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Journal of Immunology & Clinical Research

Research Article

PD1 Gene Promoter Polymorphism in Thymoma and Myasthenia Gravis

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Submitted: 02 December 2013

Accepted: 03 January 2014

Published: 20 January 2014

Keywords

- *PD-1*
- Promoter
- Thymoma
- Polymorphism
- Myasthenia gravis
- CTLA4

Abstract

Imbalance of immune regulation affects tumor-specific T-cell immunity in the cancer microenvironment and reshapes tumor progression and metastasis. Recent studies demonstrated that blockade of interactions of immune function mediates antitumor activity in preclinical models. Myasthenia gravis (MG) in thymoma patients depends critically on intratumorous generation and export of mature autoreactive T cells. On the other hands, the programmed death 1 (PD-1) molecule plays a role for negative regulator of T cells. Thus we investigated *PD1* and cytotoxic T lymphocyte associated antigen-4 (*CTLA4*) gene polymorphism by genotyping assay using TaqMan PCR methods in surgically treated thymoma cases and myasthenia gravis cases. In this study included 148 surgically removed thymoma cases and 32 myasthenia gravis cases for *PD-1* and *CTLA4* genotyping analyses. The *PD1* polymorphism at promoter -606 position (rs36084323) or at intron 2 (rs34819629) was not significantly different between myasthenia gravis patients (MG) and not with MG patients (non MG) within thymoma cases. *PD-1* polymorphism (GG) at promoter -606 position (rs36084323) was tendency towards lower in MG cases without thymoma when compared to MG with thymoma cases (p=0.1003). *CTLA4* gene polymorphism (rs231775) was not different within age, stage and MG statuses. AA genotype (3.1%) in MG without thymoma was tendency towards lower when compared to anti-acetylcholine antibody negative thymoma patients (p=0.0928). Thus *PD-1 or CTLA4* low activity might favor the development of non-thymomatous MG.

INTRODUCTION

Myasthenia gravis (MG) is considered a phenotype for antibody-mediated neuromuscular disorder and autoimmune diseases, directed against the nicotinic acetylcholine receptor. Among MG patients, those with thymoma differ from the other groups by a lack of significant human leukocyte antigen (HLA) association, absence of sex preponderance, and a poor response to thymectomy [1]. There is also good evidence that paraneoplastic MG has a different pathogenesis from the common thymic lymphofollicular hyperplasia-associated MG [2]. MG [3] or thymoma is associated with the +49A/G single nucleotide polymporphism (SNP) of the cytotoxic T-lymphocyte-associated antigen 4 (*CTLA4*) gene.

An imbalance of immune regulation affects tumor-specific T-cell immunity in the cancer microenvironment and reshapes tumor progression and metastasis [4]. The lack of immuno-stimulatory activation can be harmful if it impairs immune responses against cancer [5]. Many receptor-ligand interactions are known to trigger anti-apoptotic pathways that prevent activation-induced T-cell death [6,7]. Programmed death 1 (PD-1) protein, a T-cell coinhibitory receptor plays a central role in the ability of tumor cells to escape the host's immune system. Blockade of interactions between PD-1 and PD-1 ligands enhances immune function *in vitro* and mediates antitumor activity in preclinical models [8,9]. Recent reports suggested that antibody-mediated blockade of PD-1 [10,11] induced durable tumor regression and prolonged stabilization of disease in some patients with advanced

cancers. The PD-1 molecule is a negative regulator of T cells. One of the SNP of *PD-1* (PD1.3 G/A), a regulatory SNP located in intron 4, showed to be involved in susceptibility to SLE in Caucasian [12], however, Asian populations are not polymorphic at this SNP [13]. In addition, the *PD-1* SNP statuses were not correlated with MG in Caucasians [14]. The polymorphism at *PD-1* promoter was reported by Chinese, but vary rare in Caucasians [15]. The *PD-1* promoter SNP statuses in tumors are not well investigated.

In this paper, we have investigated the *PD-1* gene polymorphisms in Japanese thymoma with or without MG using real-time polymerase chain reaction (PCR) using TaqMan PCR in surgically treated cases. The findings were compared to the clinicopathologic features of thymoma/MG and *PD-1* gene status.

PATIENTS AND METHODS

Patients

The study group included thymoma patients (54.8±14.7 years old) and MG patients (38.4±18.9 years old) who had undergone surgery at the Department of Surgery, Nagoya City University Hospital between 1995 to 2013. All thymus tissue samples were immediately frozen and stored at -80 °C until assayed. Patient consent was obtained from the patients. The study was approved by the ethics committee of the University. The clinical and pathological characteristics of the 148 thymoma patients for *PD-1* gene genotyping analyses were as follows; 65(43.9%) were male 83 were female. 30(20.2%) were less than 40 years old. 40(27.0%) were with MG (male; 15, female; 25) and 84 were anti-acecyhlcholine receptor negative (male 43, female; 41). 49 (34.5%) were pathological stage I, 51 were stage II, 22 were stage III, 25 were stage IV and 1 unknown.

