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Gene expression profiles of TNF-like cytokine 1A (TL1A) and its receptors death receptor 3 (DR3) and decoy receptor 3 (DcR3) in multiple sclerosis

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A B S T R A C T

TL1A/DR3/DcR3 pathway is an important mediator of inflammatory responses and contributes to the pathogenesis of several chronic inflammatory diseases. Therefore, we analysed PBMC gene expression of these molecules in 30 relapsing-remitting multiple sclerosis (RRMS) patients, 8 secondary progressive MS (SPMS), 9 primary progressive MS (PPMS), 11 clinically isolated syndrome (CIS) patients, and 16 healthy controls (HCs), to evaluate their biomarker potential in MS. The results showed significant decrease in TL1A expression in RRMS compared to other study groups. TL1A as a marker of inflammation, we found its higher expression among treatment näive RRMS patients as compared to HCs and among patients who were treated with DMTs. Moreover, TL1A expression was found to be associated with the clinical and MRI findings of MS patients suggesting its possible involvement in the establishment or preservation of immune system homeostasis or in the regulation of inflammatory activity. Taken together, these findings suggest the TL1A should be evaluated further for its potential as a candidate biomarker of inflammatory activity and the marker of therapeutic response to immunomodulatory treatments in MS.

1. Introduction

Multiple Sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system (CNS), where failure in the multiple cellular and molecular mechanism mediate the disease development and progression (Dendrou et al., 2015). Increasing evidence suggests that tumor necrosis factor superfamily (TNFSF) ligands and their cognate receptors (TNFRSF) contribute to the pathology of tissue damage in inflammatory demyelinating diseases, including MS (Aggarwal, 2003; Moreno et al., 2014; Ward-Kavanagh et al., 2016). TNF superfamily of ligands and receptors consists of several proteins expressed on immune cells, and play important roles in activation, proliferation, differentiation, and migration of immune cells from periphery to CNS (Sonar and Lal, 2015). Death receptor 3 (DR3)-mediated signalling is less studied and no clinical reports are available on it in MS compared to other DR signalling such as TNF/TNF-R, Fas/FasL, TRAIL, DR6, and p75NTR in MS and experimental autoimmune encephalomyelitis (EAE) (Mc Guire et al., 2011). We recently reported upregulated gene expression levels of DR3 in relapsing-remitting multiple sclerosis (RRMS) patients (Hagman et al., 2015).

TNF-like ligand 1A (TL1A) binds with its receptor DR3, and this interaction leads to the activation, proliferation, and production of cytokines by T cells and NK cells, as well as provides the apoptotic signals to lymphocytes (Migone et al., 2002). DR3 shares closest homology to TNFR1, but it is not expressed as ubiquitously as TNFR1 (Ward-Kavanagh et al., 2016). DR3 expression is restricted on $CD4^+$ and $CD8^+$ T cells, natural killer (NK) cells, regulatory T-cells, and among the $CD4^+$ T cells it is more frequently expressed on Th17 cells than on Th1 and Th2 cells (Aiba and Nakamura, 2013). TL1A is expressed as membrane bound form in activated T cells, macrophages, monocytes, and dendritic cells, but it is also present in fully active secreted form (Meylan et al., 2011). DcR3 is a soluble decoy receptor, which is expressed mostly in T cells and antigen-presenting cells such as monocytes/macrophages and dendritic cells (Lin and Hsieh, 2011). It provides pleiotropic immunomodulatory function as it neutralizes the biological functions of ligands TL1A, FasL (TNFSF6) and LIGHT (TNFSF14) (Pitti et al., 1998; Siakavellas et al., 2015; Yu et al., 1999). Soluble TL1A and DcR3 have been widely studied for their biomarker potential in various autoimmune and inflammatory diseases such as asthma, inflammatory bowel disease, rheumatoid arthritis (RA) and psoriasis (Aiba and Nakamura, 2013; Richard et al., 2015). However, clinical reports on gene expression of DR3, DcR3, and TL1A on peripheral blood mononuclear cells (PBMCs) derived from MS patients are lacking. Accumulating evidence indicates the roles of DR3, DcR3 and

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TL1A in autoimmunity and neuroinflammation (Aggarwal, 2003; Lin and Hsieh, 2011; Sonar and Lal, 2015). Therefore the present study was undertaken to evaluate whether the expression of these genes are related to clinical features of MS (disease activity, neurological disability, disese duration, and disease progression) and usefulness of these molecules as biomarkers for discriminating different clinical forms of MS.

