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Frequencies of IL-15Rα+ cells in patients with Behçet's disease and the effects of overexpressing IL-15Rα+ on disease symptoms in mice

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ABSTRACT

It has been suggested higher serum levels of IL-15 and lower expression levels of IL-15 receptor alpha (IL-15Rα) are correlated with pathogenesis of Behçet's disease (BD). However, whether overexpressing IL-15Rα could be used as a therapeutic candidate for BD is currently unclear. Therefore, the purpose of this study was to determine whether overexpressing IL-15Rα could affect BD symptoms in a mouse model. IL-15/IL-15Rα complex expressing vector or protein complex of IL-15/IL-15Rα-Fc was used to treat BD mice. Frequencies of IL-15Rα+ cells in peripheral blood leukocytes (PBL) and lymph node cells were determined using a flow cytometer. BD symptoms in mice improved after treatment with IL-15/15Rα expression vector or IL-15/IL-15Rα-Fc protein complex. In addition, treatment with pIL-15/15Rα significantly ($p = .016$) decreased disease severity score of BD mice compared to treatment with control vector. Frequencies of IL-15Rα+ cells were also significantly ($p = .01$) higher in peritoneal macrophages of pIL-15/15Rα treated BD mice than those of mice treated with control vector. Frequencies of IL-15Rα+ PBL were also significantly higher in BD mice treated with IL-15/IL-15Rα-Fc protein complex than those in the control group. These results suggest up-regulating IL-15Rα+ cells could be used as novel therapeutic strategies to control BD in the future.

1. Introduction

Behcet's disease (BD) is a chronic multi-systemic inflammatory disease presented by oral ulcer, genital ulcer, skin ulcer, and ocular inflammation. BD frequently involves joints, intestine, and the central nervous system [1]. Its pathogenic mechanism remains elusive. However, viral, genetic, and immunological factors are likely to be involved [2]. Viral hypothesis is based on the detection of viruses in saliva and oral tissues from BD patients with ulcer [3,4]. ICR mice inoculated with herpes simplex virus (HSV) has been developed as an animal model showing BD-like symptoms such as oral ulcers, genital ulcer, skin ulcers, eye symptoms, intestinal ulcers, arthritis, neural involvement, and skin crust [5]. It has been suggested that HSV might play an important role in the pathogenesis in BD patients [6] and BD model mice [5]. HSV-1 DNA and higher serum antibodies against HSV have been reported in BD patients than those in normal controls [7,8].

Interleikin-15 (IL-15) is a pleiotropic proinflammatory cytokine produced by activated dendritic cells, macrophages, and monocytes [9–11] essential for cell survival, cell proliferation, and functional activity of immune cells such as natural killer (NK) cells, memory T cells, monocytes, macrophages, and dendritic cells. IL-15 stimulates B cells to proliferate and secrete immunoglobulins [12,13]. IL-15 is also involved in the pathogenesis of diverse inflammatory diseases including BD [14]. IL-15 exerts its effect by binding to a membrane receptor composed of high affinity binding alpha chain (IL-15Rα) [15] that forms a heterotrimeric receptor complex with IL-15Rβ and IL-15Rγ [16]. IL-15Rα is expressed independently of IL-15Rβγ in humans and mice [17]. IL-15Rα restricts aberrant immune stimulation and decreases the risk of uncontrolled IL-15 exposure [18]. IL-15Rα chain serves as a protector in the cell membrane. The importance of IL-15 for the production and survival of memory CD8 T cells has been shown using virus infected IL-15 knockout mice [19,20]. It has been reported that the combination of human IL-15 and mouse IL-15Rα-Fc results in significant proliferation of NK cells and NKT cells in mouse *in vivo* [21].

Higher expressions of IL-15 have been observed in serum, cerebrospinal fluid, and aqueous humor of BD patients [22–24]. However, whether overexpressing IL-15Rα could be used as a treatment for BD is currently unclear. Therefore, the purpose of this study was to determine whether overexpressing IL-15Rα could affect BD symptoms in a mouse model.

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Table 1
Clinical characteristics of Behçet's disease patients.

	Patient	Age	OU	GU	GI	Neu	Vas	OL	Pathergy	HLA-B51
Inactive	N = 11 (F:6, M:5)	43.5 ± 7.8	10 (90.9%)	8 (72.7%)	1 (9.1%)	0 (0%)	2 (18.2%)	6 (54.5%)	3 (27.3%)	5 (45.5%)
Active	N = 15 (F:10, M:5)	41.4 ± 8.2	15 (100%)	11 (73.3%)	1 (6.7%)	1 (6.7%)	0 (0%)	6 (40.0%)	0 (0%)	4 (26.7%)

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

Table 2
Therapeutic history of Behçet's disease patients.

