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Jalal Naghinezhad[1]*, Jalil Rohani[2], Shahriyar Gholizadeh[2], Sajjad Ehtiati[3], Jamshid Gholizadeh[4] and Hossein Ayatollahi[1]

[1]Department of Clinical Hematology and blood banking, Cancer Molecular Pathology Research center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Department of Biotechnology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Department of Clinical Biochemistry, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[4]Department of Clinical Immunology, Inflammation and inflammatory research center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

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***Corresponding author:** Jalal Naghinezhad, Inflammation and Inflammatory Diseases Division. Molecular pathology cancer research center. Hematology Dept. Ghaem Hosp. Mashhad University of Medical Sciences, Mashhad, Iran, Tel: +98 (51)3422749, (51); Email: Naghinezhadj961@mums.ac.ir

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Research Article

T-cell malignancies pathogenesis, a system hematology/oncology

Abstract

Human T-cell leukemia/lymphoma is one of the most aggressive hematologic malignancy, which associated with poor prognosis. T-cell prolymphocytic leukemia (TPLL), Sezary syndrome, and acute T cell lymphocytic leukemia (T-ALL) are included to T-cell neoplasm. It is important to understand the alteration among expression of the genes toward malignant T cells. For acquiring more insights in oncogenesis molecular events, the systems hematology analysis was done. At first, the differentially expressed genes (DEGs) were taken pairwise among the four sample sets of T-PLL .vs normal T-cell, Sezary syndrome .vs normal T-cell, and ATLL .vs normal T-cell. Then, the protein-protein interaction networks (PPINs) were reconstructed via using the hub genes. Finally, the pathways of cells proliferation and transformation were identified TPLL and Sezary syndrome and ATLL. Among all differentially expressed gene (DEG), 1538 gene has log fold change above 2 or under -2. The hub genes among DEGs were found. The results demonstrated, oncogenesis genes associated with proliferation, evade apoptosis and inflammation were significantly overexpressed in T-cell disorders. comparative investigation gene expression between T-PLL .vs normal T-cell, Sezary syndrome .vs normal T-cell, and ATLL .vs normal T-cell showed despite inflammatory genes such AP-1, AIF, NF-kB were overexpressed in T-cell disorders but in ATL it occurred significantly and important pathways like PI3K/Akt/mTOR are activated in T-cell disorders especially in ATL.

Introduction

Recent advances in cellular and molecular biology producing an excessive volume of complicated datain an interaction manner between hormones, neurotransmitters, eicosanoids, cytokines and genes. In addition, intra and extra protein-protein interaction network occurs among the cells in response to environmental triggers, which brings more intricacy Specify the outcome of an activity in a special tissue or organ to the surrounding microenvironment make it more intricacy. There are two main problems in reductionist molecular approach, the first one is producing information pollution and secondly, the systemic or physiological or physio-pathological interpretation are very hard. Therefore, using systemic approach in context of holistic program may help to understand the pathway which may produce particular consequences. Therefore, system biology programs might be helpful in such scientific situation.

T-cell lymphoproliferative disorders are a broad type of malignancy, which included several progressive cancers including T-PLL (T-cell prolymphocytic leukemia), sezary syndrome, and T-ALL .

T-PLL is one of the mature T-cell neoplasm, which accounts for 2% of all mature lymphocytic leukemia [1,2]. In this type of disease, there is post-thymic monoclonal prolymphocyte, which strongly expresses CD7, CD5, and CD2, and the lack of expression of TdT and CD1a [3,4]. Malignant cells have the normal size, high ratio of nuclear-to-cytoplasm, with a round to oval shape, and a single prominent nucleolus; the cytoplasm is agranular, with blebs [1]. Sezary syndrome is another T-cell neoplasm, which characterized by the triad phenomena. 1. Wide reddening of the skin (erythroderma), 2. Sezary cells (atypical T-lymphocytes) in peripheral blood, 3. Skin rushes. Furthermore, the most pertinent clinical aspect is erythroderma [5,6]. Generally, Sezary cells are mature monoclonal T-cell that expresses CD3+, CD4+ and CD8−; it may aberrantly not express T-cell antigens like CD7 [7].

