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Original Research Article

Abnormal expression of MAPK14-related lncRNAs in the peripheral blood of patients with multiple sclerosis

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ABSTRACT

Introduction: Contribution of MAPK14 in the pathogenesis of multiple sclerosis (MS) has been proposed by several studies. Long non-coding RNA (lncRNA) have been suggested to be functionally linked with Mitogen-activated protein kinase 14 (MAPK14).

Methods: Expression levels of *MAPK14* and its associated lncRNAs were measured in the circulation of MS patients compared with control subjects.

Results: Expression levels of *NORAD* and *RAD51-AS1* were higher in total patients compared with controls (Expression ratio (95% CI) = 1.4 (1.04–1.89), P value = 0.015 and Expression ratio (95% CI) = 1.91 (1.43–2.6), P value = 0.0001, respectively). Conversely, *ZNRD1ASP* was under-expressed in cases compared with controls (Expression ratio (95% CI) = 0.61 (0.41–0.8), P value = 0.0005). In spite of the observed abnormal expression levels of these lncRNAs in the circulation of MS patients, their expressions were not correlated with Expanded Disability Status Scale (EDSS) score, disease duration or age at disease onset.

Conclusion: To sum up, the current investigation shows dysregulation of MAPK14-related lncRNAs in MS patients.

1. Introduction

Multiple sclerosis (MS) is an inflammatory condition in the central nervous system (CNS) affecting a large number adults in the world. Similar to other autoimmune disorders, its etiology is poorly understood. Yet, it is obvious that environmental risk factors act on a vulnerable genetic context to cause this condition [1]. Among the signaling pathways involved in the pathophysiology of MS is the Mitogen-activated protein kinase (MAPK) pathway [2]. This pathway has been found to participate in the regulation of inflammatory responses in numerous cell types and release of a number of cytokines and inflammatory molecules [3]. Evidence from the animal model of disorder, namely experimental allergic encephalomyelitis (EAE) has confirmed participation of p38 MAPK pathway in this condition [4,5]. Notably, activity of p38 MAPK has been known to be increased in T cells through a MAPK kinases-independent manner that comprises autophosphorylation [6,7]. This signaling pathway can affect EAE pathogenesis through modulation of activity of Th17 cells, dendritic cells, and myeloid cells [2]. Further experiments in a relapsing-remitting EAE model have shown that administration of p38 MAPK inhibitor during the remission phase can ameliorate succeeding relapses [8]. Although not completely verified, it has been suggested that activation of p38 MAPK in CNS residing cells such as glial cells may partake in the pathogenesis of EAE [2]. Most importantly, expression of *MAPK14* gene which

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encodes p38α has been reported to be significantly increased in MS lesions [9]. Moreover, p38α-deficient mice have been shown to exhibit lower reactivity of astrogliosis and deficiency in the construction of astroglial barrier under inflammatory conditions in the CNS. Therefore, p38α has a possible role the maintenance of the CNS microcirculatory barrier [3].

Finding the function of MAPK14 in the pathogenesis of MS and clarification of detailed molecular targets and regulators of this kinase can result in design of appropriate targeted therapies for MS. Thus, evidence supports the importance of MAPK14-related pathways in the pathoetiology of MS. It has been revealed that MAPK14 has interaction with some long non-coding RNAs (lncRNAs), namely *NORAD*, *HCG11* and *ZNRD1ASP* [10]. These lncRNAs have been found by bioinformatics analyses to interact with MAPK14 through affecting expression of miRNAs that regulate expression of MAPK14 [10]. Therefore a competing endogenous RNA (ceRNA) network exists between these lncRNAs and MAPK14. Thus, changes in the MAPK14-related lncRNAs might imitate subnormal activity of this kinase, participating in the etiology of MS. In the current study, we measured expression levels of *MAPK14* and its associated lncRNAs in MS patients compared with controls.

2. Materials and methods

2.1. Study participants

A group of Iranian MS patients including 12 males and 38 females were recruited for expression assays (Table 1). Moreover, 50 age and sex matched healthy persons were enlisted as controls. Control persons had no history or sign of neurologic or autoimmune diseases. The revised McDonald criteria [11] was used for assessment of cases. Informed consent forms were signed by all MS patients and healthy controls. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1399.211).