PCR assay for *PD-1* and *CTLA4* gene

Genomic DNA was extracted from thymus tissues using Wizard SV Genomic DNA Purification System (Promega. Madison, WI, USA) according to the manufactures' instructions. DNA concentration was determined by Nano Drop ND-1000 Spectrophotometer (Nano Drop Technologies Inc., Rockland, DE, USA). The primers and TaqMan probes for *PD-1*(*-606 G/A*; codon -606 of intron; rs36084323, *+6371G/A*; inton 2; rs34819629) and *CTLA4*; +49A/G, codon 17 of exon1; rs231775) were designed at Applied Biosystems (Foster City, CA, USA). For SNP genotyping, one pair of TaqMan probes and one pair of PCR primers were used. Two TaqMan probes differ at the polymorphic site, with one probe complementary to the wild-type allele and the other to the variant allele. TaqMan PCR and genotyping analysis were performed on Applied Biosystems 7500 Real Time PCR System. The reaction mixtures were amplified in 1 µl of template DNA (10ng/µl), 12.5 µl of 2X TaqMan Universal Master Mix, 0.625 µl of 20X primer/probe mix, 10.875 µl of ddH_2O in a volume of 25 µl. The cycling conditions were as follows: initial denaturation at 95°C for 10 minutes, followed by 40 cycles at 95°C for 15 seconds and 58°C for 1 minutes. The results were analyzed on Applied Biosystems 7500 Real Time PCR System using alleic discrimination assay program.

Statistical analysis

Statistical analyses were done using the Student's t-test for unpaired samples and T_2 test for paired samples. All analysis was done using the Stat-View software package (Abacus Concepts Inc. Berkeley, CA), and was considered significant when the *p* -value was less than 0.05.

RESULTS

PD-1 polymorphisn status in Japanese thymoma and mg

We have investigated *PD-1* gene status for 148 thymoma samples tissues. The *PD-1* SNPs at promoter region (rs 36084323) were 35 AA, 71 GA and 42 GG in thymomas. The ratio was very similar to the Asian healthy control as previously reported [15]. The ratio of GG genotype was not different between MG patients (32.5%), anti-acetylcholine antibody positive patients but not with MG patients (29.2%), and anti-antibody negative patients (26.2%) within thymoma cases. The GG ratio was not significantly different between male (30.8%) and female (26.5%, p=0.5680). The GG ratio was not different whether higher than 40 years old (27.1%) or lower than 40 years old (33.3%). The GG ratio was not correlated with pathological stages, if we compared stage I-III (20.4%) vs. IV (9.5%, p=0.1214), and GG was even smaller population in stage IV (Table 1). The *PD-1* SNPs at promoter region were 10 AA, 17 GA and 5 GG (15.6%) in MG without thymoma patients. GG genotype was tendency towards lower when compared to the MG with thymoma patients (p=0.1003) (Table 2).

PD-1 gene SNP status at intron 2 (rs 34819629) was very similar to the status for rs 36084323, and 93.9% identical. The *PD-1* rs 34819629 SNPs were 35 AA, 67 GA and 46 GG in thymomas. GG genotype was not different between MG patients (35.0%), anti-antibody positive but not with MG patients (33.3%), and anti-acetylcholine antibody negative patients (28.5%). The GG ratio was not significantly different between male (33.8%) and female (28.9%, p=0.5201). The GG ratio was not different whether higher than 40 years old (29.7%) or lower than 40 years old (36.7%, p=0.4591). The GG ratio was tendency towards lower in pathological stages IV (8.7%) when compared to stage I-III (21%, p=0.0667) (Table 3). The *PD-1* SNPs at intron 2 region were 10 AA, 16 GA and 6 GG (18.8%) in MG without thymoma patients. GG genotype was not significantly different with the MG with thymoma patients (p=0.1261).

CTLA4 polymorphisn status in Japanese thymoma and MG

CTLA4 gene SNP status at exon1 (+49A/G, rs 231775) was 17 AA, 65 GA and 66 GG in thymomas. AA genotype was not different between MG patients (5%), anti-antibody positive but not with MG patients (20.8%), and anti-acetylcholine antibody negative patients (11.9%), and the ratio was lower in MG patients. The AA phenotype was significantly higher in male (20%) than in female (7.2%, p=0.0254). *CTLA-4* +49 SNP statuses was not different whether higher than 40 or lower than 40 (p=0.3190). *CTLA4* +49 SNP was not correlated with pathological stages (I-III vs IV, p=0.8548) (Table 4). The *CTLA4* SNPs at +49 were 1 AA, 13 GA and 18 GG in MG without thymoma patients. AA genotype (3.1%) was tendency towards lower when compared to anti-

acetylcholine antibody negative thymoma patients (p=0.0928). Within 10 AA -606 *PD-1* patients with non-thymomataous MG, 5 were GG at +49 *CTLA4*. Within 5 GG -606 *PD-1* patients with non-thymomatous MG, no AA at +49 *CTLA4*. Thus, *PD-1* and *CTLA4* SNP was independent.

