pathway, integrin signaling pathway, P53 signaling pathway, CCKR, TLR, FGF, DNA Damage, MAPK signaling, integrated cancer, Caspase, NF- κ B, BCL-2 family, survival complex, breast cancer, Pancreatic cancer.

Conclusions: Overall, based on scientific results in the present study, it seems the immune system via stimulation of biological processes such as cell survival, proliferation, CTLs exhaustion, and apoptosis concomitant, caused immortalization of HTLV-1 infected CD4+ T cells.

1. Background

Like some oncogenic bacteria such as *Helicobacter pylori* (*H. pylori*), Human T-cell leukemia virus-I (HTLV-1) is among the oncogenic viruses, and in other words, is the most cariogenic virus (1). Despite the lack of attention, HTLV-1 is known as one of the most oncogenic viruses for human (2). Adult T cell leukaemia/lymphoma (ATLL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) are accounted as two famous forms of infections which are caused by this virus (3). The virus identified by Galo group in 1979, but despite about 4 decades of research on the integrity of this virus, but still there is no a reliable therapeutic method for treatment of its infections (4). In addition, HTLV-1 virus is involved in the some autoimmune diseases (immune system attacks parts of own body by mistake) including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Sjogren's syndrome (SS) (5). In the patients involved with HAM/TSP disease, it seen a high production of pro-inflammatory cytokines and chemokines such as CXCL9, CXCL10, IFN- γ , and TNF- α (6). Nevertheless, the patients involved with ATLL, have high levels of immunosuppressive cytokines such as IL-10 and TGF- β (7). In the present study, we identified immune genes which are more affected than other genes following HTLV-1 infection. These gene include IL-10, IL-6, JAK, IL-15, SOCS1, TNFR6, FOXP3, PD-1, FADD, Ras, BCL2, Rb, RICTOR, RAC1, MAP2K4, BCL2A1, MAP1B, CXCR4, BRCA1, MSH2, ATM, and RIG1.

2. Methods

First, based on collected results from an international public database, The Gene Expression Omnibus Database. The database evaluated human immune-microarray with Accession number: GSE19080. Also, the

gene expression profile of CD4 + T cells in four groups, healthy donors, asymptomatic HTLV-1 carriers (ACs), HAM/TSP (HTLV-1-associated myelopathy/tropical spastic paraparesis), and ATLL (Adult T-cell leukemia/lymphoma) based on GPL9686 platform was evaluated. From 38 samples, 8 samples were healthy, and other samples were ACs (11 samples), HAM/TSP (12 samples), and ATLL (7 samples). Evaluated cell lines and providing patient details was better in this study compared to other microarray studies. Each of data was received with CEL format, and their quality was confirmed by the R software MetaQC package. All data were classified in three category including ATLL, ACs, and healthy individuals. In the next step, data was calculated by affy package, based on Log2, differentially expressed genes (DEGs), and fold change (FC) of datasets (FDR-adjusted p value < 0.05) (8). After that, by searching on Google Scholar, Scopus, and PubMed databases, related articles were studied, and gene expression variations of immune system during HTLV-1 infection were investigated. According to review of the literatures, it was determined that, 65 immune genes had variations, significantly; therefore, these genes were evaluated. Then, DGE and Log FC of considered genes was calculated. According to profile changes of considered genes, heatmap was constructed for healthy individuals, ACs, and ATLL groups. Following this step, a protein-protein interaction network (PPIN) including studied genes was provide through online server STRINGER. Finally, all 65 genes were evaluated in terms of Gene Enrichment and Gene ontology. Given that information, a signaling network was recommended based on the role of immune system changes in progression of HTLV-1 infection toward to ATLL.

3. Results

Studied genes in our research are listed in the Box 1, and other genes were deleted from study, due to lack of any significance in statistical test or lack of enough information.