2. Patients and methods

2.1. Patients

This two-year prospective follow-up study included 74 participants: 30 confirmed MS patients (McDonald et al., 2001; Polman et al., 2005) with relapsing-remitting MS (RRMS), 8 with secondary progressive MS (SPMS), 9 with primary-progressive MS (PPMS), 11 clinically isolated syndrome (CIS) patients (Miller et al., 2012), and 16 healthy controls (HCs). All patients underwent neurological and magnetic resonance imaging (MRI) examination a year before and at the time of sample collection.

The neurological examination in MS and CIS included the determination of expanded disability status scale (EDSS) score (Kurtzke, 1983) and preclinical disease activity as expressed by the number of relapses in the preceding two years before the study. The diagnosis of MS was based on the revised McDonald Criteria, and the diagnosis was definite (McDonald et al., 2001; Polman et al., 2005). CIS patients were defined as patients who had their first demyelinating event suggestive of MS (Miller et al., 2012). The HCs group consisted of 16 subjects (age 36.3 ± 13.5 years; 11 females, 5 males, mean ± SD). The study was approved by the ethics committee of Tampere University Hospital, and all participants gave informed consent. Demographic and clinical characteristics among MS and CIS patients are presented in Table 1.

2.2. MRI image segmentation and volumetric analysis

All MRI examinations were performed on a 1.5 Tesla MRI Unit (Siemens Avanto, Erlangen, Germany). The MRI protocol included a T1-weighted header followed by an axial T1-weighted magnetisation prepared rapid gradient echo (MP-RAGE), and a T2-weighted turbo spin echo (TSE), fluid attenuation inversion recovery (FLAIR), magnetisation transfer contrasts (MTC), diffusion weighted imaging (DWI), and gadolinium-enhanced T1-weighted MP-RAGE sequences. T1-weighted MP-RAGE, FLAIR and T2-weighted TSE images were used for volumetric analysis. For MP-RAGE, the imaging parameters were as follows: repetition time (TR) = 1160 ms; echo time (TE) = 4.24 ms; inversion time (TI) = 600 ms; slice thickness = 0.9 mm; and in-plane resolution = 0.45 ∗ 0.45 mm. In FLAIR, the following parameters were used: TR = 8500 ms; TE = 100 ms; TI = 2500 ms; slice thickness = 5.0 mm; and in-plane resolution = 0.45 ∗ 0.45 mm. In TSE, the following imaging scheme was used: TR = 750 ms; TE = 115 ms; slice thickness = 3.0 mm; and in-plane resolution = 0.90 ∗ 0.90 mm. Volumetric segmentation of plaques in the brain was performed using semiautomatic Anatomatic™ software operating in a Windows environment, and the images were analysed blindly.

2.3. Total RNA extraction and reverse transcription

PBMCs were separated in a Vacutainer CPT cell preparation tube (Becton Dickinson and Company, Franklin Lakes, NJ, USA) according to the manufacturer's protocol. Total RNA was isolated from stored cell lysate with a Qiagen RNeasy plus mini kit (QIAGEN GmbH, Hilden, Germany) according to the manufacturer's instructions. The total RNA was eluted with nuclease-free water, and samples were stored at −80 °C until further analyses. The concentration and purity of RNA was determined before complementary DNA (cDNA) synthesis using a NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific Inc., Wilmington, DE, USA).

Total RNA (1 μg) was reverse transcribed to cDNA in a 20 μl reaction volume using a High Capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, USA) with the standard protocol. RT reaction mixture contained 2 μl of 10× RT buffer, 0.8 μl of 25× dNTP Mix, 2 μl of 10× random hexamer primers, 1 μl of 50 U/μl MultiScribe RT enzyme, 4.2 μl of RNase-free water, and 10 μl of extracted RNA solution in RNase-free water. The tubes were loaded in the thermal cycler (Biometra UNO II) preheated at 25 °C for 10 min, incubation at 37 °C for 120 min, 5 min at 85 °C, and then held at 4 °C. The cDNA samples were stored at −20 °C until use.

