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RAB3GAP2 dysregulation in adult T-cell leukemia/lymphoma (ATLL) compared to acute lymphoblastic leukemia (ALL): a molecular perspective

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Abstract

Adult T-cell leukemia/lymphoma (ATLL) is a type of blood cancer related to human T-cell lymphotropic virus type 1 (HTLV-1). The principal aim of this study was to investigate cellular processes related to innate immune response, intracellular protein transport, and translational initiation regulation in individuals afflicted with ATLL and Acute lymphoblastic leukemia (ALL). Whole blood samples and peripheral blood mononuclear cells were collected from 10 viral ATLL patients and 10 ALL subjects. Real-time quantitative PCR was then performed to quantify mRNA expression levels of SMC6, FANCM, EIF4H, WDR7, RAB3GAP2, and IFN α/β. The study revealed some distinctions between ATLL and ALL patients. Particularly, RAB3GAP2 level ($P=0.028$) was found to be elevated in ATLL patients compared to ALL. Conversely, expression levels of IFN-β ($P=0.31$), SMC6 ($P=0.68$), WDR7 ($P=0.43$), EIF4H ($P=0.38$), and FANCM ($P=0.57$) were diminished in ATLL patients in contrast to ALL. These proteins play a pivotal role in both translation and immune activation, suggesting a potential correlation between the observed disparities and the virus-mediated progression of cancer. However, it is worth noting that the expression differences in FANCM, EIF4H, SMC6, and WDR7 between ATLL and ALL were minimal. This proposes that the underlying molecular mechanisms governing ATLL and ALL may largely overlap concerning these cellular processes. However, considerable increased expression of RAB3GAP2 was observed in ATLL compared to ALL.

Keywords ATLL, HTLV-1, ALL, Real-time PCR, Translational initiation, Intracellular protein transport, Innate immunity

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Introduction

Human T-cell Lymphotropic virus type 1 (HTLV-1) is an RNA virus classified within the Retroviridae family and the delta retrovirus genus. It possesses the capability to establish long-term infections in humans [1]. Typically, over 90% of carriers remain asymptomatic. The virus has infected nearly 10–20 million individuals globally, with prevalence rates varying across specific regions, including South America, Central Africa, South India, the Caribbean, South Japan, and West Africa. A particularly high prevalence has been observed in Iran's northeastern province of Khorasan [2]. It exhibits a gradual

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progression in infected individuals, with approximately 5% of patients eventually developing either Adult T-Cell Leukemia/Lymphoma (ATLL) or myelopathy/Tropical Spastic Paraparesis (HAM/TSP) [3].

Cancer continues to be a prominent cause of mortality in today's world, due to the development of transformed cells characterized by their remarkable capacity for rapid proliferation. This process involves a persistent dysregulation in protein synthesis, disrupting the translational control of specific transcripts that facilitate growth. Among various types of cancer, one particularly aggressive and dangerous form of lymphoma is ATLL. The primary culprit behind ATLL is HTLV-1, with the acute variant being the most prevalent. The prognosis for patients with acute ATLL is not good, with survival often limited to just a few months [4, 5]). During the process of cell infection, HTLV-1 can profoundly influence multiple cellular processes, ultimately contributing to the onset of ATLL. One critical area of influence is mRNA translation, spanning initiation, elongation, and termination stages. Ensuring the proper regulation of protein synthesis is critical for normal cellular function. However, disruptions in this regulation can lead to the development of various diseases, including cancer [6]. The precise localization of translation requires a complex interplay of proteins, translational initiation factors in eukaryotic cells, and various regulatory factors. Dysfunction in these components can disrupt cellular protein translation, resulting in abnormal proliferation and differentiation, which, in turn, can contribute to the development of cancer. SMC6 (Structural maintenance of chromosomes protein 6), FANCM (Fanconi anemia complementation group M), and EIF4H (eukaryotic translation initiation factor 4 H) are among the most important genes involved in controlling translation initiation [7–9]. The second significant cellular process implicated in cancer is protein transduction. Intracellular signal transduction refers to the transfer of molecular signals from cell receptors to the interior of the cell. When the cytoplasmic chain of these receptors is activated, it triggers multiple intracellular signal transduction processes within the cell. These cellular processes play a crucial role in fundamental cellular processes, such as cell proliferation and differentiation. RAB3GAP2 (Rab3 GTPase-activating protein catalytic subunit 2) and WDR 7 (WD repeat-containing protein 7) are among the most important genes involved in this process [10, 11]. However, cells exhibit resistance against viral infections due to the presence of innate immunity, particularly through the action of interferons. Interferons are proteins produced by the body in response to viruses and other pathogens. These molecules serve as a crucial innate defense mechanism, working to hinder viral replication or translation and reduce the virulence of the virus [12, 13]. This process can prevent the virus from replicating, while also providing a defense against cancer cells [14, 15].

