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TRIM39R, but not TRIM39B, regulates type I interferon response

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ABSTRACT

Behcet's disease (BD) is a chronic relapsing inflammatory autoimmune disease characterized by recurrent oral and genital ulcers, skin legions and uveitis and its pathogenesis is not fully elucidated. Previously we identified that two novel susceptible SNPs are associated with BD. One is located in putative RNF39 promoter region, another is located on TRIM39 coding exon. In this study, in order to identify the molecular function of TRIM39, we established gain-of-function of TRIM39 related genes and thus, performed microarray analysis. Our results indicate that TRIM39R, but not TRIM39B, regulates type I interferon response.

1. Introduction

Behcet's disease (BD) is a chronic relapsing inflammatory autoimmune disease characterized by recurrent oral and genital ulcers, skin legions and uveitis [1]. Although it is one of a systemic inflammatory disease, BD patients emerge some inflammation symptoms to several specific organs and thus pathological conditions are diverse and complex. Besides that, BD resembles another autoimmune diseases such as Rheumatoid arthritis and Familial Mediterranean fever in the symptoms [2,3]. That is the reason why it is so hard to understand the pathogenesis well.

Previous several association studies have elucidated that human leukocyte antigen *(HLA)-B*51* and *-A*26* is strongly associated with BD in various ethnic groups [4,5]. However, Among BD patients, a substantial number of them do not possess *HLA-B*51 and -A*26* allele and their contribution is not critical, thus suggesting that there still are another unidentified genetic factors. Actually, we identified using multiple logistic regression analysis that two novel susceptible SNPs located on putative *RNF39* promoter region and *TRIM39* coding exon independently of *HLA-B*51 and -A*26* allele [6]. Recently, using huge number of BD patient samples, two genome-wide association studies (GWASs) including our group's study indicate that interleukin *(IL)-10* and *IL-23R/IL-12RB2* genes were associated with BD [5,7]. It has been thought that Th1/Th17 immune response contributes to the pathological condition of BD [8]. These results confirmed that not only Th1 but also Th17 plays an important role for BD development and onset. Besides that, in susceptible individual, an elicitation of BD has been thought to be caused by viral and bacterial infection [9,10].

Recent studies suggest that a few member of tripartite motif (TRIM) family play an important role for regulation of innate immune pathway including type I interferon and defense of viral infection [11–15]. Moreover, TRIM39 fused with Rpp21, which locates nearby TRIM39, (TRIM39R) probably generated by intergenic splicing of a pre-mRNA of TRIM39 and Rpp21 [16]. In our previous study, two SNPs, rs2074474 and rs974963, which is located on *TRIM39* and *Rpp21* coding exon, respectively, was included in same susceptible linkage disequilibrium (LD) block with BD [6], suggesting that *Rpp21* and/or *TRIM39* may be involved in BD. Wherein, we established gain-of-function of TRIM39B, TRIM39R and Rpp21 in human embryonic kidney (HEK) 293T cell line, and then carried out microarray analysis in order to obtain any information concerning functional annotation and to speculate that which one is interact to BD pathology. Our microarray analysis clearly predicts that TRIM39R, but not TRIM39B, regulates defense of viral infection and type I IFN response pathway.

Abbreviations: BD, Behcet's disease; HLA, human leukocyte antigen; GWAS, genome-wide association study; IL, interleukin; TRIM, tripartite moti; LD, linkage disequilibrium; HEK, human embryonic kidney; PVDF, polyvinylidene difluoride; TBST, Tris-buffered saline containing 0.1% Tween-20; cRNA, complementary RNA; FDR, False discovery rate; OASs, oligoadenylate synthetases; IFIs, interferon alpha-induced proteins; ISGs, interferon stimulated genes; IRFs, interferon regulatory factors; MOAP, modulator of apoptosis; APC/C, anaphase-promoting complex.

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2. Materials and methods

2.1. Construction of expression vectors

Using human Bone marrow cDNA, we amplified open leading frames of TRIM39B isoform2, TRIM39R and Rpp21 with following sets of primer; the sense primer 5′-AAGAATTCATGGCAGAGACAAGTCTGTTAGAGGCTG-3′, 5′-GCAGACTCAGGGTTCCAGTAACCAGGATATCAA-3′ and 5′-AAGAATTCATGGCGGGGCCGGTGAAGGACCG-3′ and the antisense primer 5′-CAGGCCCCCAACAGATTGGGAGGATATCAA-3′, 5′-TTGATATCCTGGTTACTGGAACCCTGAGTCTGC-3′ and 5′-GCAGACTCAGGGTTCCAGTAACCAGGATATCAA-3′, respectively. PCR condition was run for 40 cycles using the following protocol: 10 s denaturation at 98 °C; 15 s annealing at 55 °C; 1 min extension at 68 °C. The amplicons were digested with EcoRI and EcoRV restriction enzymes, and inserted into the corresponding sites of the pcDNA6/V5-His B vector (Invitrogen, CA, USA).

