Russian Journal of Infection and Immunity = Infektsiya i immunitet
2021, vol. 11, no. 6, pp. 1185–1189

Инфекция и иммунитет
2021, Т. 11, № 6, с. 1185–1189

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

M. Keikha[a], M. Karbalaei[b]

[a] *Mashhad University of Medical Sciences, Mashhad, Iran*
[b] *Jiroft University of Medical Sciences, Jiroft, Iran*

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 $CD4^+$ 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 $CD4^+$ 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.*

БЛОКАДА LIRs КАК НОВЫЙ ПОДХОД К ДИАГНОСТИКЕ И ЛЕЧЕНИЮ Т-КЛЕТОЧНОГО ЛЕЙКОЗА ВЗРОСЛЫХ

Кеиха М.[1], Карбалаеи М.[2]

[1] *Мешхедский университет медицинских наук, г. Мешхед, Иран*
[2] *Исламский университет Азад, филиал Тонкабон, г. Тонкабон, Иран*

Резюме. В современной медицине одной из основных проблем в области инфекционных заболеваний является вирус Т-клеточного лейкоза человека 1 типа (HTLV-1). Важную роль в возникновении Т-клеточного лейкоза/лимфомы взрослых (ATLL) на фоне HTLV-1-инфекции играют лимфоцит-ингибирующие рецепторы (LIR). К LIR относятся LAG3, PD-1, TIGIT, CD160, TIM3 и 2B4. Для проведения исследования из базы данных Gene Expression Omnibus (http://www.ncbi.nlm.gov/geo) по таким ключевым словам, как «Т-лимфотропный вирус человека типа I (HTLV-1)», «Homo sapiens», «ATLL» и «полногеномное секвенирование», была собра-

Адрес для переписки:
Мохсен Карбалаеи
Иран, г. Джирофт, Университет медицинских наук Джирофта.
Тел.: +98 913 193-36-12.
E-mail: mohsen.karbalaei@jmu.ac.ir

Contacts:
Mohsen Karbalaei
Iran, Jiroft, Jiroft University of Medical Sciences.
Phone: +98 913 193-36-12.
E-mail: mohsen.karbalaei@jmu.ac.ir

Для цитирования:
Кеиха М., Карбалаеи М. Блокада LIRs как новый подход к диагностике и лечению Т-клеточного лейкоза взрослых // Инфекция и иммунитет. 2021. Т. 11, № 6. С. 1185–1189. doi: 10.15789/2220-7619-BOL-1635

Citation:
Keikha M., Karbalaei M. Blockade of LIRs as a new approach for diagnostics and treatment of ATLL malignancy // Russian Journal of Infection and Immunity = Infektsiya i immunitet, 2021, vol. 11, no. 6, pp. 1185–1189. doi: 10.15789/2220-7619-BOL-1635

DOI: http://dx.doi.org/10.15789/2220-7619-BOL-1635

на вся информация о результатах детекции LIR в CD4+ Т-клетках периферической крови пациентов, инфицированных HTLV-1, с помощью технологии микрочипов для изучения эволюции LIR на разных стадиях HTLV-1-инфекции. Поиск был ограничен мартом 2020 г. Принимая во внимание главную цель исследования, мы провели оценку данных, относящихся к *Homo sapiens*, в частности к линии CD4+ Т-клеток людей, инфицированных HTLV-1. Мы изучали эти рецепторы у пациентов с ATLL в сравнении со здоровыми людьми из контрольной группы (КГ) и у бессимптомных носителей HTLV-1. Из всех 18 обнаруженных исследований мы выбрали и проанализировали только три работы: GSE19080, GSE33615 и GSE57259, которые удовлетворяли критериям включения с надлежащим качественным анализом ATLL по сравнению с контролем, ATLL по сравнению с бессимптомным носительством, а также бессимптомное носительство по сравнению с контролем. К сожалению, мы не смогли проанализировать различные стадии ATLL (острая, лимфоматозная, хроническая и медленная) во всех включенных исследованиях из-за отсутствия достаточной информации. Наконец, на основе коэффициента ложного обнаружения Бенджамини–Хохберга (FDR) для нескольких категорий были отобраны дифференциально экспрессируемые гены (DEG). Таким образом, мы впервые продемонстрировали, что уровень экспрессии LIR в группе ATLL был выше, чем в группе бессимптомных носителей или здоровых доноров. В заключение следует отметить, что, по нашим предположениям, блокада LIR играет ключевую роль в диагностике и лечении злокачественных новообразований ATLL.

Ключевые слова: *ATLL, HAM/TSP, HTLV-1, LIRs, злокачественность, иммунитет.*

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

using Morpheus (https://software.broadinstitute.org/morpheus) [8]. In the final step, we have proposed the signaling network in relation to potential role of the lymphocyte inhibitory receptor genes during pathogenesis of HTLV-1 infection.

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 contribution and cooperative functions of each node as well as the color of the edges which is responsible for type of each experiments which confirmed relationship between each node.

