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Polymorphisms of Genes for Programmed Cell Death 1 Ligands in Patients with Rheumatoid Arthritis

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Abstract To investigate the role of ligands for programmed cell death 1 (PD-L) in the pathogenesis of rheumatoid arthritis (RA), 129 patients with RA and 125 unrelated healthy controls were enrolled in this study. The *PD-L1* and *PD-L2* polymorphisms were determined by the method of polymerase chain reaction (PCR)/direct sequencing or PCR/reaction fragment length polymorphisms. The genotype distributions of *PD-L1* 6777 C/G were not significantly different between the patients with RA and healthy controls. There was also no significant difference in the allele frequencies of *PD-L1* 6777 C/G polymorphisms between the patients with RA and controls. Similar findings could also be found in the phenotypes and alleles frequencies of *PD-L2* 47103 C/T and 47139 T/C polymorphisms between the patients with RA and controls. The patients with *PD-L1* 6777 G had higher prevalence of rheumatoid nodule in comparison with those without *PD-L1* 6777 G (p=0.005, OR=4.0, 95% CI= 1.5–10.9). In contrast, the *PD-L2* 47103 C/T and 47139 T/C polymorphisms were not related to the occurrence of rheumatoid nodule. This study demonstrated that the *PD-L1* and *PD-L2* polymorphisms were not associated with susceptibility to RA in Taiwan. *PD-L1* 6777 G was associated with the prevalence of rheumatoid nodule.

Keywords *PD-L1* · *PD-L2* · *PD-1* · polymorphisms · rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that may involve extraarticular organs in addition to joints. Genetic and environmental factors are related to the pathogenesis of RA [1].

In many populations, *HLA-DR4* plays an important role in the susceptibility to RA. Our previous study also showed that *HLA-DR4*, especially *DRB1*0405*, was associated with the susceptibility to and clinical manifestations of RA in Taiwan [2]. However, the shared-epitope hypothesis accounted for only about half of our patients. Therefore, non-*HLA* genes may also play important roles in the pathogenesis of RA.

Programmed cell death 1 (PD-1) is an immunoinhibitory receptor expressed by activated T cells, B cells, and myeloid cells [3]. The ligands for PD-1 (PD-L1 and PD-L2, also known as B7-H1 and B7-DC) are type I transmembrane protein structurally related to the B7 family. They can be induced in monocytes, dendritic cells, endothelial cells, keratinocytes, B cells, and tumor cells [3–8]. However,

PD-L1 expression is different from that of PD-L2. PD-L1 is also expressed on activated T cells, placental trophoblasts, myocardial endothelium, and cortical thymic epithelial cells. In contrast, PD-L2 can also be presented on placental endothelium and medullary thymic epithelial cells [7]. The interactions of PD-1 with PD-L1 and PD-L2 result in the inhibition of T-cell receptor-mediated lymphocyte proliferation and cytokine secretion, and they also inhibit CD28-mediated costimulation. The relative levels of inhibitory PD-L1 and costimulatory CD80/CD86 signals on antigen-presenting cells determine the extent of T-cell activation and the threshold between tolerance and autoimmunity. Therefore, PD-L1 expression on nonlymphoid tissues and its interaction with PD-1 may determine the extent of immune responses at sites of inflammation [3].

Recent studies using anti-PD-L1 mAbs have suggested a role for PD-L1 in regulating autoimmune diseases. PD-L1 blockade rapidly precipitated diabetes in prediabetic female nonobese diabetic mice [9]. PD-L2 blockade in animals also resulted in augmentation of experimental autoimmune encephalomyelitis [10]. These studies demonstrated that PD-1-PD-L blockade was related to the development of autoimmune diseases.

The polymorphisms in exons of *PD-L1* and *PD-L2* may result in amino acid substitution, structural changes, and different expressions of PD-L1 and PD-L2. The consequent interactions between PD-L1 or PD-L2 and PD-1 may also be changed. Therefore, *PD-L1* and *PD-L2* polymorphisms may be related to the pathogenesis of autoimmune diseases. Our previous study showed that *PD-L2* polymorphisms are associated with susceptibility to systemic lupus erythematosus (SLE) in Taiwan [11]. RA is a T-cell-related autoimmune disease. PD-L determines the extent of T-cell activation. Therefore, the *PD-L* polymorphisms may also be associated with the development of RA. A report in regard to the association of *PD-L* polymorphisms with RA is still unavailable. The purpose of this study is to investigate the associations of *PD-L1* and *PD-L2* polymorphisms with susceptibility and clinical manifestations of RA in Taiwan.

