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What Is Adult T-Cell Leukemia Pathogenesis? System Virology as a Solution of This Puzzle

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Dear Editor,

Human T-cell leukemia virus type 1 (HTLV-1) is a causative agent of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and the adult T-cell leukemia/lymphoma (ATLL) (1). There are 20 million HTLV-1 infected individuals worldwide. Of which, approximately 2% to 4% of HTLV-1 infected cases were developed to ATL; although, 90% of HTLV-1 infected individuals remain as an asymptomatic carrier (ACs) during their lives (2, 3).

ATLL is a progressive lymphoid malignancy, which characterized with an uncontrollable proliferation of CD4+ T cells after a long-lasting period of infection with HTLV-1 in ACs cases (3). The main mechanism of ATL remains unknown; however, it is suggested that cytokines and the immune system play a key role in the development of ATL (3, 4). Due to the existence of several inquiries regarding the ATL pathogenesis; this study was done for the analysis of the main changes in ATL patients compared to ACs via transcriptomic information during a system biology report.

In this study, the differentially expressed genes (DEGs) were retrieved from gene expression omnibus (GEO) datasets (accession number: GSE19080). DEGs were limited to immune-system, apoptosis, cell cycle, and cell growth was analyzed using Benjamini-Hochberg FDR-adjusted $P < 0.05$ in two different groups of ATLs and ACs individuals. Then, the protein-protein interaction network (PPIN) for significant genes was constructed via STRING online server. Finally, the signaling network for ATLs was proposed for completion of ATL pathogenesis model.

According to our analysis, there are over-expression of different genes including NF-kB, mTOR, PI3K/Akt, transactivation factor, T cell surface molecule as well as anti-apoptotic genes in ATLs; whereas downregulation of IFNG, Caspase, Foxp3, JAK-STAT, or cytokine such as TGF-β in this group. Several of these changes are predictable, for example, downregulation of IFN-γ production followed the destruction of functionality T cells; or decline of TGF-β in ATLs, which inhibits by HTLV-1 (HTLV-1 is inducing production of T cells whereas suppresser effects of TGF-β on T cells proliferation). In addition, our analysis showed that Foxp3 was downregulated in ATLs; given that T regulatory cells are limited T cell proliferation. Therefore, the expression levels of Foxp3 should be down-regulated in ATLs, which was confirmed in this study. Moreover, Janus tyrosine kinases (JAKs) is cause to proliferation or NF-kB and IL-2 was essential for T cell activation and proliferation. Therefore, JAK-STAT, NF-kB signaling pathway, and IL-2 production should be over-expressed in ATLs for T cells proliferation and develop to ATL, which is confirmed in our data analysis (Table 1) (2-5). According to the review of the literatures, *Tax* is induction of the transcription factors such as CREB, SRF, and AP-1, which is confirmed in our analysis (4, 5).

According to PPIN, PI3K/Akt, mTOR, JAK-STAT, NF_kB, and transactivation genes have central roles in ATL pathogenesis, which are located in central nodes. Cytokines, cyclin, T cell surface molecules, and anti-apoptosis genes are located in external nodes, which influenced by central nods (Figure 1).

Based on the signaling network, HBZ and Tax can promote T cells for cell growth and proliferation using several signaling pathways including NF_kB, PI3K, and MAPK signaling pathway, which lead to ATL during lengthy induction by HTLV-1 (Figure 2).

In summary, there is limited information regarding

Table 1. The Expression Profiles of ATLs and ACs Compared with Healthy Individuals