Box 1
The names of 65 interfering immune genes during HTLV-1 infection

IL-6	IL-4	IL-2	TGF- β	IL-10
STAT5	STAT3	JAK	CD4	IL-13
SOCS1	NFKB1	IRF4	IL-12	IL-15
RORYt	FOXP3	Smad4	TNFR6	IFN- γ
Bak	Bad	Caspase 8	Caspase 3	PD-1
AP-1	MyD88	TP53	CytC	FADD
IRF5	IRF3	CREB	AKT	MAPK7
BCL2	Ras	PTEN	DAXX	Fas
EGF	RICTOR	Rb	CDK4	C-myc
MDM2	CDC42	RAC1	iNOS	Elk1
Tsc2	MAP1B	BCL2A1	JunD	MAP2k4
TLR5	NFAT	MSH2	BRCA1	CXCR4
SDF-1	RIG1	FGFR1	HSPG2	ATM

Regarding of assessments, it was cleared that in ATLL individuals compared with healthy ones, the expression of some of genes were upregulated, while other genes were dysregulated (Table 1).

Table 1
Expression level of 65 immune genes in ATLL subjects compared to healthy ones

Status	All 65 studied immune genes involved in ATLL infection							
Upregulated genes	IL-2	IL-13	STAT3	STAT5	IL-12	SDF-1	NFKB1	SCOS1
	PD-1	Caspase 3	Caspase 8	Bad	Bak	FADD	CytC	AP-1
	Ras	BCL2	C-myc	RICTOR	Elk1	RAC1	BCL2A1	Tsc2
	NFAT	HPG2	RIG1	IFN- γ	Fas	CXCR4		
Downregulated genes	IL-10	TGF- β	IL-4	IL-6	CD4	JAK	IL-15	IRF4
	Smad4	FOXP3	RORYt	TP53	MyD88	MAPK7	AKT	CREB
	IRF5	DAXX	PTEN	CDK4	Rb	EGF	iNOS	CDC42
	MAP2k4	JunD	MAP1B	BRCA1	MSH2	TLR5	ATM	FGFR1
	IRF3	MDM2	TNFR6					

Expression gene profile was almost exclusive in each of the three modes, healthy donors, ACs, and ATLL patients. Notably, between these gene, expression changes in some genes was clearer than others. These gene include IL-10, IL-6, JAK, IL-15, SOCS1, TNFR6, FOXP3, PD-1, FADD, Ras, BCL2, Rb, RICTOR, RAC1, MAP2K4, BCL2A1, MAP1B, CXCR4, BRCA1, MSH2, ATM, and RIG1 (Table 2, and Figure 1).

Table 2
Comparison of Logarithm Fold-Change (Log FC) in Normal, ACs, and ATLL groups with each other.

Gene	Normal vs. ACs	Normal vs. ATLL	ACs vs. ATLL
IL-10	-0.02	-1.82	-0.03
TGF- β	-0.9	-0.08	-0.27
IL-2	0.5	0.18	-0.46
IL-4	-0.09	-0.3	0.42
IL-6	-1.37	-0.22	0.05
IL-13	0.10	-0.02	-0.084
CD4	-0.4	-0.64	-0.24
JAK	-0.03	1.37	0.001
STAT3	0.4	-0.04	-0.48
STAT5	0.24	0.52	0.27
IL-15	-1.12	-1.58	-0.44
IL-12	0.02	0.27	0.24
IRF4	-0.40	0.39	0.79
NFKB1	0.75	0.54	-0.26
SOCS1	1.72	0.37	-1.34
IFN- γ	0.92	0.38	-0.54
TNFR6	-1.12	-0.66	0.26
Smad4	-0.24	-0.42	-0.33
foxp3	-0.79	-1.31	-0.52
RORYt	-0.37	-0.33	0.03
PD-1	0.40	1.21	0.80
Caspase 8	0.74	0.13	-0.60
Caspase 3	0.43	-0.07	-0.51
Bad	0.66	0.53	-0.13
Bak	0.19	0.20	0.01
FADD	0.12	1.91	1.52
Cytochrome C	0.02	0.76	-0.12
TP53	-0.46	0.51	-0.67

