

## Letter to Editor

# HTLV1-Associated Myelopathy Tropical Spastic Paraparesis Mechanism from System Virology Approach

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### Dear Editor;

Human T-cell leukaemia virus type I (HTLV-I) is retrovirus type C which has been identified since 30 years ago from cutaneous T-cell lymphoma (by Poiesz et al) as the first human retrovirus [1]. Given that literatures, approximately 10-20 million people have been infected with HTLV-1 which most HTLV-1-infected individuals are living in endemic countries including Japan, Caribbean, South America, Africa, Australia and Northeast of Iran (specially Mashhad, Neyshabour and Sabzevar).

HTLV-1 is transmitted throughout unsafe-sexual contact, blood transfusion, drug injection and breastfeeding [2-3]. HTLV-1 can cause adult T-leukemia (ATL), HTLV1-associated myelopathy tropical spastic paraparesis (HAM/TSP), arthritis, uveitis, infective dermatitis and lymphadenitis or Sjogren syndrome [3].

Although 90% of HTLV-1 infected individuals remain as asymptomatic carriers during their lives; 3- 0.25–4% of HTLV-1 infected persons develop HAM/TSP but accurate mechanism of

HAM/TSP remains unknown. There is limited information about risk factor of developing asymptomatic carriers into HAM/TSP [4]. Also, HTLV-1 does not have efficient specific standard chemotherapy and combination of IFN- $\alpha$  plus Zidovudine is only available option for treatment of HTLV-1 infection based on the empirical results [5].

According to the current evidence, HTLV-1 infected iTreg cells are reservoir and travel to central nervous system (CNS) and spinal cord via CD4+ T cells; disability and clinical symptoms develop following tissue destruction due to cytotoxic lymphocytes (CTLs) activities and chronic progressive inflammation in spinal cord [6]. The pro-inflammatory cytokines, such as IL-4, IL-6, IL-8, IFN- $\gamma$  and TNF- $\alpha$ , adhesion molecules, Fas/FasL play important role in HAM/TSP pathogenesis [7]. Determination of correct HAM/TSP pathogenesis is necessary for diagnosis and introduction of efficient treatment [4]. Obviously, transcriptome information is reliable source for infectious disease pathogenesis [4,7-8].

The aim of this study was the expression of novel evidence in HAM/TSP pathogenesis using system virology method. The gene expression profiles of PBMCs in individuals infected with the Human T-Lymphotropic virus Type 1 (HTLV-1) was obtained from NCBI Gene Expression Omnibus (GEO) database (Accession number: GSE29312; GPL6947 platform). Then, the GEO2R was employed for determination of differentially expressed genes (DEGs) and evaluation of fold

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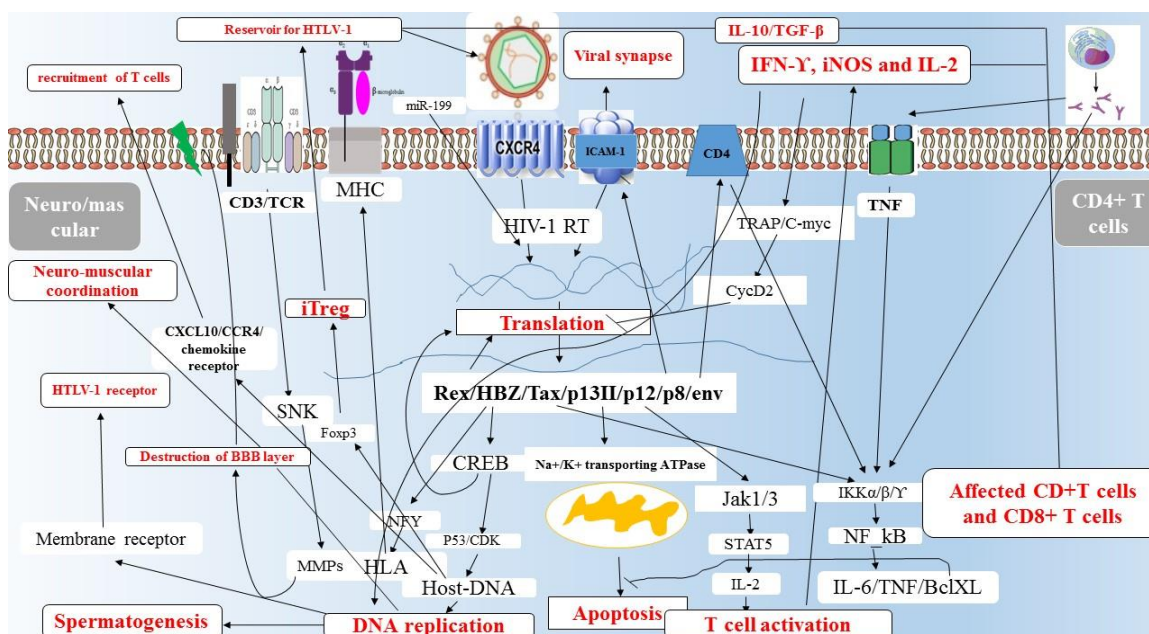