According to KEGG and wikiPathway databases in relation to the effects of the lymphocyte inhibitory receptor genes and their alternation in normal signaling pathway during HTLV-1 infection, constant stimulation and continuous expression of LIRs on HTLV-1 infected $CD4^+$ T cells could cause: 1) 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]. 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

Table. LogFC of ATLL vs ASCs or HC, as well as ATLL subtypess

GEO studies	Population setting	LAG3	PD1	ADAM10/17	TIGIT	CD160	TIM3	2B4
GSE19080	ATLL vs. ASCs	0.78	0.80	NA	NA	0.11	NA	0.18
	ASCs vs. HC	0.55	0.29	NA	NA	0.16	NA	0.42
	ATLL vs. HC	0.48	1.2	NA	NA	0.47	NA	0.61
GSE57259	ATLL vs. HC	2.47	2.79	–0.97	NA	3.19	0.06	0.31
GSE33615	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

Note. LogFC — logarithm fold-change, ASCs — infected-asymptomatic carriers, HC — healthy control.

on exaggerative 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 ATTL malignancy. For example, Pembrolizumab, which is a monoclonal antibody against PD-1, has successfully passed phase II of 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 (1302TiP 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. Feeney 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 M. 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/jjhr.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/jjcdc.93351*
12. Keikha M., Eslami M., Yousefi B., Ali-Hassanzadeh M., Kamali A., Yousefi M., Karbalaei M. HCV genotypes and their determinative role in hepatitis C treatment. *VirusDisease, 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: 104198. doi: 10.1016/j.micpath.2020.104198*
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 myelopathy/tropical 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., Iyoda 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.V128.22.2516.2516*
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. 1, 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 leukemia/lymphoma 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: 10.1158/1538-7445.AM2018-5629*
21. Lipson E.J., Long G.V., Tawbi H., Schadendorf D., Atkinson V.G., Maurer M., Simonsen K.L., Harbison C., Hodi F.S. CA224-047: a randomized, double-blind, phase II/III study of relatlimab (anti-LAG-3) in combination with nivolumab (anti-PD-1) versus nivolumab alone in previously untreated metastatic or unresectable melanoma. *Ann. Oncol., 2018, vol. 29, no. 8, pp. viii464–viii465. doi: 10.1093/annonc/mdy289.058*
22. Menguy T., Briaux A., Jeunesse E., Giustiniani J., Calcei A., Guyon T., Mizrahi J., Haegel H., Duong V., Soler V., Brousset P., Bensussan A., Raymond Letron I., Le Bouteiller P. Anti-CD160, alone or in combination with bevacizumab, is a potent inhibitor of ocular neovascularization in rabbit and monkey. *Invest. Ophthalmol. Vis. Sci., 2018, vol. 59, no. 7, pp. 2687–2698. doi: 10.1167/iovs.18-24024*
23. Mori N., Gill P.S., Mougdil 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.*
24. Mozhgani S.H., Zarei-Ghobadi M., Teymoori-Rad M., Mokhtari-Azad T., Mirzaie M., Sheikhi M., Jazayeri S.M., Shahbahrami 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., 2018, vol. 119, no. 5, pp. 3968–3979. doi: 10.1002/jcb.26546*
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., Chew G.M., Jones R.B., Tanaka Y., Neto W.K., Sanabani S.S., Ostrowski M.A., Segurado A.C., Nixon D.F., Kallas E.G. HTLV-1 tax specific $CD8^+$ T cells express low levels of Tim-3 in HTLV-1 infection: implications for progression to neurological complications. *PLoS Negl. Trop. Dis., 2011, vol. 5, no. 4: e1030. doi: 10.1371/journal.pntd.0001030*
26. Odorizzi 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.1100038*
27. Ouaguia L., Mrizak D., Renaud S., Moralès O., Delhem N. Control of the inflammatory response mechanisms mediated by natural and induced regulatory T-cells in HCV-, HTLV-1-, and EBV-associated cancers. *Mediators Inflamm., 2014: 564296. doi: 10.1155/2014/564296*
28. Rodríguez-Zúñiga M., Cortez-Franco F., Qujiano-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*
29. 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*
30. 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*
31. 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(200208)32:8<2255::AID-IMMU2255>3.0.CO;2-A.*
32. 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*
33. Zarour H.M. Reversing T-cell dysfunction and exhaustion in cancer. *Clin. Cancer Res., 2016, vol. 22, no. 8, pp. 1856–1864. doi: 10.1158/1078-0432.CCR-15-1849*

Авторы:
Кеиха М., к.н., кафедра микробиологии и вирусологии медицинского факультета, Мешхедский университет медицинских наук, г. Мешхед, Иран;
Карбалаеи М., к.н., кафедра микробиологии и вирусологии медицинской школы, Университет медицинских наук Джирофта, г. Джирофт, Иран.