2.2. Expression studies

Five milliliters of whole peripheral blood were obtained from recruited persons. Then, these samples were subjected to RNA extraction by Hybrid-RTM blood RNA extraction kit (GeneAll, South Koera). In brief, plasma was removed and WBC were transferred in another tube for further steps of RNA extraction. Subsequently, cDNA was synthesized from RNA using High-Capacity cDNA Reverse Transcription kit (Applied Biosystems). Expression of *MAPK14* and associated lncRNAs were quantified in all samples according to the methods described previously [10].

2.3. Statistical analysis

Data was analyzed using GraphPad Prism software version 9.0 (La Jolla, CA, USA). Expression of *MAPK14* gene and lncRNAs was calculated using the comparative –delta Ct method. The normal/gaussian distribution of the values was assessed using the Shapiro-Wilk test. Mann-Whitney *U* test was used to identify differentially expressed genes between patients and healthy subjects. The two-way ANOVA and Tukey post hoc tests were used to analyze the effect of disease and gender on gene expression. Correlations between levels of genes expression were measured with Spearman's rank correlation coefficient. Receiver operating characteristic (ROC) curves were depicted to appraise the diagnostic power of expression levels of differentially expressed genes. P value < 0.05 was considered as significant.

Table 1
General information about cases.

Parameters	Groups	Values
Sex (number)	Male	12
	Female	38
Age (Years, mean ± SD)	Male	37.5 ± 10.8
	Female	40.13 ± 9.52
Duration (Years, mean ± SD)	Male	4.5 ± 3.03
	Female	7.26 ± 6.18
Age of onset (Years, mean ± SD)	Male	32.83 ± 11.23
	Female	32.86 ± 9.32
Expanded Disability Status Scale score	Male	3.41 ± 1.57
	Female	2.85 ± 1.26

3. Results

3.1. General demographic/clinical information

The study included 12 male MS patients and 38 female MS patients. Table 1 shows information about enlisted MS patients.

3.2. Expression assays

We assessed expression of four lncRNAs (NR_027451.1, NR_026790.1, NR_040058.1 and NR_026751.2) and MAPK14. Table 2 shows characteristics of selected genes.

Expression levels of *NORAD*, *RAD51-AS1* and *ZNRD1ASP* were different between cases and controls (Fig. 1). *NORAD* levels were higher in MS cases compared with controls (P value < 0.05). *RAD51-AS1* was also up-regulated in MS cases (P value < 0.001). However, *ZNRD1ASP* was down-regulated in patients compared with controls (P value < 0.01). Finally, *MAPK14* and *HCG1*1 had similar expression patterns between cases and controls.

There was a disease- and sex-differentiated expression for *NORAD* lncRNA gene (p values = 0.03 and 0.002, respectively) in studied groups (Fig. 2). However, the interaction between sex and disease had no significant effect on expression level of *NORAD* in subgroups (Fig. 2). Also, the interaction between sex and disease had significant effect on expression levels of *RAD51-AS1* in subgroups (p value = 0.02) (Fig. 2). Disease had remarkable impact on expression level of *NORAD*, *RAD51-AS1* and *ZNRD1ASP* lncRNAs genes.

We reported up-regulation of *NORAD* in total patients compared with controls (Expression ratio (95% CI) = 1.4 (1.04–1.89), P value = 0.015) and in female controls compared with male controls (Expression ratio (95% CI) = 2.3 (1.22–4.34), P value = 0.004). Moreover, *RAD51-AS1* expression was reported to be elevated in total cases compared with total healthy persons (Expression ratio (95% CI) = 1.91 (1.43–2.6), P value = 0.0001) and in male patients compared with male controls (Expression ratio (95% CI) = 3.7 (1.4–9.8), P value = 0.003). Lastly,

Table 2
Information about selected genes.

