



# IL-2/IL-2 antibody immune complex regulates HSV-induced inflammation through induction of IL-2 receptor alpha, beta, and gamma in a mouse model

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## ARTICLE INFO

### Article history:

Received 6 February 2015

Received in revised form 28 May 2015

Accepted 7 July 2015

Available online 17 July 2015

### Keywords:

IL-2/IL-2 antibody immune complex

Behçet's disease

Mouse model

HSV

IL-2R $\alpha\beta\gamma$

## ABSTRACT

The differences of serum IL-2 levels were not consistent between Behçet's Disease (BD) patients and healthy controls, however, the correlation of interleukin-2 receptor (IL-2R) and BD has not been investigated. IL-2R is composed of three subunits; alpha, beta, and gamma. The expression frequencies of IL-2R subunits were analyzed in the peripheral blood mononuclear cells, spleens, and lymph node (LN) cells. The expression of IL-2R subunits was different between BD mice and controls. IL-2R beta expressing cell frequencies were also different between BD patients and healthy controls. The IL-2/anti-mIL-2 antibody complex administration regulated the IL-2R subunits in mice. The change of expression in IL-2R was accompanied by the increase of CD8+CD44+ memory T cells, CD3-NK1.1+CD11b+CD27+ natural killer cells, and improvement of symptoms. In this study, we elucidated the role of IL-2R subunits on BD, a finding that can be connected to therapeutic strategy for patients based on the results from the treatment of BD mice.

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## 1. Introduction

The serum levels of soluble interleukin-2 receptors (sIL-2R) were significantly higher in active Behçet's Disease (BD) patients than in inactive patients (Alpsoy et al., 1998; Evereklioglu et al., 2002; Uchio et al., 1999). Several papers reported that serum levels of IL-2 were significantly higher in BD patients than in healthy controls (Ahn et al., 2006; Akdeniz et al., 2004; Alpsoy et al., 1998), whereas other papers have reported that IL-2 levels are not much different between BD patients and healthy controls (Aktas Cetin et al., 2013; Pekiner et al., 2012). According to Sugi-Ikai et al. (1998) the frequencies of IL-2 producing CD4+ and CD8+ cells in active

patients are significantly higher than those in inactive patients (Sugi-Ikai et al., 1998). Sakane et al. (1986) suggested that the impairment of IL-2 responsiveness in concanavalin-A activated lymphoblasts was due to a decrease in the density of IL-2 receptors on T cells and this may thus contribute to the immunologic aberrations in BD.

For the signaling of IL-2, IL-2 and IL-2 receptor (IL-2R) interaction is important (Gaffen, 2001). From previous reports, the serum IL-2 levels were not consistent and there were no reports related to the frequencies of IL-2 receptor-expressing leukocytes in BD patients. Higher serum levels of sIL-2R may have a reverse correlation with the expression of membrane bound IL-2R on leukocytes. Therefore, this study focused on the expression and regulation of IL-2R on peripheral blood mononuclear cells (PBMC) in a BD mouse model and BD patients. BD mice were produced by herpes simplex virus (HSV) inoculation on the scratched earlobe and they showed BD-like symptoms, including major symptoms such as oral, genital, eye inflammation, and minor symptoms such as arthritis and intestinal involvement (Sohn et al., 1998).

IL-2R is composed of alpha (CD25), beta (CD122), and gamma (CD132) subunits (Pekalski et al., 2013; Voss et al., 1992). IL-2R $\alpha$ ,

**Abbreviations:** BD, Behçet's disease; BDN, BD normal; HSV, herpes simplex virus; IL-2/S4B6-1, IL-2/anti-mIL-2 antibody complex; IL-2R, interleukin-2 receptor; ip, intraperitoneal; LN, lymph node; NK, natural killer; PBMC, peripheral blood mononuclear cells; PBS, phosphate buffered saline; rIL-2, recombinant IL-2; sc, subcutaneous; sIL-2R, soluble IL-2 receptor; TNF, tumor necrosis factor.

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<http://dx.doi.org/10.1016/j.imbio.2015.07.004>

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**Table 1**  
Clinical characteristics of Behcet's disease patients.

