International Immunopharmacology 112 (2022) 109188

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Analysis of expression of regulatory T cell related lncRNAs in inflammatory demyelinating polyneuropathies

Mohammad Taheri [a,b], Shayeste Roustapour [c], Mahdi Gholipour [d], Bashdar Mahmud Hussen [e,f], Solat Eslami [g,h], Soudeh Ghafouri-Fard [i,*], Arezou Sayad [i,*]

[a] Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Institute of Human Genetics, Jena University Hospital, Jena, Germany
[c] School of Medicine, Qazvin University of Medical Sciences, Qazvin, Iran
[d] Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[e] Department of Pharmacognosy, College of Pharmacy, Hawler Medical University, Kurdistan Region, Erbil, Iraq
[f] Center of Research and Strategic Studies, Lebanese French University, Erbil, Kurdistan Region, Iraq
[g] Department of Medical Biotechnology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran
[h] Dietary Supplements and Probiotic Research Center, Alborz University of Medical Sciences, Karaj, Iran
[i] Department of Medical Genetics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
FLICR
NEST
RMRP
TH2-LCR
lncRNA
Inflammatory demyelinating polyneuropathies

ABSTRACT

Long non-coding RNAs that regulate function of regulatory T cells can affect pathoetiology of autoimmune disorders, such as inflammatory demyelinating polyneuropathies. In the current case-control study, we compared expression of four of these lncRNAs, namely FLICR, NEST, RMRP and TH2-LCR between patients with inflammatory demyelinating polyneuropathies and healthy subjects. Expressions of RMRP, NEST and FLICR were higher in total patients compared with controls. However, there was no significant difference in their expressions between acute and chronic demyelinating polyneuropathies. In addition, interaction of gender and disease factors had significant effect on expression levels of RMRP and TH2-LCR genes in subgroups. RMRR was superior to other lncRNAs in terms of AUC, sensitivity and specificity values in total patients and both subgroups of patients. This lncRNA could separate total patients, female patients and male patients from corresponding controls with AUC values (±SD) of 0.9 ± 0.03, 0.86 ± 0.07 and 0.93 ± 0.03, respectively. FLICR ranked second in this regard, since it could separate total patients, female patients and male patients from corresponding controls with AUC values (±SD) of 0.81 ± 0.03, 0.72 ± 0.07 and 0.87 ± 0.04, respectively. Therefore, our study provides evidence for participation of regulatory T cells-related lncRNAs in the pathoetiology of inflammatory demyelinating polyneuropathies.

1. Introduction

Inflammatory demyelinating polyneuropathies comprise a group of diseases with either acute or chronic course (acute inflammatory demyelinating polyneuropathy (AIDP) versus chronic inflammatory demyelinating polyneuropathy (CIDP)). Abnormal function of different groups of immune cells has been shown to be implicated in the pathogenesis of these conditions [1]. For instance, experiments in animal models have revealed that early diminution of regulatory T cells (Tregs) intensifies the clinical severity of experimental autoimmune neuritis, enhances proliferation of myelin specific T cells and promotes histological features of inflammatory response in peripheral nerves. Thus, Tregs can influence severity of autoimmune neuropathies in animal models during the early priming stage of disorder [1,2]. Tregs are a group of CD4+ T cells that are described by the transcription factor FoxP3. These cells are considered as central players in preserving immune homeostasis, by diminishing activity of numerous immunocytes lineages [3,4]. Moreover, Tregs have been shown to suppress antigen-stimulated proliferation of splenocytes, induce an upsurge in CD4(+) IL-10(+) cells and suppress spontaneous autoimmune polyneuropathy [5].

Other experiments have indicated significant impairment of Treg functions in CIDP cases [6,7]. Moreover, Tregs could ameliorate neuritis stimulated by T cell transfer from NOD.ICAM1^{tm1Jcgr} mice [2]. Besides,

* Corresponding authors.
E-mail addresses: s.ghafourifard@sbmu.ac.ir (S. Ghafouri-Fard), ar.sayad@yahoo.com (A. Sayad).

https://doi.org/10.1016/j.intimp.2022.109188
Received 17 July 2022; Received in revised form 18 August 2022; Accepted 19 August 2022
Available online 27 August 2022

B7-2 costimulatory molecules have been shown to exert crucial role in prevention of peripheral tolerance to P0 antigen which might occur through reduction of Treg generation [8].

