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Altered Expression of Cell Cycle Regulators in Adult T-Cell Leukemia/ Lymphoma Patients

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Abstract

Background: Adult T-cell leukemia/lymphoma (ATLL) is caused by human T-cell lymphotropic virus type-1 (HTLV-1). HTLV-1 oncogenes can induce malignancy through controlled gene expression of cell cycle checkpoints in the host cell. HTLV-I genes play a pivotal role in overriding cell cycle checkpoints and deregulate cellular division. In this study, we aimed to determine and compare the HTLV-1 proviral load and the gene expression levels of cyclin-dependent kinase-2 (CDK2), CDK4, p53, and retinoblastoma (Rb) in ATLL and carrier groups.

Methods: A total of twenty-five ATLL patients (12 females and 13 males) and 21 asymptomatic carriers (10 females and 11 males) were included in this study. TaqMan real-time polymerase chain reaction assay was used for evaluation of proviral load and gene expression levels of CDK2, CDK4, p53, and Rb. Statistical analysis was used to compare proviral load and gene expression levels between two groups, using SPSS version 18.

Results: The mean scores of the HTLV-1 proviral load in the ATLL patients and healthy carriers were 13067.20±6400.41 and 345.79±78.80 copies/10^4 cells, respectively (P=0.000). There was a significant correlation between the gene expression levels of CDK2 and CDK4 (P=0.01) in the ATLL group.

Conclusions: Our findings demonstrated a significant difference between the ATLL patients and healthy carriers regarding the rate of proviral load and the gene expression levels of p53 and CDK4; accordingly, proviral load and expression levels of these genes may be useful in the assessment of disease progression and prediction of HTLV-1 infection outcomes.

Keywords: Adult T-cell leukemia/ lymphoma, CDKs, HTLV-I, p53, Retinoblastoma

Introduction

Adult T-cell leukemia-lymphoma (ATLL) is caused by the proliferation of human T-cell leukemia virus type 1 (HTLV-1)-infected CD4+ T cells (1). HTLV-1 is endemic in the Middle East, Central Africa, Southwestern Japan, the Caribbean Basin, the Melanesian Islands, and South America (2, 3). In Iran, endemic areas are Khorasan Razavi, Northern Khorasan, Alborz, Golestan, and East Azarbayejan (3-5). The majority of HTLV-1 virus

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carriers do not present any clinical symptoms, and approximately 1-2% of them show symptoms during a 20-40 years period (6). Regulatory proteins in HTLV-1 such as Tax and HTLV-1 basic leucine zipper factor (HBZ) were expressed in HTLV-1-infected human CD4+ T-cells to provide virus survival and dissemination (3).

The cell cycle is controlled at three checkpoints, including G1/S, S, and G2/M that are controlled by cycling-dependent kinase-2 (CDK2), CDK4, and CDK6(7). Activation of kinase proteins leads to phosphorylation of the cell cycle proteins, which improves cell proliferation (7). Tax expression in HTLV-1 represses a number of cellular genes and initiates stimulation of cytokines, stress signals, growth factors, and oncogenes; thus, Tax excessively activates CDK4, CDK6, and CDK inhibitors in the host cell cycle (8).

Retinoblastoma (Rb), as a tumor suppressor gene, is the key protein in the G1 phase that is phosphorylated by CDK4-cyclinD. Rb protein controls cell cycle through binding to E2F and inhibiting this protein. In resting cells, cyclinD/CDK4/6 complex inhibitors keep the Rb in a hypophosphorylated state and therefore Rb remains attached to the E2F transcription factor. Phosphorylation of Rb changes the structure of this protein and induces the release of E2F (9). The Rb protein is inactivated in ATLL patients by the HTLV-1 Tax protein (10).