2.4. TaqMan gene expression assays

The gene expression of DR3 (TNFRSF25, Assay ID: Hs00980365_g1), DcR3 (TNFRSF6B, Assay ID: Hs00187070_m1), TL1A (TNFSF15, Assay ID: Hs00270802_s1) and GAPDH (Assay ID: Hs99999905_m1) were analysed with Taqman assays using the Applied Biosystems® 7900 Real-Time PCR System (Thermo Fisher Scientific). Each PCR reaction was performed in 10 μl reaction volume in the 384 well plate (Greiner Bio-one International), which contained 0.5 μl of 20× Taqman® gene Expression Assay, 5 μl of 2× TaqMan® Gene Expression Master Mix (Thermo Fisher Scientific), 2.5 μl of RNase/Dnase free water and 2 μl of

Table 1
Demographic and clinical characteristics among MS and CIS patients.

Parameters	CIS	RRMS	SPMS	PPMS
	n = 11	n = 30	n = 8	n = 9
Gender F/M[a]	9/2	23/7	5/3	6/3
Age (years)[b]	35.4 ± 10.2 (23–53)	36.6 ± 10.3 (19–54)	51.2 ± 8.3 (39–62)	60.7 ± 8.0 (46–73)
Disease duration from diagnosis (years)[b]	NA	4.0 ± 3.9 (0.0 ± 13.7)	16.3 ± 11.0 (1.4–32.4)	18.7 ± 8.2 (3.3–27.2)
Time from first symptoms (years)[b]	3.0 ± 1.7 (1.7–6.8)	8.7 ± 7.0 (1.7–30.0)	21.4 ± 9.2 (7.9–33.2)	25.0 ± 13.8 (6.8–48.1)
EDSS[b]	0.2 ± 0.4 (0–1)	1.7 ± 1.9 (0–7)	5.7 ± 2.0 (2.0–7.5)	4.8 ± 1.8 (1.5–6.5)
Annualized relapse rate[b]	0.0 ± 0.0	2.0 ± 1.6 (0–6.4)	0.4 ± 0.4 (0.0–1.0)	0.0 ± 0.0 (0–1)
Pre-study disease activity[b,c]	0.8 ± 0.6 (0–2)	1.7 ± 1.7(0–7)	0.0 ± 0.0	0.0 ± 0.0
Progression index [b]	NA	2.7 ± 2.9 (0.0–11.3)	2.7 ± 1.7 (0.8–5.4)	4.7 ± 2.7 (0.5–9.9)
Treatment (NT/IFN/GA/MX)[a]	NA	0/17/1/1	0/0/0/0	0/0/0/0
T1 lesions (cm^3)[b]	0.3 ± 0.3 (0.0–0.9)	3.2 ± 5.2 (0.0–26.4)	9.0 ± 8.2 (0.4–24.7)	4.8 ± 9.4 (0.4–29.8)
FLAIR lesions (cm^3)[b]	1.7 ± 2.4 (0.00–0.92)	12.0 ± 14.2 (0.0–66.0)	21.5 ± 13.9 (0.2–43.3)	14.3 ± 16.3 (1.4–53.1)

CIS: clinically isolated syndrome, RRMS: relapsing-remitting MS, PPMS: primary progressive MS, HCs: healthy controls, EDSS: expanded disability status scale, NT: no treatment, IFN: interferon, GA: glatiramer acetate, MX: mitoxantrone, and NA: not applicable.

[a] Number of patients.

[b] Mean ± SD (range).

[c] Number of relapses 2 years before the study.