Table I Frequencies of *PD-L1* Polymorphisms in the Patients with RA and Controls

Polymorphisms of *PD-L1*	RA, n=129 (%)	Controls, n=125 (%)
Genotype		
1072 G/G	129 (100)	125 (100)
1113 G/G	129 (100)	125 (100)
6777 C/C	95 (73.6)	104 (83.2)
C/G	32 (24.8)	19 (15.2)
G/G	2 (1.6)	2 (1.6)
Allele		
1072 G	258 (100)	250 (100)
1113 G	258 (100)	250 (100)
6777 C	222 (86.0)	227 (90.8)
G	36 (14.0)	23 (9.2)

The *PD-L1* 1072 C and *PD-L1* 1113 A alleles could not be detected in Taiwanese. There were no significant differences in the genotype and allele frequencies of *PD-L1* 6777 polymorphisms between the patients with RA and controls.

Table II Frequencies of *PD-L2* Polymorphisms in the Patients with RA and Controls

Polymorphisms of *PD-L2*	RA, n=129 (%)	Controls, n=125 (%)
Genotype		
24293 G/G	129 (100)	125 (100)
47103 C/C	102 (79.1)	84 (67.2)
C/T	18 (28.0)	30 (24.0)
T/T	9 (33.5)	11 (8.8)
47139 T/T	106 (92.1)	111 (88.8)
C/T	23 (17.8)	13 (10.4)
C/C	0 (0)	1 (0.8)
Allele		
24293 G	258 (100)	250 (100)
47103 C	222 (86.0)	198 (79.2)
T	36 (14.0)	52 (20.8)
47139 T	235 (91.1)	235 (94.0)
C	23 (4.0)	15 (6.0)

The *PD-L2* 24293 C allele could not be found in this study.

Materials and Methods

One hundred twenty-nine patients with RA (94 females, 35 males) and 125 age- and sex-matched unrelated healthy controls (93 females, 32 males) were enrolled in this study. All of the patients and controls are Taiwanese. The diagnosis of RA was according to the American College of Rheumatology 1987 revised criteria for the classification of RA. DNA was extracted from peripheral leukocyte with commercial kit. This study has been approved by the Institutional Review Board of Kaohsiung Medical University Hospital.

The polymorphisms in the exons of *PD-L1*, which were determined in this study, included *PD-L1* 1072 G/C (rs 12551333; exon 3, amino acid 49, Asp→His), 1113 G/A (rs 4278201; exon 3, amino acid 62, Lys→Lys, synonymous), and 6777 C/G (rs 17718883; exon 4, amino acid 146, Pro→Arg). The primers and conditions for polymerase chain reaction (PCR) were the same as those in our previous study [11].

The polymorphisms of *PD-L1* 1072 G/C and 1113 G/A were determined by the method of PCR/direct sequencing. The sequences of primers were 5′- TGTGGTAGAGTATGG-TAGC- 3′ and 5′- CTGTCTGTAGCTACTATGC - 3′. The amplification conditions consisted of initial denaturation at 96°C for 3 min, followed by five cycles of denaturation at 95°C for 1 min, annealing at 56°C for 1 min, and extension

Table III Associations of *PD-L1* and *PD-L2* Polymorphisms with Rheumatoid Nodule in the Patients with RA

Polymorphisms of *PD-L*		Rheumatoid nodule		*p*	OR (95% CI)
		+	–		
		n=19 (%)	*n*=110 (%)		
PD-L1 6777 C	(+)	18 (94.7)	109 (99.1)	NS	
	(–)	1 (5.3)	1 (0.9)		
6777 G	(+)	10 (52.6)	24 (21.8)	0.005	4.0 (1.5–10.9)
	(–)	9 (47.4)	86 (78.2)		
PD-L2 47103 C	(+)	18 (94.7)	102 (92.7)	NS	
	(–)	1 (5.3)	8 (7.3)		
47103 T	(+)	3 (15.8)	24 (21.8)	NS	
	(–)	16 (84.2)	86 (78.2)		
47139 T	(+)	19 (100.0)	110 (100.0)	NS	
	(–)	0 (0)	0 (0)		
47139 C	(+)	4 (21.1)	19 (17.3)	NS	
	(–)	15 (78.9)	91 (82.7)		