MyD88	-0.09	0.49	0.58
AP-1	0.74	0.65	-0.64
MAPK7	-0.25	-0.1	0.23
AKT	-0.23	-0.27	-0.04
CREB	-0.31	-0.57	-0.57
IRF3	-0.16	0.08	0.25
IRF5	-0.57	-0.99	-0.41
Fas	0.42	0.65	0.23
DAXX	-0.64	-0.54	0.09
PTEN	-0.30	-0.48	-0.18
Ras	1.16	-1.07	0.43
BCL2	0.66	-0.09	-1.48
C-myc	0.65	0.75	-0.57
CDK4	-0.45	-0.64	-0.18
Rb	-0.16	-1.63	0.84
RICTOR	0.46	1.41	0.95
EGF	-0.87	-0.17	0.002
Elk1	0.48	0.25	-0.23
iNOS	-0.16	-0.56	0.45
RAC1	1.16	1.40	0.24
CDC42	-0.02	-0.16	-0.14
MDM2	-0.87	-0.98	-0.09
MAP2k4	-0.08	0.99	1.07
JunD	-0.12	-0.19	0.01
BCL2A1	0.60	1.63	1.03
MAP1B	-0.68	-1.20	-0.54
Tsc2	0.55	0.65	0.25
CXCR4	1.73	2.33	0.59
BRCA1	-0.74	-1.38	-0.56
MSH2	-0.73	-1.05	-0.31

NFAT	0.53	0.73	0.2
TLR5	-0.08	0.85	0.94
ATM	-1.47	-2.36	-0.88
HSPG2	0.55	-0.27	-0.58
FGFR1	-0.62	-0.74	-0.84
RIG1	0.60	1.19	0.58
SDF-1	0.34	0.70	0.36

As well as, the genes that had been dysregulated in their expression in healthy group were compared to ATLL and ACs groups are listed in Table 3.

Table 3
Dysregulation of gene expression in healthy group compared to ACs and ATLL groups

Status	Gene manes							
Upregulated genes	IL-2	STAT5	IL-12	NFKB1	SOCS1	IFN-γ	PD-1	Caspase 8
	Bad	Bak	FADD	CytC	AP-1	Fas	C-myc	RICTOR
	Elk1	RAC1	BCL2A1	Tsc2	CXCR4	NFAT	RIG1	SDF-1
Downregulated genes	IL-10	TGF-β	IL-4	IL-6	CD4	IL-5	TNFR6	Smad4
	FOXP3	RORYt	MAPK7	AKT	CREB	IRF5	DAXX	PTEN
	CDK4	Rb	EGF	iNOS	CDC42	MDM2	JunD	MAP1
	BRCA1	MSH2	ATM	FGFR1				

The PPI network was constructed for prediction of role and relevance of immune system in progression toward to ATLL. This network included 71 nodes, 729 edges, clustering coefficient 0.66, and p value $< 1.0e^{-16}$ (Figure 2). The distance between each node was representative for interaction between that node with its adjacent nodes, and different colors are representative for this interaction based on different databases. According to received data from STRING database, it was found that the PPI network effects on various biological processes such as cell communication, cytokine signaling, signal transduction, cell death, protein kinase, and microtubule rearrangement. In this network, some elements such as signal transduction factors, MAPK, signaling death, PI3K, mTOR, and NF-κB in center of network surrounded by interleukins. On the other, based on scientific assessments it was clear that these processes occur at the nucleoplasm, cytosol, and cell membrane levels. In addition, 34 of these genes had an impact in pathogens cancer, and 14 of them in host-virus interaction.