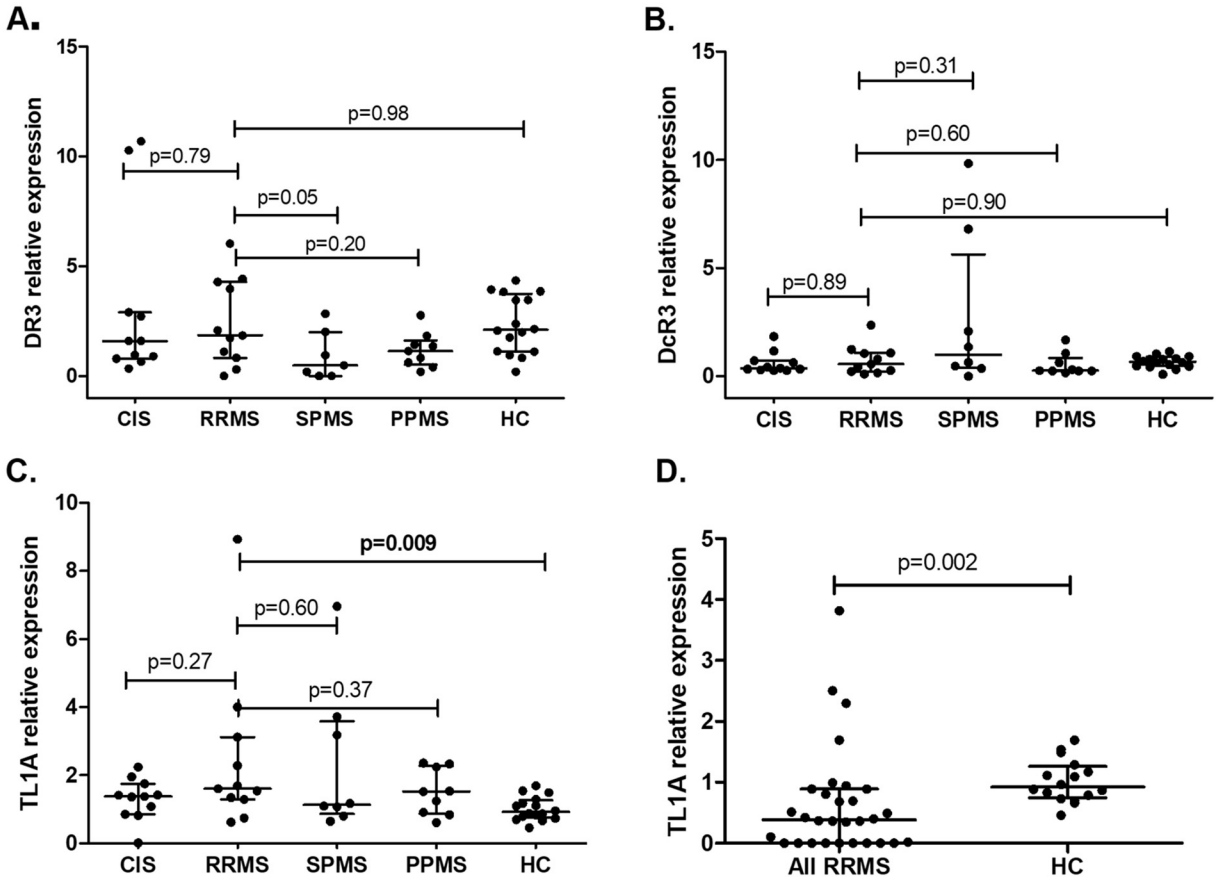

Fig. 1. Scatter plot showing the relative gene expression levels of DR3, DcR3, and TL1A in different MS patients, CIS and HCs. Figures A, B and C include RRMS patients who were treatment naïve whereas fig. D includes all RRMS patients including treated ones. The bars indicate the median and interquartile range.

cDNA. Samples were run in three replicates and no template controls were run in each run. Quantitative-PCR reactions was run under standard conditions: initial denaturation at 95 °C for 10 min, after which 40 amplification cycles of 15 s denaturation in 95 °C and 1 min annealing and extension in 60 °C was performed. The gene expression data were analysed with RQ manager software (Applied Biosystems) using the comparative Ct method (ΔΔCt). The housekeeping gene glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used to normalize the results, and a healthy control sample, in each plate, was used as a calibrator in the data analysis.

2.5. Statistical analysis

Statistical analyses were performed using SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Due to the skewed distributions, a non-parametric, Kruskal-Wallis test or two-tailed Mann–Whitney *U* was used to compare the differences between the clinical parameters, and relative gene expression levels in study groups. For correlation analyses, spearman's correlation coefficient was used to explore the association between relative gene expression levels and clinical or MRI parameters. A p-value $< .05$ was considered statistically significant. Significant values were adjusted by the Bonferroni correction for multiple tests. Figures were prepared using GraphPad Prism 5.02 software (GraphPad Software Inc., La Jolla, CA, USA).