NS Not significant

at 72°C for 1 min, and 35 cycles of denaturation at 95°C for 1 min, annealing at 52°C for 1 min, and extension at 72°C for 1 min, and then a final extension phase at 72°C for 7 min. The nucleotide sequence was determined by the method of direct sequencing with the BigDye Terminator Cycle Sequencing Kit (Applied Biosystem Co.). The polymorphisms of *PD-L1* 6777 C/G were determined by the PCR/restriction fragment length polymorphism (RFLP) method. The sequences of primers were 5′- TACGTAGTTCTGTGCTCAG- 3′ and 5′- GTTGATTCTCAGTGTGCT G- 3′. PCR was carried out under the following conditions: initial denaturation at 95°C for 3 min and five cycles of denaturation at 94°C for 1 min, annealing at 55°C for 1 min, and extension at 72°C for 1 min, and then 30 cycles of denaturation at 94°C for 1 min, annealing at 50°C for 1 min and extension at 72°C for 1 min. A final extension phase was also performed at 72°C for 7 min. The restriction enzyme Bsr I was used to determine the 6777 C/G polymorphisms.

There are three nonsynonymous polymorphisms in *PD-L2* including *PD-L2* 24293 G/C (rs 12339171; exon 3, amino acid 58, Ser→Thr), 47103 /T (rs 7854303; exon 5, amino acid 229, Ser→Phe), and 47139 T/C (rs 7854413; exon 5, amino acid 241, Ile→Thr). These polymorphisms were also determined by the method of PCR/RFLP in this study. To determine the *PD-L2* 24293 G/C polymorphisms, the primers 5′- AGCATGGCAGCAATGTGAC- 3′ and 5′- CACTCACCTTTGACTTTCAG- 3′ were used. PCR was performed under the following conditions: initial denaturation at 95°C for 3 min and five cycles of denaturation at 95°C for 1 min, annealing at 56°C for 1 min, and extension at 72°C for 1 min, and then 35 cycles of denaturation at 95°C for 1 min, annealing at 54°C for 1 min and extension at 72°C for 1 min. A final extension phase was also performed at 72°C for 7 min. Then, the PCR product was digested with Bsr I.

The primers 5′- CCTGTTGGTCTACCTCTTAG- 3′ and 5′-TGAAAGCAG CAAGCCATAGG- 3′ were used to determine the *PD-L2* 47103 C/T and 47139 T/C polymorphisms. The PCR conditions were as follows: initial denaturation at 96°C for 3 min, followed by five cycles of denaturation at 95°C for 1 min, annealing at 58°C for 1 min, and extension at 72°C for 1 min, and 25 cycles of denaturation at 95°C for 1 min, annealing at 53°C for 1 min, and extension at 72°C for 1 min, and then a final extension phase at 72°C for 7 min. Then, the nucleotide sequence was determined by the method of direct sequencing.

The associations of PD-L1 and PD-L2 polymorphisms with clinical manifestations of RA were also evaluated.

The chi-square test or Fisher's exact test was used for statistical analysis. Odds ratio (OR) and its 95% confidence interval (CI) were calculated by using the SPSS statistic program.

Results

The distributions of *PD-L1* and *PD-L2* genotypes were compatible with Hardy–Weinberg equilibrium in the controls. The *PD-L1* 1072 C and *PD-L1* 1113 A alleles could not be detected in this study. Moreover, there was no significant difference in the genotype frequencies of *PD-L1* 6777 C/G polymorphisms between the patients with RA and the controls (Table I). Similar findings could also be concluded in their allele frequencies.

PD-L2 24293 C allele could not be found in the patients and controls in this study; all of the patients and the controls had *PD-L2* 24293 G. This study demonstrated that

there was no significant difference in the genotype distributions of *PD-L2* 47103 C/T and *PD-L2* 47139 T/C polymorphisms between the patients with RA and the controls in Taiwan (Table II). Similar findings could also be concluded in the allele frequencies of *PD-L2* 47103 C/T and *PD-L2* 47139 T/C polymorphisms.

The associations of *PD-L1* and *PD-L2* polymorphisms with rheumatoid nodule in the patients with RA are demonstrated in Table III. The prevalence of rheumatoid nodule was significantly higher in the patients with *PD-L1* 6777 G(+) than in the *PD-L1* 6777 G (−) patients ($p = 0.005$, OR=4.0, 95% CI=1.5–10.9).

Discussion

This study demonstrated that *PD-L1* and *PD-L2* polymorphisms were not related to the susceptibility to RA in Taiwan. However, *PD-L1* 6777 G was associated with the development of rheumatoid nodule in patients with RA.