2.2. Cells and transfection

HEK293T cell were cultured in DMEM (Invitrogen, CA, USA) containing 10% fetal bovine serum (FBS, Thermo Fisher Scientific, MA, USA) at 37 °C with 5% CO_2. To optimize transfection condition, we introduced pcDNA6-emGFP into the cells using fugeneHD (promega, WI, USA) according to manufacturer's instructions. After that, we introduced pcDNA6/V5-His B, pcDNA6/V5-His-TRIM39B, -TRIM39R or -Rpp21 and pcDNA6-emGFP into the cells. After checking fluorescence of emGFP, we collected the cells and then, the cells were lysed with RIPA buffer or with Trizol reagent (Life Technologies, CA, USA).

2.3. Western blotting

We used antibodies anti-RNF23 (ab-49312, abcome, UK), -Rpp21 (ab-118681, abcome, UK) and -V5epitope (P/N46-0705, Life Technologies, CA, USA) to detect TRIM39, Rpp21 and v5, respectively. Equal amount of protein samples were subjected to 12.5% SDS–PAGE before being transferred polyvinylidene difluoride (PVDF) membranes. The membranes were then exposed to each primary antibody, and subsequently, were exposed to HRP-conjugated secondary antibody. The membranes were blocked with 5% skim milk/Tris-buffered saline containing 0.1% Tween-20 (TBST) at room temperature for 1 h, after which the samples were incubated overnight at 4 °C with each primary antibodies. The membranes were then washed three times with TBST, followed by an hour incubation at room temperature with secondary antibody. The membranes were then washed six times with TBST and were visualized using ECL + Western Blotting Detection System (Amersham Pharmacia Biotech, NY, USA).

2.4. RT-PCR analysis

The principal methods for total RNA extraction and RT-PCR were described in previous paper [17]. RT-PCR primers for human TRIM39B, TRIM39R and Rpp21 were same as mentioned above for cloning of each open reading frame. The PCR reaction was performed using prime star GXL polymerase (TaKaRa, Japan) and template with 1 μl of the RT product. 40 cycles were carried out at 98 °C for 10 sec (denaturing), 55 °C for 5 sec (annealing) and 68 °C for 2 min (extension).