Adult T cell leukemia/Lymphoma (ATLL) is viral (HTLV) associated T-cell neoplasm, which characterized by abnormal T-cell in peripheral blood [8]. Despite the HTLV-1 is endemic in some region, however, only the minority of infected subjects

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express ATLL (2-5%) and the majority of them remain asymptomatic [9]. ATL has a poor prognosis with a survival rate of very short around 11 months in lymphomatous and acute forms.

HTLV-1 is the first discovered oncovirus which bearing two oncogenic proteins, Tax and HBZ. Tax is a viral tans-activator, the immune-dominant protein of HTLV-1 which induces cell cycle and growth factors such as IL-2, IL-2Rα, GM-CSF. Therefore, HTLV-1 tax is necessary for cell transforming, while due to immunogenicity the virus decrement its expression by producing HBZ to escape from host immune system. Therefore, Tax inducing malignancy, but HBZ necessary for maintenance of the cancerous cells.

It is important to investigate and find hub genes that expressed in T-cell leukemia /lymphoma and analyze their role in this disease. So more investigation to find the hub DEGs expression among T-cell leukemia/lymphoma is necessary.

Material and Method

Gene expression microarray dataset

The gene expression profile of CD3 positive T-cells comprise a platform, GPL10558 Illumina HumanHT-12 V4.0 expression beadchip was obtained from NCBI Gene Expression Omnibus (GEO) database (Accession number: GSE107397 for T-PLL and sezary syndrome, GSE55851 for ATL with platform GPL10332 Agilent-026652 Whole Human Genome Microarray 4x44K v2).

Analysis of differentially expressed genes (DEGs)

The dataset was normalized by GEO2R. Differentially expression genes (DEGs) were identified through GEO detabase. In the same part fold change (FC) are also calculated. The DEGs were recognized between different data sets as three categories includes: 1) TPLL vs. normal T-cell, 2) sezary vs. normal T-cell, and 3) ATL vs. normal T-cell. Based on adjusted p-values <0.05 the DEGs was selected. The upregulated (positive logFC) and downregulated (negative logFC) genes recognized by Log FC. The heatmap was drawn by using package pheatmap in R 3.2.5.

Construction of PPIN and centrality analysis

For create the PPINs, we used the online STRING database. The cut off to analyze the PPINs were considered upper than 0.4 and we considered All interaction origins comprise physical and functional that may derive from co-expression, genomic context, high-throughput experiments, and previous. Then we used the Network Analyzer app in Cytoscape (3.7.0) for analyzation the PPINs. We calculate degree, closeness, and betweenness parameter by this software. The degree is a number of edges which are connected to each node. The closeness centrality is the shortest path between every two nodes. Another centrality parameter is the betweenness that is the number of their visiting during the crossing from all shortest paths. In the next step, each of the functional modules of T-PLL vs normal T-cell, Sezary syndrome vs normal T-cell, and ATL vs normal T-cell.

Finally, the Enrichr were utilized to enrich the identified hub DEGs in KEGG pathway to comprehend further intuition about communications. The hub genes of T-PLL vs normal T-cell, Sezary syndrome vs normal T-cell, and ATL vs normal T-cell were enriched in PI3K-Akt signaling, Ras signaling cancer, cancer, Pancreatic cancer, B cell receptor signaling cancer, and Adherence junction so the results confirm the cells proliferation, evade apoptosis, migration, and transformation due to change in aberrant signaling pathways.

Results

Correlation analysis of sample-sample

Correlation map (Figure 1) is the first figure of this paper and showed the distances of sample versus sample. Based on the sample correlation, this map compares the expression data and computed the results (expression of genes). The range of map color is from blue to red. Red shows no difference or higher correlation and blue indicates a low level of correlation (Figure 2).