There is still much to uncover about the impact of the HTLV-1 virus on molecular processes, especially in the context of translation initiation, control, and intracellular changes. Currently, a significant number of individuals worldwide are affected by this virus, each carrying the potential risk of developing ATLL.

This research endeavor utilizes high-quality data from individuals suffering from ATLL to compare the expression levels of seven genes involved in three cellular processes (translation initiation regulation, intracellular protein transport, and immune response to viral infection) between ATLL caused by HTLV-1 and ALL, using Real-Time qPCR. Moreover, the clinical data is analyzed using flow cytometry. By unraveling the pathological processes of HTLV-1 and identifying key factors contributing to its pathogenesis, this study aims to enhance our understanding of the virus. In addition, it holds the potential to pave the way for the development of novel diagnostic techniques and medications thus making significant strides in combating HTLV-1.

Materials and methods

Study population

Overall, 20 patients (with a ratio 1:1 of viral ATLL and ALL) were admitted to the oncology departments of Imam-khomeini, Imam-Hossein, and Shariati Hospital from 2021 to 2022. Among ATLL patients, 8 were male and 2 were female. The ALL patients consisted of 4 males and 6 females.

Sample collection

6 mL of blood samples were collected in sterile tubes containing EDTA anticoagulant and promptly transported to the virology laboratory while maintaining cold chain conditions to confirm the infection. The research included individuals with newly diagnosed cases of ATLL and ALL (with confirmation of ALL from laboratory and expert physician). To ensure a clear assessment, only participants who had not received any prior medications and had no history of autoimmune diseases or ongoing infectious illnesses, such as HIV, HCV, and HBV, were selected. The study was approved by the ethics committee of Tehran University of Medical Sciences, Tehran, Iran, and each participant provided signed consent (Ethical code: IR.TUMS.SPH.REC.1399.112).

ELISA assessment

Confirmation of clinical symptoms in the study subjects was based on diagnostic criteria. After obtaining initial consent, blood sampling and serology tests (ELISA) were performed to screen the presence of the antibodies, followed by PCR for confirmation. The ELISA test utilized

the DIA Pro kit manufactured in Italy to detect antibodies against the HTLV-1 virus in the samples. The cut-off value was determined based on the light absorption at 450 nm (NC) negative control, and the results were interpreted using the corresponding table provided by the kit. If the obtained number was lower than 0.9, the sample was considered negative for HTLV-1.

RNA extraction and cDNA synthesis

RNA extraction from PBMCs was performed using RNJia Kit (ROJE, Iran) according to the manufacturer's instructions to purify total RNA. Subsequently, RNA elution was treated with RNase-free DNase (Qiagen, Germany), and cDNA was synthesized using 5 µl of the extracted RNA and 1 µl of random hexamer primers using the RT-ROSET Kit (ROJE, Iran) as outlined by the manufacturer's protocol. RNA concentrations were quantified spectrophotometrically at 260/280 nm using a NanoDrop spectrophotometer.

Table 1 Designed primers for selected genes in this study for detection by RT-qPCR are shown below.