Authors:
Keikha M., PhD, Department of Microbiology and Virology, Faculty of Medicine, Mashhad University Medical Sciences, Mashhad, Iran;
Karbalaei M., PhD, Department of Microbiology and Virology, School of Medicine, Jiroft University of Medical Sciences, Jiroft, Iran.

Поступила в редакцию 10.11.2020
Отправлена на доработку 28.03.2021
Принята к печати 10.04.2021

Received 10.11.2020
Revision received 28.03.2021
Accepted 10.04.2021

Иллюстрации к статье «Блокада LIRs как новый подход к диагностике и лечению Т-клеточного лейкоза взрослых» (авторы: М. Кеиха, М. Карбалаеи) (с. 1185–1189)

Illustrations for the article “Blockade of LIRs as a new approach for diagnostics and treatment of ATLL malignancy” (authors: Keikha M., Karbalaei M.) (pp. 1185–1189)

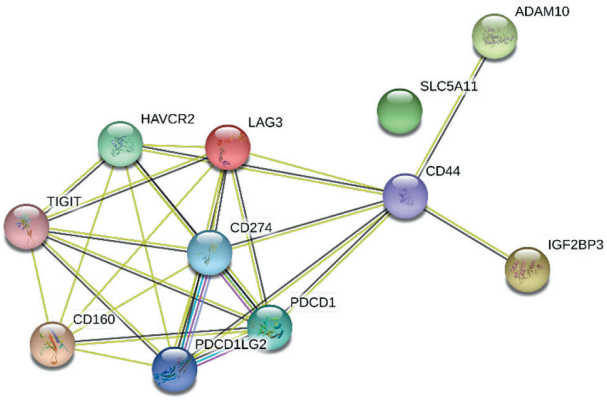

Figure 1. The protein network interaction between various lymphocyte inhibitory receptors (LIRs)

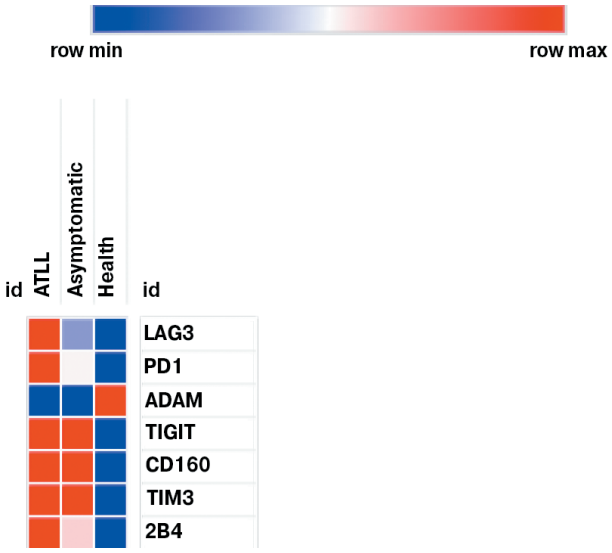

Figure 2. The heatmap of the lymphocyte inhibitory receptors expressed genes in HTLV-1 infected patients; colors demonstrate the expression level of each gene

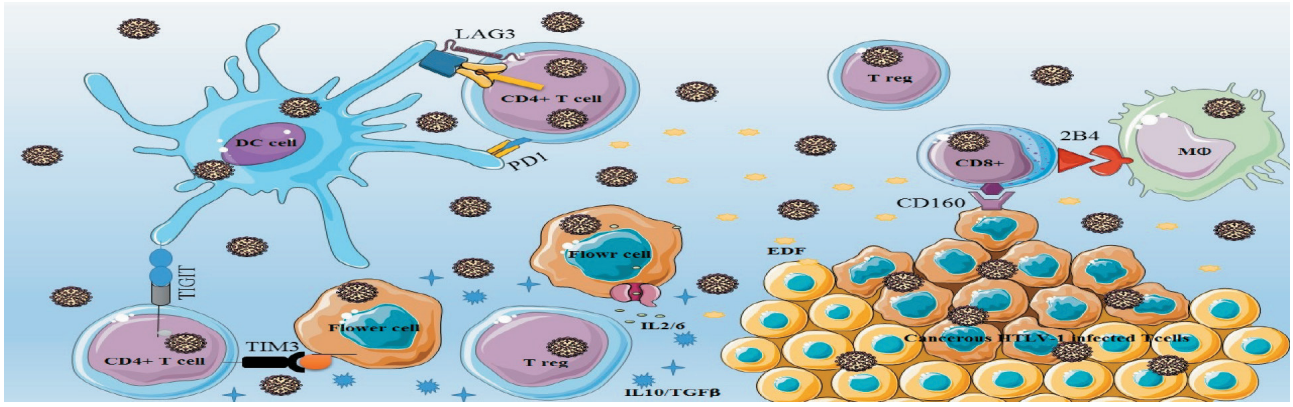

Figure 3. Proposed hypothesis network to determine the crucial role of lymphocyte inhibitory receptors in alternation of signaling pathway in tumor microenvironment of ATLL patients