In the heat map, the first 70 genes (ordering by variance)

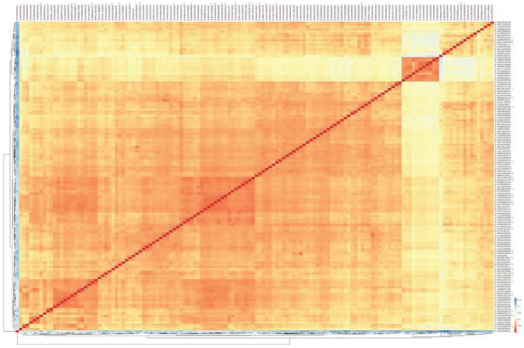

Figure 1: The heatmap of the pairwise sample correlation across different GSMs. The colors demonstrate the relative correlation between 70* samples as specified in the color key.

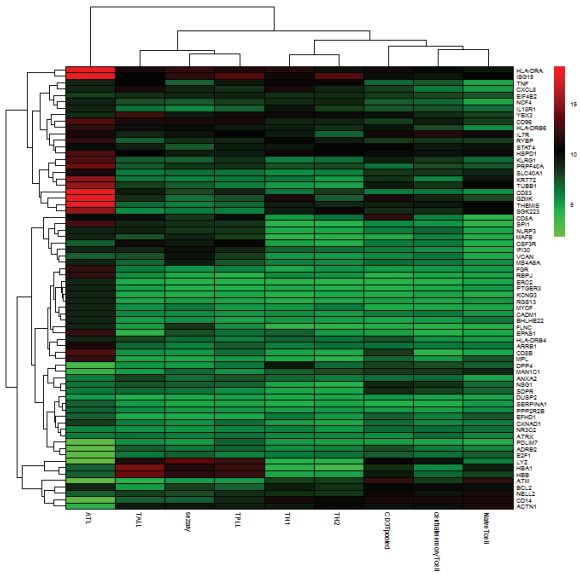

Figure 2: Heatmap: The heatmap of the hub genes over three* sample categories. The colors show the expression level of each gene.

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belonging to each group were plotted. In this map, mean gene expression in each sample was calculated. Based on variance difference the top 70 genes among five sample sets were elected. Upregulated genes are specified as red and downregulated genes are identified as green.

Analysis of DEGs

Based on adjusted P-value <0.05 as the criteria, 4487, 1799, and 31580 genes with remarkable differential expressions were found for five categories of Normal vs. ATL, Normal vs. sezary syndrome, and Normal vs. T-PLL respectively.

The identification of hub genes and common genes

To examine the stock relationship between the determined hub genes and the development of ATL, sezary syndrome, and TPLL the PPINs were utilized. The node size demonstrates the degree. The node color was ordered according to the closeness centrality. The edge color showed betweenness. Red color demonstrates low closeness and blue shows high closeness centrality.

PPIN construction

In gene ontology biological process (GO Biological Process) of enrichr website, each of the functional modules of TPLL vs. normal T-cell, sezary syndrome vs. normal T-cell, and ATL vs. normal T-cell were individually enriched. Afterward, based on inclusion of the gene, the meaningful modules were elected. Most of the nodes associated with cell proliferation, FC gamma receptors signaling and evade of apoptosis and inflammation. In addition, nucleotide-excision repair was upregulated (Figure 3).

The identification of functional modules and their ontology enrichment

Each of the functional modules of Normal vs. ATL, TPLL, and sezary syndrome were individually in gene ontology biological process (GO Biological Process) enriched. Most of the nodes associated with apoptosis and nucleotide-excision repair were upregulated, while the majority of the nodes associated with the negative regulation of cell differentiation were downregulated in ATL, TPLL, and sezary syndrome.