Another tumor suppressor is the p53 with important functions to prevent the development of cancer. There is p53 mutations in at least half of all human tumors (11). This protein is activated during DNA damage and impedes cell cycle in G1/S checkpoint until DNA repair (12). In HTLV-1 infected cell lines, Tax expression hinders the function of p53 and promotes oncogenesis in host cells (10). Given the important role of CDK2, CDK4, p53, and retinoblastoma genes in cell cycle regulaion and the significance of HTLV-1 genes in oncogenesis induction in host cells through thier effects on cell cycle regulators, in this study, we evaluated and compared the levels of expression of CDK2, CDK4, p53, and Rb genes in ATLL patients and healthy carriers. Our study provides important information to disclose the role of CDK2, CDK4, p53, and retinoblastoma genes and proviral load (PVL) value in the course of HTLV-1- mediated disease progression.

Materials and Methods

Study population

This cross-sectional study was conducted on twenty-five ATLL patients and 21 healthy carriers in Ghaem and Imam Reza hospitals, affiliated to Mashhad University of Medical Sciences, Mashhad, Iran, during July 2012-April 2015. ATLL diagnosis was based on clinical history, pathological and experimental findings by two expert hematologists. HTLV-1 infection was diagnosed using HTLV-1 antibody serological test and it was confirmed by polymerase chain reaction (PCR) for Tax gene and long terminal repeat regions as previously described (4). Patients were classified into two subtypes using the Shimoyama criteria (13). The presence study protocol was approved by the ethics committee of Mashhad University of Medical Sciences, Mashhad, Iran. Informed consent was obtained from all patients before their entry to study for the performance of different blood tests.

Isolation of PBMCs and cDNA synthesis

Peripheral blood mononuclear cells (PBMCs) were separated from whole blood using Ficoll density gradient (Inno-train, Germany) for DNA and RNA extraction. Total RNA was extracted from PBMCs using a Tripure isolation reagent (Roche, Germany) based on the manufacturer's instruction. Complementary DNA (cDNA) was synthesized using random primers and reverse transcriptase based on the manufacturer's instruction (Bioneer, South Korea). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) primers were used to check correct cDNA synthesis. The GAPDH forward primer was 5'-CAAGGTCATCCATGACAACTTTG-3' and GAPDH reverse primer was 5'-GTCCACCACCCTGTTGCTGTAG-3'.

Primer design and real-time PCR

After detection of the desired sequence of genes (CDK2, CDK4, p53, and Rb) using the National Center for Biotechnology Information (NCBI, Genebank), primers and probes were designed by AlleleID, version 5. Real-time PCR was performed using TaqMan method. Real-time PCR was performed for CDK2, CDK4, Rb, and p53 genes, as well as cellular reference gene (β2-microglobulin)

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on Rotor-Gene 6000 cycler (Corbett, Hilden, Germany), using TaqMan Reagents (Applied Biosystems, USA) in accordance with the manufacturer's instruction. Specific primers and probes used to amplify the desired genes are provided in Table 1.

Table 1. Primer and probe sequences used in quantitative real-time polymerase chain reaction.

Gene	Primer Name	Sequences (5'->3')	Length	Tm[a]	GC%[b]
CDK2[c]	Forward	ATTCTGAGATTGACCAGCTCTTCC	24	59.3	45.8
	Reverse	CTTGGCTTGTAATCAGGCATAGAAG	25	59.1	44
	Probe	CCACACCACCTCATCTGGGGTCCC	24	67.3	66.7
CDK4	Forward	AAATTGGTGTCGGTGCCTATGG	22	61.2	50
	Reverse	CACGAACTGTGCTGATGGGAAG	22	61.76	54.55
	Probe	ACAAGGCCCGTGATCCCCACAGTGG	25	69.6	64
Rb[d]	Forward	CCTATCTCCGGCTAAATACACTTTG	25	59.3	44
	Reverse	TTGGTCCAAATGCCTGTCTCTC	22	60.55	50
	Probe	AACGCCTTCTGTCTGAGCACCCAGA	25	67	56
p53	Forward	CAGCATCTTATCCGAGTGGAAGG	23	60.8	52.17
	Reverse	GTTGTAGTGGATGGTGGTACAGTC	24	60.86	50
	Probe	CTCAGGCGGCTCATAGGGCACCAC	24	68.1	66.7

[a]Melting Temperature, [b]Guanine-Cytosine content, [c]Cyclin-Dependent Kinase-2, [d]Retinoblastoma