Name/Gene symbol	Accession number	Location	Full name	Function
NORAD	NR_027451.1	20q11.23	non-coding RNA activated by DNA damage	lncRNA class (gene expression regulation)
HCG11	NR_026790.1	6p22.2	HLA complex group 11	lncRNA class (gene expression regulation)
RAD51-AS1	NR_040058.1	15q15.1	RAD51 antisense RNA 1	lncRNA class (gene expression regulation)
ZNRD1ASP	NR_026751.2	6p22.1	zinc ribbon domain containing 1 antisense, pseudogene	lncRNA class (gene expression regulation)
MAPK14	NM_001315.3	6p21.31	mitogen-activated protein kinase 14	Protein kinase

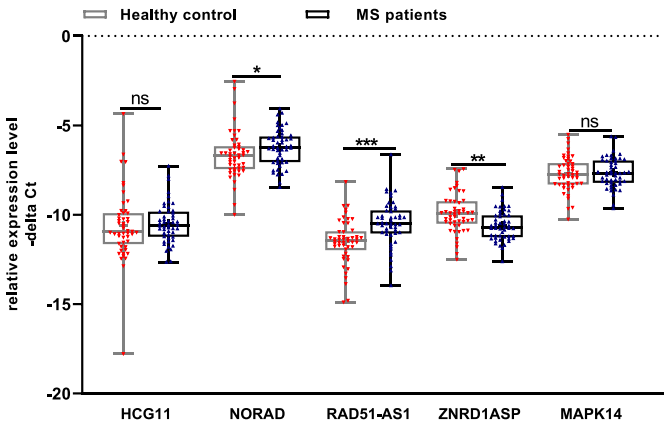

Fig. 1. Relative expression levels of *MAPK14* gene and four related lncRNAs in MS patients and healthy controls as described by –delta Ct values (Ct Housekeeping gene- Ct Target gene). Mann-Whitney *U* test was used to identify differentially expressed genes between two groups (*P value < 0.05 and ***P value < 0.001).

expression of *ZNRD1ASP* was down-regulated in total patients compared with total controls (Expression ratio (95% CI) = 0.61 (0.41–0.8), P value = 0.0005) and in female patients compared with female controls (Expression ratio (95% CI) = 0.64 (0.42–0.97), P value = 0.03). Other comparisons yielded no significant results. Particularly, expression of none of the assessed genes was different between female patients and male patients (Table 3).

We assessed correlations between all pairs of genes (Table 4). The most robust correlations were found between *NORAD* and *MAPK14* (correlation coefficient = 0.7), between *NORAD* and *RAD51-AS1* (correlation coefficient = 0.66), and *HCG11* and *NORAD* (correlation coefficient = 0.63) in MS patients.

ROC curves were made by plotting the true positive rate (sensitivity) against the false positive rate at numerous thresholds. ROC curve analyses showed that expression levels of *NORAD*, *RAD51-AS1* and *ZNRD1ASP* could differentiate MS patients and controls with AUC values 0.63, 0.71 and 0.7 (Fig. 3 and Table 5).

RAD51, *ZNRD1ASP* and *NORAD* could differentiate between MS patients and healthy controls with P values of 0.0002, 0.0006 and 0.02, respectively (Table 5).

Then, we assessed correlation between expression of genes and demographic/clinical data of MS patients using Pearson correlation. Expression of genes was not correlated with disease duration, sex, Expanded Disability Status Scale (EDSS) score, age at onset or patients' age (Table 6). As expected, there were correlations between age at disease onset and disease duration (correlation coefficient = −0.341) and between age and age at disease onset (correlation coefficient = 0.769).

4. Discussion

Several lncRNAs have been shown to be dysregulated in MS. Among these lncRNAs are NEAT1, PANDA and TUG1 [12]. Moreover, a number of cancer-associated lncRNAs, namely SPRY4-IT1, HOXA-AS2, LINC-ROR, and MEG3 have been down-regulated in MS patients [13].