There are several clues pointing to the role of non-coding RNAs in the modulation of function and differentiation of Tregs [9]. This bulk of evidence also reveals that abnormal expression of non-coding RNAs can influence the etiology of conditions that are linked with the impairment of Treg function. In the present study, we assessed circulatory levels of four Treg-related long non-coding RNAs (lncRNAs) in AIDP and CIDP patients. Selected lncRNAs are FLICR (FOXP3 Regulating Long Intergenic Non-Coding RNA), NEST (IFNG-AS1), RMRP (RNA Component of Mitochondrial RNA Processing Endoribonuclease) and TH2-LCR (Th2 Cytokine Locus Control Region). RMRP has an established role in the regulation of Th17 cell effector functions [10]. Since Th17 and Treg cells have comparable developmental requirements, this lncRNA might also be involved in the regulation of Treg functions. Moreover, RMRP has been found to act as a molecular sponge for miR-206 [11], a miRNA that regulates T17/Treg ratio [12] and its expression in T cells has been regarded as a novel biomarker for Th17-type immune responses [13]. FLICR has been found to regulate expression of Foxp3 and facilitate development of a group of Tregs with reduced levels of FoxP3. FLICR is also involved in the development of some autoimmune conditions such as autoimmune diabetes [14]. TH2-LCR has important functions in the modulation of production of Th2 cytokines and development of the immune-related condition allergic asthma [15]. Finally, NEST is another lncRNA that affects methylation of the *IFN-G* locus and regulates expression of IFN-γ [16]. Production IFN-γ by Foxp3+ Tregs has an essential role for regulation of immune responses [17]. Moreover, NEST has been shown to decrease Th1-stimulated proliferation of Treg cells [18]. We have recently assessed expressions of these lncRNAs in patients with autism spectrum disorder and reported dysregulation of some of these lncRNAs [19].

2. Materials and methods

2.1. Patients and controls

Totally, 32 CIDP patients and 25 AIDP patients were enlisted in the current study as cases. The patients cohort was the same as our recently published study [20]. Moreover, 79 normal subjects were recruited as controls. Patients were diagnosed using clinical, electrophysiological, and CSF tests according to the criteria proposed previously [21,22]. CIDP and AIDP cases were in remission. They were not on any chronic immunotherapeutic regimen. In AIDP patients, blood samples were obtained after clinical recovery. Chronic infection, cancer, or any systemic diseases were regarded as exclusion criteria. Control subjects had no history of recent or chronic infection, cancer, or systemic diseases. The study protocol was permitted by the ethical committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1400.662). All cases and controls signed the informed consent forms.

2.2. Experiments

RNA was extracted from blood samples using the RNJia Kit (Tehran, Iran). Then, 50–70 ng of extracted RNA was transformed to cDNA using AddScript cDNA synthesis kit (AddBio, Korea). Expressions of FLICR, NEST, RMRP, TH2-LCR were enumerated in all blood samples using Ampliqon master mix (Denmark). Reactions were executed in StepOnePlus Real-Time PCR System. Primers sequences are demonstrated in Table 1.

2.3. Statistical analysis

Analyses were performed using GraphPad Prism version 9.0 (La Jolla, CA, USA). Expression levels of four Treg-related lncRNAs, namely TH2-LCR, RMRP, IFNG-AS1 (NEST) and FLICR were measured in peripheral blood samples obtained from 24 AIDP cases, 32 CIDP cases and 79 healthy controls. Expression levels of these lncRNA were calculated using the comparative –delta Ct method. The normal/gaussian distributions of the values were assessed using the Shapiro-wilk test. The non-parametric Kruskal-Wallis test was used to identify differentially expressed genes between patients (AIDP cases, CIDP cases and total patients) and healthy controls. A two-way ANOVA and Tukey post hoc test were used to analyze the effects of main factors (disease and gender) and the interaction between them on gene expression levels. Because data was not normally distributed, correlations between expression levels of lncRNAs in both patients and control samples were measured with Spearman's rank correlation coefficient. The receiver operating characteristic (ROC) curves were illustrated and AUC values were calculated. P value < 0.05 was considered as significant.

Table 1
Primers and size of amplified regions.

Gene	Sequence 5 → 3	Primer Length (bp)
B2M	F-AGATGAGTATGCCTGCCGTG	20
	R-GCGGCATCTTCAAACCTCCA	20
FLICR	F-GGG CTT TTC CAG AAG GGT CT	20
	R-AGC CCA GGG TTC TAG TCG	18
NEST	F-AGC TGA TGA TGG TGG CAA TCT	21
	R-TGA CTT CTC CTC CAG CGT TTT	21
RMRP	F-GTA GAC ATT CCC CGC TTC CCA	21
	R-GAG AAT GAG CCC CGT GTG GTT	21
TH2-LCR	F-GCT CCC CAG GCT TTT GAG ATA	21
	R-TGG TGA TGC TGA AGG GAG AC	20

3. Results

3.1. General information about patients and controls

Table 2 shows the demographic data of patients and controls.