According to Gene enrichment analysis, it was determined that hub genes in present study are able effect on various pathways such as apoptosis, proliferation and T cell activation, Ras signaling pathway, integrin signaling pathway, P53 signaling pathway, CCKR, TLR, FGF, DNA Damage, MAPK signaling, integrated cancer, Caspase, NF- κ B, BCL-2 family, survival complex, breast cancer, Pancreatic cancer (WikiPathways 2019, Panther 2016, and Jensen compartments). According to review of the scientific documentations, noted pathways play pivotal role in proliferation and transformation of cells, as well as in progression on immune cells toward ATLL (Figure 3).

Based on performed assessments, it was known that the main transcription factors which activated under the effect of these genes, are including E2F1, NFKB1, TP53, IRF1, RELA, GLI1, STAT1/3, PML, CEBPB, SMAD3, and JUN (Figure 4a and b). Also, by searching in miRTar Base database, it was found that some microRNA molecules such as miR-574-3p, miR-34a-5p, miR-146a-5p, miR-21-5p, and mir-223-3p can to be caused dysregulation in network (Figure 4c).

Finally, in order to determination of effects of immune gene changes on ATLL infection, a signaling network was drew based on received Gene ontology information from KEGG, Wiki pathway, and Panther databases. This pathway drew with regards to hub genes and proteins that have the most interaction with them. The basis of this network was on signaling pathways such as NF- κ B, PI3K-Akt, mTOR, MAPK, TP53, Ras, apoptosis, DNA damage, and cell cycle. Considering the results of this study, the components of immune system by affecting processes such as inflammation, apoptosis, DNA damage, cell proliferation, T cell activation, invasion, angiogenesis, cell survival, and cell migration cause the progression of HTLV-1 towards ATLL cancer (Figure 5).

The results of Gene enrichment showed that some of microRNAs play pivotal role in regulation of our studied genes (hub genes). Between these elements, hsa-miR-574 is considered as an appropriate candidate for prediction of ATLL cancer (9-11). Also, based on Cui et al. studies, hsa-miR-574 can be effective on treatment of colorectal cancer (10). Based on Garcia et al. studies, it was found that hsa-miR-146a can via concomitant of BRCA1 expression has both preventive and therapeutic roles in breast and ovarian cancers (11). Another element is hsa-miR-21 can stimulate proliferation of tumor mass, and concomitant of activation of this molecule leads to tumor metastases (12). Using by Kaplan-Meier Plotter database, we assessed the important of microRNAs in prognosis of cancer, and according of collected results, the changes of these molecules can be accounted as suitable candidates for prognosis of tumors (Figure 6).

4. Discussion

CD4 + T cells play a critical role in HTLV-1 infection and HTLV-1 preferentially infects these cells (13). Despite four decades of researches on HTLV-1, many ambiguity remain about the pathogenicity mechanism and key proteins involved in diverse pathological pathways. In this study, we investigated the gene expression profile of CD4 + T cells in healthy donors, asymptomatic HTLV-1 carriers (ACs), and ATLL based on GPL9686 platform. Among 65 immune genes studied (Box1), we identified immune genes which are more affected than other genes following HTLV-1 infection including: IL-10, IL-6, JAK, IL-15, SOCS1, TNFR6, FOXP3, PD-1, FADD, Ras, BCL2, Rb, RICTOR, RAC1, MAP2K4, BCL2A1, MAP1B, CXCR4, BRCA1, MSH2, ATM, and RIG1. These genes affect on difference processes of immune system such as inflammation, apoptosis, DNA damage, cell

