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Letter

Research letter

The synchronized gene expression of retrotransposons and type I interferon in dermatomyositis

To the Editor: Dermatomyositis (DM) is an autoimmune, multiorgan disease. The type I interferon signature is characteristic in DM, and viral infection may be a contributing factor.[1] Retrotransposons are divided into 2 groups: non-long terminal repeat retrotransposons include long interspersed nuclear element-1 (LINE-1), Alu, and short interspersed nuclear elements (SINE)-variable number of tandem repeats (VNTR)-Alu (SVA), whereas long terminal repeat retrotransposons include endogenous retroviruses.[2] LINE-1 is a representative retrotransposon

Table I. Clinical characteristics of DNA and RNA virus detection in patients with posttreatment dermatomyositis

					DNA and RNA virus detection			
					After treatment		Before treatment	
Patient	Age, y	Sex	Antibody	Therapy (per day)	Serum	Extracted RNA	Serum	Extracted RNA
1	55	F	ARS	PSL 10 mg, CyA 50 mg	ND	-	ND	ND
2	55	F	MDA5	PSL 30 mg, Tac 3 mg, IVCY	ND	CMV	ND	ND
3	41	F	TIF1γ	PSL 8 mg	-	-	ND	ND
4	55	F	Mi2	PSL 40 mg	-	CMV	ND	ND
5	51	F	MDA5	Unknown	-	-	ND	ND
6	50	M	MDA5	PSL 10 mg, Aza 100 mg	-	-	ND	ND
7	75	F	negative	PSL 5 mg	-	-	ND	ND
8	43	M	negative	PSL 5 mg	-	-	ND	ND
9	72	F	negative	PSL 5 mg	-	EBV	ND	ND
10	54	F	negative	PSL 5 mg	-	-	ND	ND
11	45	F	negative	PSL 4 mg	-	-	ND	ND
12	40	F	ARS	PSL 10 mg	-	-	ND	ND
13	66	M	TIF1γ	-	-	-	ND	ND
14	52	M	Mi2	PSL 3 mg	-	-	ND	ND
15	76	F	TIF1γ	PSL 5 mg	-	-	ND	ND
16	46	F	ARS	PSL 5 mg	-	-	ND	ND
17	68	F	TIF1γ	PSL 6 mg	-	-	ND	ND
18	68	F	negative	PSL 1 mg	-	-	ND	ND
19	63	F	negative	PSL 1 mg	-	HHV7	ND	ND
20	38	M	negative	PSL 4 mg	-	-	ND	ND
21	51	M	TIF1γ	PSL 5 mg	-	-	ND	ND
22	53	M	Mi2	PSL 6 mg	-	-	ND	ND
23	63	F	negative	PSL 5 mg	-	-	ND	ND
24	60	F	negative	PSL 4 mg	-	-	ND	ND
25	43	M	negative	PSL 5 mg	-	-	ND	ND
26	59	F	MDA5	Unknown	-	CMV, EBV	ND	ND
27	54	F	MDA5	Unknown	-	-	ND	ND
28	52	F	MDA5	Unknown	ND	EBV	ND	ND
29	58	M	negative	-	ND	ND	-	-
30	60	M	unknown	-	ND	ND	-	-
31	71	M	unknown	-	ND	ND	-	-
32	44	F	MDA5	-	ND	ND	-	ND
33	10	F	MDA5	-	ND	ND	-	ND
34	45	M	MDA5	-	ND	ND	-	ND
35	57	F	MDA5	-	ND	ND	-	ND

The detected viruses were rhino/enterovirus, enterovirus 68, parechovirus, coronavirus, HSV, CMV, parvovirus B19, VZV, HHV6, HHV7, HHV8, and EBV.

Aza, Azathioprine; *CMV,* cytomegalovirus; *CyA,* cyclosporine A; *EBV,* Epstein-Barr virus; *F,* female; *HHV,* human herpesvirus; *HSV,* herpes simplex virus; *IVCY,* intravenous cyclophosphamide; *M,* male; *ND,* not described; *PSL,* prednisolone; *Tac,* tacrolimus; *VZV,* varicella zoster virus; -, negative.