Gene name	Forward primer	Reverse primer	Annealing	Amplicon size
GAPDH	TGGACCTGACCT GCCGTCTA	GGAGGAGT GGGTGTCGC TGTT	62	152
Tax	GGATAGCAAAC CGTCAAGCAC	GGTGAGGGGT TGTCGTCAA	58	195
HBZ	ACGTCGCCCGG AGAAAACA	CTCCACCTCG CCTTCCAACT	60	152
LTR	GGCTCGCATCTC CCCTTCAC	GAGCAAGC AGGGTCAGG CAA	62	221
SMC6	AAATGGCTTGG GCAGTGGTCA	CCATACATTC TGGTGCTCGT GCAT	60	213
FANCM	GGGCATCCTGTT CCAAGTCAAGA	TCCTTTCCACC ACCATGCGAT	60	222
EIF4H	CGGACTTCG ACACCTACGA CGAT	AGCCGTACAC TCCTTATGCT GAGA	59	211
RAB3GAP2	CTGTTGGCTGG AGTGGTTCCT	CACAATGCA GGTCCAGTCA GGA	59	122
WDR7	CCCAAACTTCCT CCACACAGCA	TTGTTTCTCGG CATCGGCACA	60	169
IFN α	GGCTGAAACCA TCCCTGTCCT	CCCCCTGTATC ACACAGGCTT	62	160
IFN β	AGTGTCAGAA GCTCCTGTGG CAA	TAGATGGTC AATGCGGCG TCCT	62	133

Abbreviations: GAPDH, Glyceraldehyde-3-phosphate dehydrogenase; SMC6 Structural maintenance of chromosomes protein 6; FANCM, FA Complementation Group M; EIF4H, Eukaryotic translation initiation factor 4 H; RAB3GAP2, RAB3 GTPase Activating Non-Catalytic Protein Subunit 2; WDR7, WD repeat-containing protein 7; IFN α, Interferon alpha; IFN β, Interferon beta

Quantitative Real-time PCR

The initial screening for HTLV-1 infection in the subjects was conducted using ELISA (DIA Pro Kit, Version ULTRA, Italy), and the results were confirmed by PCR targeting Tax, HBZ, and LTR regions of the virus. The mRNA expression of WDR7, RAB3GAP2, FANCM, SMC6, and IFN α/β were measured using Real-time qPCR assay. The sequences of the PCR primers are provided in Table 1. The Real-time qPCR assay was performed following the manufacturer's instructions. To determine the expression index, the relative copy number of the mRNA of interest was normalized by dividing it by the relative mRNA copy number of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) with human origin. This yielded the normalized expression value for each gene. All samples were compared to the expression of an appropriate reference gene, and the standard deviation was calculated. The reaction consisted of an initial denaturation at 94 °C for 45 s, followed by 45 cycles of amplification with the specific annealing temperature for each primer, and a final extension at 72 °C for 20 s.

Flow cytometry assessment and CD4 + and CD8 + T-cell subsets flow cytometric analysis

After preparing the appropriate suspension from collected whole blood, the cells were stained with conjugated fluorochrome (PE-CD4) and (FITC- CD8+) and then examined by BD facscalibur flow cytometer and analyzed by Flowjo 10 software. The antibodies were purchased for CD4 and CD8 from Biolegend. All experiments were done within the lymphocyte gate and was defined using FSC vs. SSC plot.

Statistical analysis

GraphPad Prism software was utilized to perform statistical analysis, including t-test, and Mann–Whitney U test to detect the level of significance and differences between the studied groups. To assess the correlation among different genes, the Spearman's rank correlation test was utilized. In this study, a *P*-value lower than 0.05 was deemed to be significant.

Results

Demographic data

The research analyzed the interactions between the virus and the host by examining changes in gene expression of 10 individuals with viral ATLL and 10 individuals with ALL. The t-test analysis revealed no significant differences based on gender between two groups (P-value = 0.213). The mean age of the viral ATLL group was 52.6 years, while the ALL group had an average age of 38.6 years (Table 2). The results of comparing the age of the two groups showed significant differences between individuals with viral ATLL and ALL (P-value = 0.0005).