proliferation, T cell activation, invasion, angiogenesis, cell survival, and cell migration. Based on various studies, several changes in the cytokine/cytokine receptor signaling cascades are altered in HTLV-I-infected cells (14). It has been shown that the proliferation of HTLV-1 CD4 + T cells is due to JAK/STAT signaling pathway in response to some interleukins, specifically IL-2, IL-6, and IL-15 (15–17). The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway plays critical roles in orchestrating of immune system, especially cytokine receptors (18). The activation of this pathway leads to lymphocyte proliferation. Interleukin-6 (IL-6) is a multifunctional cytokine with a pleiotropic effect on inflammation, immune response, and hematopoiesis (19). The result of our study show that the upregulated of IL-6 gene expression in ATL patients compared to other groups, ACs and healthy donors. It has been reported that the Tax protein involved in the constitutive expression of IL-6 in cells infected with HTLV-I (20). Moreover, previous studies demonstrated that in ATL patients, serum level of IL6 are significantly higher than in the AC's and healthy control and survival decrease with increasing in IL6 (21). Several studies showed that the expression of both IL-15 and IL-15 receptor increased in HTLV-I-transformed cells lines (22, 23). Azimi et al. (24, 25) demonstrated that the IL-15 promoter is transactivated by Tax and the level of IL-15 mRNA is increased 3–4-fold in HTLV-I-transformed cells lines. In consistent with observations of Mariner et al. (26), Pise-Masison et al. (27) showed that the level of IL-15R elevated 5–10-fold in the HTLV-I-infected cell samples. Also, in the present study, it was concluded that the expression level of IL-10, TGF- β , and FOXP3 in ATLL cases had increased compared to other groups, ACs and healthy donors. It seems that, increase in expression of IL-10, TGF- β , FOXP3 and PD-1 caused to induction of production of T regulatory cells, immune-suppression and CTLs exhaustion. ATLL is associated with high levels of IL-10 and TGF- β . These immunosuppressive cytokines could promote a protumoral micro-environment. In one study demonstrated that the levels of IL-10 increased in sera from ATL patients compared with sera from healthy subject. Moreover, IL-10 is constitutively produced by ATL cells and HTLV-I-infected cell lines (28). In recent study it has been shown that the anti-inflammatory cytokine IL-10 and its downstream signals through the STAT3 and IRF4 pathways, potentially act as a switch for proliferation in HTLV-1-infected cells (29). It is suggested that an importance function of IL-10 in ATL may be inhibitory activities on macrophages and Th1 and also as a means of escaping host defenses. It has been implicated that the negative regulatory programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) pathway has an important role in the induction of CTL exhaustion during chronic viral infection and tumor (30–32). According to previous studies, suppression of immune responses and CTLs exhaustion lead to progression of disease to ATLL (33). In one study, Kozako et al. demonstrated that the PD-1 expression was significantly up-regulated on lymphocytes in ACs and ATLL patients compared to non-HTLV-1-infected individuals (33). In the present study, our result showed an increase in the LogFC of PD-1 in normal people Vs ATLL patient. Then the activity of PD-1/PD-L1 pathway during persistent viral infection may induce the exhausted of CTLs in HTLV-1 infected individuals, which may lead to immune evasion in ACs and ATLL patients. DNA damage also is one of the most important predisposing factors for tumor (34). In our research, expression level of BRCA1 and ATM genes had increased in ATLL patients. these genes are accounted as one of most important biomarkers which upregulated during the DNA damage in this group and defect in BRCA1 and ATM leads to DNA replication errors and cancer growth (35, 36). Breast cancer type 1 susceptibility protein (BRCA1) is a tumor suppressor gene that encodes a nuclear phosphoprotein, which is involved in repair damaged DNA and maintain genome stability. It has been shown that the expression of BRCA1 gene in ATLL patients is significantly reduced compared to normal individuals due to the effects of TAX protein and it is rationally in favor of increasing the tumor state (37). ATM (ataxia telangiectasia) gene like BRCA1