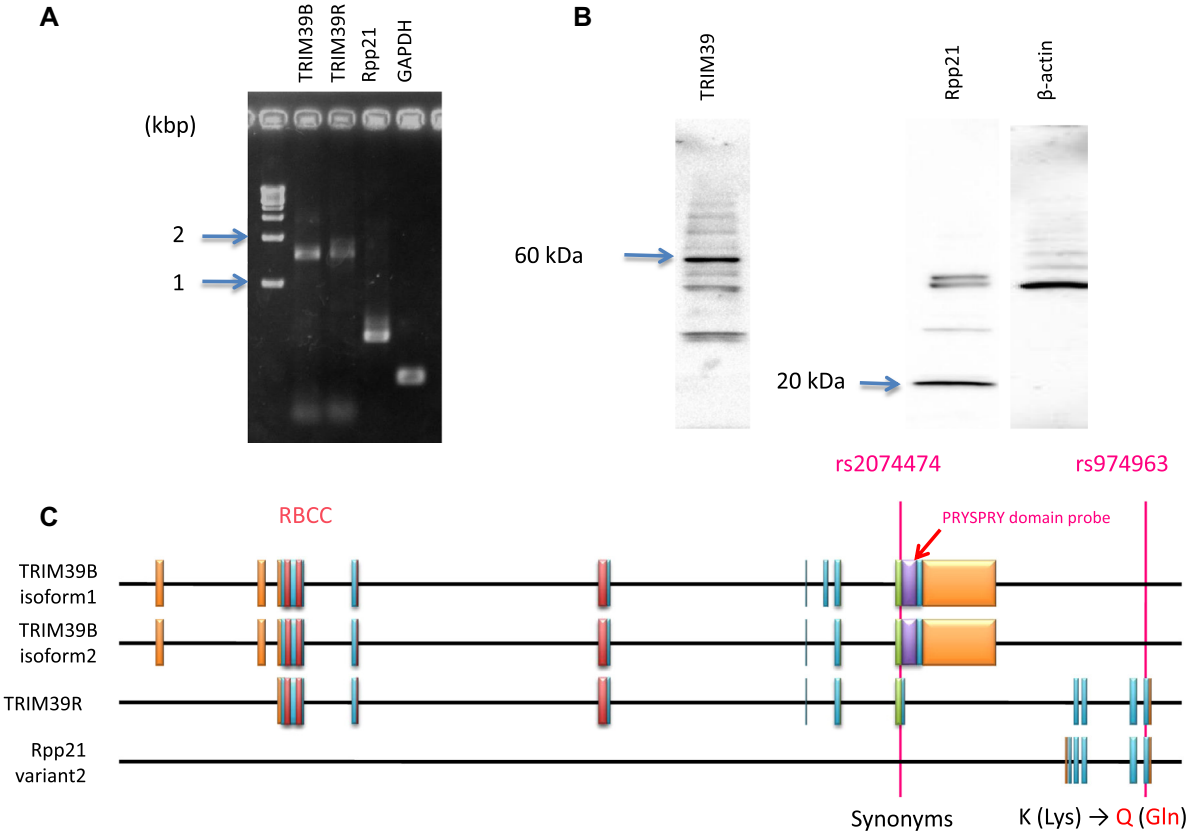


Fig. 1. TRIM39B, TRIM39R and Rpp21 are endogenously expressed in HEK293T cell. (A) RT-PCR was performed as described in Section 2. The product of each gene was run on 2% agarose gel stained with ethidium bromide. One kilobase ladder as a molecular marker was run at the left lane. (B) Cell lysates were analyzed by Western blotting using an antibody that was specific for TRIM39, Rpp21 or beta-actin. (C) This chart indicates TRIM39B, TRIM39R and Rpp21 genome structure. Rectangle indicates exons of each transcript. Two SNPs we previously identified are shown by red vertical line. Red arrow shows TRIM39B probe on PRYSPRY domain, which is included as probe in microarray used in this study.