Fig. 1. The signaling network in HAM/TSP pathogenesis in CD4+ T cells and neuro/muscular cell lines.

change (FC) among two groups including asymptomatic carriers (ACs) and HAM/TSP using log<sub>2</sub> transformation and Benjamini-Hochberg FDR-adjusted p-values <0.05 for different genes limited to the immune-system and neuro-muscular network that is upregulated (positive logFC) and downregulated (negative logFC) in ACs vs HAM/TSP groups. Also, Protein-Protein interaction network (PPIN) is constructed via STRING online database [8]. Finally, HAM/TSP pathogenesis signaling network was built based on KEGG pathway and DEGs data analysis (Figure 1).

Given that our screening criteria, there are 83 different genes with remarkable differential expression between two groups (Table 1). According to different gene expression profiles of ACs vs HAM/TSP; There are remarkable changes in fold change expression of three class of Immune-system, nervous and muscular system. Various different class of signaling pathway, trans-membrane receptors, DNA-repair, apoptosis, cell survival and proliferative, Immune-modulatory and neuro-muscular related genes are dysregulated from ACs to HAM/TSP patients.

Totally, proliferation, persistent-inflammation, apoptosis and tissue destruction, and immune dysregulation are observed during progress of HAM/TSP pathogenesis. Of which, increase of

Immune-related cytokines, surface cell receptors and Foxp2/3 genes are interested, it is suggested that HTLV-1 is selected T regulatory cells as reservoir due to long half-life; Then, following tissue damage (because of IFN- $\gamma$  and inflammation) the clinical symptoms including walking disruption, urinary disturbance, faintness, constipation, and inferior backache (Table 1) [9-10].

HTLV-1 increased expression of surface receptors to influenced un-infected cells and induce inflammatory response to produce immune-suppressive cytokines such as IL-10 and TGF- $\beta$  for production of novel induce T regulatory cells (iTreg) (Figure 1).

In summary, our present system virology is confirmed current hypothesis about HAM/TSP pathogenesis with more details. It seems that Immune-dysregulation especially different cytokines expression in ACs individuals has key role in develop to HAM/TSP. In the other hand, HTLV-1 is successive intracellular pathogens which advantage from human host for hosting, replication and expansion in the human host using viral proteins specially HTLV-1 reverse transcriptase, protease, integrase, Tax and HBZ and provoke inflammatory process for production of Immune-suppressive cytokines during long-time inflammation and induction of iTregs as

reservoir sources; In addition, astrocytes gene expression patterns can help to this process via production of chemokines receptors for recruitment of CD4+ T cells into spinal cord. Moreover, clinical symptoms are appeared following constituted inflammation process. Therefore, targeting immune-cytokines and surface receptors could be as novel therapeutic option for HAM/TSP patients.