Quantification of HTLV-1 proviral load

To assess the HTLV-1 proviral load, PBMCs were isolated and DNA was extracted from PBMCs by DNA extraction kit (Cinnagen, Iran). Real-time PCR was performed by a Rotorgene Q Real-Time PCR machine (Qiagen, Germany) using a commercial absolute quantification kit (Novin Gene, Iran) and specific primers and a fluorogenic probe to measure the proviral load of HTLV-1. The HTLV-1 copy number was reported as an actual amount of cellular DNA by means of quantification of the albumin gene as the reference gene. Each two copies of albumin genes are equal one cell. HTLV-1 and albumin DNA concentrations were calculated from two 5-point standard curves. The normalized value of the HTLV-1 proviral load was calculated as the ratio of (HTLV-1 DNA copies number/albumin DNA copies number /2) $\times 10^4$ and expressed as the number of HTLV-1 proviruses per 10^4 PBMCs.

Statistical analysis

Data analysis was carried out in SPSS version 18 and the results were reported as mean±SD. Kolmogorov–Smirnov test was carried out to test the normality of the variables distribution. Statistical analysis was performed in the two groups using Mann–Whitney U test. Moreover, the Spearman's rank correlation coefficient was used to determine the correlation between the study variables. A P-value less than 0.05 was considered statistically significant.

Results

In this study, twenty-five ATLL patients (12 females and 13 males) and 21 asymptomatic carriers (10 females and 11 males) were enrolled. The mean score of age in the ATLL group was 54.83±1.25 years, while it was 40.83±2.14 years in the carrier group. According to the results, eight patients were in acute type and seventeen were lymphoma type. The mean scores of HTLV-1 proviral load in the ATLL and carrier groups were 13067.20±6400.41 and 345.79±78.80 copies/10^4 cells, respectively. The mean scores of expression for each gene in patients and carriers are demonstrated in Table 2.

Table 2. Mean scores of proviral load and expression of CDK2, CDK4, Rb, and P53 genes in the ATLL patients and carrier groups.

Gene	Group (n)	Mean± SD[b]
Proviral load	ATLL[a] (25)	13067.20±6400.41
	Carriers (21)	345.79±78.80
CDK2[c]	ATLL (25)	2.51±1.77
	Carriers (21)	0.45±0.25
CDK4	ATLL (25)	0.12±0.09
	Carriers (21)	0.04±0.02
Rb[d]	ATLL (25)	0.75±0.42
	Carriers (21)	0.22±0.05
p53	ATLL (25)	0.002±0.0008
	Carriers (21)	0.049±0.012

aAdult T-cell Leukemia/Lymphoma, bStandard Deviation, cCyclin-Dependent Kinase-2, dRetinoblastoma

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Comparison of the mean scores for each gene revealed that expression of CDK2, CDK4, and Rb genes in ATLL group was slightly higher than the carrier group but only CDK4 gene expression reached a significant increase in the patients compared with carriers. At the same time, p53 gene expression was dramatically higher in the carriers and this rise was statistically significant. In addition, there was a significant correlation between CDK2 and CDK4 genes expression in ATLL patients (r=0.530, P=0.01). The Stem-and-Leaf Plot in figure 1 (Fig. 1) exhibits the difference in expression levels of CDK4 and p53 genes between the carrier and ATLL groups.