3.2. Expression assays

Fig. 1 shows relative expression levels of Treg-associated lncRNAs in patients versus controls. We used the non-parametric Kruskal-Wallis test to find differentially expressed genes between patients (AIDP, CIDP and total patients) and healthy controls groups. Then, expressions of all genes were compared between all groups using Dunn test for correction of multiple comparisons.

Expression levels of RMRP, NEST and FLICR were significantly higher in total patients compared with controls. However, there was no significant difference in their expressions between AIDP and CIDP cases (data not shown).

We detected significant effect of group (disease) factor on expression levels of RMRP, NEST and FLICR. Also, we reported significant effect of gender factor on expression levels of RMRP and NEST lncRNAs. In addition, interaction of gender and disease factors had significant effect on expression levels of RMRP and TH2-LCR genes in subgroups (Table 3).

While RMRR was shown to be up-regulated in total patients and both

Table 2
General data of patients and controls.

Study groups	Parameters	Values		
Patients	Sex (number)	Male	39	18 AIDP 21 CIDP
		Female	18	7 AIDP 11 CIDP
	Age (Years, mean ± SD)	Male	52.68 ± 18.24	
		Female	55.16 ± 13.36	
Controls	Sex (number)	Male	40	
		Female	39	

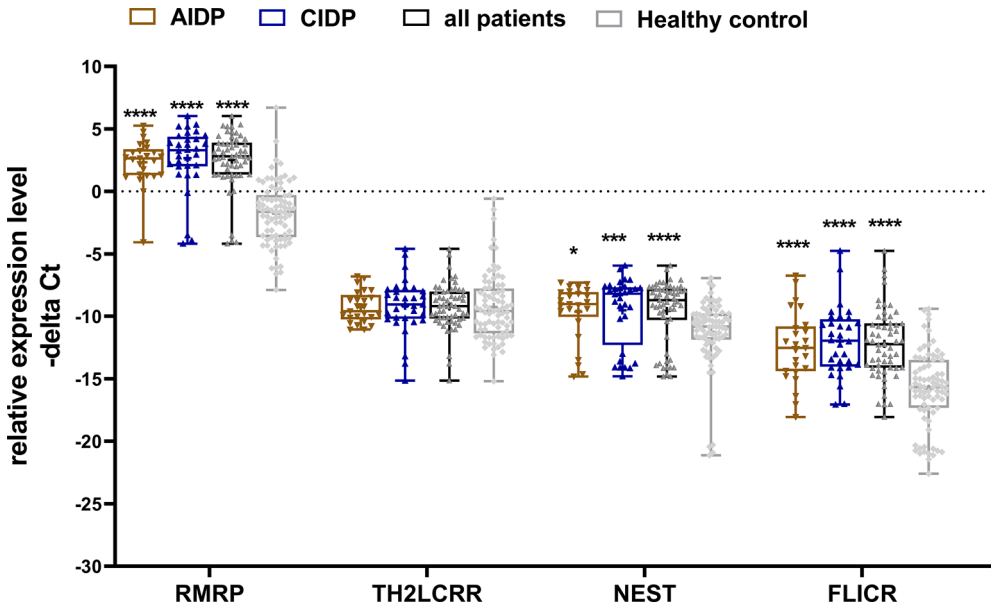

Fig. 1. Relative expression levels of four Treg related lncRNAs (A-D) in demyelinating polyneuropathy patients (total), CIDP, AIDP and healthy controls as described by –delta Ct values. The non-parametric Kruskal-Wallis test was used to find differentially expressed genes between patients (AIDP, CIDP and total patients) and healthy controls groups. (*P value < 0.05, ***P value < 0.001 and ****P value < 0.0001.)

Table 3
Graphpad prism output from analysis of effect of Group and Gender (Tests of Between-Subjects Effects) on expression of four Treg related lncRNAs in total patients compared to healthy controls.

Source of Variation	Group effect			Gender effect			Interactions		
	SS[a]	F[b]	P value	SS	F	P value	SS	F	P value
RMRP	552.1	102.8	**P < 0.0001**	28.64	5.33	**P = 0.022**	30.5	5.68	**0.018**
TH2-LCR	0.16	0.029	0.86	1.55	0.28	0.59	23.67	4.3	**0.039**
NEST	103.6	15.59	**0.0001**	39.68	5.97	**0.016**	1.63	0.24	0.62
FLICR	362	42.88	**P < 0.0001**	1.82	0.21	0.64	29.98	3.55	0.06

[a] Sum of Squares.
[b] F of Variance.

male and female patients compared with the corresponding controls, the highest expression ratio was reported in male patients versus male controls (expression ratio (95 % CI) = 38.5 (14.6–101)). Similar findings were reported for FLICR with the highest expression ratio (95 % CI) being 21.8 (6.7–71) among male subgroups (Table 4).