**Table 1. Different gene expression between ACs vs HAM/TSP individuals.**

Gene symbol	Gene name	LogFC
CARD17	caspase recruitment domain family member 17	-1.24
FCRL1	Fc receptor like 1	-1.30
DNAH12	dynein axonemal heavy chain 12	-1.57
HLA-C	major histocompatibility complex, class I, C	-3.98
IFITM3	interferon induced transmembrane protein 3	-1.17
KCNIP2	potassium voltage-gated channel interacting protein 2	-2.17
HLA-DRB6	major histocompatibility complex, class II, DR beta 6 (pseudogene)	-1.91
EPSTI1	epithelial stromal interaction 1 (breast)	-1.10
TNFRSF6B	TNF receptor superfamily member 6b	-3.67
FCGR1B	Fc fragment of IgG receptor 1b	-1.16
FCGR1A	Fc fragment of IgG receptor 1a	-1.15
GGT8P	gamma-glutamyl transferase 8 pseudogene	-1.86
NBEAP1	neurobeachin pseudogene 1	-4.80
BEX-1	brain expressed X-linked 1	-1.22
NRP2	neuropilin 2	-1.72
CASP5	caspase 5	-1.07
TLX2	T-cell leukemia homeobox 2	-3.30
NBPWR2	neuropeptides B/W receptor 2	-1.32
MYRF	myelin regulatory factor	-2.01
KIR2DL5A	killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 5A	-2.51
CD274	CD274 molecule	-2.24
MSC	musculin	-1.20
NBPF15	neuroblastoma breakpoint family member 15	-1.53
IL33	interleukin 33	-4.7
PMP22	peripheral myelin protein 22	-2.57
FOXP2	forkhead box P2	-1.09
ACER2	alkaline ceramidase 2	-1.17
TLR8	toll like receptor 8	-1.13
MIR99AHG	mir-99a-let-7c cluster host gene	-3.29
MBLN1	Muscle blind like splicing regulator 1	-2.45
MRAS	muscle RAS oncogene homolog	-1.36
HCG4	HLA complex group 4 (non-protein coding)	-1.20
SYN3	synapsin III	-1.10
RAX88	retina and anterior neural fold homeobox	-1.88
NXPE4	neurexophilin and PC-esterase domain family member 4	-1.79
NKIN1	Na+/K+ transporting ATPase interacting 1	-1.24
GABRA1	gamma-aminobutyric acid type A receptor alpha1 subunit	-1.25
NLGN4X	neuroligin 4, X-linked	-1.88
NETO1	neuropilin and tolloid like 1	-1.08
BAALC	brain and acute leukemia,	-1.05