Discussion

The pathogenesis mechanism result from T-cell malignancies are not well recognized so far. Hub genes that involved in the development of the TPLL, ATL, and Sezary syndrome highlighted by network analysis. Sixty-two, fifty-eight, and forty-nine (Table 1,2) DEGs were found from TPLL Sezary syndrome, and ATL vs normal T-cells, respectively. These genes may involve in the pathogenesis pathway. Information extracted from KEGG demonstrated that these DEGs have a role in proliferation, evade of apoptosis, immune signaling pathways. DEGs between TPLL vs normal T-cell, Sezary vs normal T-cell, ATL vs. normal T-cell were enriched in GO Biologocal Process (Figure 4) and revealed the functions of these genes in positive regulation of transcription,

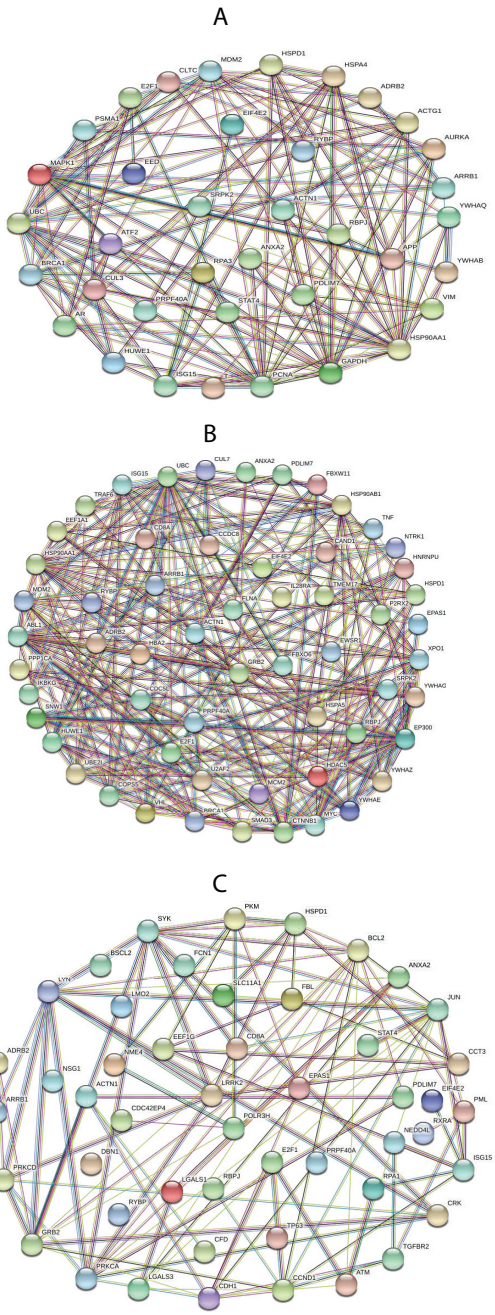

Figure 3: Protein-Protein interaction networks (PPINs) (Cytoscape): The Protein-Protein interaction networks (PPINs) formed between the identified hub DEGs of a (group1 vs. group2), b (group1vs. group3), and c (group2 vs. group3). The node size is indicative of degree of nodes and the node color is representative of the closeness centrality of nodes ranging from red (low value) to blue (high value). Also thickness of edges and edge color represent betweenness centrality. High values indicated by thick line and dark color (blue).

desensitization G protein receptor signaling, and regulate apoptosis signaling. In addition, some genes upregulated that have a role in lymphocyte activation and induce inflammation such NF-kB and AP-1.

Some events exist that proposed to induce tumorigenesis, which comprised of inflammation, cell survival, apoptosis inhibition, DNA repair blocking through deregulation of the related gene expression. Lymphocyte activation is the essential

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Table 1: List of the upregulated (positive logFC) and downregulated (negative logFC) hub genes in each group.

