学位論文

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ABSTRACT

Plasmacytoid dendritic cells (pDCs) are characterized by an exclusive expression of nucleic acid sensing Toll-like receptor 7 (TLR7) and TLR9, and production of high amounts of type I interferon (IFN) in response to TLR7/9 signaling. This function is crucial for both antiviral immunity and the pathogenesis of autoimmune diseases. An Ets family transcription factor, i.e., Spi-B (which is highly expressed in pDCs) is required for TLR7/9 signal-induced type I IFN production and can transactivate IFN-α promoter in synergy with IFN regulatory factor-7 (IRF-7). Herein, we analyzed how Spi-B contributes to the transactivation of the *Ifna4* promoter. We performed deletion and/or mutational analyses of the *Ifna4* promoter and an electrophoretic mobility shift assay (EMSA) and observed an Spi-B binding site in close proximity to the IRF-7 binding site. The EMSA results also showed that the binding of Spi-B to the double-stranded DNA probe potentiated the recruitment of IRF-7 to its binding site. We also observed that the association of Spi-B with transcriptional coactivator p300 was required for the Spi-B-induced synergistic enhancement of the *Ifna4* promoter activity by Spi-B. These results clarify the molecular mechanism of action of Spi-B in the transcriptional activation of the *Ifna4* promoter.

1. Introduction

Dendritic cells (DCs) play essential roles in the connection between innate and adaptive immunity by being activated through pathogen sensors such as Toll-like receptors (TLRs) and by producing various cytokines [1–3]. DCs are divided into two subsets: plasmacytoid dendritic cells (pDCs) and conventional dendritic cells (cDCs) [4]. As a unique subset within the DC lineage, pDCs are capable of producing high levels of type I interferon (IFN) through TLR7 or TLR9 signaling [5]. Type I IFN contributes to antivirus defense and to the pathogenesis of autoimmune diseases including systemic lupus erythematosus (SLE), myositis, Sjögren's syndrome (SS) and systemic sclerosis (SSc) [6].

pDCs express constitutively high levels of Spi-B, which is a member of the Ets family transcription factors [7,8]. Our earlier findings demonstrated that Spi-B plays a critical role in TLR7/9 signal-induced type I IFN production in pDCs [9]. Spi-B transactivates the type I IFN promoters in synergy with transcription factor IFN regulatory factor 7 (IRF-7). IRF-7 also plays a key role in the production of type I IFN in pDCs. IRF-7 is localized in the

Abbreviations: CBP, CREB binding protein; CREB, cAMP response element-binding protein; DCs, dendritic cells; HAT, histone acetyltransferase; IFN, interferon; IRF, IFN regulatory factor; pDC, plasmacytoid DC; PEST, proline-, glutamic acid-, serine- and threonine-rich; TA, transactivation; TLR, Toll-like receptor.

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cytoplasm and activated by phosphorylation. The activated IRF-7 then translocates into the nucleus and binds to the promoter region of type I IFN genes [10]. The Ets family transcription factors consists of approx. 30 proteins that share a DNA-binding Ets domain which binds to the consensus sequence, 5′-GGAA/T-3' [11,12]. Spi-B associates with IRF-7 through its Ets domain and synergistically augments the IRF-7-induced transactivation of the IFN-α promoter [9]. However, little is known about the mechanism of action of Spi-B. Herein, we analyzed the detailed molecular mechanisms of the Spi-B-mediated enhancement of the *Ifna4* promoter activity.