Table 2 Demographic data of patients participated in the study

Variables	ATLL (No = 10) Male Female	ALL (No = 10) Male Female
Gender	8 (80%) 2 (20%)	6 (60%) 4 (40%)
Age		
18–29	0 (0%) 0 (0%)	3 (30%) 0 (0%)
30–39	1 (10%) 1 (10%)	1 (10%) 1 (10%)
40–49	1 (10%) 1 (10%)	2 (20%) 1 (10%)
≥ 50	6 (60%) 0 (0%)	0 (0%) 2 (20%)
Mean age (y)	52.6	38.6
Surgery	5 (50%) 2 (20%)	2 (20%) 3 (30%)
Blood Transfusion	3 (30%) 0 (0%)	4 (40%) 0 (0%)
Hospitalization	7 (70%) 0 (0%)	1 (10%) 2 (20%)
Tattooing	5 (62.5%) 1 (10%)	1 (10%) 0(0%)
Dentistry	8 (80%) 2 (20%)	6 (60%) 4 (40%)
Cupping	3 (30%) 1 (10%)	2 (20%) 2 (20%)

Gene assessment

SMC6, FANCM, and EIF4H

In this investigation, the average expression of SMC6 mRNA was found to be 0.00076 ± 0.0006 in ATLL patients with the virus and 0.000677 ± 0.0005 in ALL ($P > 0.05$) (Fig. 1a). The average expression of FANCM mRNA was found to be 0.09048 ± 0.032 in ATLL patients with the virus and 0.05959 ± 0.091 in ALL ($P > 0.05$) (Fig. 1b). The mean expression of EIF4H mRNA in the group of ATLL and ALL patients was 0.2544 ± 0.015 and 0.1727 ± 0.019 respectively ($P > 0.05$) (Fig. 1c).

RAB3GAP2 and WDR7

A significant difference in RAB3GAP2 mRNA expression was observed between the two groups ($P = 0.028$). The mean expression of RAB3GAP2 (viral ATLL 0.4 ± 0.276; ALL 0.16 ± 0.155) was pairwise compared by the Mann-Whitney U test (Fig. 1d).

The mean WDR7 mRNA expression in the ATLL patients and ALL was reported as 0.017 ± 0.015 and 0.025 ± 0.019, respectively ($P = 0.43$) (Fig. 1e).

In addition, the correlations are provided in Table 3.

Interferon α/β

Interferon is a key component for innate immune response. The mean expression for IFN α was found to be 0.044 ± 0.0321 in the ATLL group and 0.045 ± 0.0326 in the ALL group ($P > 0.05$). The mean expression of IFN β was 0.072 ± 0.089 and 0.053 ± 0.027 in ATLL and ALL groups, respectively ($P > 0.05$). Therefore, there were no significant differences in the expressions of IFN α and IFN β between two groups (Fig. 1f and g).

