BLOCKADE OF LIRs AS A NEW APPROACH FOR DIAGNOSTICS AND TREATMENT OF ATLL MALIGNANCY

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Abstract. In the new world of medicine, one of the main concerns in the field of infectious diseases has been focused on Human T-cell Leukemia Virus type 1 (HTLV-1). During the infection, lymphocyte inhibitory receptors (LIRs) play a prominent role in the occurrence of adult T-cell leukemia/lymphoma (ATLL). These receptors include LAG3, PD-1, TIGIT, CD160, TIM3, and 2B4. First, we have collected all microarray information on the profile of HTLV-1 infected patients from the Gene Expression Omnibus (http://www.ncbi.nlm.gov/geo) database until March 2020, in order to identify the microarray related to evolutionary development of LTRs during various phases of HTLV-1 infection in human peripheral blood CD4\textsuperscript{+} T cells by searching for keywords such as “Human T-lymphotropic virus type I (HTLV-1)”, “Homo sapiens”, “ATLL”, and “Whole genome sequencing”. Considering the main goal of the study, we have only assessed data related to Homo sapiens particularly CD4\textsuperscript{+} T cell lineage from human subjects infected with HTLV-1. We evaluated these receptors in ATLL patients compared to healthy control (HC) individuals and HTLV-1 infected-asymptomatic carriers (ASCs). Out of all 18 identified records, we only selected and analyzed three studies: GSE19080, GSE33615, and GSE57259, which satisfied inclusion criteria with proper quality analysis of ATLL vs. normal, ATLL vs. asymptomatic carrier as well as asymptomatic carrier vs. normal. Unfortunately, we could not analyze various stages of ATLL malignancy (acute, lymphomatous, chronic and smoldering) in all included studies due to the lack of sufficient information. Finally, based on Benjamini–Hochberg False discovery rate (FDR), the differentially expressed genes (DEGs) were selected for several categories. Hence, for the first time we demonstrated that the expression rate of LIRs in ATLL group was higher than either in asymptomatic carrier or healthy donor groups. As a conclusion, it seems that the blockade of LIRs has a pivotal role in diagnostics and treatment of ATLL malignancy.

Key words: ATLL, HAM/TSP, HTLV-1, LIRs, malignancy, immunity.
Introduction

In recent years, it has been demonstrated that high expression of inhibitor receptors on lymphocytes leads to modulation of function of co-stimulatory receptors and finally decreased T cell activity, tissue damage, and autoimmunity [1, 33]. According to in vitro evidence, about 24 h after stimulation of lymphocytes, lymphocyte inhibitory receptors (LIRs) begin to express and reach to their highest levels after 48 h [31]. Hence, it seems that long stimulation of lymphocytes increases the expression of LIRs genes, which in turn leads to the T cells dysfunction, and finally cancer [26, 33]. Based on recent studies, chronic inflammation by viral infection can cause excessive expression of LIRs and as a result downregulation of lymphocyte proliferation and dysregulation of cytokine release [30]. Like hepatitis C virus, Human T-cell leukemia virus type 1 (HTLV-1) is one of the most important single-stranded RNA viruses [2, 12]. Once it enters human circulatory system, HTLV-1 creates persistent infection and chronic inflammation through inhibition and escape mechanisms from facing immune responses. Therefore, it is likely that the activity of LIRs can have a positive impact on pathogenesis of HTLV-1 virus with clinical symptoms [14, 17]. This oncogenic virus belongs to Retroviridae family which has infected about 15–20 million people worldwide [15]. Although most infected individuals remain asymptomatic, 2–6% of them progress to adult T-cell leukemia/lymphoma (ATLL), and 2–3% to HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) [10, 13, 15]. ATLL is one of the most severe types of leukemia in which CD4+ T cells increase dramatically [28]. Although the pathogenesis of ATLL is still unknown, its most well-known features include immortalization of the infected CD4+ T cells, continuous lymphocyte proliferation, CD4+ T cell exhaustion and the increase in the number of regulatory (Treg) T cells of TGF-β and IL-10 cytokines [7, 11]. However, LIRs play an important role in the development of ATLL [9]. The aim of this study was to investigate the differences of expression of LIRs genes such as LAG3, PD-1, TIGIT, CD160, TIM3, and 2B4 in ATLL patients compared to healthy control (HC) individuals and HTLV-1 infected-asymptomatic carriers (ASCs).