recognizes DNA damage or broken DNA strands. During DNA damages several phosphoproteins of the DDR pathway (H2AX, ATM, CHK1-2, P53, BRCA1) activated that lead to arrest the cell cycle transiently or lead to apoptosis and senescence but it has been demonstrated that the Tax inhibits the DDR machinery by sequestering key signaling pathway components (38). So, in infected people, the expression level of the ATM gene is higher than normal individuals, which is as follows: ATLL > asymptomatic carriers > normal peoples (39). DNA mismatch repair protein Msh2 also known MSH2 is a tumor suppressor gene which involved in many different forms of DNA repair (40). In line with other studies (41), in the present study, it appears that the expression of this gene is decreased in AC and ATLL. Apoptosis play an critical role in destroying malignant cells (42). It has been demonstrated that in HTLV-1 infection, the virus through Tax, enhances expression of family inhibitor of apoptotic BCL2 and Bcl-xL (43, 44) and suppress expression Bax gene which have role in inducing apoptosis (45). In this regard, our result showed that the expression level of these genes and anti-apoptosis markers (i.e. BCL2, CytC, and BCL-XL) had been upregulated in ATLL. Moreover, in normal individuals compared to asymptomatic carriers with a LogFC = 0.66, indicating an increase in BCL activity in normal individuals and consequently suppression of apoptosis. Various studies showed that BCL2A1 overexpressed in hematological malignancies and solid tumors and may contribute to tumor progression (46). In addition, BCL2A1 by decrease in apoptosis and MDM2 by containment of TP53 caused stimulation of CDKs and protection of cell survival. Regarding of assessments in present study, it was cleared that the expression of BCL2A1 were upregulated in ATLL individuals compared with healthy ones. FADD (Fas associated via death domain) is a cytoplasmic protein that has an important role in apoptosis (47). It has been demonstrated that HTLV-1 transactivator protein Tax inhibits Fas-mediated apoptosis by induction of c-FLIP through activation of NF- κ B, as a negative regulator of apoptosis by binding to the DED of FADD (48). Our result indicated that the expression of the FADD is higher in normal people than ATL patient (log FC: 1.99) and therefore the level of apoptosis in ATL patient is decreased. Another protein that affected by Tax is Ras. Ras family proteins have a key role in control intracellular signaling networks. Moreover Ras regulated different processes such as actin cytoskeletal integrity, cell differentiation, cell proliferation, apoptosis, and cell migration (49). It has been reported that Ras family proteins are often deregulated in cancers, leading to increased invasion and metastasis, and decreased apoptosis (50). HTLV-1 infected cells increased RAS expression follow TAX expression, which increase sensitivity to apoptosis by using the antagonist Farnesyl thiosalicylic acid (51). In our study the expression of the RAS gene have been shown an increase in asymptomatic carrier as compared to normal individual and in normal individuals it was less expressed in lymphoma patients. Accordingly, during HTLV-1 infection the expression of TAX as follow as Ras were increased, leading to the proliferation and transformation of cells into malignancies and resistance to apoptosis (52). One of the hallmarks features of tumors is tissue invasion and chemokines and their receptors play a key role (53). Moreover, It is well known that chemokines and their receptors have a role in pathogenesis of HTLV-1 such as: inflammation in the central nervous system (CNS) in cases of HAM/TSP, T cell immortalization and tissue infiltration (54). Several chemokine receptors has been identified in ATLL including: CCR4 (55), CCR7 (56), CCR8 (54), and CXCR4 (57). One of chemokine receptor which is overexpressed in HTLV-1 infection is CXCR4 which interaction with stromal cell-derived factor 1 (SDF1)/CXCL12 play a paramount role in the migration of ATL cells (56). In this study our result indicated that the expression of CXCR4, FGF, EGF, RAC1, and MAPKs were increased in ATLL group and confirmed this hypothesis. Moreover, interestingly, it has been demonstrated that the absence of Rapamycin-insensitive companion of mTOR (RICTOR) increased the expression of CCR2, CCR4 and CXCR4, which associated with