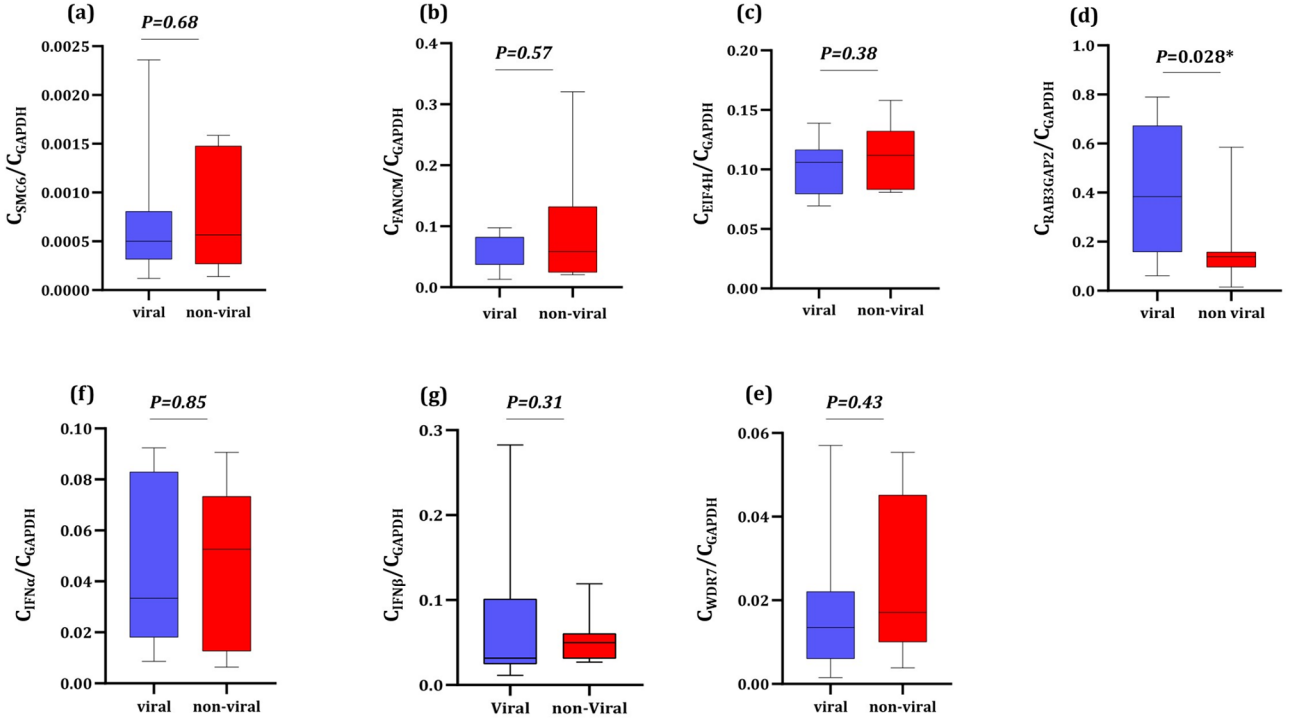

Fig. 1 Expressions are mentioned as viral (ATLL) and non-viral (ALL). (**a**) The average expression of SMC6 was 0.00076 ± 0.0006 in viral ATLL samples and 0.000677 ± 0.0005 in non-viral ALL samples ($P > 0.05$). (**b**) The average expression of FANCM was 0.09048 ± 0.032 in ATLL samples and 0.05959 ± 0.091 in ALL samples ($P > 0.05$). (**c**) The mean expression of EIF4H in ATLL and ALL samples was 0.10± 0.02 and 0.11 ± 0.02 respectively ($P > 0.05$). (**d**) The average expression of RAB3GAP2 was 0.4 ± 0.276 in ATLL samples and 0.16 ± 0.155 for ALL ($P = 0.028$). (**e**) The average expression of WDR7 in the ATLL patients and ALL was 0.017 ± 0.015 and 0.025 ± 0.019, respectively ($P > 0.05$). (**f**) The mean expression for IFN α was 0.044 ± 0.0321 in ATLL samples and 0.045 ± 0.0326 in ALL samples ($P > 0.05$). (**g**) The IFN β mean expression were 0.072 ± 0.089 and 0.053 ± 0.027 in ATLL and ALL groups respectively ($P > 0.05$)

Table 3 Correlation and significance (*P-value*) divided by genes

No.	Gene	Correlation and *P-value*	IFN α	IFN β	Smc6	WDR7	EIF4H	FANCM	RAB3GAP2
1	IFN α	Correlation	1	−0.74	−0.262	**0.685****	0.423	**0.465***	−0.068
		P-value		0.758	0.264	**0.001**	0.063	**0.039**	0.777
2	IFN β	Correlation		1	0.200	0.218	−0.164	−0.247	−0.215
		P-value			0.397	0.355	0.490	0.294	0.363
3	Smc6	Correlation			1	−0.273	−0.472	**−0.452***	0.090
		P-value				0.244	0.036	**0.045**	0.705
4	WDR7	Correlation				1	**0.566****	**0.653****	−0.196
		P-value					**0.009**	**0.002**	0.408
5	EIF4H	Correlation					1	**−0.774****	−0.291
		P-value						**0.000**	0.213
6	FANCM	Correlation						1	−0.271
		P-value							0.248
7	RAB3GAP2	Correlation							1
		P-value							