The highest correlation coefficient was detected between TH2LCR and RMRP among patients (Correlation coefficient = 0.5). In addition, among patients, expression of RMRP was correlated with expression of FLICR with correlation coefficient of 0.34. Other correlations were weaker, based on the calculated correlation coefficients (Table 5).

Finally, we assessed AUC values of RMRP, FLICR and NEST in total patients, female patients and male patients, respectively (Fig. 2).

RMRR was superior to other lncRNAs in terms of AUC, sensitivity and specificity values in total patients and both subgroups of patients. This lncRNA could separate total patients, female patients and male patients from corresponding controls with AUC values (±SD) of 0.9 ± 0.03, 0.86 ± 0.07 and 0.93 ± 0.03, respectively. FLICR ranked second in this regard, since it could separate total patients, female patients and male

Table 4
The results of expression study of four Treg related lncRNAs, namely RMRP, TH-2LCR, NEST and FLICR in peripheral blood of patients with demyelinating polyneuropathy compared with healthy subjects.

Studied Genes		Total patients vs controls (57 vs 79)	AIDP patients vs controls (25 vs 79)	CIDP patients vs controls (32 vs 79)	Male patients vs male controls (19 vs 30)	Female patients vs female controls (11 vs 11)
RMRP	Expression ratio (95 % CI)	19.23 (10.77–34.25)	18.7 (9.7–35.2)	27.28 (13.54–51.98)	38.5 (14.6–101)	9.6 (2.8–32.4)
	Adjusted P Value	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
TH2-LCR	Expression ratio (95 % CI)	0.95 (0.53–1.69)	0.8 (0.44–1.54)	1.37 (0.67–2.62)	1.75 (0.67–4.5)	0.51 (0.15–1.7)
	Adjusted P Value	0.86	0.9	0.9	0.41	0.48
IFNG-AS1 (NEST)	Expression ratio (95 % CI)	2.2 (1.15–4.16)	3.28 (1.89–5.5)	4.29 (2.22–7.1)	4.2 (1.48–11.9)	3 (0.81–11.8)
	Adjusted P Value	**0.0001**	**0.012**	**0.0004**	**0.0026**	0.12
FLICR	Expression ratio (95 % CI)	10.95 (5.31–22.47)	8.95 (3.6–22.3)	12.15 (5.38–29.6)	21.8 (6.7–71)	5.5 (1.2–24.2)
	Adjusted P Value	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**0.018**

Table 5
Spearman's correlations between RNA expression levels among the DP patients ($N = 57$) and healthy controls ($N = 79$).

	RMRP		NEST		FLICR	
	Patients	Control	Patients	Control	Patients	Control
TH2LCR	0.5**	0.28*	−0.01	0.32*	0.1	0.32*
RMRP			0.18	0.27*	0.34*	0.15
NEST					−0.11	0.24*

* Significance level of $p < 0.05$.
** Significance level of $p < 0.001$.

patients from corresponding controls with AUC values (±SD) of 0.81 ± 0.03, 0.72 ± 0.07 and 0.87 ± 0.04, respectively (Table 6). We also combined transcript levels of three mentioned genes for depiction of ROC curves, but the AUC values did not improve.

Fig. 3 shows ROC curves stratified by disease condition.

4. Discussion

Tregs are a certain group of immunosuppressive T cells that have crucial roles in the maintenance of immune homeostasis. These cells sustain self-tolerance, suppress autoimmunity, and function as important negative regulators of inflammatory response [23]. Function of these cells are modulated by a number of lncRNAs such as those assessed in the current study. The quantity and suppressive functions of Tregs have been reported to be reduced in the patients with CIDP. In addition, Tregs isolated from CIDP patients have been shown to express lower level of FoxP3 transcripts [24].

The results of current study indicated significant up-regulation of RMRP, NEST and FLICR in patients with inflammatory polyneuropathy compared with controls. Since the patients were in remission, altered expression of these lncRNAs is not related with disease activity. However, the altered expression could reflect underlying genetic variation in these genes that might predispose to the development of these diseases. In other words, dysregulation of these genes might predispose to disease rather than being the result of the disease.

Yet, there was no significant difference in their expressions between AIDP and CIDP cases representing comparable roles of these transcripts in the pathogenesis of CIDP and AIDP.

RMRP has been shown to affect Th17 cell effector functions [10]. While Th17 and Treg cells have distinct functions, they have comparable developmental requirements. In fact, TGF-β, IL-6, and ATRA have been found to regulate differentiation of antigen-naïve *T*-cells to either Th17 or Tregs [25]. Up-regulation of RMRP has been found to enhance activity of cardiac fibroblasts through regulation of miR-613 [26]. This miRNA has a presumed role in the pathogenesis of immune-related conditions, since it enhances apoptosis of synovial fibroblasts of patients with rheumatoid arthritis through down-regulating DKK1 [27].