3. Results

3.1. Clinical and MRI data

RRMS patients had lower EDSS compared to SPMS and PPMS ($p < .0001$), who also were younger and had shorter disease duration ($p < .001$). Nineteen out of 30 (63%) RRMS patients were on treatment with immunomodulatory drugs (17 patients with interferon-beta (IFN-β), 1 with glatiramer acetate, and 1 with mitoxantrone). Majority of the treated RRMS patients ($n = 19$), were free of clinical disease activity during the two years before study enrollment. Eleven RRMS patients (37%) showed disease activity: 4 patients had 1 relapse, 6 had 2 relapses, and 9 had 3 to 7 relapses.

The volumes of hypointense T1-weighted were lower in RRMS compared to SPMS ($p = .021$) but not as compared to PPMS ($p = .073$) whereas SPMS and PPMS patients had similar volumes of both T1- and FLAIR lesions ($p > .05$). CIS patients had lowest volumes of T1 and FLAIR lesions compared to MS subtypes ($p < .001$).

3.2. Assessment of relative gene expression levels of DR3, DcR3, and TL1A expression levels

Relative gene expression levels of DR3 and DcR3 were similar among all study groups (Fig. 1A–B). However, TL1A expression levels were higher among treatment naïve RRMS patients as compared to HCs ($p = .009$, Fig. 1C). When analysed among whole RRMS group including both treated with disease modifying therapies (DMTs) and treatment naïve patients, TL1A expression levels were significantly lower compared to HCs ($p = .002$, Fig. 1D). Such difference in DR3 and DcR3 expression levels did not exist among whole RRMS group as compared to SPMS, PPPMS, CIS and HCs (data not shown).

Next, we explored the effect of DMTs on DR3, DcR3, and TL1A gene expression levels among the RRMS patients who were treated with DMTs and those who were treatment naïve. Those patients who were treated ($n = 19$) showed significantly decreased expression of DcR3 and