MAPK14 is a protein kinase being induced by cell stress and inflammatory stimuli such as proinflammtory cytokines or TLR ligands [2]. This kinase influences inflammatory response and cell death [14,15]. Thus, this molecule is a possible target for design of therapeutic targets for MS [2]. In the current investigation, we reported up-regulation of two MAPK14-related lncRNAs i.e. *NORAD* and *RAD51-AS1*, while down-regulation of a MAPK14-related lncRNA, namely *ZNRD1ASP* in the circulation of patients with MS. Notably, despite the change in the expression of regulatory lncRNAs, expression of the MAPK14 gene was not changed which is not expected based on the

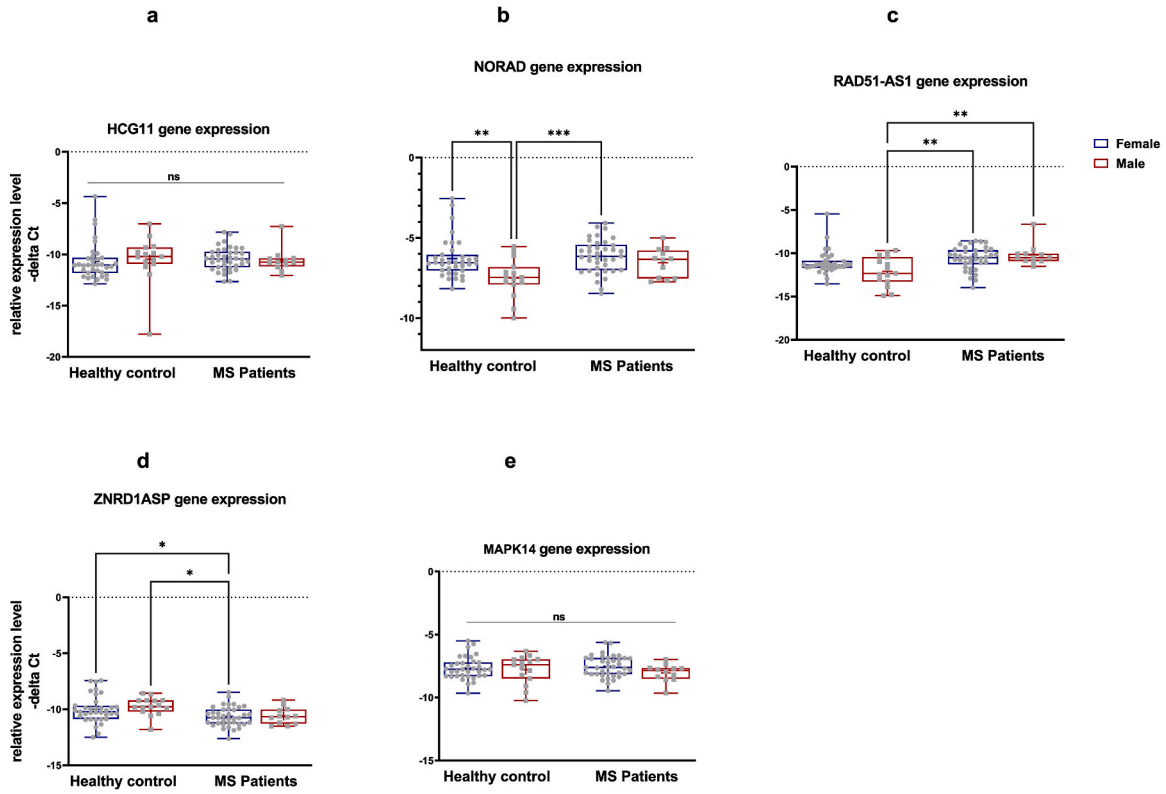

Fig. 2. Relative expression levels of *MAPK14* gene and four related lncRNAs in Multiple Sclerosis (MS) patients (male and female) versus control subgroups (male and female) as described by –delta Ct values. Two-way ANOVA and Tukey post hoc tests were used to analyze the effects of main factors (disease and gender) and the interaction on gene expression levels in subgroups (*P value < 0.05, **P value < 0.01 and ***P value < 0.001).

Table 3
The results of expression ratio (fold change) of *MAPK14* and four related lncRNAs genes in MS patients compared to healthy controls.