	Colchicine	Steroid	Pentoxifylline	Minocycline	Salazopyrine	Empynase	Rebamipide
Inactive (N = 11)	10 (90.9%)	2 (18.2%)	6 (54.5%)	0 (0%)	1 (9.1%)	1 (9.1%)	8 (72.7%)
Active (N = 15)	8 (53.3%)	2 (13.3%)	6 (40.0%)	3 (20.2%)	2 (13.3%)	5 (33.3%)	7 (46.7%)

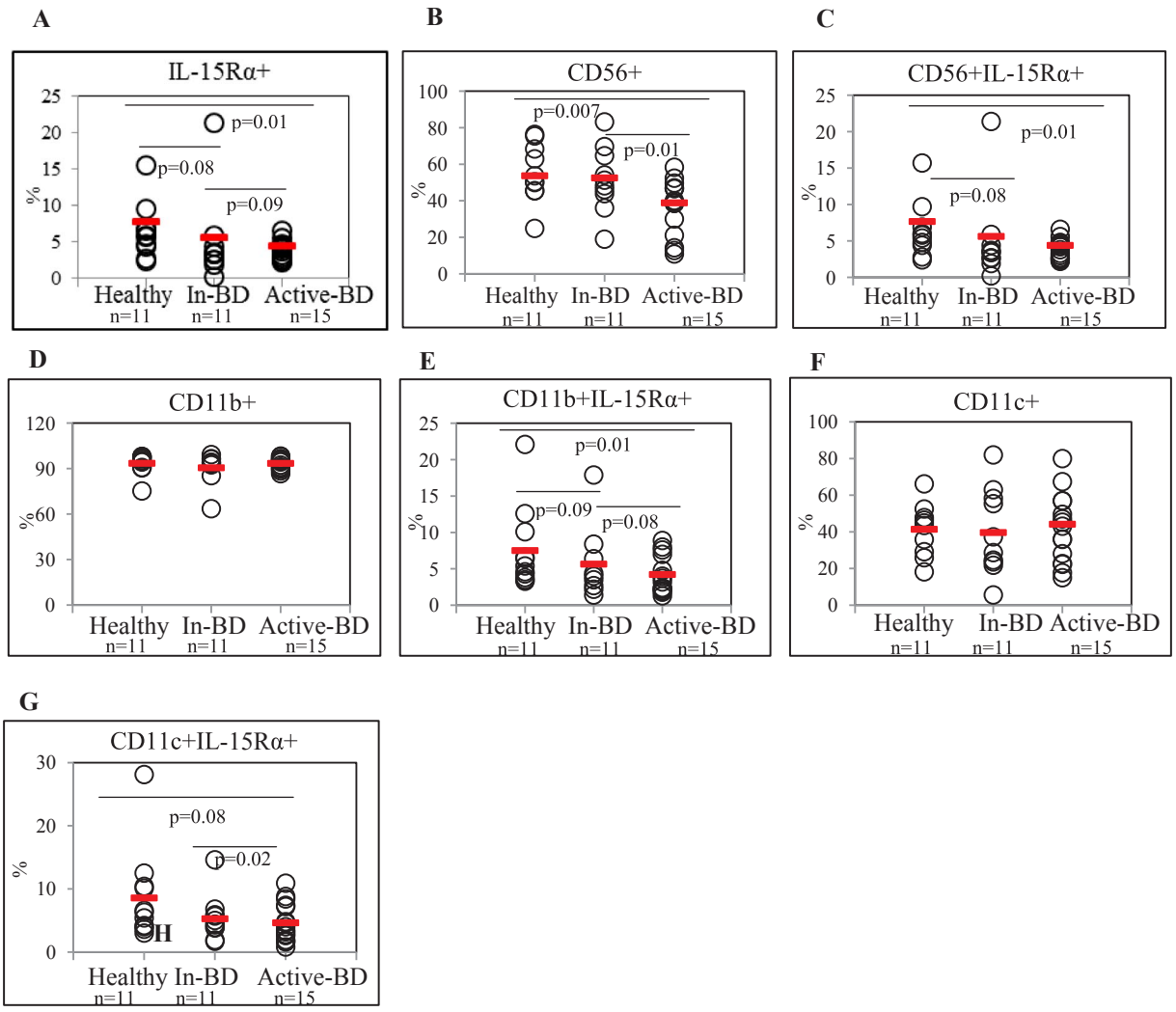

Fig. 1. Frequencies of IL-15Rα + cells were decreased in granulocytes of patients with Behçet's disease. (A) Frequencies of IL-15Rα + cells in granulocytes were down-regulated in active BD patients than those in healthy controls. (B, C) Frequencies of CD56 + IL-15Rα + cells were also lower in active BD patients than those in healthy controls. (D, F) Frequencies of CD11b + and CD11c + were not significantly different among these groups. However, frequencies of CD11b + IL-15Rα + cells (E) and CD11c + IL-15Rα + (G) cells were down-regulated in active BD patients than those in healthy controls. (H) Representative histograms of double positive cell populations for CD56 + IL-15Rα +, CD11b + IL-15Rα +, and CD11c + IL-15Rα + cells. n indicates the number of patients used in this analysis. Cell populations were quantified by FACS.