*. Correlation is significant at the 0.01 level

**. Correlation is significant at the 0.05 level

HTLV-1 infection is correlated to inversion of the CD4/CD8 T-cell ratio in patients with ATLL

We have presented the results of a flow cytometry analysis of samples obtained from participants with viral ATLL disease. To determine T helper and cytotoxic cell populations, Phico-erythrin (PE) anti-CD4 antibody (bio legend company cat no: 317409) and PE anti-CD8 antibody (bio company cat no: 301007) were employed. Cells (either CD4 + or CD8+) are shown in Fig. 2. Cells located in the upper left quadrant of the figure exhibited CD4 + expression on their surface, with an average of 4.21%. Cells located in the lower right quadrant, on the other hand, exhibited CD8 + expression on their surface, with an average of 1.35%. The CD8+/CD4 cell ratio within samples was determined to be 0.32 ($P > 0.05$). The samples related to the result of flow cytometry in people with ALL cancer after analysis with FlowJo software are also shown. All cells shown in this figure were CD4+/CD8 + lymphocytes. Cells positioned on the left side and the upper side of the quadrant expressed CD4 + on their surface, with an average of 8.1%. CD8 + population was observed in the right and lower quadrants, with an average of 1.55%. In our samples, the ratio of CD8+/CD4 + cells was calculated to be 0.19 ($P > 0.05$). The ratio and total amounts of CD4 + cells were significantly higher in patients with ALL compared to viral ATLL (Fig. 2a and b).

Discussion

HTLV-1 is recognized as one of the most significant viruses in endemic countries. Although some cellular protein interactions following HTLV-1 infection have been investigated in previous studies, there remains a lack of investigation in this research area. Considering its importance, we conducted a study to examine the mRNA expression of specific host factors, namely SMC6, FANCM, EIF4H, RAB3GAP2, WDR7, and IFN α/β. Our findings revealed altered gene expression in several cellular processes, particularly RAB3GAP2, which is involved in intracellular protein transport. In addition, downregulation in WDR7, SMC6, and FANCM was observed in the viral ATLL group.

HTLV-1 can induce the production of various cytokines and interferons. HTLV-1-infected individuals have been observed to exhibit elevated levels of IFN-α expression. Some studies suggest a correlation between HTLV-1 infection and increased levels of IFN-α [16]. Moreover, there is evidence indicating that IFN-α exerts antiviral by inhibiting HTLV-1 assembly through the prevention of raft interaction with the virus [17]. However, the transactivating transcriptional regulatory protein (Tax) of the virus can modulate this response by inducing the suppressor of cytokine signaling 1 (SOCS1), thus promoting virus replication within the cell [18, 19].