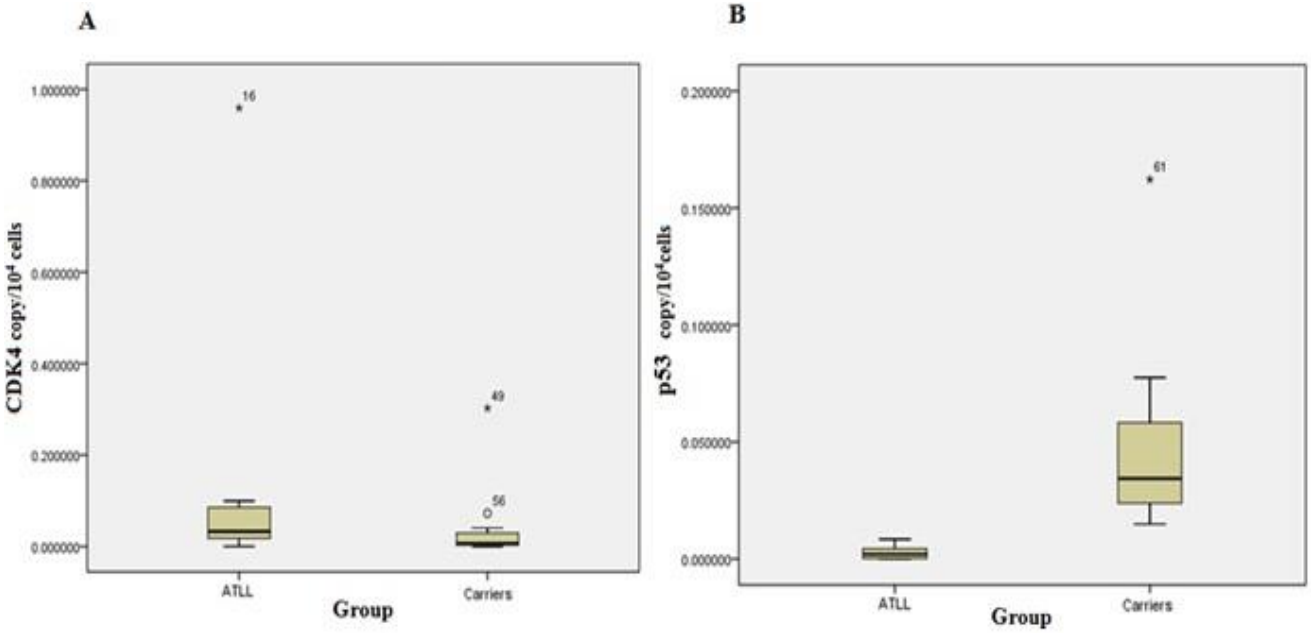


Fig. 1. Comparison of the expression levels of CDK4 (A) and p53 (B) genes between the carrier and ATLL groups.

The mean score of proviral load was significantly different between ATLL and carrier groups (P=0.000). The Stem-and-Leaf Plot in figure 2 (Fig. 2) exhibits the difference proviral load between the carrier and ATLL groups.

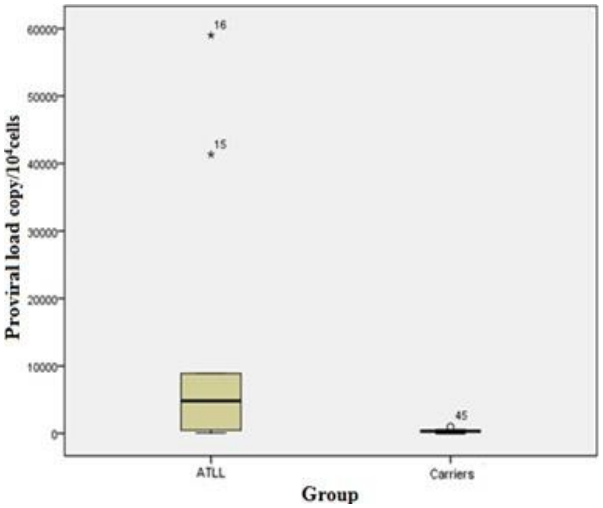


Fig. 2. Comparison of the proviral load value between the carrier and ATLL groups.

Discussion

In the current study, we evaluated and compared HTLV-I proviral load and expression levels of CDK2, CDK4, p53 and Rb genes in ATLL patients and healthy carriers. Cell cycle progression is controlled by consecutive activation of CDK components and it is inactivated by CDKIs (10). Tax effects on cell cycle factors, leads to excessive cell cycle and promotes multipolar mitosis; thus, produces cancer cells, in addition to Tax, HBZ gene is thought to play an important role in oncogenesis (14, 15).