Gene Symbol	Description	Function	ATLs	ACs
BIRC5	Baculoviral IAP repeat containing 5	Apoptosis inhibitor	-0.38	-0.59
CDC2	Cell division cycle 2	Cell proliferation	-0.46	0.21
CDKN2A	Cyclin dependent kinase inhibitor 2A	Cell proliferation	0.26	-0.13
KCNAB1	Potassium voltage-gated channel subfamily a member regulatory beta subunit 1	Potassium channel	0.31	0.16
CREB1	CAMP responsive element binding protein 1	Transactivation	-0.54	0.001
CD25	Interleukin 2 receptor subunit alpha	IL-2 receptor	-0.53	-1.07
NFKBIE	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsilon	Pro- inflammatory response	0.24	0.25
mTOR	Mechanistic target of rapamycin kinase	Cell survive	1.15	0.37
Jak1	Janus kinase 1	Inflammation	0.11	0.04
TP53	Tumor protein P53	Tumor suppressor	0.74	-0.26
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase	Cell proliferation	0.08	-0.02
C-myc	C-myc myelocytomatosis viral oncogene	Cell proliferation	-0.78	-0.72
CCR5	C-C motif chemokine receptor 5	Fusion co-receptor	0.06	1.09
CDK6	Cyclin dependent kinase 6	Cell cycle regulators	0.31	0.41
Jun	Jun proto-oncogene	Transcription	-0.25	0.08
CDKN1A	Cyclin dependent kinase inhibitor 1A	Cell cycle regulators	0.07	-0.004
IRF-1	Interferon regulatory factor 1	Transactivation	0.48	0.63
SYK	Spleen associated tyrosine kinase	Inflammation	0.09	-0.85
NFKB1	Nuclear factor kappa B subunit 1	Inflammation	0.70	1.27
TGFB	Transforming growth factor-beta	Suppression of immune-system	-0.06	0.23
Foxp3	Forkhead box P3	Transcription	-0.49	-0.07
TRAF	TNF receptor associated factor	Inflammatory response	0.11	-0.024
ATF3	Activating transcription factor 3	Transcription	0.07	0.3
CREB	cAMP response element binding protein	Transcription	0.57	0.30
CXCR4	C-X-C motif chemokine receptor 4	Viral receptor	3.4	2.96
EF2	Eukaryotic translation elongation factor 2	Transcription	0.23	-0.72
STAT6	Signal transducer and activator of transcription 6	Transcription	-1.26	-0.19
IL-15	Interleukin 15	Inflammation	-0.25	0.13
SRF	Serum response factor	Transcription	0.45	0.51
BCL2	B-cell lymphoma 2	Cell survive	0.77	1.13
CASP9	Caspase 9 (apoptotic inducer)		-1.27	-0.98
IFNG	Interferon gamma	Inflammation	1.76	1.78

ATL pathogenesis; KEGG pathway (hsa05166) is not enriched enough and future investigation for ATL pathogenesis is needed. This information can be useful for the development of diagnosis, monitoring, and treatment of ATL patients. According to the present analysis, the immune-system changes, particularly cytokines, can have influenced several vital signaling pathways such as NF-kB, MAPK, and PI3K-Akt/mTOR signaling pathways, which regulate cell proliferation and is responsible for developing to adult T-cell leukemia/lymphoma.

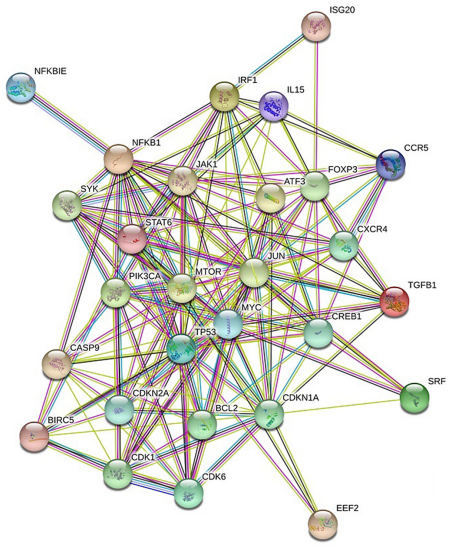

Figure 1. The protein-protein interaction networks among ATLs analyzed group

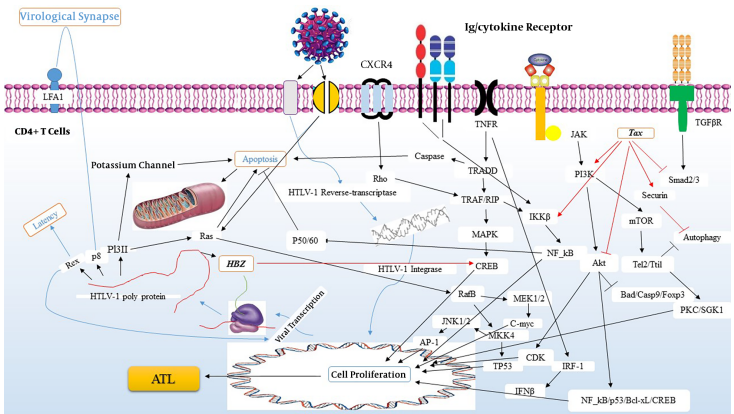

Figure 2. The signaling network in ATL pathogenesis in CD4+ T cells

Footnotes

Conflict of Interests: The authors declared no conflict of interests.

Ethical Approval: The Ethics Committee of Mashhad University of Medical Sciences approved the study.

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