T-PLL vs normal T-cell		Sezary syndrome vs normal T-cell		ATL vs. normal T-cell	
Group1		Group2		Group3	
gene	logFC	gene	logFC	gene	logFC
E2F1	1.545432	NSG1	3.574519	STAT4	4.766895
ACTN1	1.06548	CD8A	3.150694	ACTN1	4.738796
RYBP	0.000765	STAT4	2.665425	ADRB2	4.248545
P2RX2	-0.11866	BCL2	2.49808	ARRB1	2.754718
TRAF6	-0.12748	TGFBR2	1.939543	APP	2.534831
CAND1	-0.15035	ATM	1.847538	PDLIM7	1.470234
CCDC8	-0.15052	ACTN1	1.777966	ATF2	-1.19377
VHL	-0.15421	FBL	1.768289	YWHAB	-1.19853
CUL7	-0.1549	RPA1	1.560724	YWHAQ	-1.34111
TMEM17	-0.16458	NME4	1.459423	HSPD1	-1.5186
YWHAG	-0.16611	DBN1	1.385098	MAPK1	-1.36513
CTNNB1	-0.17541	JUN	1.311091	ACTG1	-1.40582
GRB2	-0.18745	ADRB2	1.271	SRPK2	-1.43103
SRPK2	-0.19608	ANXA2	1.160805	HUWE1	-1.44426
MDM2	-0.1963	BSCL2	1.022361	PRPF40A	-1.45781
XPO1	-0.19959	CCT3	1.021859	HSPD1	-1.5186
ARRB1	-0.21034	PRKCA	1.018382	RBPJ	-1.58271
HUWE1	-0.21694	EEF1G	1.011577	EED	-1.61715
EWSR1	-0.23672	HSPD1	0.982609	EIF4E2	-1.62316
SNW1	-0.26237	HSPD1	0.982609	PSMA1	-1.6642
IKBKG	-0.26419	E2F1	0.891407	MDM2	-1.67015
PRPF40A	-0.27067	POLR3H	0.856254	RPA3	-1.681
ADRB2	-0.27456	CRK	-0.75889	HSPA4	-1.71179
HSPD1	-0.27456	LRRK2	-0.87036	GAPDH	-1.72972
NTRK1	-0.28097	RYBP	-0.90736	UBC	-1.78407
U2AF2	-0.29949	ARRB1	-0.9194	VIM	-2.11818
SMAD3	-0.31983	PRPF40A	-1.06064	PCNA	-2.17529
FBXW11	-0.34794	PKM	-1.0707	AURKA	-2.22123
UBE2I	-0.44742	PML	-1.07293	HSP90AA1	-2.28656
PDLIM7	-0.45358	RBPJ	-1.07795	RYBP	-2.65012
HDAC5	-0.48648	EPAS1	-1.08363	ANXA2	-2.90753
PPP1CA	-0.51775	PRKCD	-1.24591	CUL3	-3.0883
BRCA1	-0.53356	TP63	-1.33703	ISG15	-3.44707
EEF1A1	-0.55179	EIF4E2	-1.3602	BRCA1	-3.60192
RBPJ	-0.56595	GRB2	-1.40439	E2F1	-3.62836
HSPA5	-0.59293	LGALS3	-1.44806	AR	-4.3343
ABL1	-0.63564	CDC42EP4	-1.51235	EPAS1	-4.70134
YWHAZ	-0.68842	SYK	-1.5806		
COPS5	-0.70717	CCND1	-1.65001		
FLNA	-0.73114	PDLIM7	-1.76604		
IFNLR1	-0.79562	LMO2	-1.8425		
HNRNPU	-0.82901	RXRA	-1.94858		
EP300	-0.85891	LYN	-2.26973		
MYC	-0.88357	LGALS1	-2.31846		
FBXO6	-0.90107	NEDD4L	-2.39347		
EIF4E2	-0.91195	ISG15	-2.62421		
ISG15	-0.99293	CDH1	-2.75653		
HSP90AB1	-1.00027	FCN1	-3.80347		
HSP90AA1	-1.02422	CFD	-3.85889		
YWHAE	-1.11065	SLC11A1	-3.93497		
CDC5L	-1.11447				
UBC	-1.12304				
EPAS1	-1.3641				
MCM2	-1.47236				
ANXA2	-2.13503				
TNF	-3.48695				
TCL1A	-3.53427545				
CD8A	-3.87245				
HBA2	-3.91181				

Table 2: The common hub genes which identified.