the homing and migration of T-cells (58). RICTOR is a key component of the PI3K/AKT/mTOR signal transduction pathway an essential component of the mTORC2 of mTOR complex (59). It is indicated that the RICTOR down-regulation suppresses cell proliferation and tumor formation (60, 61). Log Fc in RICTOR gene in this study shown 1.61 fold change in normal individual compare to ATLL patient that mean dysfunction in RICTOR in ATLL, leading to an error in T cell proliferation and by affecting the expression of chemokine receptor genes in cells and it may affect the homing and migration of virus-infected cells (58, 62). P53 and Rb are the main tumor suppressors, which lead to inhibition of proliferation (63, 64). HTLV-1 oncogenes can induce malignancy through their effects on gene expression of cell cycle checkpoints such as P53 and Rb in the host cell (65). It has been demonstrated that HTLV-1 Tax protein hinders the function of p53 and Rb protein in host cells and lead to deregulate cellular division (66, 67). In line with other studies, in this study, we found decrease in expression of these genes in ATLL group. So, HTLV-1 oncogenes by their effects on function and expression of p53 and Rb induce oncogenesis in host cells.

5. Conclusions

Overall, based on scientific results in the present study, it seems the immune system via stimulation of biological processes such as cell survival, proliferation, CTLs exhaustion, and apoptosis concomitant, caused immortalization of HTLV-1 infected CD4 + T cells. As well as, this system via angiogenesis stimulation and cellular growth factors causes Tissue invasion phenomenon. In addition, this system through stimulation of angiogenesis and cellular growth factors in malignant tissues, and has an important role to progression of HTLV-1 to ATLL cancer. Also, immune system targeting by microRNA molecules as a new and effective approach, is accounted for development of new generation drugs against ATLL.

Abbreviations

Human T-lymphotropic virus type 1: HTLV-1

Adult T cell leukaemia/lymphoma: ATLL

HTLV-1-associated myelopathy/tropical spastic paraparesis: HAM/TSP

Asymptomatic HTLV-1 carriers: ACs

Helicobacter pylori: H. pylori

Differentially expressed genes: DEGs

Fold change: FC

Declarations

- Ethics approval and consent to participate

Not applicable (this paper was provided based on researching in global databases)

- Consent for publish

Not Applicable

- Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files

- Competing interests

There is no any conflict of interest among the all authors.

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- Authors' Contributions

1. MK1 have contributed to design of the work and analysis of data
2. MA have contributed to design of the work and analysis of data
3. RB have contributed to design of the work and analysis of data
4. MK2 have drafted the work and substantively revised it

All authors read and approved the final manuscript

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Figures

Figure 1

Heatmap of upregulation and downregulation of 65 immune genes in Normal, ACs, and ATLL patients. The color of each gene is representative for expression rate of it. Regard to the changes of colors from green (higher expression to red (lower expression) it to be resulted identification of gene expression rate of each gene. Between these gene, expression changes in some genes are higher than others. These gene include IL-10, IL-6, JAK, IL-15, SOCS1, TNFR6, FOXP3, PD-1, FADD, Ras, BCL2, Rb, RICTOR, RAC1, MAP2K4, BCL2A1, MAP1B, CXCR4, BRCA1, MSH2, ATM, and RIG1.

Figure 3

Gene enrichment analysis. It was determined that hub genes in our studies were effective on various pathways. These pathway is noted in the text.

Figure 4

Gene enrichment analysis. A) The best transcription factors are STAT1, ASAT5, PML, CEBPB, and JUN. B) The best transcription factors are NFKB1, E2F1, TP53, IRF1, RELA, and GLI1. C) Dysregulating microRNA molecules are including miR-574-3p, miR-34a-5p, miR-146a-5p, miR-21-5p, and mir-223-3p.

Figure 5

The components of immune system effect on processes such as inflammation, apoptosis, DNA damage, cell proliferation, T cell activation, invasion, angiogenesis, cell survival, and cell migration. Eventually, this interaction lead to the progression of HTLV-1 towards ATLL cancer.

Figure 6

Gene enrichment results about the properties of miRNA molecules. The hsa-miR-574 molecule is predicted as an appropriate candidate for treatment of ATLL cancer. The has-miR-164a concomitant of BRCA1 expression,

and has preventive and therapeutic roles in breast and ovarian cancers. Has-miR-21 can stimulate proliferation of tumor mass, concomitants cancer metastases.