		Total patients vs. Controls (50 vs. 50)	Male patients vs. Male Controls (12 vs. 15)	Female patients vs. Female Controls (38 vs. 35)	Female patients vs. Male patients (38 vs. 12)	Female controls vs. Male Controls (35 vs. 15)
NORAD	Expression ratio (95% CI)	1.4 (1.04–1.89)	1.9 (0.87–4.28)	1.1 (0.68–1.79)	1.32 (0.67–2.6)	2.3 (1.22–4.34)
	Adjusted P Value	**0.015***	0.13	0.94	0.7	**0.004***
RAD51-AS1	Expression ratio (95% CI)	1.91 (1.43–2.6)	3.7 (1.4–9.8)	1.39 (0.77–2.49)	0.75 (0.32–1.72)	2 (0.93–4.37)
	Adjusted P Value	**0.0001***	**0.003***	0.45	0.81	0.08
ZNRD1ASP	Expression ratio (95% CI)	0.61 (0.41–0.8)	0.55 (0.27–1.1)	0.64 (0.42–0.97)	0.96 (0.53–1.74)	0.83 (0.47–1.43)
	Adjusted P Value	**0.0005***	0.12	**0.03***	0.99	0.81

Table 4
Spearman's correlations between *MAPK14* and four related lncRNAs expression levels among the patients ($N = 50$) and healthy controls ($N = 50$).

	NORAD Cases Controls	RAD51-AS1 Cases Controls	ZNRD1ASP Cases Controls	MAPK14 Cases Controls
HCG11	0.63 0.37	0.6 0.45	0.38 0.43	0.6 0.53
NORAD		0.66 0.5	0.49 0.29	0.7 0.59
RAD51-AS1			0.31 0.32	0.43 0.4
ZNRD1ASP				0.5 0.4

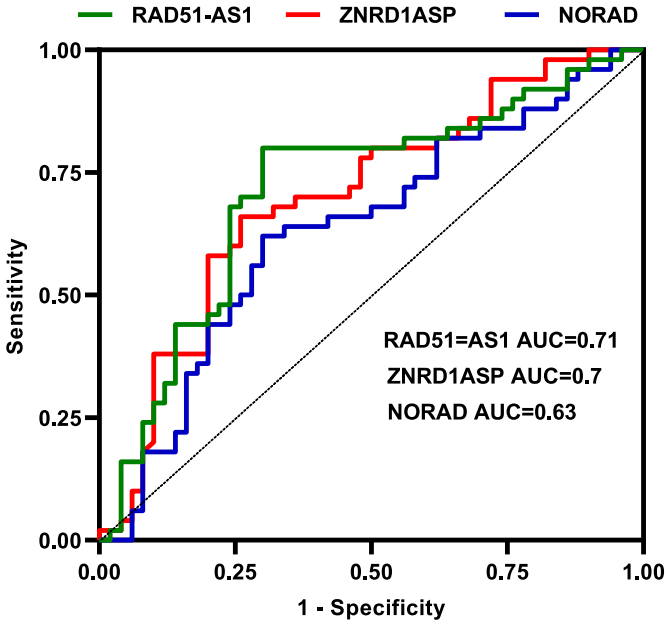

Fig. 3. Receiver operating characteristic (ROC) curves of *RAD51-AS1*, *ZNRD1ASP* and *NORAD* lncRNAs transcript levels in MS (AUC shows area under curves).

available literature on the role of this MAPK in the regulation of inflammatory responses. This might reflect the involvement of several other regulatory mechanisms for fine-tuning of expression of MAPK14. Alternatively, these lncRNAs might affect pathoetiology of MS through MAPK14-unrelated pathways.

NORAD has an essential role in the maintenance of genomic stability [16,17]. This process might be changed in MS, since polymorphisms within DNA repair system have been associated with risk of this disorder [18]. Therefore, changes in the expression of *NORAD* might affect the efficiency of DNA repair system in MS patients. In addition, this lncRNA has a possible impact on inflammatory responses, as its silencing has suppressed inflammation through regulation of activity of the miR-485/NRF1 axis [19]. Notably, miR-485 is among dysregulated miRNAs in MS [20]. miR-485–3p has also been shown to affect differentiation and proliferation of neural stem cells through regulation of expression of TRIP6 [21]. Thus, abnormal expression of *NORAD* in MS patients is expected to alter levels of miR-485–3p, influencing both immune responses and differentiation of neural stem cells. Cumulatively, *NORAD* can participate in the etiology of MS through various routes.