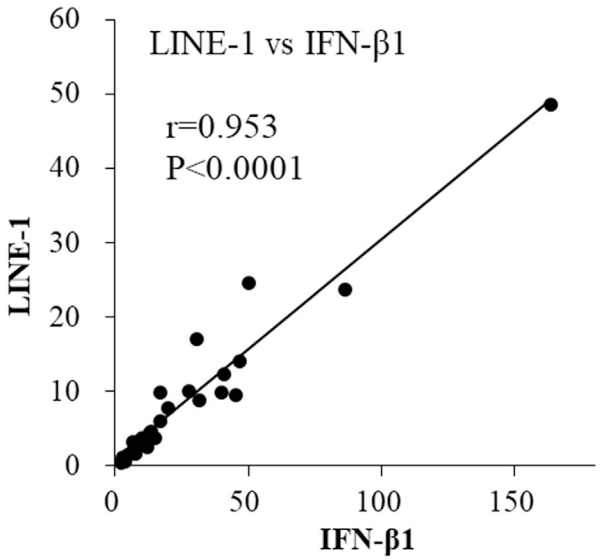

Fig 1. The correlation of *IFN-β1* and LINE-1 mRNA in the blood cells of patients with DM. The correlation of the relative messenger RNA level of *IFN-β1* with LINE-1. The results were tested for statistical significance by the nonparametric Spearman test. *DM,* Dermatomyositis; *mRNA,* messenger RNA.

that regulates the expression of type I interferon through the MDA5 pathway.[3] The expression of LINE-1 is observed in autoimmune diseases, such as systemic lupus erythematosus and Sjögren syndrome[4]; however, its expression pattern in DM is unknown. We investigated viral infections and the expression of retrotransposons.

We enrolled 7 pre- and 28 posttreatment patients with DM and 10 healthy individuals recruited from Gunma University. The autoantibody and treatment profiles and detected viruses by polymerase chain reaction are shown in Table I. Only a few DNA viruses, which are known to chronically infect humans, were detected among peripheral white blood cells after treatment. Next, quantitative polymerase chain reaction was performed to compare the expression of messenger RNA (mRNA) from peripheral white blood cells in posttreatment patients with DM with that in healthy control individuals. Two-group comparisons were assessed using the Mann-Whitney *U* test. The expression levels of LINE-1 and other retrotransposon mRNAs were significantly upregulated in patients with DM (LINE-1, 2.70 ± 3.19 vs 0.30 ± 0.19; HERVK14C, 3.54 ± 6.24 vs 0.27 ± 0.19; and SVA, 2.71 ± 2.74 vs 0.44 ± 0.20; all $P < .0001$). This upregulation was seen in not only anti-MDA5 antibody−positive patients but also in other autoantibody-positive patients as well as autoantibody-negative patients. To clarify whether altered DNA methylation contributes to the inappropriate expression of retrotransposons, expression levels of the methylation enzymes DNA methyltransferase (DNMT) 3A and DNMT3B were detected and showed significant down- and upregulation, respectively (0.62 ± 0.44 vs 1.15 ± 0.59 and 2.00 ± 3.00 vs 0.30 ± 0.19, respectively; $P < .05$). The expression levels of *IFN-α2* and *IFN-β1* were significantly increased (2.59 ± 4.59 vs 0.27 ± 0.18 and 4.08 ± 5.11 vs 0.31 ± 0.24, respectively; $P < .0001$). The LINE-1 promoter methylation was assessed by pyrosequencing, showing significant hypomethylation of LINE-1 promoter in patients with DM (78.12% ± 1.21% vs 80.24% ± 1.25%; $P < .005$, Mann-Whitney *U* test). Furthermore, the significant positive correlation was found between retrotransposon (LINE-1, HERVK14C, and SVA) and *IFN-β1* expression (*IFN-β1*: $r = 0.953$, $r = 0.941$, and $r = 0.948$, respectively; all $P < .0001$; nonparametric Spearman test) (LINE-1 vs *IFN-β1* in Fig 1) as well as DNMT3B and retrotransposons (DNMT3B: $r = 0.906$, $r = 0.717$, and $r = 0.833$, respectively).

In the present study, we detected elevated type I interferon expression of mRNA, even in posttreatment samples from patients with DM. We confirmed a strong positive correlation between the expression of retrotransposons and *IFN-β1*. In addition, the dysregulation of methylation enzymes was observed in our study. Although LINE-1−induced type I interferon regulates the activity and propagation of LINE-1,[5] the precise mechanisms underlying the mutual regulation between LINE-1 and type I interferon need further investigation.

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