FLICR is another lncRNA that regulates expression of Foxp3, resulting in development of a group of Tregs with reduced levels of FoxP3. Notably, FLICR has an important effect in IL-2 deficiency situations. From a mechanistical point of view, FILCR modulates chromatin configuration in a certain part of Foxp3 locus to restrain activation of Tregs. Moreover, FLICR induces development of autoimmune diabetes,

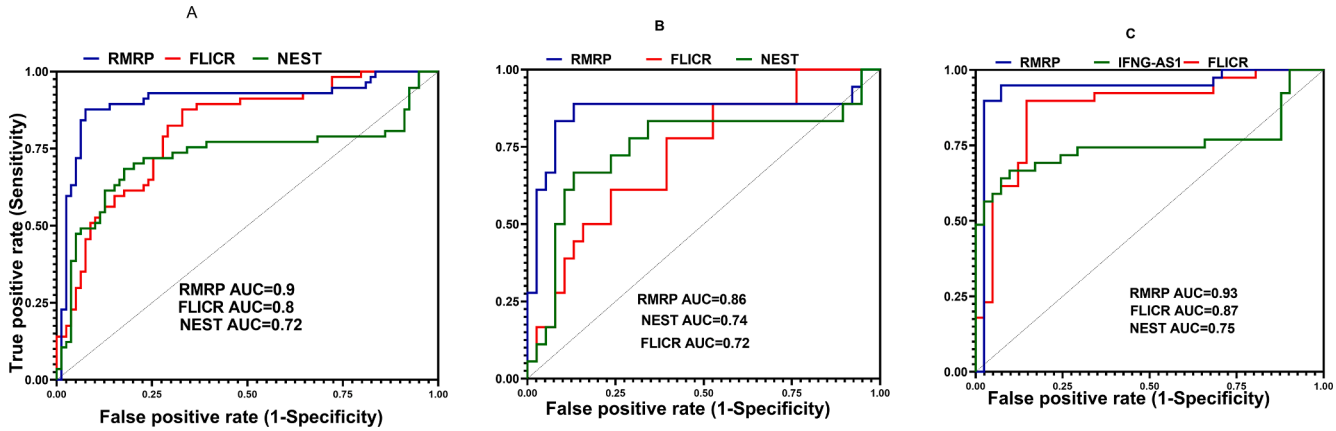

Fig. 2. ROC curves of RMRP, FLICR and NEST lncRNAs transcript levels in total patients (AIDP + CIDP) versus total controls (A), in female patients versus female controls (B), and male patients versus male controls (C). All three lncRNAs perform well in separation of male patients from male controls.

Table 6
The results of ROC curve analysis in total patients (AIDP + CIDP), female and male subgroups as well as AIDP and CIDP cases compared with corresponding controls.

	RMRP				NEST				FLICR			
	AUC ± SD	Sensitivity	Specificity	P Value	AUC ± SD	Sensitivity	Specificity	P Value	AUC ± SD	Sensitivity	Specificity	P Value
Total patients vs total normal controls (57 vs 79)	0.9 ± 0.03	0.88	0.92	<0.0001	0.72 ± 0.05	0.68	0.82	<0.0001	0.81 ± 0.03	0.87	0.67	<0.0001
Female patients vs female controls (18 vs 38)	0.86 ± 0.07	0.88	0.86	<0.0001	0.74 ± 0.08	0.66	0.86	0.003	0.72 ± 0.07	0.77	0.6	0.0069
Male patients vs male controls (39 vs 41)	0.93 ± 0.03	0.95	0.93	<0.0001	0.75 ± 0.06	0.66	0.9	0.0001	0.87 ± 0.04	0.89	0.85	<0.0001
AIDP patients vs total normal controls (25 vs 79)	0.92 ± 0.03	0.88	0.92	<0.0001	0.79 ± 0.05	0.88	0.63	<0.0001	0.73 ± 0.06	0.76	0.77	0.004
CIDP patients vs total normal controls (32 vs 79)	0.89 ± 0.04	0.87	0.93	<0.0001	0.82 ± 0.04	0.9	0.67	<0.0001	0.71 ± 0.06	0.69	0.83	0.0004