Sets		Common Hub genes
Set1	Group1 vs Group2 & Group2 vs Group3 & Group1 vs Group3	ACTN1, ADRB2, ANXA2, HSPD1, E2F1, RYBP, ARRB1, PRPF40A, RBPJ, EPAS1, EIF4E2, PDLIM7, ISG15, ATM, TP53
Set2	Group1 vs Group3 & Group1 vs Group2	ACTN1, ADRB2, ARRB1, PDLIM7, PRPF40A, HSPD1, RBPJ, EIF4E2, RYBP, ANXA2, ISG15, E2F1, EPAS1, ATM, TP53
Set3	Group1 vs Group2 & Group2 vs Group3	ACTN1, ADRB2, ARRB1, PDLIM7, PRPF40A, HSPD1, RBPJ, EIF4E2, RYBP, ANXA2, ISG15, E2F1, EPAS1, ATM, TP53
Set4	Group2 vs Group3 & Group1 vs Group3	ACTN1, ADRB2, ANXA2, HSPD1, E2F1, RYBP, ARRB1, PRPF40A, RBPJ, EPAS1, EIF4E2, PDLIM7, ISG15, ATM, TP53
Set5	Group1 vs Group2	STAT4, ACTN1, ADRB2, ARRB1, PDLIM7, PRPF40A, HSPD1, RBPJ, EIF4E2, RYBP, ANXA2, ISG15, E2F1, EPAS1, ATM, TP53
Set6	Group1 vs Group3	ACTN1, ADRB2, ARRB1, PDLIM7, SRPK2, HUWE1, PRPF40A, HSPD1, RBPJ, EIF4E2, MDM2, UBC, HSP90AA1, RYBP, ANXA2, ISG15, BRCA1, E2F1, EPAS1, ATM, TP53
Set7	Group2 vs Group3	CD8A, ACTN1, ADRB2, ANXA2, HSPD1, E2F1, RYBP, ARRB1, PRPF40A, RBPJ, EPAS1, EIF4E2, GRB2, PDLIM7, ISG15, FCN1, ATM, TP53

aim of up- and down-regulated genes in ATLL progression. All of the three ways of lymphocyte activation are smart in ATL; I) NF-kappa B activation that lead to the upregulation of BCL2A1, II) Upregulation of MAP2K4 that result in activation of AP1 and III) Actuation of NFAT gene controlled from upregulation of CALM 1. Furthermore, to lymphocyte activation, NF-kappa B can stimulate cell survival, inflammatory responses, and apoptosis inhibition. Also, NF-kappa B is aroused by an increase of TLR5 and can be under direct influence of Tax protein [10].

One of the bold difference between ATL and other T-cell neoplasm is inflammation induced by HTLV-1. Some genes were overexpressed only in ATL that may stimulate through HTLV-1. HSPG2 takes part in the fundamental interaction between the HTLV-1 and the cell. On the other hand, HSPG2 works as a HTLV-1 receptor. The essential region of HSPG is endorepellin (C-terminal Domain V), which appended to the VEGFR2 upon endothelial cells and special integrin receptor