2. Materials and methods

2.1. Plasmids

The *Ifna4* promoter-driven luciferase reporter plasmids were prepared as described [13]. Deletion mutants of the *Ifna4* promoter were generated by polymerase chain reaction (PCR) and subcloned into the pGL3 vector (Promega, Madison, WI, USA). The Flag-tagged murine IRF-7 expression vector (pEF-BOS-FLAG-mIRF-7) and the HA-tagged murine Spi-B (HA-SpiB-IRES2-venus, HA-SpiBdTA-IRES2-venus and HA-SpiBdEts-IRES2-venus) were generated as described [9,13]. Point mutants in the *Ifna4* promoter and HA-tagged murine Spi-B (Ser-149-Ala) mutant were generated by using the QuikChange II Site-Directed Mutagenesis Kits (Agilent Technologies, Santa Clara, CA). The Myc-tagged human p300 expression vector (pEF-BOS-p300-Myc) was kindly provided by Dr. K. Nakashima (Kyushu University).

2.2. Luciferase assay

For the assay of luciferase activity, 293T cells were seeded in 24-well plates (1×10^5 cells/well) and cultured overnight. These cells were transiently transfected with 75 ng of a luciferase reporter plasmid together with a combination of expression plasmids for Spi-B, IRF-7, and/or p300 using ScreenFect A (Fujifilm Wako Pure Chemical, Tokyo). Cell lysates were prepared 20–24 h after transfection, and the luciferase activity was measured by the Dual-Glo luciferase assay system (Promega).

2.3. Electrophoretic mobility shift assay (EMSA)

We performed an electrophoretic mobility shift assay (EMSA) as follows: 293T cells (9×10^6 cells) were seeded in a 10-cm dish and transfected with 6 μg of expression plasmid for IRF-7 using ScreenFect A and then cultured overnight. The nuclear extracts containing Flag-tagged murine IRF-7 were prepared as described [13]. The protein concentrations of the nuclear extracts were determined with the use of BCA Protein Assay Reagent (Thermo Scientific, Waltham, MA). The HA-tagged murine Spi-B was generated using a cell-free protein synthesis system (PURExfrex 1.0, GeneFrontier, Kashiwa, Japan).

The EMSA was performed as described [13]. The following double-stranded oligonucleotides corresponding to regions from −167 to −144 of the *Ifna4* promoter were ^{32}P-labeled and used: wild-type probe (5′-TAAAGAAAGTGAAAAGAGAATTGG-3′), and mutant probe (5′-TAAAGAAAGTGAAAAGACAATTGG-3′). The supershift assay was performed by preincubating reaction mixtures with 200 ng of rat anti-HA antibody (3F10, Roche Diagnostics, Indianapolis, IN) and/or 2 μg of mouse anti-FLAG antibody (1E6, Fujifilm Wako Pure Chemical) before the addition of the labeled probe. Rat IgG1κ (eBRG1, eBioscience, San Diego, CA) and/or mouse IgG2bκ (MG2b-57, BioLegend, San Diego, CA) were used as control antibodies.

2.4. Immunoprecipitation and western blot analysis

293T cells were transiently transfected with a combination of plasmids using Lipofectamine 2000 (Invitrogen, Carlsbad, CA). Cell lysates were prepared 24 h after transfection and incubated with anti-HA polyclonal antibody (561, 1:200 dilution, MBL, Nagoya, Japan), anti-Myc antibody (013-26513, 1:240 dilution, 10D11, Fujifilm Wako Pure Chemical) or anti-FLAG M2 antibody (F1804, 1:200 dilution, Sigma, St. Louis, MO). The immune complexes were collected with Dynabeads Protein G (Invitrogen). Western blot experiments were performed as described [13].

3. Results

3.1. The synergistic enhancement of the Ifna4 promoter by Spi-B

Spi-B can synergistically enhance the IRF-7-induced transactivation of the *Ifna4* promoter [9]. To investigate how Spi-B synergistically activates the *Ifna4* promoter, we first searched for Spi-B binding site(s) in the *Ifna4* promoter. Spi-B has a DNA-binding Ets domain. There are five potential Ets-binding motifs in the *Ifna4* promoter; they consist of the purine-rich GGAA/T consensus sequences (−486 to −55) (Suppl. Fig. S1) [12]. We constructed two mutant reporter plasmids containing the *Ifna4* promoter (Suppl. Fig. S1), and observed that Spi-B could augment the IRF-7-induced transactivation of the *Ifna4* promoter even though all five potential Ets-binding motifs were mutated (mtEts5) (Fig. 1A).