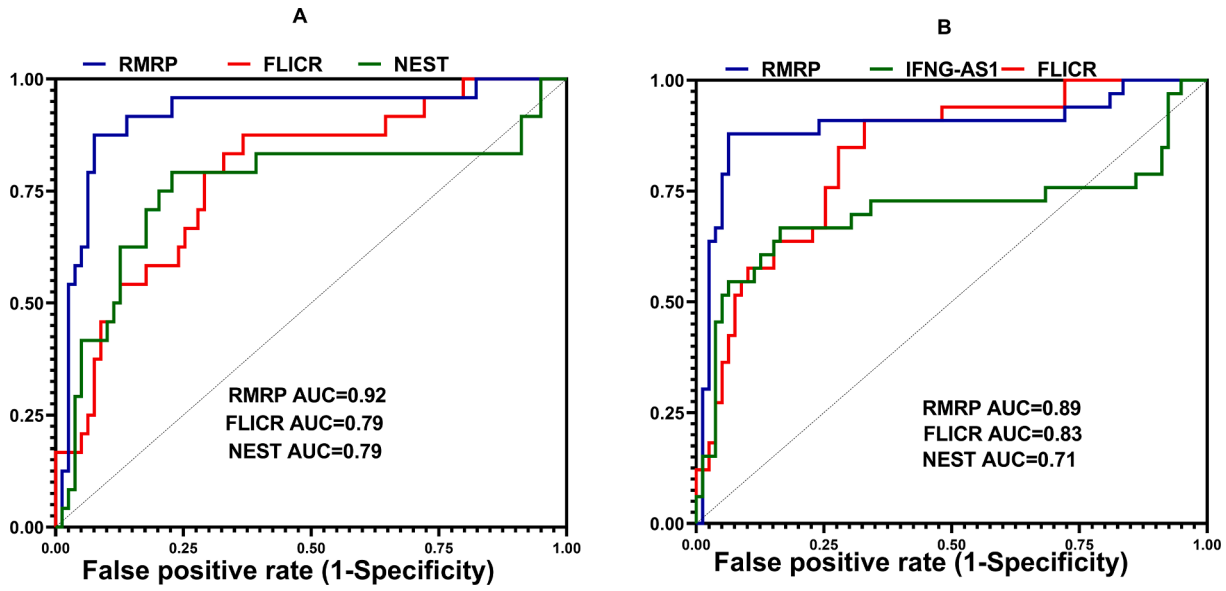

Fig. 3. ROC curves of RMRP, NEST and FLICR lncRNAs transcript levels in AIDP patients (A), and CIDP patients (B).

but limits antiviral responses [14].

TH2-LCR has important functions in the regulation of immune response via modulation of expression of Th2 cytokines. Its impacts in the pathoetiology of allergic asthma has been confirmed [15]. Finally, NEST is another lncRNA that binds to WDR5, a constituent of the H3K4 methytransferase complex which can modify H3 methylation at the *IFN-G* locus, therefore influencing expression of IFN-γ [16]. NEST has a role in down-regulation of CD40L and TFT-bet in CD4+ T cells, therefore decreasing Th1-stimulated proliferation of Treg cells [18].

Dysregulation of these lncRNAs in the circulation of AIDP and CIDP patients implies possible role of these lncRNAs in the pathoetiology of abnormal immune responses in this disorder. We have also reported dysregulation of RMRP, NEST and FLICR in autism spectrum disorder, another neurological condition which is associated with abnormal immune responses [19]. Thus, these lncRNAs are putative candidate for further functional studies in these conditions.

Moreover, it is worth to state that these lncRNAs regulate other physiological processes in addition to Treg differentiation. For example, RMRP functions as a miR-34a-5p sponge to promote cell proliferation and repress cell apoptosis [28]. Notably, miR-34a-5p has been shown to affect chemokine signaling through modulation of CXCL10/CXCL11/CXCR3 axis in immune cells [29]. Thus, it is possible that these lncRNAs participate in inflammatory demyelinating polyneuropathies via other pathways, not only regulation of Treg differentiation.

RMRR had the best performance in separation of total patients and both subgroups of patients from corresponding controls, and FLICR ranked second in this regard. Although the AUC, sensitivity and specificity values were appropriate, these lncRNAs are not likely to be used as general diagnostic markers for autoimmune polyneuropathies, since the diagnosis of these disorders are mainly based on clinical manifestations. The observed dysregulation of Treg-related lncRNAs in autoimmune polyneuropathies represent a possible venue for design of novel therapeutic options for these disorders. Moreover, the observed changes in the expression of Treg-related lncRNAs are not specific to CIDP or AIDP.

Thus, we demonstrated dysregulation of RMRP, NEST and FLICR lncRNAs in the blood of patients with autoimmune polyneuropathies. Future studies are needed to elaborate the alterations in the expressions of these lncRNAs in the course of autoimmune polyneuropathies in relation with response of patients to administrated drugs. We also state small sample size as a limitation of our study. In addition, lack of assessment of Treg levels in blood and their activity is another limitation of our study. As a direction for future studies, it is suggested to assess the polymorphisms of these genes in patients with autoimmune polyneuropathies as compared with normal population.