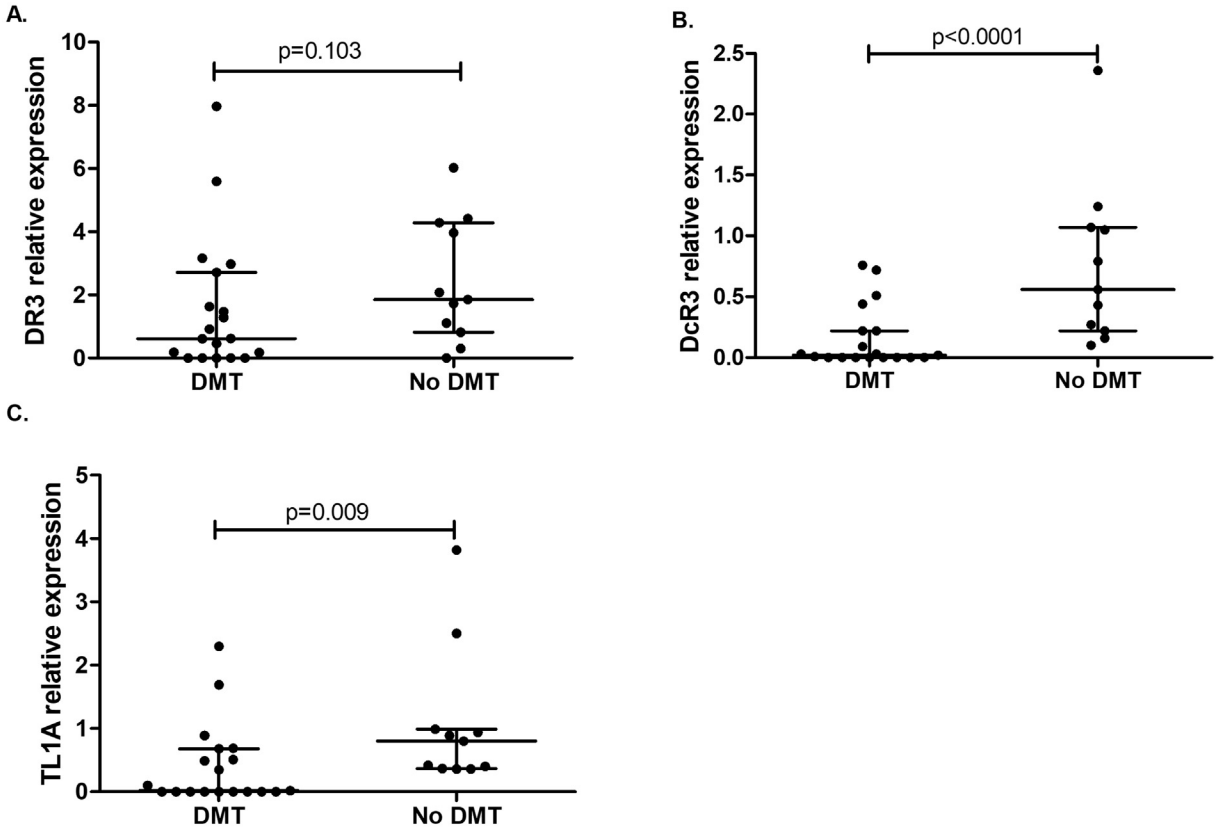

Fig. 2. Relative DR3, DcR3, and TL1A gene expression levels among RRMS patients who were treated with DMTs versus those who were treatment naïve. The bars indicate the median and interquartile range.

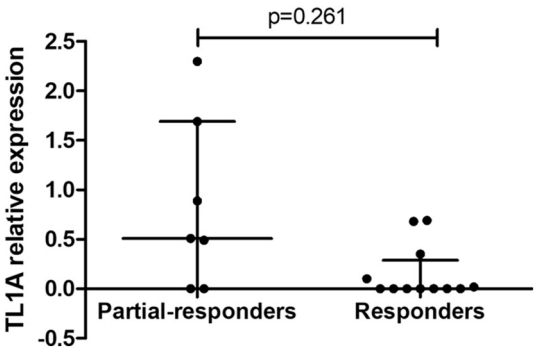

Fig. 3. Relative TL1A gene expression levels among partial-responders and responders in RRMS patients. The bars indicate the median and interquartile range.

TL1A compared to patients who were treatment naïve ($p < .01$, $n = 19$, Fig. 2B–C) whereas DR3 expression did not differ between these groups ($p = .103$, Fig. 2A).

Next, we categorized the DMT-treated RRMS patients ($n = 19$) into responders (those patients who had no further relapses and were without deterioration in the EDSS score during one year of treatment, $n = 13$), and remaining ones as partial responders ($n = 6$). When we compared the TL1A expression between these two groups, partial responders had increased TL1A expression than responders, however, the difference was not statistically significant ($p = .261$, Fig. 3).

3.3. Association of DR3, DcR3, and TL1A gene expressions with clinical and MRI parameters in MS patients

When we explored the association of relative gene expressions of DR3, DcR3, and TL1A with clinical parameters of RRMS, SPMS, PPMS, and CIS patients, the results did not show any correlations. Later we grouped all MS patients (RRMS, SPMS and PPMS) as clinically definite MS (CDMS, $n = 47$), as a single group, and performed the correlation analyses. Among the three genes analysed, only the TL1A expression levels significantly correlated with MS disease parameters: EDSS score ($r = 0.484$, $p = .001$, Fig. 4A), MS disease duration ($r = 0.417$, $p = .004$, Fig. 4B), time from the first symptoms ($r = 0.458$, $p = .001$, Fig. 4C), the volume of T1-weighted lesions ($r = 0.291$, $p = .050$, Fig. 4D), and FLAIR lesions ($r = 0.337$, $p = .022$, Fig. 4E). Moreover, TL1A expression did not correlate with preclinical disease activity. Among CIS patients, none of the genes reveal any correlations with clinical or MRI parameters. Since the status of disease activity may affect the TL1A expression, we further selected and classified RRMS patients into two groups i) patients with relapses and ii) patients without relapses preceding two years of sample collection. The result showed no change in TL1A expression levels among these groups ($p = .172$, data not shown).

4. Discussion

Due to the evidence indicating the association of DR3, DcR3, and TL1A with neuroinflammation (Sonar and Lal, 2015), we analysed their gene expression in PBMC obtained from MS patients to evaluate whether these molecules may contribute as biomarkers in MS.