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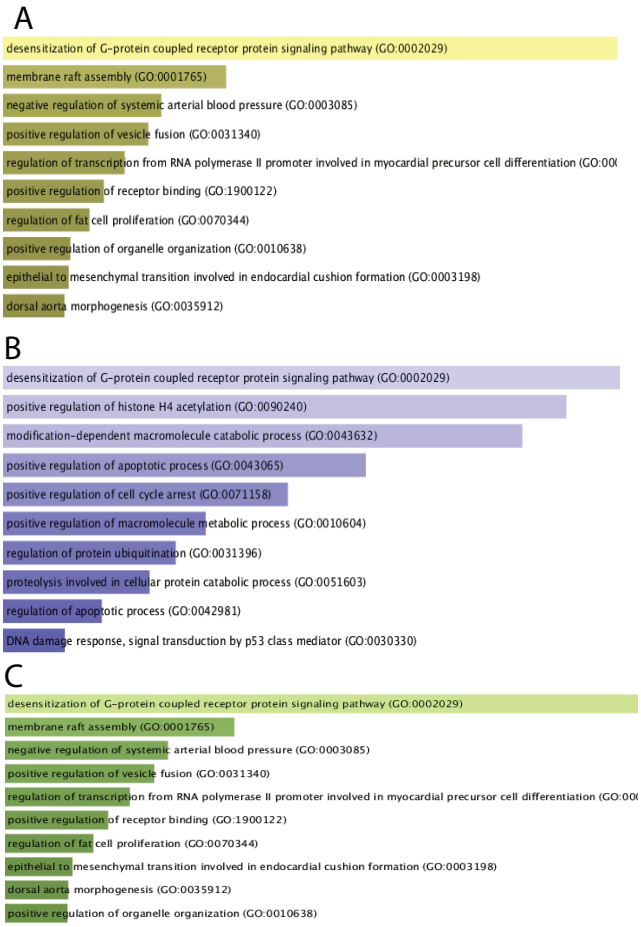

Figure 4: Gene ontology and biological process sorted by combined score (Enrichr): The functional modules identified from networks of (a) Group1, (b) Group2, (c) Group3. The most significant GO biological process term in top ranks of combined score was specified in each module.

(α2β1) [12]. CXCR3 was overexpressed significantly in just ATL, although in other malignant T-cell is slightly upregulated. This lead to enhances shift T-helper to TH-1 and induce inflammation and result in more progression of ATL [11]. Another important chemokine receptor that overexpressed in ATL is CXCR7, which regulates the interaction between endothelial cells and tumor cells in intra- and extravasation and exerts an anti-apoptotic action. Inflammatory proteins like allograft inflammatory factor 1 (AIF) is found in an immune cell in response to inflammatory cytokines like IL1 and INF gamma. In ATL upregulated significantly and lead to cell proliferation in response of inflammation. ISG 15 could be induced by HTLV-1 directly and upregulated common between T-PLL, ATL, sezary syndrome. ISG15 stimulate inflammation by activation of RIG1 and NF-kB.

In T-PLL and sezary syndrome development, the similar pathways to ATLL such mTOR and NF-kappa B pathways are influenced by different genes and lead to the same results. In T-PLL, TCL1A demonstrated the highest dysregulation. TCL1A as a booster of T-cell signaling input, its upregulation was associated with deregulations of TCR pathway modulators, suggesting a net improvement of antigen receptor and cytokine signaling in T-PLL. This included decreased expressions of the membranenegative-costimulatory CTLA4, reduce the suppressive T–T homotypic receptor SLAMF6, or of the T cell pro-apoptotic GIMAPs, andsignificant overexpression of TNF, also known to shape TCR signals. In addition, Upregulation of immunosuppressive CD83 result in more immune evasive properties [13]. In addition, TCL1A induce activation of NF-kB and result in activation and proliferation of malignant lymphocyte. Importantly this protein activates PI3K/Akt/mTOR pathway and interact with ATM. So has central role in T-PLL progression.

Over-activated pathways in TPLL, ATL, and sezary syndrome

PI3K/Akt/mTOR signaling pathway is activated in these malignancies in different ways. For example, in sezary syndrome, PTEN gene deletion leads to hyperactivation of this pathway and in ATL viral onco-proteins stimulate this pathway. This pathway is pivotal signaling pathway, which has a role in proliferation, survival, migration and evades of apoptosis [14]. This pathway regulates key proteins like MDM2, P27, P21, FKHR, caspase9, and NF-kB [15]. Activation of NF-kB lead to cell activation so has central role tumorgenesis. Furthermore, PI3K/AKT/mTOR regulate cell nutrition level and increase GLUT4 in the cell surface [16]. In term of anti-apoptotic function, this pathway downregulates BAD, BAX and upregulates BCL-2, BCL-xL, and MCL-1 [17]. In term of inflammation this pathway upregulates NF-kB. This pathway enhances cell proliferation through induce cap dependent translation by activation of mTOR.