Importantly, *NORAD* expression differed between male and female healthy control patients but not MS patients. This might show possible effects of sex on expression of this gene in helathy controls. This effect is possibly modulated by the presence of MS.

RAD51-AS1 is an lncRNA which is involved in inhibition of DNA repair [22]. Moreover, it can target three important cytokines [23]. Abnormal expression pattern of this lncRNA in MS patients is in line with the possibility of defective DNA repair system in these patients. The function of *ZNRD1ASP* has not been assessed in immune-related disorders. However, polymorphisms within *ZNRD1* have been associated with viral load in patients infected with HIV [24].

Then, we evaluated ROC curves for assessment of *NORAD*, *RAD51-AS1* and *ZNRD1ASP* in MS. These genes could differentiate MS patients

Table 6
The results of Pearson correlation between expression of *MAPK14* and four related lncRNAs, age, disease duration, sex, age at onset and EDSS.

	age	sex	EDSS	Age at onset	Disease duration
HCG11	−.009	−.127	.088	−.163	.012
NORAD	−.051	−.172	.01	.067	−.272
RAD51-AS1	−.004	.063	.000	−.011	−.04
ZNRD1ASP	−.071	.016	.04	.031	−.15
MAPK14	−.123	−.258	−.035	−.01	−.246
Age		−.136	.024	**.769**	.157
Sex			.09	−.063	−.112
EDSS				.045	−.194
Age at onset					**−.341***

Disease duration was classified into 3 ranges (1–3, 4–10 and more than 10 years). Age of onset was classified into 3 ranges (<30, 31–40 and more than 40 years). EDSS was classified into 2 ranges (1–2, and greater than 2).

Table 5
The results of ROC curve analysis for three differentially expressed genes in patients with MS disease and healthy controls.

RAD51				ZNRD1ASP				NORAD			
AUC±SD	Sensitivity	Specificity	P Value	AUC±SD	Sensitivity	Specificity	P Value	AUC±SD	Sensitivity	Specificity	P Value
0.71 ± 0.05	0.8	0.7	0.0002	0.7 ± 0.05	0.64	0.74	0.0006	0.63 ± 0.05	0.62	0.7	0.02

and controls with AUC values 0.63, 0.71 and 0.7. Thus, none of them could individually separate MS patients from healthy controls with appropriate diagnostic values.

In spite of the observed dysregulation of these lncRNAs in the circulation of MS patients, their expressions were not correlated with EDSS, disease duration or age at disease onset. However, all of these genes were correlated with each other in both study subgroups highlighting their involvement in the MAPK14-related network. In brief, the current investigation shows dysregulation of MAPK14-related lncRNAs in MS patients. Our study has limitations regarding sample size and lack of functional studies.

We propose conduction of additional functional studies to unravel the underlying mechanism of their contribution in the pathoetiology of MS. Further in vitro studies are needed to find the consequences of dysregulation of these lncRNAs at cellular level. Finally, the relation between other lncRNAs and MAPK14 and the impact of MS on the expression of these lncRNAs should be assessed in future studies.

Ethics approval and consent to participant

All procedures were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration. 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.1399.211).

Consent of publication

Not applicable

Data availability statement

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Funding

Not applicable

CRediT authorship contribution statement

Soudeh Ghafouri-Fard: wrote the manuscript and revised it, All authors read and approved the submitted manuscript. **Mahdi Gholipour:** collected the data and performed the experiment, Data curation, All authors read and approved the submitted manuscript. **Solat Eslami:** analyzed the data, Formal analysis, Data curation, All authors read and approved the submitted manuscript. **Bashdar Mahmud Hussen:** collected the data and performed the experiment, Data curation, All authors read and approved the submitted manuscript. **Mohammad Taheri:** designed and supervised the study, Supervision, All authors read and approved the submitted manuscript. **Mohammad Samadian:** collected the data and performed the experiment, Data curation, All authors read and approved the submitted manuscript. **Mir Davood Omrani:** designed and supervised the study, Supervision, All authors read and approved the submitted manuscript.

Declaration of competing interest

The authors declare they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ncrna.2023.03.006.

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