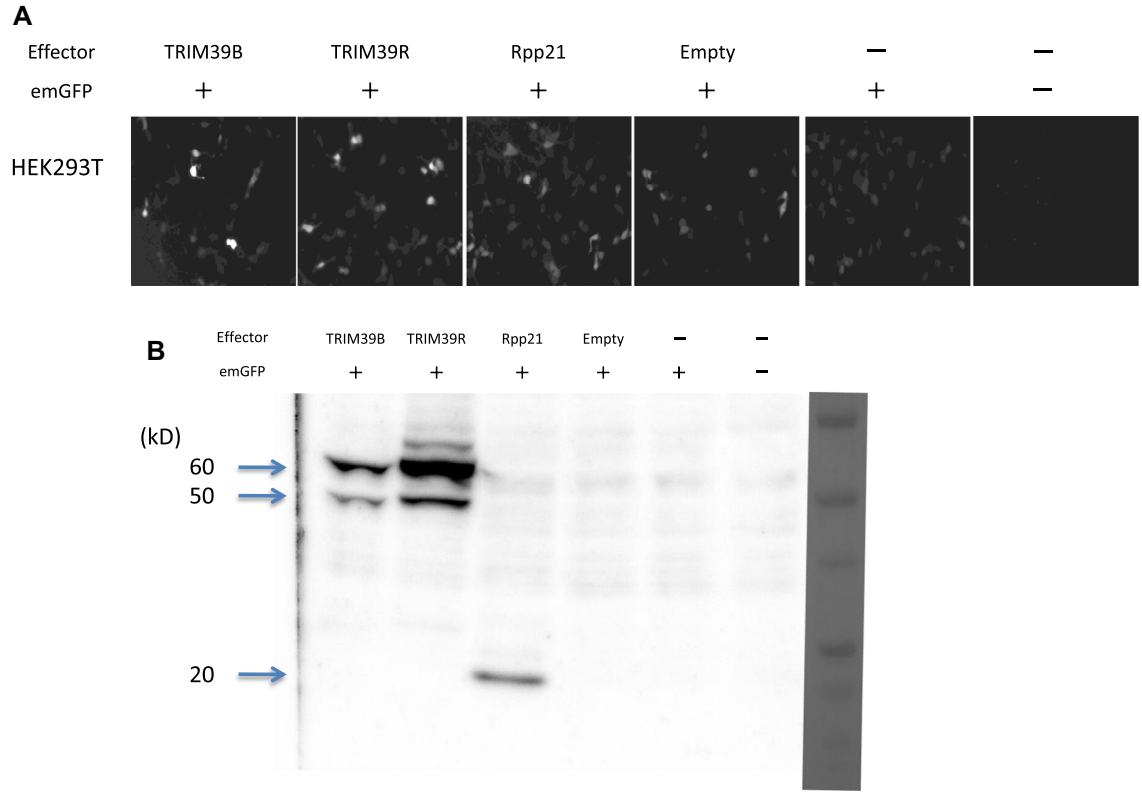


Fig. 2. Establishment of gain-of-function of TRIM39B, TRIM39R and Rpp21. (A) Fluorescence of emGFP in each transfectant was detected under a fluorescence microscope. (B) Exogenous TRIM39B, TRIM39R and Rpp21 were analyzed by Western blotting using anti-V5 epitope tag.

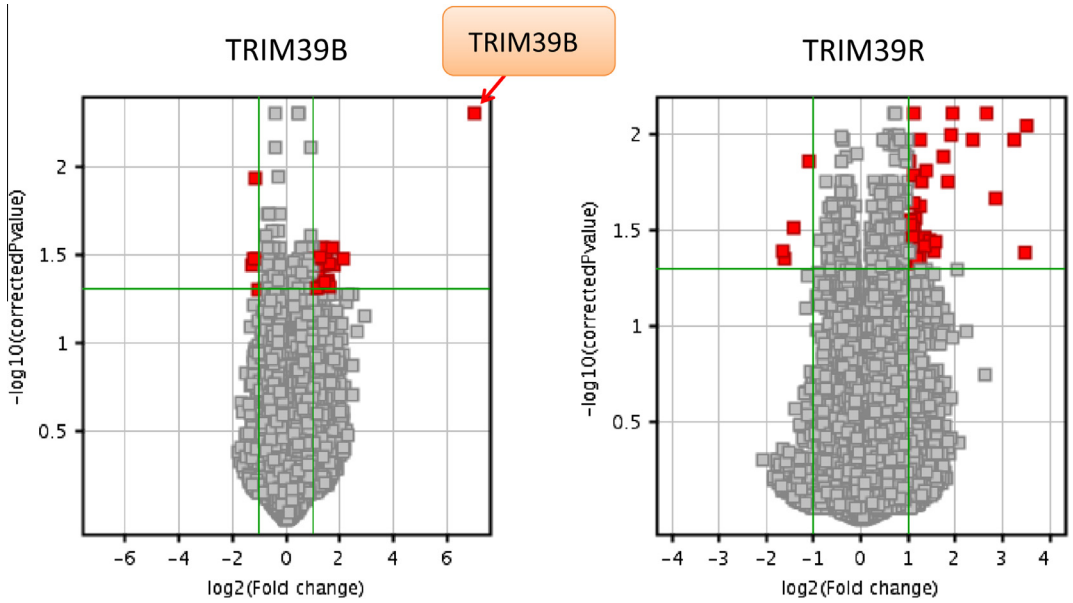
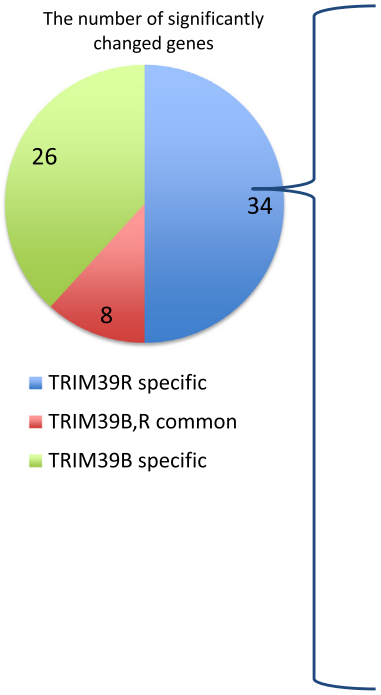


Fig. 3. TRIM39B and TRIM39R, but not Rpp21, induces significant changes in gene expression. Volcano plot based on gene profile in gain-of-function of TRIM39B (left panel) and TRIM39R (right panel). Two vertical green line indicates that *P* value and fold changes (more than 2.0-fold) between each comparison from each gene were calculated. Horizontal green line indicates that False discovery rate (FDR) (*q* values less than 0.05) was calculated by Gene Spring GX according to Benjamini and Hochberg's method. Small red square indicates significant changed probes. Red arrow indicates overexpression of TRIM39B.