DISCUSSION

In this study, we focused on one of the programmed death 1, *PD-1* gene SNP to know whether it might be new molecular mechanism for thymoma. We have found that *PD-1* gene SNP was tendency towards lower in MG patients (without thymoma) when correlated to MG with thymoma patients.

Human cancers harbor numerous genetic and epigenetic changes, generating neoantigens that are potentially recognizable by immune system [16]. Tumors develop multistep resistance systems, including local immuno-suppression, induction of tolerance, and systemic dysfunction in T-cell signaling [17-20]. In addition, tumors utilize several pathways to escape immune destruction. PD1 is a key immune-checkpoint receptor expressed by activated T-cells and mediates immuno-suppressions. Thus *PD-1* might also act as a molecule target for tumor progression in cancers. In *in vitro*, inhibition of the interaction between PD-1 and PD-L1 could enhance T-cell responses and mediate preclinical antitumor activity [8, 9]. These observations made us our intensive efforts to develop immunotherapeutic approaches for cancer, including immune-checkpoint-pathway inhibitors such as anti-CTLA-4 antibody [21,22] and anti-PD-L1 therapy [11,12]. Anti-PD-1 antibody study has been started in advances solid tumors [23]. The recent studies by Brahmer et al. [11] and Topalian et al. [12] have been reporting the safety and activity of anti-PD1 or PD-L1 immunotherapy in cancers. However, in our analysis, *PD-1* or *CTLA-4* polymorphism did not correlate with thymoma progression. PD-1 polymorphSNPs at thymoma patients were very similar to Asian healthy controls. These molecules might not have a role in thymoma itself.

The PD-1 belongs to the immunoglobulin receptor superfamily, encodes a 55-kd type 1 transmembrane inhibitory immunoreceptor, and is responsible for the negative regulation in T-cell activation and peripheral torelance [24]. Expression of PD-1 was observed only in activated T and B cells and early lymphoid precursors [25]. Previous reports indicate that PD-1 is markedly upregulated on surface of exhausted virus-specific CD8+ T cells in mice with lymphocytic choriomeningitis virus infection [26], and in humans with human immunodeficiency virus (HIV) infection [27,28]. *PD-1* -606G allele showed a significant association with Japanese subacute sclerosing panencephalitis (SSPE) [29]. A haplotype having -606G allele with high promoter activity was associated with the development of SSPE [29]. Relative PD1 expression was higher in SSPE patients than in control [29]. PD-1 pathway might play a central role for the T cell dysfunction. Previous report demonstrated that -606G/A (previously called PD-1.1 at -531G/A) was associated with rheumatoid arthritis (RA) in Chinese [30]. However, this *PD-1* SNP is rare in Europeans (1%) and Africans (4%) [15]. Other *PD-1* SNP statuses were not significantly associated with MG in Sweden [14]. There is large variation in the frequencies of *PD-1* SNP among different ethnic groups.

Studies on PD-1 deficient mice in different genetic backgrounds showed the development of lupus-like autoimmune diseases [30] and autoimmune cardio myopathy [31]. Various studies indicated that *PD-1* gene SNP polymorphisms were associated with autoimmune diseases such as SLE [32], multiple sclerosis [33], rheumatoid arthritis (RA) [34] and type 1 diabetes [35], although most of the SNPs were Caucasian specific. Some reports on transcriptional levels have shown decreased

Table 1: Clinico-pathological data of 148 thymoma patients.

		PD-1		
		No. of AA+GA	**No. of GG**	**p-value**
Factors		**patients**	**patients**	
Mean age (years)	54.8±14.7	106 55.1±14.5	42 54.7±15.7	0.9078
Stage				
I II III IV		35(33.7%) 33(31.7%) 15(14.4%) 21(20.2%)	14(33.3%) 18(42.9%) 7(16.7%) 4(9.5%)	I-III vs. IV 0.1212
MG status				
MG+		27(25.5%)	13(31.0%)	N. S.
AchR Ab+		17(16.0%)	7(16.7%)	
Negative		62(58.5%)	22(52.4%)	
Gender				
Male		45(42.5%)	20(47.6%)	0.5680
Female		61(57.5%)	22(52.4%)	
Age				
40≦		20(18.9%)	10(23.8%)	0.5002
>40		86(81.1%)	32(76.2%)	

* MG: Myasthenia Gravis; AchR: Acetylcholine Receptor; Ab; antibody. N.S.: not significant

Table 2: Comparison of -606G/A genotype.