The PD-1-PD-L pathway regulates the immune response in both lymphoid and nonlymphoid organs. The interactions between PD-1 and PD-L inhibit lymphocyte activation. Although positive effects of PD-1-PD-L interaction have been found [5, 6, 12, 13], the negative effects are well-documented. It is still unknown whether the positive effects are caused by the inhibition of negative signaling or by other stimulatory receptors.

Mice deficient in *PD-1* developed spontaneous autoimmune diseases, which suggested a negative costimulatory function [14–18]. PD-1-PD-L pathway may play an important role in the induction and maintenance of peripheral tolerance. PD-1-PD-L interaction inhibits adverse immune response in two ways. PD-Ls on antigen presenting cells inhibit T-cell activation and induce peripheral tolerance. Moreover, PD-Ls on target cells inhibit the effector function of T-cells to maintain tolerance. PD-L on nonlymphoid organs prevents tissue destruction by suppressing the effector function of autoreactive lymphocytes. PD-L1 on islet cells suppresses the effector function of diabetogenic T cells [19]. PD-L1 on tumor cells suppresses the cytolytic activity of $CD8^+$ T cells [20, 21]. Blocking PD-1-PD-L interaction will accelerate tumor eradication. A PD-1-PD-L blockade may activate the immune system of tumor-bearing hosts to eradicate tumors.

Resting dendritic cells induce inactivation or anergy of T cells and $CD8^+$ T-cells tolerance through the PD-1-PD-L pathway [22]. Virus- or parasite-infected cells will induce PD-L1 expression on dendritic cells and then induce T-cell anergy, which will result in immune paralysis against viruses or parasites [23, 24]. However, activated dendritic cells express lower levels of PD-L than costimulatory and MHC molecules. The activating signals overcome the inhibitory signal of PD-1, and T-cell activation will result.

PD-1-PD-L interaction inhibits adverse immune responses to prevent autoimmunity. The *PD-1* or *PD-L* polymorphisms may interfere with the interaction between PD-1 and PD-L and then diminish the prevention of autoimmune responses. Several studies revealed that *PD-1* polymorphisms were associated with some immune-mediated diseases including RA, SLE, and type I diabetes [25–30]. Our previous study also revealed an association between *PD-L2* polymorphisms and the development of SLE [11]. This study showed that the polymorphisms in the exons of *PD-L1* and *PD-L2* were not associated with susceptibility to RA in Taiwan. We also found that *PD-L1* 6777 G(+) was associated with the development of rheumatoid nodule in patients with RA. Meanwhile, the correlations between nodule development and disease duration, age at disease onset, or positivity of rheumatoid factor could not be found in this study (data not shown).

The *PD-L1* 6777 C/G polymorphisms result in an amino acid substitution in exon 4. *PD-L1* 6777 G encodes arginine instead of proline in *PD-L1* 6777 C. Arginine has a polar and hydrophilic side chain, whereas proline is nonpolar and hydrophobic. An aromatic side chain is also noted in proline. Further investigation is needed to determine whether the polarity of amino acid is related to the occurrence of rheumatoid nodule. Dong et al. [31] demonstrated that the autoantibodies to PD-L1 were found in 29% of patients with RA, and the existence of the autoantibodies was correlated with the disease activity of RA. The immobilized anti-PD-L1 autoantibodies can stimulate the proliferation of $CD4^+$ T cells in vitro. The autoantibodies against PD-L1 may contribute to the progression of RA by inducing aberrant T-cell responses. It is still unknown whether the development of rheumatoid nodule is associated with the aberrant immune responses caused by amino acid substitution.

In our previous study, *PD-L2* 47103 T is associated with susceptibility to SLE [11]. A similar finding could not be demonstrated in patients with RA. The expression of PD-L2 is different from that of PD-L1. Moreover, PD-L1 and PD-L2 are differentially regulated by Th1 and Th2 cells [32]. Th1 and Th2 cells differentially upregulate PD-L1 and PD-L2 expression on inflammatory macrophage. PD-L1 and PD-L2 have different functions in regulating type 1 and type 2 immune responses. Many studies showed that SLE was a Th2-mediated disease [33–35]. In contrast, a dominant Th1 drive was evident in RA [36]. *PD-L1* polymorphisms may influence type 1 immune responses and also be related to the pathogenesis of RA.

In summary, this study revealed that *PD-L1* polymorphisms were not related to the susceptibility to RA in

Taiwan. *PD-L1* 6777 G allele is associated with the development of rheumatoid nodule in RA patients.

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