	cytoplasmic	
IGHD	immunoglobulin heavy constant delta	-1.11
NSG1	neuron specific gene family member 1	1.41
KIR2DL5B	killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 5B	1.64
HSPG2	heparan sulfate proteoglycan 2	1.30
GGTLC1	gamma-glutamyl transferase light chain 1	1.59
TRAT1	T cell receptor associated transmembrane adaptor 1	2.58
NMBR	neuromedin B receptor	1.42
PAMR1	peptidase domain containing associated with muscle regeneration 1	2.99
DNAAF5	dynein axonemal assembly factor 5	2.90
CHRM3	cholinergic receptor muscarinic 3	2.85
ANTXR1	anthrax toxin receptor 1	1.09
NTRK2	neurotrophic receptor tyrosine kinase 2	5.15
IL6ST	interleukin 6 signal transducer	1.04
NTRK2	neurotrophic receptor tyrosine kinase 2	2.60
NRXN3	neurexin 3	3.41
MAG	myelin associated glycoprotein	2.73
NEU2	neuraminidase 2	4.28
CD34	CD34 molecule	1.85
AMER2	APC membrane recruitment protein 2	5.6
LENG9	leukocyte receptor cluster member 9	2.19
FGFR4	fibroblast growth factor receptor 4	4.85
KCNV1	potassium voltage-gated channel modifier subfamily V member 1	2.10
TLX1	T-cell leukemia homeobox 1	1.04
KLK9	kallikrein related peptidase 9	3.57
BCL11B	B-cell CLL/lymphoma 11B	1.02
OR2T5	olfactory receptor family 2 subfamily T member 5	3.20
CD177	CD177 molecule	1.51
MMP28	matrix metalloproteinase 28	1.23
ITGB4	integrin subunit beta 4	1.41
MFSD4A	major facilitator superfamily domain containing 4A	4.38
SOHLH1	spermatogenesis and oogenesis specific basic helix-loop-helix 1	3.59
MADD	MAP kinase activating death domain	2.19
NOSTRIN	nitric oxide synthase trafficking	1.74
CNOT6L	CCR4-NOT transcription complex subunit 6 like	1.67
NEUROD1	neuronal differentiation 1	1.01
TTY6B	testis-specific transcript, Y-linked 6B	1.20
CDKN2B	cyclin dependent kinase inhibitor 2B	1.60
NOS1	nitric oxide synthase 1	1.93
MASP1	mannan binding lectin serine peptidase 1	1.22
IL17RC	interleukin 17 receptor C	1.11
WBSCR17	Williams-Beuren syndrome chromosome region 17	1.04
FAIM	Fas apoptotic inhibitory molecule	1.04
CT45A1	cancer/testis antigen family 45, member A1	1.19

### Conflict of Interests

Nothing to declare

## Ethical Considerations

The Ethics Committee of Mashhad University of Medical Sciences was approved the study.

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## References

- Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc Natl Acad Sci U S A* 1980;77:7415-7419.
- Fani M, Rezayi M, Meshkat Z, Rezaee SA, Makvandi M, Abouzari-Lotf E, et al. Current approaches for detection of human T-lymphotropic virus Type 1: A systematic review. *J Cell Physiol*. 2019;234(8):12433-41.
- Rafatpanah H, Hosseini RF, Pourseyed SH. The Impact of immune response on HTLV-I in HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP). *Iran J Basic Med Sci*. 2013;16(3):235.
- Mozhgani SH, Zarei-Ghobadi M, Teymoori-Rad M, Mokhtari-Azad T, Mirzaie M, Sheikhi M, et al. Human T-lymphotropic virus 1 (HTLV-1) pathogenesis: A systems virology study. *J Cell Physiol*. 2018;119(5):3968-79.
- Alizadeh AA, Bohlen SP, Lossos C, Martinez-Climent JA, Ramos JC, Cubedo-Gil E, et al. Expression profiles of adult T-cell leukemia-lymphoma and associations with clinical responses to zidovudine and interferon  $\alpha$ . *Leuk Lymphoma*. 2010;51(7):1200-16.
- Yamano Y, Sato T. Clinical pathophysiology of human T-lymphotropic virus-type 1-associated myelopathy/tropical spastic paraparesis. *Front Microbiol*. 2012;3:389.
- Futsch N, Prates G, Mahieux R, Casseb J, Dutartre H. Cytokine Networks Dysregulation during HTLV-1 Infection and Associated Diseases. *Viruses*. 2018;10(12):691.
- Tattermusch S, Skinner JA, Chaussabel D, Banchereau J, Berry MP, McNab FW, et al. Systems biology approaches reveal a specific interferon-inducible signature in HTLV-1 associated myelopathy. *PLoS Pathog*. 2012;8(1): e1002480.
- Fuzii HT, da Silva Dias GA, de Barros RJ, Falcão LF, Quaresma JA. Immunopathogenesis of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). *Life Sci*. 2014;104(1-2):9-14.
- Keikha M, Karbalaie Zadeh Babaki M, Augusto Marcondes Fonseca L, Casseb J. The Relevance of HTLV-1-associated Myelopathy/Tropical Spastic Paraparesis in Iran: A Review Study. *Rev Clin Med*. 2019;6(2):60-65.