Methods

First, we have collected all microarray information on the profile of HTLV-1 infected patients from Gene Expression Omnibus (http://www.ncbi.nlm.gov/geo) database till the end of March 2020, in order to identify the microarray related to evolutionary development of lymphocyte inhibitory receptor genes during various phases of HTLV-1 infection in CD4+ T cells of human subjects. The keywords such as “Human T-lymphotropic virus type I (HTLV-1)”, “Homo sapiens”, “ATLL”, and “Whole genome sequencing” were being used repeatedly. Considering the main goal of the study, we have only assessed data related to Homo sapiens particularly CD4+ T cell line of human subjects infected with HTLV-1. Quality and consistency of data was done using R package MetaQC. In the next step, both differentially expressed genes (DEGs) and Logarithm fold-change (logFC) were measured for several different categories such as: 1) ATLL vs. HC individuals; 2) ATLL vs. ASCs; 3) ASCs vs. HC individuals; 4) combination of various subtypes of ATLL by GEO2R; DEGs were selected according to Benjamini–Hochberg False discovery rate (FDR) with p value < 0.05. The positive logFC represents upregulation, whereas negative logFC represents downregulation. The lymphocyte inhibitory receptor genes were selected by Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, one of the best Enricher web tools based on the top combined scores. In addition, the super-network comprises protein interaction network between LIRs which was constructed by STRING online database version 10.5. Also, the heatmap plots were generated.
Results and discussion

From total of 18 identified records, we only selected and analyzed three studies: GSE19080 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE19080), GSE33615 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE33615), and GSE57259 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE57259); they all met our inclusion criteria with proper quality analysis of ATLL vs. normal, ATLL vs. asymptomatic carrier as well as asymptomatic carrier vs. normal. Unfortunately, we could not analyze various stages of ATLL malignancy (acute, lymphomatous, chronic and smoldering) in all included studies due to lack of information. Overall, the expression rate of LIRs in ATLL group was higher than either of asymptomatic carrier and healthy donor groups (Fig. 1, III cover).

It is notable that the expression rate of LIRs was also higher in ASCs in comparison with HC donors (Table). Among all, the analysis of GSE33615 study showed that expression of LIRs in particular PD-1 and LAG3 genes was significantly related to severity of the disease (p value < 0.001). In addition, ADAM10/17 gene is coded a transmembrane metalloprotease which is cleavage LAG 3 which is downregulated in precancerous phase (Table).

According to STRING network, a close relationship was observed among interfering genes in lymphocyte inhibitory process (Fig. 2, III cover). The PPIN networks consist of 11 nodes and 35 edges; the distance between each nodes represents a close relationship of the nodes. There is a dysregulation of function of LIRs expressing T cells which have been infected by HTLV-1; for example, Ouaguia et al. (2014) showed that the number of Treg type 1 (Tr1) cells which produce cytokines such as IL-10, TGF-β, CD18 and LAG3 increases in patients affected by ATLL [23]. Konnai et al. (2013) in their study on bovine leukemia virus (BLV), discovered that the expression of LAG3 increases on the surface of lymphocytes of bovis affected by leukemia [24]. In 2016, Yasuma et al. illustrated that HTLV-1 bZIP factor inhibits the cytotoxicity function of T CD8+ cells via induction of T-Cell Immunoglobulin and ITIM Domain (TIGIT) [32]. Ndhlovu et al. (2011) by monitoring the HAM/TSP patients, discovered that HTLV-1 tax specific CD8+ T cells decreases the expression of TIM3 receptor. They also realized that some unknown factors, through their non-inhibitory effects on HTLV-1 infected CD4+ T cells could cause a) apoptosis of HTLV-1 specific CD8+ T cells; 2) anergy; 3) expression of immune suppressor cytokines e.g. IL-10 and TGF-β; 4) support of Treg cells; 5) cell-proliferation and 6) HTLV-1 infected T cells develop into ATLL malignancy (Fig. 3, III cover).