Among the three genes analysed in this study, only the TL1A expression was found to be significantly decreased among RRMS compared to HCs. Although TL1A has been considered as a marker of active inflammation, we were unable to find its elevated levels in RRMS patients compared to SPMS, PPMS, CIS, and HCs. This could be due to the stable disease activity of the RRMS patients and the effect of treatment with DMTs. All RRMS patients enrolled in this study had relatively

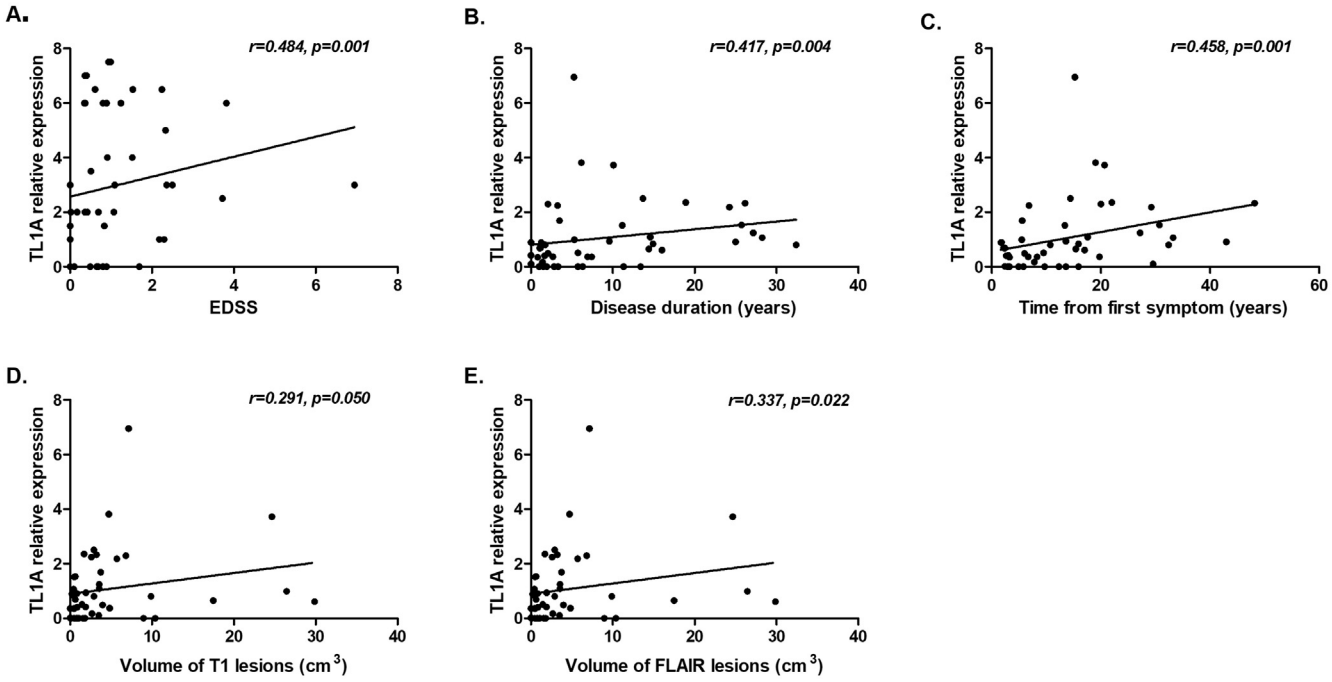

Fig. 4. Association of TL1A gene expression to disease parameters: A. EDSS, B. Disease duration, C. Time from the first symptoms, D. Volumes of T1 lesions in MRI, and E. volumes of FLAIR lesions in MRI.

stable clinical disease activity at the time of sample collection, therefore, lower TL1A expression could be attributed to the state of reduced inflammatory activity or the state of immune system homeostasis, which are mediated by the tight regulation of apoptosis (Macchi et al., 2015). In MS, inflammatory and apoptotic responses may occur either at the peripheral level or at the CNS, and in particular, stable phase of the disease is characterized by the inhibition of peripheral inflammatory response, as in the case of our patients with RRMS (Gurevich and Achiron, 2012; Macchi et al., 2015). TL1A binding to DR3 induces activation of NF-kappaB, and thus promoting inflammation, but this interaction also regulates cell apoptosis by activating caspase cascade (Oh and Ghosh, 2013; Schreiber et al., 2010; Schreiber and Podack, 2013). Since TL1A is expressed on several activated immune cells such as T cells, monocytes, B cells and dendritic cells (Siakavellas et al., 2015), change in the ratio of these cell subsets can affect the TL1A expression, therefore future study is needed to show the TL1A expression levels in the most affected cell subset by flow cytometry.