2.5. Microarray analysis

Gene Expression microarray for Sure Print G3 Human Gene Expression (G4851A; 8 × 60K) and all of the reagents for microarray were obtained from Agilent Technologies (Palo Alto, CA, USA). Quadruplicate total RNA were extracted from each cells transfected with empty vector or each genes using Trizol reagent as described [17] and its integrity was assessed using an Bioanalyzer 2100 (Agilent Technology, CA, USA). Each aliquots of total RNA was reverse transcribed into complementary DNA and



GO Term	p-value
type I interferon-mediated signaling pathway	8.56×10^{-11}
response to type I interferon	9.45×10^{-11}
cellular response to type I interferon	8.56×10^{-11}
response to cytokine stimulus	1.76×10^{-7}
innate immune response	1.43×10^{-7}
cytokine-mediated signaling pathway	3.68×10^{-7}
cellular response to cytokine stimulus	7.19×10^{-7}
response to virus	1.45×10^{-6}
cellular response to interferon-alpha	4.20×10^{-6}
immune response	1.37×10^{-5}
response to interferon-alpha	1.40×10^{-5}
response to organic substance	1.71×10^{-5}
defense response	2.45×10^{-5}
immune system process	4.33×10^{-5}
positive regulation of viral genome replication	6.27×10^{-5}
negative regulation of viral reproduction	7.65×10^{-5}
negative regulation of viral genome replication	7.65×10^{-5}
nBAF complex	9.18×10^{-5}
response to other organism	1.31×10^{-4}
response to interferon-gamma	1.74×10^{-4}
response to biotic stimulus	1.69×10^{-4}

Fig. 4. Gene Ontology analysis clearly indicates TRIM39B regulates type I interferon response and defense of viral infection. Pie chart indicates the number of genes significantly changed by TRIM39B (green), TRIM39R (blue) or both of them commonly (carmine). Right chart shows the results of Gene Ontology analysis including predicted pathway involved in type I interferon (red circle) and in viral infection (green circle).

subsequently transcribed into complementary RNA (cRNA) using the Low Input Quick Linear Amp Labeling Kit (Agilent Technology, CA, USA). The quality of each cRNA was confirmed by total yield and specificity calculated using NanoDrop ND-1000 spectrophotometer (Thermo Fisher Scientific, MA, USA). Labeled cRNAs were used for hybridization. Slides for microarray were incubated at 65 °C for 17 h in microarray hybridization chambers. After hybridization, slides were washed according to the protocol suggested by Agilent. Images for each of arrays were scanned with an Agilent DNA microarray scanner (model G2505C) and saved as TIFF format. For data normalization, 75 percentile normalization using a per-chip 75 percentile of all measurements were performed by Gene Spring GX software (Agilent Technologies, CA, USA). *P* value and fold changes (more than 2.0-fold) between each comparison from each gene were calculated. False discovery rate (FDR) (*q* values less than 0.05) were calculated by Gene Spring GX according to Benjamini and Hochberg's method. Differentially expressed genes were analyzed using Gene spring GX's Gene Ontology data set to predict biological significance.

3. Results

3.1. Expression of endogenous TRIM39 and Rpp21

To examine TRIM39B, TRIM39R and Rpp21 expression in human cells, we performed RT-PCR and Western blotting analysis. Our results show that not only TRIM39B and Rpp21 but also TRIM39R is endogenously expressed in HEK293T cell, Jurkat, T cell line, Raji, B cell line and primary cultured human chondrocyte (Fig. 1A, B and data not shown). The PCR product was subjected to sequence analysis showed 100% homology with human TRIM39B isoform 2, TRIM39R and Rpp21 variant 2. TRIM39R possesses the sequence as TRIM39B isoform 2 fused with Rpp21 variant 2 (Fig. 1 C, Supplementary Fig.). We also detected specific band of endogenous TRIM39 and/or TRIM39R proteins, which was identical to around 60 kDa, as well as Rpp21, which was around 20 kDa although antibody for TRIM39 used in this study detects both of them (Fig. 1B).