Based on the results obtained in the present study, we demonstrated a significant increase in the expression of genes associated with lymphocyte inhibitory effect and their relationship with severity of the disease, in particular PD-1 and LAG3 genes in patients affected by ATLL. Some alterations such as cell proliferation, T cell exhaustion, and immune dysregulation are among the main factors related to the occurrence of HTLV-1 infected CD4+ T cells [24]. Recently, studies have shown that the number of T cells (CD4+ and CD8+) which express PD-1, would increase in ATLL patients [19, 29]. Either of two HBZ and Tax proteins of HTLV-1 virus can increase the expression of IL-10 by HTLV-1 infected CD4+ T cells. Also, the induction of Treg cells function in infected patients leads to the enhancement of IL-10, TGF-β, and secretion of epidermal growth factor (EGF), these changes could cause continuous proliferation and immortalization of HTLV-1 infected T cells, and are considered as risk factors for ATLL [7, 16, 23, 24]. There is a dysregulation of function of LIRs expressing T cells which have been infected by HTLV-1; for example, Ouaguia et al. (2014) showed that the number of Treg type 1 (Tr1) cells which produce cytokines such as IL-10, TGF-β, CD18 and LAG3 increases in patients affected by ATLL [23]. Konnai et al. (2013) in their study on bovine leukemia virus (BLV), discovered that the expression of LAG3 increases on the surface of lymphocytes of bovis affected by leukemia [24].

| GEO studies | Population setting | LAG3 | PD1 | ADAM10/17 | TIGIT | CD160 | TIM3 | 2B4 |
|-------------|------------------|------|-----|-----------|-------|-------|------|-----|
| GSE19080    | ATLL vs. ASCs    | 0.78 | 0.80| NA        | 0.11  | NA    | NA   | 0.18|
|             | ASCs vs. HC      | 0.55 | 0.29| NA        | 0.16  | NA    | NA   | 0.42|
|             | ATLL vs. HC      | 0.48 | 1.20| NA        | 0.47  | NA    | NA   | 0.61|
| GSE57259    | ATLL vs. HC      | 2.47 | 2.79| −0.97     | 3.19  | 0.06  | 0.31 |
|             | ATLL vs. HC      | 2.13 | −0.65| 0.45      | 1.13  | 0.31  | 1.29 | 1.39|
|             | Acute vs. Chronic| 0.29 | 0.03| −0.59     | −0.20 | −0.71 | 0.43 | −0.45|
|             | Acute vs. Smoldering| 2.51 | 1.30| 0.89      | 2.65  | −1.01 | 0.54 | 0.84|
|             | Chronic vs. Smoldering| 2.69 | 1.39| 1.50      | 2.73  | −0.23 | −0.11| 1.27|
|             | Lymphomatous vs. other types | 0.36 | 2.48| −0.54     | −1.50 | −1.21 | −1.69| −0.44|

Notes: LogFC — logarithm fold-change, ASCs — infected-asymptomatic carriers, HC — healthy control.
on exaggerated responses in immune system, could develop chronic progressive inflammation status [25]. In 2014, Chibueze et al. demonstrated that the expression of CD160 molecule on HTLV-1 specific CD8+ T cells will have an inhibitory effect on their function, and must be considered as a risk factor in developing the infection into ATLL [4]. In another related study, Ezinne et al. (2014) declared that blocking 2B4/CD48 interaction can increase functional capacity of the infected CD+ T cells (Fig. 3, III cover) [5].

In recent years, various studies have focused on the impact of LIRs blocking drugs for treating ATLL malignancy. For example, Pembrolizumab, which is a monoclonal antibody against PD-1, has successfully passed phase II clinical trial among T cell-lymphoma patients [3]. Relatlimab (CA224-060), as an anti-LAG3 has passed phase II of clinical trial [6]. Another Relatlimab (1302TP CA224-047) in combination with Nivolumab (anti-PD-1) is in phase II/III of the study [21]. Sym023, a human anti-TIM3, is a well-known antibody which inhibits TIM3 in vitro [20]. TSR-022, is a potent anti-human TIM-3 therapeutic antibody. Anti-CD160, alone or in combination with Bevacizumab, is considered as an inhibitor of ocular neovascularization in rabbit and monkey models [22]. Hence, it seems that blocking LIRs through supporting cytotoxicity of CD8+ T cells can be considered as an important strategy in containment and treatment of lymphoma, particularly in ATLL patients [13].