5. Ethics approval and consent to participant

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent forms were obtained from all study participants. Informed consent forms were obtained from all study participants. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1400.662). All methods were performed in accordance with the relevant guidelines and regulations.

6. Consent of publication

Not applicable.

7. Authors' contributions

SGF wrote the manuscript and revised it. MT and AS designed and supervised the study. BMH, MG and SR collected the data and performed the experiment. SE analyzed the data. All authors read and approved the submitted manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgement

This study was financially supported by Shahid Beheshti University of Medical Sciences.

References

[1] A. Safa, T. Azimi, A. Sayad, M. Taheri, S. Ghafouri-Fard, A review of the role of genetic factors in Guillain-Barré syndrome, J. Mol. Neurosci.: MN 71 (5) (2021) 902–920.

[2] G. Meyer zu Hörste, S. Cordes, A.K. Mausberg, A.L. Zozulya, C. Wessig, T. Sparwasser, C. Mathys, H. Wiendl, H.-P. Hartung, B.C. Kieseier, FoxP3+ regulatory T cells determine disease severity in rodent models of inflammatory neuropathies, PLoS one 9(10) (2014) e108756.

[3] S.Z. Josefowicz, L.-F. Lu, A.Y. Rudensky, Regulatory T cells: mechanisms of differentiation and function, Annu. Rev. Immunol. 30 (1) (2012) 531–564.

[4] K.S. Smigiel, S. Srivastava, J.M. Stolley, D.J. Campbell, Regulatory T-cell homeostasis: steady-state maintenance and modulation during inflammation, Immunol. Rev. 259 (1) (2014) 40–59.

[5] S. Quan, J. Sheng, P. Abraham, B. Soliven, Regulatory T and B lymphocytes in a spontaneous autoimmune polyneuropathy, Clin. Exp. Immunol. 184 (1) (2016) 50–61.

[6] L.J. Chi, W.H. Xu, Z.W. Zhang, H.T. Huang, L.M. Zhang, J. Zhou, Distribution of Th17 cells and Th1 cells in peripheral blood and cerebrospinal fluid in chronic inflammatory demyelinating polyradiculoneuropathy, J. Peripheral Nervous Syst. 15 (4) (2010) 345–356.

[7] L.J. Chi, H.B. Wang, W.Z. Wang, Impairment of circulating CD4+ CD25+ regulatory T cells in patients with chronic inflammatory demyelinating polyradiculoneuropathy, J. Peripheral Nervous Syst. 13 (1) (2008) 54–63.

[8] S. Quan, H.-J. Kim, D. Dukala, J.R. Sheng, B. Soliven, Impaired dendritic cell function in a spontaneous autoimmune polyneuropathy, J. Immunol. 194 (9) (2015) 4175–4184.

[9] Y. Luo, H. Wang, Effects of non-coding RNA on regulatory T cells and implications for treatment of immunological diseases, Front. Immunol. 11 (2020) 612060.

[10] W. Huang, B. Thomas, R.A. Flynn, S.J. Gavzy, L. Wu, S.V. Kim, J.A. Hall, E. R. Miraldi, C.P. Ng, F. Rigo, S. Meadows, N.R. Montoya, N.G. Herrera, A. I. Domingos, F. Rastinejad, R.M. Myers, F.V. Fuller-Pace, R. Bonneau, H.Y. Chang, O. Acuto, D.R. Littman, DDX5 and its associated lncRNA Rmrp modulate TH17 cell effector functions, Nature 528 (7583) (2015) 517–522.

[11] X. Wang, L. Peng, X. Gong, X. Zhang, R. Sun, J. Du, LncRNA-RMRP promotes nucleus pulposus cell proliferation through regulating miR-206 expression, J. Cell Mol. Med. 22 (11) (2018) 5468–5476.

[12] X. Ye, Q. Lu, A. Yang, J. Rao, W. Xie, C. He, W. Wang, H. Li, Z. Zhang, MiR-206 regulates the Th17/Treg ratio during osteoarthritis, Mol. Med. 27 (1) (2021) 1–9.

[13] J.D. Haas, K. Nistala, F. Petermann, N. Saran, V. Chennupati, S. Schmitz, T. Korn, L. R. Wedderburn, R. Förster, A. Krueger, I. Prinz, Expression of miRNAs miR-133b and miR-206 in the Il17a/f locus is co-regulated with IL-17 production in αβ and γδ T cells, PLoS ONE 6(5) (2011) e20171.

[14] D. Zemmour, A. Pratama, S.M. Loughhead, D. Mathis, C. Benoist, Flicr, a long noncoding RNA, modulates Foxp3 expression and autoimmunity, Proc. Natl. Acad. Sci. 114 (17) (2017) E3472–E3480.