HTLV-1 instigates proliferation of CD4+ T-cell lymphocytes thereby virus is reproduced (14). There are various risk factors for progression from carrier status to ATLL, including advanced age, family history of ATLL, and high proviral load (16). In ATLL patients, development of HTLV-I through HTLV-I proviral load is utmost importance (17). Similar of previous studies results, our results showed that viral load was significantly higher in the

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ATLL patients than the carrier group (16, 18). In healthy carriers, HTLV-1 proviral load value was measured as important predictor of development of ATLL (16).

Cell cycle factors are controlled in normal cells regularly, while the dysregulation of CDK components in cancer cells leads to the survival of cancer cells (19). The G1-phase progression is regulated by the several CDKs, especially CDK4 and CDK6. According to previous studies, cell cycle checkpoints in most types of cancers are controlled through elevated expression of CDK, especially CDK2 and CDK4 (20, 21). Our results showed that the mean expression levels of CDK2 and CDK4 genes in ATLL patients were more than healthy carriers due to the effects of HTLV-I oncogenes on ATLL patients. HTLV-1 Tax protein stimulates CDKs activity, especially CDK2, CDK4 and CDK6 and increases G1- to S-phase Transition in T Lymphocytes of ATLL patients moreover the suppression of Tax synthesis leads to the significant reduction of the CDK4 and CDK6 activity (22, 23).

Normal cells respond to anti-proliferative signals by dephosphorylating Rb in G1 checkpoint. In infected cells with HTLV-I, Tax gene expression can induce hyperphosphorylation and degradation of Rb by activation of CDK-4 and CDK-6, which then hyperphosphorylatd Rb releases the E2F transcription factor and accelerates cell cycle transition from G1 to S (24). The current study showed that gene expression level of Rb in ATLL patients is more than healthy carriers. It has been reported recently that overexpression of Rb is associated with progression of the disease in subjects with advanced bladder cancer or follicular lymphoma. Therefore Rb controls tumor proliferation not only as a cell cycle regulator, but also by other mechanisms, possibly by apoptosis inhibition. Rb plays a critical role in its hypophosphorylated form for the development of ATLL, as well as a cell cycle stimulator in hyperphosphorylated form (25).

Despite previous genes, activation of p53 such as a tumor suppressor gene prevents the development of cancer cells through impeding cycle cell and inducing apoptosis (26). Ellis et al. indicated that overexpression of p53 in lung cancer cells forcefully induces autophagy (26). Nowadays, induced overexpression of p53 in cancer cells is used as a treatment method (27). Ariumi et al. (28) and Gatza et al. (29) reported that in infected cells with HTLV-I, Tax protein indirectly inhibits p53 function, moreover, this protein inhibits the expression of p53 by transcription repression of this gene (30). Accordingly, in the current study expression of p53 in ATLL patients was significantly lower than healthy carriers, which can leads to oncogenesis.

In addition to Tax, the HBZ gene promotes the proliferation of cancer cells in ATLL patients. Therefore, it is believed that HBZ gene is necessary for leukemogenesis (18). In infected cells, Tax and HBZ genes expression in the early and late stages of ATLL respectively may play a major role in HTLV-1 biology and the development of leukemia through deactivating effects of transcription mediators and/or attenuating cellular gene expression (8). Wright et al. reported that HBZ reduces transcription of p53-responsive genes, p21/CDKN1A and GADD45A, which contributes to cell cycle arrest (31). Our results revealed that the rate of p53 expression in ATLL was significantly lower than the carriers. Therefore, HTLV-1 oncogenes in different stages of ATLL can potentially induce oncogenesis in host cells by their effects on function and expression of p53 and Rb.

According to these results, there was a significant difference between the ATLL patients and carriers regarding the rate of PVL and the genes expression of p53 and CDK4; therefore, it seems that PVL, CDK4 and P53 measurements might help in the assessment of disease progression and prediction of HTLV-1 infection outcomes. This research demonstrates the possible correlation between virus oncogenes and altered expression of the cell cycle regulators of ATLL patients. Further molecular studies are necessary for better understanding of virus genes and host cell cycle interaction, which can lead to find selective therapeutic agents for ATLL.

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