Patient	Age	Sex	OU	GU	GI	NEUR	VAS	OL	Pathergy	HLA-B51
Inactive										
1	35	F	+	+				+	+	+
2	34	M	+					+		+
3	44	F	+	+					–	–
4	50	F	+	+	+			+		+
5	42	F	+	+					–	
6	54	F	+	+						–
7	36	M	+	+			+			–
8	57	F	+	+				+	+	+
9	40	M	+					+	–	–
10	48	M					+	+	+	+
11	39	M	+	+						
Active										
1	38	M	+					+		–
2	40	F	+		+					–
3	36	F	+	+				–		+
4	46	F	+	+				–		–
5	50	M	+	+		+		+		+
6	39	F	+	+						–
7	49	F	+	+						–
8	41	F	+					+		
9	43	F	+	+						–
10	41	M	+	+				+		
11	41	F	+	+				+		
12	45	F	+	+						–
13	23	F	+	+						+
14	41	M	+					+	–	+
15	49	M	+	+						–
16	44	F	+	+					–	+
17	32	F	+	+					–	+
18	53	F	+	+				+	–	–
19	47	M	+	+				+	–	+
20	22	F	+	+					–	–
21	51	M	+	+					–	+

Note—M: male, F: female, OU: oral ulcers, GU: genital ulcers, GI: gastrointestinal inflammation, NEUR: neurological involvement, VAS: vasculitis, OL: ocular lesions.

CD25, is a well-known marker of regulatory T cells, as CD4+CD25+ cells (Turka and Walsh, 2008). IL-2R $\beta$ , CD122, is the common receptor for IL-15 receptor beta (Pillet et al., 2009). IL-2R $\gamma$ , CD132, is the common gamma chain of receptor for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 (Vosshenrich et al., 2005). Recently, the IL-2/anti-IL-2 monoclonal antibody complex was found to display an extended lifespan, beyond that of IL-2 alone *in vivo*, and to have the biological activity for proliferation of memory CD8+ T cells (Boyman et al., 2010; Mostbock et al., 2008) and expansion of CD4+CD25+ regulatory T cells (Polhill et al., 2012). In HSV-induced BD mice, up-regulation of memory CD8+ T cells and CD4+CD25+ regulatory T cells were correlated to the improvement of symptoms (Choi et al., 2013a; Shim et al., 2011). In this study, the expression of IL-2R  $\alpha$ ,  $\beta$ , and  $\gamma$  was analyzed in BD mice and the regulation of the receptor subunits through IL-2/anti-IL-2Ab complex was applied to BD mice for the resolution of inflammation by expansion of regulatory T cells, or memory T cells, or the regulation of natural killer (NK) cell maturation.

## 2. Materials and methods

### 2.1. BD symptoms in a mouse model

ICR male mice (4–5 weeks old) were infected with HSV type 1 ( $1 \times 10^6$  pfu/mL, F strain) grown in Vero cells, as previously described (Sohn et al., 1998). Virus inoculation was conducted twice with a 10 day interval in between, and after the second HSV inoculation, mice were observed from 4 weeks to 32 weeks. Animals were handled in accordance with a protocol approved by the animal care committee of Ajou University School of Medicine (AMC-102). BD manifestations were shown as several different

symptoms in mice. Of the total HSV-infected mice, 15% developed BD-like symptoms. Symptoms included oral ulcerations, genital ulcerations, erythema, skin pustules, skin ulcerations, joint-arthritis, diarrhoea, red eye (right, left), reduced vision (right, left), loss of balance, discoloration, and swelling of the face. Oral, genital and other skin ulcers and eye symptoms were classified as major symptoms. Arthritis, intestinal ulcers, and neurological involvement were identified as minor symptoms. Mice with  $\geq 1$  major and 1 minor symptom were classified as having BD. The score of each symptom was one, and the sum of the symptoms was used to determine the severity of BD. The disappearance of symptoms or 20% or greater decrease in the lesion size were classified as improvements. The calculation of severity of BD was followed by that of the BD activity index, as outlined in the BD Activity Form ([www.behcet.ws/pdf/BehcetsDiseaseActivityForm.pdf](http://www.behcet.ws/pdf/BehcetsDiseaseActivityForm.pdf)). The control group was inoculated with HSV, but asymptomatic healthy mice were used as a BD normal (BDN) control, as previously described.

### 2.2. BD patients

The patient population consisted of 32 patients with BD, who presented for the first time or were monitored at the Department of Dermatology, Ajou University Hospital and Yonsei University Severance Hospital. Clinical characteristics and therapeutic histories of these patients are shown in Tables 1 and 2. According to the International Study Group for BD criteria, the presence of any two of the following symptoms in addition to recurrent oral ulcerations is considered to be sufficient for a BD diagnosis recurrent genital ulceration, uveitis, large-vessel vasculitis, cutaneous erythema nodosum, and a positive pathergy test. The active patients group ( $n=21$  (male 7, female 14),  $41.5 \pm 8.2$  years) had at least one of the

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