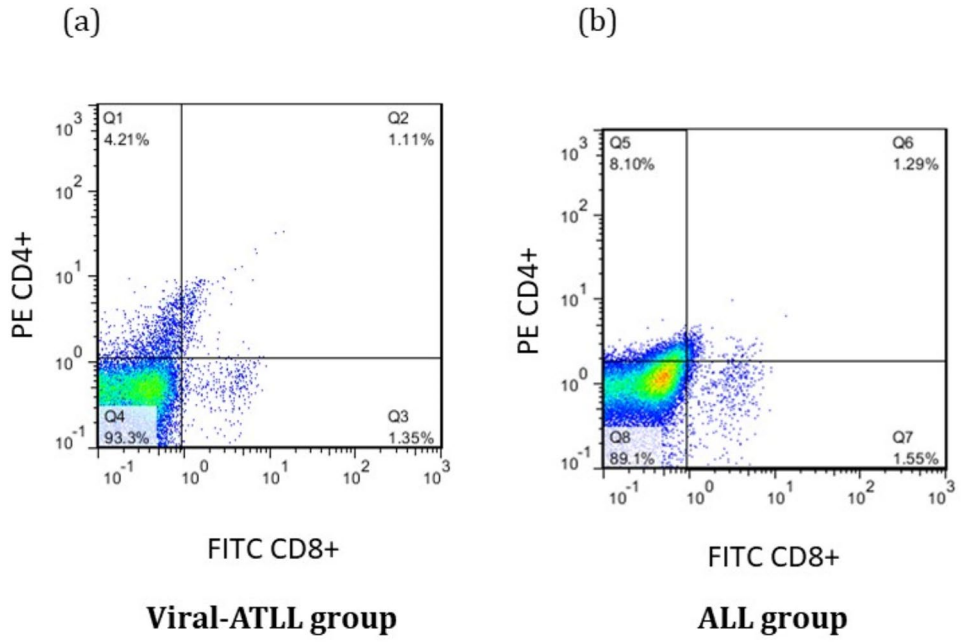

Fig. 2 The ratio of CD4 + and also CD8 + cells in individuals with viral-ATLL (**4a**) and ALL (**4b**) is shown. However, this increase is notably more pronounced within the CD4 + population

IFN-β, similar to IFN-α, is a protein that plays a crucial role in the immune response against viral infections. Numerous studies have reported on the significance of IFN-β in this context [20, 21]. IFN-β can activate T cells and facilitates their proliferation, potentially contributing to the development of ATLL. Furthermore, IFN-β can stimulate the expression of major histocompatibility complex class I molecules (MHC-1), which may enhance viral antigen presentation and promote T-cell activation [22, 23].

However, we observed no significant changes in IFN-α expression among HTLV-1-infected individuals (P-value = 0.85).

SMC6, a member of the structural maintenance of chromosome (SMC) family of proteins, is involved in the maintenance of chromosome structure and organization during cell division. Some research studies suggest that SMC6 may also participate in the immune response to viral infections [24, 25].

One study examined the expression of SMC6 in patients infected with HTLV-1. The findings of this study revealed that SMC6 expression was upregulated in HTLV-1-infected T-cells compared to uninfected T-cells. Additionally, the study identified a positive correlation between the expression of SMC6 and several cytokines and chemokines involved in the immune response, providing further evidence for its involvement in the immune response to HTLV-1 infection [26]. However, in the context of our study, we did not observe any significant differences in the expression of SMC6 between viral ATLL compared ALL.

Another study conducted a comprehensive investigation into the role of SMC6 in the immune response to viral infections. The results of this study demonstrated that SMC6 plays a critical role in inhibiting virus transcription and triggering the activation of the interferon response against viral infections. The study also reported that SMC6 is necessary for the expression of various interferon-stimulated genes (ISGs), which are important for innate defense [27, 28]. Furthermore, there is a study that highlights the variations in SMC6 levels within cells in the context of different types of cancers [29].

In a study conducted by Dupont L et al., SMC6 was found as the potential protein acting against HIV. The study revealed that SMC6 has the ability to silence unintegrated HIV within the cell. However, it was observed that the Vpr protein of HIV can antagonize the action of SMC6 [30].

In our study, we observed a decrease in SMC6 expression among viral ATLL patients compared to the ALL group (P-value = 0.68). It could potentially be attributed to HTLV-1 protein interactions with SMC6, similar to what has been observed following HIV infection. However, further research is required to fully understand the precise role of SMC6 in viral infections such as HTLV-1.

Collectively, these studies provide evidence suggesting that SMC6 may have a role in the immune response to viral infections, including HTLV-1 infection.

WDR7 is a protein-coding gene involved in various biological processes, including the regulation of transcription, apoptosis, and cell cycle progression. Although there is no direct evidence linking WDR7 expression to

HTLV-1 infection, several studies have investigated its role in cancer development [31].

A study conducted in 2017 demonstrated that the expression of WDR7 is decreased in breast cancer cell lines, and inhibiting WDR7 resulted in increased proliferation [32].

In our research, we observed a decrease in WDR7 expression among viral ATLL patients, which could contribute to proliferation and cancer development (P-value = 0.43). This finding suggests that the virus may affect WDR7 expression during the transformation process, either before or during the onset of cancer.