3.2. Gain-of-function of TRIM39B, TRIM39R and Rpp21

To analyze the functions of TRIM39B, TRIM39R and Rpp21, we tried to establish each gain-of-function models using CMV promoter-driven overexpression. We co-transfected with the vector containing each gene and CMV vector containing emGFP into 293T cells. 48 h after transfection, we confirmed the efficiency of the transfection using emGFP expression (Fig. 2A). All of them had at least over 80% efficiency of transfection (Fig. 2A and data not shown). After that, we also confirmed exogenous each gene expression using V5 epitope tag, thus we could detect substantial amount of TRIM39B, TRIM39R or Rpp21 expression (Fig. 2B).

3.3. TRIM39B and TRIM39R, but not Rpp21, induces significant changes in gene expression

We succeeded in establishing gain-of-function of each gene and thus tried to obtain gene expression profile using microarray. Overexpression of TRIM39B significantly changed 57 probes, which contained 5 down-regulated probes and 52 up-regulated probes, while, that of TRIM39R changed 83 probes, which contained 6 down-regulated probes and 77 up-regulated probes (Fig. 3 and data not shown). Unexpectedly, that of Rpp21 did not significantly change any probes (data not shown). Our volcano plot analysis clearly indicated that TRIM39R, but not TRIM39B, changes larger number of genes and its effect is also larger (Fig. 3). We also confirmed overexpression of TRIM39B (123-fold rise) although included probe, which is located on SPRY domain of TRIM39B, can only detect TRIM39B (Figs. 1C and 3).

3.4. Gene Ontology analysis

Finally, to identify biological significance of TRIM39B or TRIM39R, using obtained gene sets, we performed Gene Ontology analysis. Our result of Gene Ontology clearly indicated that TRIM39R regulates type I interferon-related pathway (Fig. 4 red circles) and response to viral infection (Fig. 4 green circles). However, data set of TRIM39B could not any significant category (Fig. 4 and data not shown). Indeed, TRIM39 significantly affected many molecules involving in defense of viral infection such as 2′-5′-oligoadenylate synthetases (OASs), interferon alpha-induced proteins (IFIs), interferon stimulated genes (ISGs), interferon regulatory factors (IRFs), chemokines and interleukins (data not shown). We also examined the number of significantly changed genes by both of them, however only 8 genes are regulated by TRIM39B and TRIM39R commonly (Fig. 4 pie chart).

4. Discussion

Our results show for the first time that TRIM39R regulates type I interferon and defense of viral infection although among most of TRIM family proteins, their physiological and pathological functions have yet to be identified. TRIM39B was firstly identified novel gene as RING finger domain proteins in human *HLA* class I using degenerate PCR [18]. Lee et al. demonstrated that TRIM39B physically interacts modulator of apoptosis (MOAP)-1, which plays an important role for apoptosis, especially in Bax/Bak-dependent pathway and enhances stability of MOAP-1 protein via inhibition of polyubiquitylation [19]. Further study reveals that TRIM39 directly inhibits polyubiquitylation of MOAP-1 by anaphase-promoting complex (APC/C), which is its E3 ubiquitin ligase [20]. In agreement with them, etoposide-induced apoptosis was enhanced by TRIM39 via stabilizing MOAP-1 [19,20]. Two more recent studies demonstrated that TRIM39B directly binds p21 and enhances its stability via inhibiting $CRL4^{cdt2}$-mediated polyubiquitylation [21] and that TRIM39B directly binds and ubiquitylates p53, resulting in proteasomal degradation [22]. These reports indicate TRIM39B plays an important role for cell cycle and apoptosis. In this study, we could not obtain any data involving in apoptosis and cell cycle from gene profile of TRIM39B-overexpression. Taken together, TRIM39B function is not involved in immune response and inflammation.

In contrast to TRIM39B, physiological functions of TRIM39R remains to be clarified. There is only one study about TRIM39R that cGMP-dependent protein kinase I binds and phosphorylates both TRIM39B and TRIM39R [16]. Most recent study examined whether all of human TRIM proteins regulates type I interferon response and viral infection or not [23]. Around half of TRIM proteins enhanced RIG-I-induced type I interferon response although TRIM39B didn't have ability to elicit the type I interferon response [23]. Beside that, it makes no reference to whether TRIM39R induces the type I interferon response or not [23].

In conclusion, we for the first time established the gain-of-function of TRIM39B and TRIM39R and demonstrated that TRIM39R, but not TRIM39B, induces many genes involving in type I interferon response and defense of viral infection. Thus, we hypothesizes that TRIM39R-induced type I interferon response possibly elicited by viral infection may affect the onset and the pathogenesis of BD.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2013.05.064.

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