On the other hand, three findings in the present study support the potential of TL1A as a marker of inflammation in RRMS. First, significant increase in TL1A expression among RRMS patients who were treatment näive compared to HCs. Second, increased TL1A expression among the treatment naïve RRMS patients compared to patients who were treated with DMTs. This finding indicates reduced TL1A expression treated patients as a result of treatment effect. In consistent with our findings, Bamias et al., had also reported decreased serum levels of TL1A as a response to treatment effect in patients with other inflammatory autoimmune disease (Bamias et al., 2010). IFN-β has immunoregulatory properties and the treatment induces the expression of large number of genes that encodes proteins, which have immunomodulatory and apoptosis promoting functions (Dhib-Jalbut and Marks, 2010; Sellebjerg et al., 2008). Third, the increased TL1A expression levels in patients with partial DMT responders in comparison to DMT responders, however the difference lacked statistical significance which could be due to the small number of patients. In this regard, these findings may be relevant to support TL1A expression as an indicator of inflammation in RRMS patients and may hold the ability to reflect the therapeutic response to immunomodulatory treatment in MS. However, since we only presented TL1A levels at baseline, it is necessary to measure the TL1A in longitudinal PBMC samples, before and after the treatment, to confirm the effect of anti-inflammatory therapies on TL1A expression.

TL1A is not well studied in MS and until today, there are no reports of its association with clinical or radiological parameters. In the present study, TL1A among CDMS group, correlated positively with EDSS score, disease duration, volumes of hypointense T1 and FLAIR lesions but not with pre-clinical disease activity. However such correlations was absent when analysed among individual MS group, probably due to the small sample size. Some experimental studies have revealed the association of TL1A to EAE disease pathogenesis mediated through Th1- and Th17 T-cells (Meylan et al., 2008; Pappu et al., 2008). Moreover, TL1A was shown to be associated with disease activity profiles in several other diseases such as Crohn's disease, RA and SLE (Bamias et al., 2008; Xu et al., 2017). We did not observe correlation of TL1A with pre-clinical disease activity probably due to the remission phase of disease activity in RRMS patients. EDSS is the measure of neurological disability in MS patients and currently there are no or very few blood biomarkers available that can predict the disability progression in MS (Gajofatto et al., 2013). Since our study included small number of progressive MS patients, it is difficult to comprehend if the association of TL1A with EDSS in CMDS group indicates neurodegenerative phase of progressive patients or the inflammatory state of RRMS patients. Therefore this correlation should be confirmed in future studies including larger MS patients with progressive forms. Currently CSF as well as serum levels of neurofilament light chain is emerging as a promising biomarkers for relapse rate, EDSS, brain atrophy and disability progression (Harris et al., 2017). Among few studies, which attempted to show TNFSF as biomarkers in MS, a study has reported Fas and FasL mediated apoptosis as a predictor of long-term disability progression in MS (Lopatinskaya et al., 2006). Nevertheless, additional studies are needed to explain the biological role of TL1A that is responsible for increased disability and it remains a subject of follow-up study in a larger cohort to clarify if TL1A can be used as surrogate marker for disability progression in MS patients.

5. Conclusions

Our results support the value of lower TL1A expression as a marker of stable disease activity in MS. Given that the TL1A is a marker of active inflammation, we found its higher expression among treatment näive RRMS patients as compared to HCs and patients treated with DMTs. Moreover, TL1A expression was found to be associated with the clinical and MRI findings of MS patients suggesting its involvement in the establishment or preservation of immune system homeostasis or in the regulation of inflammatory activity. Taken together, these findings suggest the TL1A should be evaluated further for its potential as a candidate biomarker of inflammatory activity and the marker of therapeutic response to immunomodulatory treatments in MS. Nonetheless, additional studies are needed to validate these preliminary findings.

Declaration of Competing Interests

The authors have no conflict of interests to declare.

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