Conclusion

In summary, in the present study, we first showed that LIRs such as LAG3, PD-1, TIGIT, TIM3, CD160 and 2B4 were overexpressed in ATLL patients compared to asymptomatic carriers and healthy individuals. Hence, LIRs are considered as a significant biomarker in development of the infection to ATLL. On the other hand, LIRs blocking drugs can be used as the best candidates for treatment of ATLL malignancy. As noted before, several anti-LIRs are being used in both human and animal cases, including Pembrolizumab and Nivolumab (anti-PD-1), Relatlimab (anti-LAG3), Sym023 and TSR-022 (anti-TIM-3), and monoclonal antibodies against CD160, TIGIT, and 2B4.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References

1. Andrews L.P., Marciscano A.E., Drake C.G., Vignali D.A. LAG 3 (CD223) as a cancer immunotherapy target. Immun. Rev., 2017, vol. 276, no. 1, pp. 80–96. doi: 10.1111/imr.12519
2. Bangham C.R. Human T cell leukemia virus type 1: persistence and pathogenesis. Annu. Rev. Immunol., 2018, vol. 36, pp. 43–71. doi: 10.1146/annurev-immunol-042617-053222
3. Barta S.K., Zain J., MacFarlane A.W. 4th, Smith S.M., Ruan J., Fung H.C., Tan C.R., Yang Y., Alpaugh R.K., Dulaimi E., Ross E.A., Campbell K.S., Khan N., Siddharta R., Fowler N.H., Fisher R.I., Oki Y. Phase II study of the PD-1 inhibitor pembrolizumab for the treatment of relapsed or refractory mature T-cell lymphoma. Clin. Lymphoma Myeloma Leuk., 2019, vol. 19, no. 6, pp. 356–364.e3. doi: 10.1016/j.clml.2019.03.022
4. Chibueze C.E., Yoshimitsu M., Arima N. CD160 expression defines a uniquely exhausted subset of T lymphocytes in HTLV-1 infection. Biochem. Biophys. Res. Commun., 2014, vol. 453, no. 3, pp. 379–384. doi: 10.1016/j.bbrc.2014.09.084
5. Ezinne C.C., Yoshimitsu M., White Y., Arima N. HTLV-1 specific CD8+ T cell function augmented by blockade of 2B4/CD48 interaction in HTLV-1 infection. Plos One, 2014, vol. 9, no. 2: e87631. doi: 10.1371/journal.pone.0087631
6. Feehey K., Kelly R., Lipton LR., Chao J., Acosta-Rivera M., Earle D., Lei M., Kollia G., Tebbutt N.C. CA224-060: a randomized, open label, phase II trial of relatlimab (anti-LAG-3) and nivolumab with chemotherapy versus nivolumab with chemotherapy as first-line treatment in patients with gastric or gastroesophageal junction adenocarcinoma. Am. J. Clin. Oncol., 2019, vol. 37, no. 15: TPS4143. doi: 10.1200/JCO.2019.37.15_suppl.TPS4143
7. Futsch N., Prates G., Mahieux R., Casseb J., Dutartre H. Cytokine networks dysregulation during HTLV-1 infection and associated diseases. Viruses, 2018, vol. 10, no. 12: 691. doi: 10.3390/v10120691
8. Ghazvini K., Youssefi M., Keikha R. Expression changes of cytotoxicity and apoptosis genes in HTLV-1-associated myelopathy/tropical spastic paraparesis patients from the perspective of system virology. Access Microbiol., 2020, vol. 2, no. 3: acmi000088. doi: 10.1099/acmi.0.000088
9. Hude I., Sasse S., Engert A., Bröckelmann P.J. The emerging role of immune checkpoint inhibition in malignant lymphoma. Haematologica, 2017, vol. 102, no. 1, pp. 30–42. doi: 10.3324/haematol.2016.150656
10. Karbalaei M., Keikha M. Curcumin as an herbal inhibitor candidate against HTLV-1 protease. Jentashapir J. Health Res., 2019, vol. 10, no. 1: e92813. doi: 10.5812/jhr.92813
11. Karbalaei M., Keikha M. What is adult T-cell leukemia pathogenesis? System virology as a solution of this puzzle. Jundishapur. J. Chronic. Dis. Care, 2019, vol. 8, no. 3: e93351. doi: 10.5812/jccdc.93351
12. Keikha M., Eslami M., Yousefi B., Ali-Hassanzadeh M., Kamali A., Yousefi M., Karbalaei M. HCV genotypes and their determining role in hepatitis C treatment. VirusesDisease, 2020, vol. 31, no. 3, pp. 235–240. doi: 10.1007/s13337-020-00592-0
13. Keikha M., Ghazvini K., Eslami M., Yousefi B., Casseb J., Yousefi M., Karbalaei M. Molecular targeting of PD-1 signaling pathway as a novel therapeutic approach in HTLV-1 infection. Microb. Pathog., 2020, vol. 144: 104498. doi: 10.1016/j.micpath.2020.104498
14. Keikha M., Karbalaei M. Overview on coinfection of HTLV-1 and tuberculosis: mini-review. J. Clin. Tuberc. Other Mycobact. Dis., 2021, vol. 23: 100224. doi: 10.1016/j.jctube.2021.100224
15. Keikha M., Karbalaei Zadeh Babaki M., Marcondes Fonseca L.A., Casseb J. The relevance of HTLV-1-associated myeloproliferative/sarcoid spastic paraparesis in Iran: a review study. Rev. Clin. Med., 2019, vol. 6, no. 2, pp. 60–65. doi: 10.22038/RCM.2019.38759.1266