As reported [9,14], the IRF-binding site was necessary for IRF-7-induced activation of the *Ifna4* promoter in our protocol, and thus to define the precise binding site(s) for Spi-B in the *Ifna4* promoter, we made a series of *Ifna4* promoter deletion mutants and performed luciferase assays (Fig. 1B). Spi-B was still observed to augment the IRF-7-induced transactivation of the *Ifna4* promoter −176/−55 deletion mutant. The transactivation of the *Ifna4* promoter was not detectable in the −146/−55 deletion mutant. These results thus indicated that the 30-bp promoter region (from −176 to −147) containing an IRF-binding site was required for the Spi-B-dependent augmentation of the promoter activity.

To identify the binding site(s) for Spi-B in the 30-bp promoter region (−176/−147) of the *Ifna4* gene, we constructed several point mutants. Spi-B failed to enhance the IRF-7-induced transactivation of the mutant *Ifna4* promoter (g150c), which was carrying a single base substitution (g to c) at position −150 (Fig. 1C). The position g150 in the *Ifna4* promoter is flanked by an IRF-binding site (Suppl. Fig. S2). We observed that IRF-7 could transactivate both the mutant (g−150c) and the WT *Ifna4* promoter in a dose-dependent manner (Fig. 1D).

3.2. Spi-B binds to the Ifna4 promoter

For the evaluation of the binding of Spi-B to the *Ifna4* promoter, we analyzed the DNA-binding activities of HA-Spi-B by performing an EMSA using 24-bp probes derived from the *Ifna4* promoter. As expected, HA-Spi-B bound to the WT probe, and this probe-binding activity was supershifted with anti-HA antibody (Fig. 2A). HA-Spi-B did not bind to the mutant probe harboring a single base substitution (g−150c). FLAG-IRF-7 bound to both the WT and mutant probes (data not shown).

The 24-bp probe-binding activities of the mixture of HA-Spi-B and FLAG-IRF-7 were also analyzed by EMSA. The WT probe-binding activity was supershifted with anti-FLAG antibody or anti-HA antibody (Fig. 2B). When both anti-FLAG antibody and anti-HA antibody were added to the reaction mixture containing the WT probe, the supershifted band migrated more slowly,