Another important signaling pathway that activated in this type of malignancy is RAS signaling which has a pivotal role in proliferation and survival [18]. Ras signaling pathway activate important transcription factors like JUN, FOS, E2F.

Wnt/B catenin signaling pathway is critical pathway in pathogenesis of T-cell malignancies. This pathway has important role in tumorgenesis. This pathway activated from different rout. AKT can inhibit GSK3B (B catenin inhibitor) and activate this pathway. Besides Wnt binding to its receptor leads to activation of this pathway.

The JAK-STAT signaling pathway is an important signaling pathway that has a key role in T-cell malignancies, especially in T-PLL. This signaling pathway is associated with an important process like immunity, cell division, cell death, and tumor formation. This pathway can stimulate through different way such cytokine receptor and integrin.

Hub DEGs that contribute in TPLL, ATL, and sezary syndrome pathogenesis

A. downregulated hub genes: TP53 is an important protein, which has a pivotal role in cell cycle regulation, apoptosis, and angiogenesis. In ATL the operation of TP53 can be influenced by Tax protein as indirectly, downregulation of RPL5 and ATM genes, indirect increase NF-kappa B function, and effect on p38 [10]. As reported before, the reduction of p38 function can happen via downregulation of MAP2K6 and HSPG2 [12]. TP53 also downregulated in TPLL, and sezary syndrome.

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ATM is another important protein that downregulated in T-cell malignancy and leads to stimulate the perturbation in DNA repair through the reduction of BRCA1 expression level. In ATL interaction of HTLV-1 p30 with ATM lead to increases viral spread via facilitating cell survival (12).

B. Upregulated hub genes: NTRK1, Neurotrophic Tyrosine Kinase Receptor Type 1, is membrane receptor tyrosine kinase, when bind to its ligand, phosphorylates itself and members of the MAPK pathway. This provides an instructor that is essential for nerve cell development and survival [19]. Upregulation of NTRK1 that happened in TPLL, ATL, and sezary syndrome result in more T-cell proliferation and survival. In addition, activation of the MAPK pathway, induce activation of NFAT and NF-kB therefor stimulate inflammation.

Upregulation of BCL2 and BCL9 occurred in these T-cell malignancies and result in enhancing the survival of malignant cell and activation of Wnt/B catenin.

A membrane protein that highly expressed in the surface of malignant T-cell is DPPIV. This protein has an important function like immune regulation, signal transduction, and apoptosis. CD26/DPPIV plays an important role in tumor biology and is useful as a marker for various cancers [7].

Both LYN and FYN are members of Src kinase, which express in T-cell and neuronal signaling and defined as a proto-oncogene. Deregulation of these signaling is highlighted information of several cancers. FYN encoded a membrane-associated tyrosine kinase that regulates cell growth. FYN induce activation of Janus kinase (JAK), Abl, Src and focal adhesion kinase. LYN activation triggers a cascade of signaling events mediated by Lyn phosphorylation of tyrosine residues within the immune receptor tyrosine-based activation motifs (ITAM) of the receptor proteins. Deregulation of FYN and LYN happened in TPLL and sezary syndrome [20].

In conclusion, a significant aspect of our analyses is the expression alteration of genes accompanied by the inflammation and immune response in ATLL, T-PLL and sezary syndrome developments. Probably, these events are possible strategies that are used in the T-cell malignancies pathogenesis. Eventually, the comprehensive researches based on the low- and high-throughput evaluations are required to accelerate our finding of the complex diseases.

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Conflict of interest

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