[15] B.H. Koh, S.S. Hwang, J.Y. Kim, W. Lee, M.-J. Kang, C.G. Lee, J.-W. Park, R. A. Flavell, G.R. Lee, Th2 LCR is essential for regulation of Th2 cytokine genes and for pathogenesis of allergic asthma, Proc. Natl. Acad. Sci. 107 (23) (2010) 10614–10619.

[16] J.A. Gomez, O.L. Wapinski, Y.W. Yang, J.-F. Bureau, S. Gopinath, D.M. Monack, H. Y. Chang, M. Brahic, K. Kirkegaard, The NeST long ncRNA controls microbial susceptibility and epigenetic activation of the interferon-γ locus, Cell 152 (4) (2013) 743–754.

[17] C. Koenecke, C.-W. Lee, K. Thamm, L. Föhse, M. Schafferus, H.-W. Mittrücker, S. Floess, J. Huehn, A. Ganser, R. Förster, I. Prinz, IFN-γ production by allogeneic Foxp3+ regulatory T cells is essential for preventing experimental graft-versus-host disease, J. Immunol. 189 (6) (2012) 2890–2896.

[18] M. Luo, X. Liu, H. Meng, L. Xu, Y.i. Li, Z. Li, C. Liu, Y.-B. Luo, B.o. Hu, Y. Xue, Y. u. Liu, Z. Luo, H. Yang, IFNA-AS1 regulates CD4+ T cell activation in myasthenia gravis though HLA-DRB1, Clin. Immunol. 183 (2017) 121–131.

[19] M. Akbari, R. Eghtedarian, B.M. Hussen, S. Eslami, M. Taheri, S.M. Neishabouri, S. Ghafouri-Fard, Assessment of expression of regulatory T cell differentiation genes in autism spectrum disorder, Front. Mol. Neurosci. 15 (2022), 939224.

[20] M. Gholipour, M. Taheri, J. Mehvari Habibabadi, N. Nazer, A. Sayad, S. Ghafouri-Fard, Dysregulation of lncRNAs in autoimmune neuropathies, Sci. Rep. 11 (1) (2021) 1–9.

[21] D.R. Cornblath, A. Asbury, J. Albers, T. Feasby, Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP), Neurology (1991).

[22] F. Van der Meché, P. Van Doorn, J. Meulstee, F. Jennekens, Diagnostic and classification criteria for the Guillain-Barré syndrome, Eur. Neurol. 45 (3) (2001) 133–139.

[23] S.S. Duffy, B.A. Keating, C.J. Perera, G. Moalem-Taylor, The role of regulatory T cells in nervous system pathologies, J. Neurosci. Res. 96 (6) (2018) 951–968.

[24] L.J. Chi, H.B. Wang, W.Z. Wang, Impairment of circulating CD4+CD25+ regulatory T cells in patients with chronic inflammatory demyelinating polyradiculoneuropathy, J. Peripheral Nervous Syst.: JPNS 13 (1) (2008) 54–63.

[25] S. Omenetti, T.T. Pizarro, The Treg/Th17 axis: a dynamic balance regulated by the gut microbiome, Front Immunol 6 (2015) 639.

[26] M. Bai, J. Li, H. Yang, H. Zhang, Z. Zhou, T. Deng, K. Zhu, T. Ning, Q. Fan, G. Ying, Y. Ba, miR-135b delivered by gastric tumor exosomes inhibits FOXO1 expression in endothelial cells and promotes angiogenesis, Mol. Ther.: J. Am. Soc. Gene Ther. 27 (10) (2019) 1772–1783.

[27] L. Liu, Y. Zuo, Y. Xu, Z. Zhang, Y. Li, J. Pang, MiR-613 inhibits proliferation and invasion and induces apoptosis of rheumatoid arthritis synovial fibroblasts by direct down-regulation of DKK1, Cell. Mol. Biol. Lett. 24 (1) (2019) 1–14.

[28] X. Xiao, Y. Gu, G. Wang, S. Chen, c-Myc, RMRP, and miR-34a-5p form a positive-feedback loop to regulate cell proliferation and apoptosis in multiple myeloma, Int. J. Biol. Macromol. 122 (2019) 526–537.

[29] M. Hart, L. Nickl, B. Walch-Rueckheim, L. Krammes, S. Rheinheimer, C. Diener, T. Taenzer, T. Kehl, M. Sester, H.-P. Lenhof, Wrinkle in the plan: miR-34a-5p impacts chemokine signaling by modulating CXCL10/CXCL11/CXCR3-axis in CD4 +, CD8+ T cells, and M1 macrophages, J. ImmunoTher. Cancer 8 (2) (2020).