EIF4H is an RNA-binding protein that plays an important role in translational regulation [33, 34]. Several studies have explored the relationship between EIF4H expression and HTLV-1 infection. Dysregulated expression of EIF4H has been linked to cancer progression, as patients with higher levels of EIF4H have exhibited poor prognosis and reduced response to chemotherapy [33]. Additionally, another study revealed that EIF4H is essential for the efficient translation of retroviruses' viral proteins, and decreased EIF4H levels lead to reduced viral protein expression and diminished virus production [35].

However, our study found no significant differences in EIF4H expression levels between viral and ALL patients (P-value = 0.38), suggesting that this molecule may exhibit a similar pattern during the onset of ATLL regardless of the viral or non-viral etiology.

FANCM is a DNA repair protein that participates in maintaining genomic stability and preventing cellular transformation [36]. One study suggested that the decreased expression of FANCM observed in cancer may contribute to genomic instability and transformation, which aligns with the findings of our research where ANCM expression was decreased in viral-ATLL patients [37]. Additionally, a study by Lopes et al. reported that FANCM is mutated in cases of ovarian cancer, highlighting its importance in chromosomal stability [38]. Recent studies have provided evidence supporting the tumor suppressor effects of FANCM [39].

Another study conducted by Fu S et al. reported that certain viruses, including HIV, can exploit the FANCM for their integration into the host genome [40].

In our study, we observed a decrease in FANCM expression in the viral group compared to the ALL group; however, the difference was not statistically significant (P-value = 0.57). Although the decrease in FANCM expression was not substantial, it appears that the ATLL cancer process may be influencing this trend. Furthermore, it seems that the impact of the virus on this protein is either insignificant or ineffective.

RAB3GAP2 is a protein-coding gene that is involved in the regulation of intracellular vesicle trafficking. Numerous studies have reported an elevation in RAB3GAP2 expression in various cancers, including cervical cancer, osteosarcoma, and breast cancer [41–43]. Additionally, there are studies highlighting the crucial role of RAB3GAP2 in neurodevelopment [44].

Our study revealed a significant increase in RAB3GAP2 expression in the viral group (P-value = 0.028), indicating that the virus may affect this protein, potentially leading to enhanced cellular proliferation and survival. Considering that this gene is much higher elevated in this cancer (ATLL), it may be due to presence of the virus and is likely affected by the HTLV-1 proteins. Further research is required regarding the interaction of virus proteins with cellular factors, especially RAB3GAP2 to elucidate the differences between ATLL compared to other types of cancer and the exact mechanism of this interaction.

The current study provides valuable data on gene expression alterations following infection and has the potential to guide future investigations. Our study employed a suitable population and conducted rigorous statistical analysis; however, further studies with larger sample sizes are recommended to obtain more robust statistical information. In addition, it is important to investigate the expression of these genes concerning HAM/TSP and confirm their association with protein production to gain a better understanding of the underlying mechanisms of virus pathogenesis.

Conclusion

Our study revealed a significant increase in RAB3GAP2 expression among viral ATLL patients compared to ALL cases. The development of ATLL cancer has been associated with both viral and genetic factors. However, once the cancer has established itself and undergone characteristic alterations, the progression of the disease may follow a more consistent path. While different cancers may exhibit diverse pathways of progression, there may be shared factors underlying the malignant progression of the disease through distinct mechanisms. Therefore, comprehensive investigations of individual cancers cannot be generalized to all neoplasms and are limited to specific subtypes. Similar principles may apply to ATLL, where intracellular markers and molecular transformations during viral and non-viral pathogenesis occur concurrently upon entering the neoplastic phase.

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Author contributions

S.P, A.L: writing original draft, tables and figures, investigation, methodology. G.M: Investigation. M.N, SH.M: supervision, investigation, validation, review and editing.

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Data availability
Data will be made available on reasonable request from corresponding author (Dr. Sayed Hamidreza Mozhgani).

Declarations

Ethics approval and consent to participate
informed consent to participate was obtained from all of the participants in the study. In addition, this study was approved at Tehran University of Medical Sciences by the Ethics Committees of Medical Sciences Research (IR.TUMS.SPH.REC.1399.112). This study adhered to the Declaration of Helsinki.

Consent for publication
N/A.

Competing interests
The authors declare no competing interests.

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