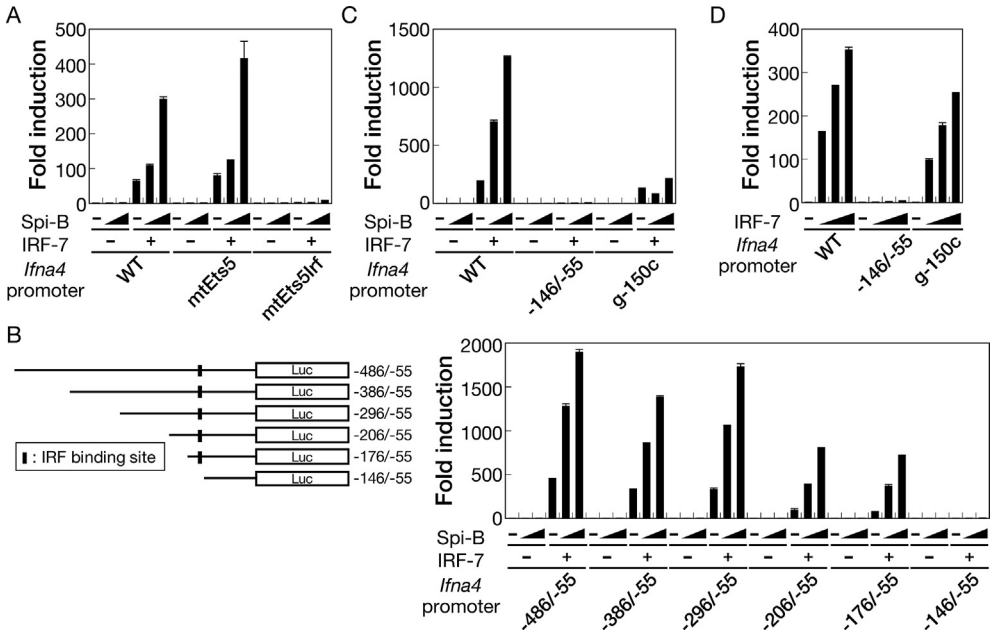

Fig. 1. Analysis of the Spi-B binding site in the *Ifna4* promoter. (A) The following mutant promoters were used for the luciferase assay. mtEts5: the *Ifna4* promoter lacking five Ets-binding motifs, mtEts5Irf: the *Ifna4* promoter lacking five Ets-binding motifs and an IRF-binding site. 293T cells were transiently transfected with these luciferase reporter plasmids together with a combination of expression vectors for Spi-B (0, 21, or 84 ng/well) and IRF-7 (0 or 16.8 ng/well). After 20 h, cell lysates were prepared and subjected to the luciferase assay. (B) A series of deletion mutants of the *Ifna4* promoter were generated as indicated. The expression vectors for Spi-B (0, 21, or 84 ng/well) and IRF-7 (0 or 8.4 ng/well) were used. The luciferase assay was carried out as indicated in (A). (C) The following mutant promoter was used for the luciferase assay. g−150c, the *Ifna4* promoter carrying a single base substitution (g to c) at position −150. The luciferase assay was carried out as indicated in (A). (D) 293T cells were transiently transfected with an *Ifna4* promoter luciferase reporter plasmid together with IRF-7 expression vector (0, 4.2, 8.4, or 16.8 ng/well). The luciferase assay was carried out as indicated in (C). Data are representative of three independent experiments (mean ± SD).

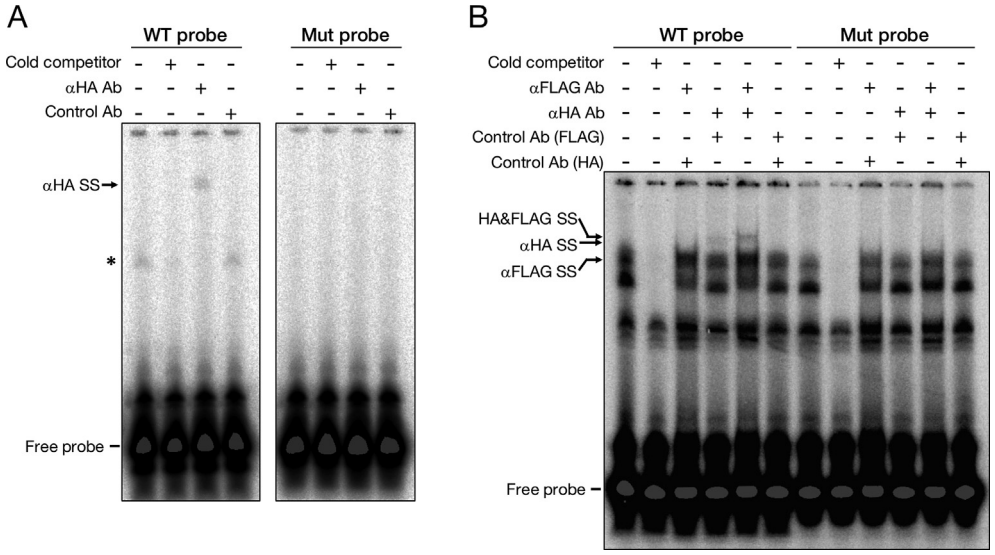

Fig. 2. The EMSA analysis of Spi-B binding to the labeled wild-type (WT) or mutant (g−150c) probes. (A) HA-Spi-B was incubated with ^{32}P-labeled probes containing the predicted binding site of Spi-B. The probe binding activity (*asterisks*) was then determined by EMSA. (B) Mixtures of HA-Spi-B and nuclear extract containing FLAG-IRF-7 were incubated with labeled probes. The probe binding activity was then determined by EMSA. Each EMSA was performed in the presence and the absence of a 100-fold molar excess of unlabeled probe as a specific competitor (cold competitor). Supershifted bands (SS) are indicated by *arrows*. A representative autoradiogram from three independent experiments is shown in (A) and (B).