	AA	AG	GG
Thymoma (n=148)	23.60%	48.00%	28.40%
MG (Non-thymoma; n=32)	31.30%	53.10%	15.60%
*RA	13.90%	51.10%	35.00%
*Control (Chinese; n=647)	24.90%	47.80%	27.30%

*Kong et al. 2005 Arthritis Rheum

Table 3: Clinico-pathological data of 148 thymoma patients.

PD-1			
	No. of AA+GA	**No. of GG**	**p-value**
Factors	**patients**	**patients**	
Mean age (years)	102 55.2±14.5	46 54.6±15.6	0.8994
Stage			
I II III IV	34(34.0%) 31(31.0%) 14(14.0%) 21(21.0%)	15(32.6%) 20(43.5%) 7(15.2%) 4(8.7%)	I-III vs. IV 0.1345
MG status			
MG+	26(25.5%)	14(30.4%)	N. S.
AchR Ab+	16(15.7%)	8(17.4%)	
Negative	60(58.8%)	24(52.2%)	
Gender			
Male	43(42.2%)	22(47.8%)	0.5201
Female	59(57.8%)	24(52.2%)	
Age			
40≦	19(18.6%)	11(23.9%)	0.4591
>40	83(81.4%)	35(76.1%)	

Table 4: Clinico-pathological data of 148 thymoma patients.

CTLA-4			
	No. of GG+GA	**No. of AA**	**p-value**
Factors	**patients**	**patients**	
Mean age (years)	131 55.4±14.5	17 52.1±17.2	0.3896
Stage			
I II III IV	45(34.6%) 44(33.8%) 19(14.6%) 22(16.9%)	4(25.0%) 7(43.8%) 2(12.5%) 3(18.8%)	I-III vs. IV 0.8584
MG status			
MG+	38(29.0%)	2(11.8%)	N. S.
AchR Ab+	74(56.5%)	5(29.4%)	
Negative	19(14.5%)	10(58.8%)	
Gender			
Male	54(41.2%)	11(64.7%)	0.0254
Female	77(58.8%)	6(35.3%)	
Age			
40≦	25(19.1%)	5(29.4%)	0.319
>40	106(80.9%)	12(70.6%)	

expression in Japanese DM 1 patients [36]. We have found the tendency towards lower GG phenotype at *PD-1* promoter in MG without thymoma when compared to MG with thymoma patients. Thus *PD1* low activity might favor the development of non-thymomatous MG. We could not demonstrate any significant association of the *PD-1* gene SNP to MG, the possible reason could be sample size, fewer number of SNPs analyzed.

CTLA4 is a receptor mainly displayed on activated T-cells. CTLA4 plays a critical role in down regulating immune responses. Mice who lack the *CTLA4* gene develop a lethal phenotype with massive T-cell activation and T-cell infiltrates in virtually all organs [37]. SNP of the *CTLA4* gene. +49A/G in exon 1 has been shown to affect gene expression [38]. The frequency of allele G and genotype G/G at position +49 was increased in MG thymoma patients than healthy controls in Sweden [3]. In contrast, +49 A/A genotype were reported to be higher in MG thymomas than non-MG thymomas from German [1]. Our results were similar to the results from Wang et al. [3]. There might be also a large variation in the frequencies of *CTLA4* SNP among different ethnic groups. AA might be lower in Asian [40]. Our AA ratio in thymomas is very similar to the previous Asian report [40].

In summary, PD-1 might have no role in thymomas. However, lower GG phenotype at promoter region of *PD-1*, as well as lower AA phenotype at *CTLA4* +49 provided a candidate of its function as the autoimmune process. *PD1* or *CTLA4* low activity might favor the development of non-thymomatous MG. Larger cohort may be needed to determine the exact role of PD-1 and CTLA4 in MG.

ACKNOWLEDGEMENT

The authors thank Miss. Yuka Toda and Ito Yamamoto for their excellent technical assistances. This work was supported by Grants-in-Aid for Scientific Research, Japan Society for the Promotion of Science (JSPS) (Nos, 25293303, 24592097, 23659674) and the Health and Labour Sciences Research Grant on Intractable Diseases (Nueroimmunological Diseases) from the Ministry of Health, Labour and Welfare of Japan.

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Cite this article

Sasaki H, Tatematsu T, Shitara M, Hikosaka Y, Okuda K, et al. (2014) PD1 Gene Promoter Polymorphism in Thymoma and Myasthenia Gravis. J Immunol Clin Res 2(1): 1011.