16. Kinosada H., Yasunaga J.I., Shimura K., Miyazato P., Onishi C., Iwata T., Inaba K., Matsuoka M. HTLV-1 bZIP factor enhances T-cell proliferation by impeding the suppressive signaling of co-inhibitory receptors. PLoS Pathog., 2017, vol. 13, no. 1: e1006120. doi: 10.1371/journal.ppat.1006120

17. Kinosada H., Yasunaga J.I., Shimura K., Matsuoka M. Functional impairment of co-inhibitory receptors promotes T-cell proliferation in HTLV-1-associated adult T-cell leukemia cells. Blood, 2016, vol. 128, no. 22, p. 2516. doi: 10.1182/blood.V112.22.2516.2516

18. Konnai S., Suzuki S., Shirai T., Ikebuchi R., Okagawa T., Sunden Y., Mingala C.N., Onuma M., Murata S., Ohashi K. Enhanced expression of LAG-3 on lymphocyte subpopulations from persistently lymphocytotic cattle infected with bovine leukemia virus. Comp. Immunol. Microbiol. Infect. Dis., 2013, vol. 36, no. 6, pp. 63–69. doi: 10.1016/j.cimid.2012.09.005

19. Kozako T., Yoshimitsu M., Fujiwara H., Masamoto I., Horai S., White Y., Akimoto M., Suzuki S., Matsushita K., Uozumi K., Tei C., Arima N. PD-1/PD-L1 expression in human T-cell leukemia virus type 1 carriers and adult T-cell lymphoma/leukemia patients. Leukemia, 2009, vol. 23, no. 2, pp. 375–382. doi: 10.1038/leu.2008.272

20. Lindsted T., Gad M., Grandal M.V., Frölich C., Bhatia V.K., Gjetting T., Lantto J., Horak I.D., Kragh M., Koefoed K., Pedersen M.W. Preclinical characterization of Sym023 a human anti-TIM3 antibody with a novel mechanism of action. AACR, 2018, vol. 78, no. 13: 5629. doi: 10.1155/2018/5629

21. Lipson E.J., Long G.V., Tawbi H., Schadendorf D., Atkinson V.G., Maurer M., Simonsen K.L., Harbison C., Hodi F.S. CA224-Sym023 in combination with nivolumab in patients with progressing exclusive melanoma. J. Immunol., 2018, vol. 188, no. 7, pp. 3972–3985. doi: 10.1111/jimm.14290

22. Mori N., Gill P.S., Moundi T., Murakami S., Eto S., Prager D. Interleukin-10 gene expression in adult T-cell leukemia. Blood, 1996, vol. 88, no. 3, pp. 1035–1045.

23. Mozghani S.H., Zarei-Gholami B., Meymouri-Rad A., Mohktari-Azad T., Mirzaie M., Sheikhzadeh M., Keshavarz M., Shahbarami R., Ghourchian H., Jafari M., Rezaee S.A., Norouzi M. Human T-lymphotropic virus 1 (HTLV-1) pathogenesis: a systems virology study. J. Cell Biochem., 2017, vol. 119, no. 5, pp. 3968–3979. doi: 10.1002/jcb.26546

24. Ndhlovu L.C., Leal F.E., Hasenkrug A.M., Jha A.R., Carvalho K.I., Eccles-James I.G., Bruno F.R., Vieira R.G., York V.A., Tei C., Arima N. PD-1/PD-L1 expression in human T-cell leukemia virus type 1 carriers and adult T-cell leukemia/lymphoma patients. Leukemia, 2009, vol. 23, no. 2, pp. 375–382. doi: 10.1038/leu.2008.272

25. Ndhlovu L.C., Leal F.E., Hasenkrug A.M., Jha A.R., Carvalho K.I., Eccles-James I.G., Bruno F.R., Vieira R.G., York V.A., Tei C., Arima N. PD-1/PD-L1 expression in human T-cell leukemia virus type 1 carriers and adult T-cell leukemia/lymphoma patients. Leukemia, 2009, vol. 23, no. 2, pp. 375–382. doi: 10.1038/leu.2008.272

26. Oo K., Kato Y., Shimauchi T., Kabashima K., Nakashima D., Sugita K., Yamada Y., Tokura Y. Augmented expression of programmed death-1 in both neoplastic and non-neoplastic CD4+ T-cells in adult T-cell leukemia/lymphoma. Viruses, 2019, vol. 11, no. 12, pp. 2585–2590. doi: 10.3390/v11122585

27. Oo K., Kato Y., Shimauchi T., Kabashima K., Nakashima D., Sugita K., Yamada Y., Hino R., Tokura Y. Augmented expression of programmed death-1 in both neoplastic and non-neoplastic CD4+ T-cells in adult T-cell leukemia/lymphoma. Int. J. Cancer, 2007, vol. 121, no. 12, pp. 2585–2590. doi: 10.1002/ijc.23042

28. Orduzzi P.M., Wherry E.J. Inhibitory receptors on lymphocytes: insights from infections. J. Immunol., 2012, vol. 188, no. 7, pp. 2957–2965. doi: 10.4049/jimmunol.1100388

29. Ouagui L., Mriazik D., Renaud S., Moralès O., Delhem N. Control of the inflammatory response mechanisms mediated by natural and induced regulatory T-cells in HCV-, HTLV-I-, and EBV-associated cancers. Mediators Inflamm., 2014: 56296. doi: 10.1155/2014/56296

30. Rodríguez-Zúñiga M., Cortez-Franco F., Quijano-Gomero E. Adult T-cell leukemia/lymphoma. Actas Dermosifiliogr. (Engl. Ed.), 2018, vol. 109, no. 5, pp. 399–407. doi: 10.1016/j.ad.2017.08.014

31. Shimauchi T., Kabashima K., Nakashima D., Sugita K., Yamada Y., Hino R., Tokura Y. Augmented expression of programmed death-1 in both neoplastic and non-neoplastic CD4+ T-cells in adult T-cell leukemia/lymphoma. Int. J. Cancer, 2007, vol. 121, no. 12, pp. 2585–2590. doi: 10.1002/ijc.23042

32. Virgin H.W., Wherry E.J., Ahmed R. Redefining chronic viral infection. Cell, 2009, vol. 138, no. 1, pp. 30–50. doi: 10.1016/j.cell.2009.06.036

33. Workman C.J., Rice D.S., Dugger K.J., Kurschner C., Vignali D.A. Phenotypic analysis of the murine CD4 related glycoprotein, CD223 (LAG-3). Eur. J. Immunol., 2002, vol. 32, no. 8, pp. 2255–2263. doi: 10.1002/1521-4141(2002)32:8<2255::AID-IMMU2255>3.0.CO;2-A

34. Yasuma K., Yasunaga J.I., Takemoto K., Sugata K., Mitobe Y., Takenouchi N., Nakagawa M., Suzuki Y., Matsuoka M. HTLV-1 bZIP factor impairs anti-viral immunity by inducing co-inhibitory molecule, T cell immunoglobulin and ITIM domain (TIGIT). PLoS Pathog., 2016, vol. 12, no. 1: e1005372. doi: 10.1371/journal.ppat.1005372

35. Zarour H.M. Reversing T-cell dysfunction and exhaustion in cancer. Clin. Cancer Res., 2012, vol. 18, no. 2, pp. 1856–1864. doi: 10.1158/1078-0432.CCR-13-1849
Figure 1. The protein network interaction between various lymphocyte inhibitory receptors (LIRs)

Figure 2. The heatmap of the lymphocyte inhibitory receptors expressed genes in HTLV-1 infected patients; colors demonstrate the expression level of each gene

Figure 3. Proposed hypothesis network to determine the crucial role of lymphocyte inhibitory receptors in alternation of signaling pathway in tumor microenvironment of ATLL patients