indicating that Spi-B and IRF-7 could bind simultaneously to the WT probe. The mutant probe-binding activity was supershifted with anti-FLAG antibody, albeit to a lesser extent, suggesting that Spi-B binding to the probe leads to an efficient binding of IRF-7 to the probe. When both anti-FLAG antibody and anti-HA antibody were added to the reaction mixture containing the mutant probe, a slowly migrating supershifted band was not detected.

3.3. Requirement of Ser149 in Spi-B for the transactivation of the Ifna4 promoter

Spi-B is comprised of an N-terminal transactivation (TA) domain, a proline-, glutamic acid-, serine- and threonine-rich (PEST) domain, and a C-terminal Ets domain. We reported that the Ets domain of Spi-B is essential for both the transactivation of

the type I IFN promoter and the association of Spi-B with IRF-7 [9]. To further investigate the mode of action of Spi-B, we created an Spi-B mutant carrying a Ser-149-Ala amino acid substitution (S149A) in the PEST domain (Suppl. Fig. S3). The results of a luciferase assay demonstrated that the Spi-B (S149A) mutant failed to augment the IRF-7-induced transactivation of the *Ifna4* promoter (Fig. 3A).

We then examined whether the Spi-B (S149A) mutant could associate with IRF-7 and bind to the *Ifna4* promoter. Spi-B (S149A) mutant was coimmunoprecipitated with IRF-7 (Fig. 3B). The EMSA results showed that the Spi-B (S149A) mutant exhibited the same WT probe-binding properties as the WT Spi-B (Fig. 3C), suggesting that the Ser149 in Spi-B played an essential role in the transactivation of the *Ifna4* promoter. We therefore hypothesized that the S149A mutation in Spi-B inhibited the recruitment of one or more additional factors — which synergistically enhanced transcriptional activity — to the *Ifna4* promoter.

3.4. The requirement of coactivator p300 for the maximal transactivation of the Ifna4 promoter

p300 and CBP are transcriptional coactivators that promote transcription by interacting with numerous transcription factors including Spi-B [15,16]. We thus examined the association between the Spi-B (S149A) mutant and p300. Coimmunoprecipitation experiments revealed that the association between these molecules was abrogated in the Spi-B (S149A) mutant (Fig. 4A). A luciferase assay showed that p300-mediated enhancing effects of transcriptional activation were cancelled by S149A mutation in Spi-B (Fig. 4B). These results suggested that the Ser149 in the PEST domain of Spi-B was critical for the binding of Spi-B to coactivator p300, and that the Ser149 was required for the enhanced transactivation of the *Ifna4* promoter by Spi-B.

4. Discussion

The initiation of transcription is regulated by two stages: chromatin remodeling, followed by the interaction of polymerase and accessory factors with the promoter [17]. Our present results identified an Spi-B binding site around position g−150 in the *Ifna4* promoter. The nucleotide sequence we found is not compatible with the consensus sequence (GGAA/T). Our findings demonstrated that the binding of Spi-B to the *Ifna4* promoter is necessary for the synergistic transactivation of the *Ifna4* promoter.

The EMSA results obtained by our use of the g−150c mutant probe suggest that Spi-B binding to the *Ifna4* promoter induces an efficient recruitment of IRF-7 to the promoter. These results are consistent with the transcriptional regulation machinery of the IFN-α gene in pDC. Upon stimulation with TLR7/9 ligands, IRF-7 is phosphorylated and activated by signaling molecules including IκB

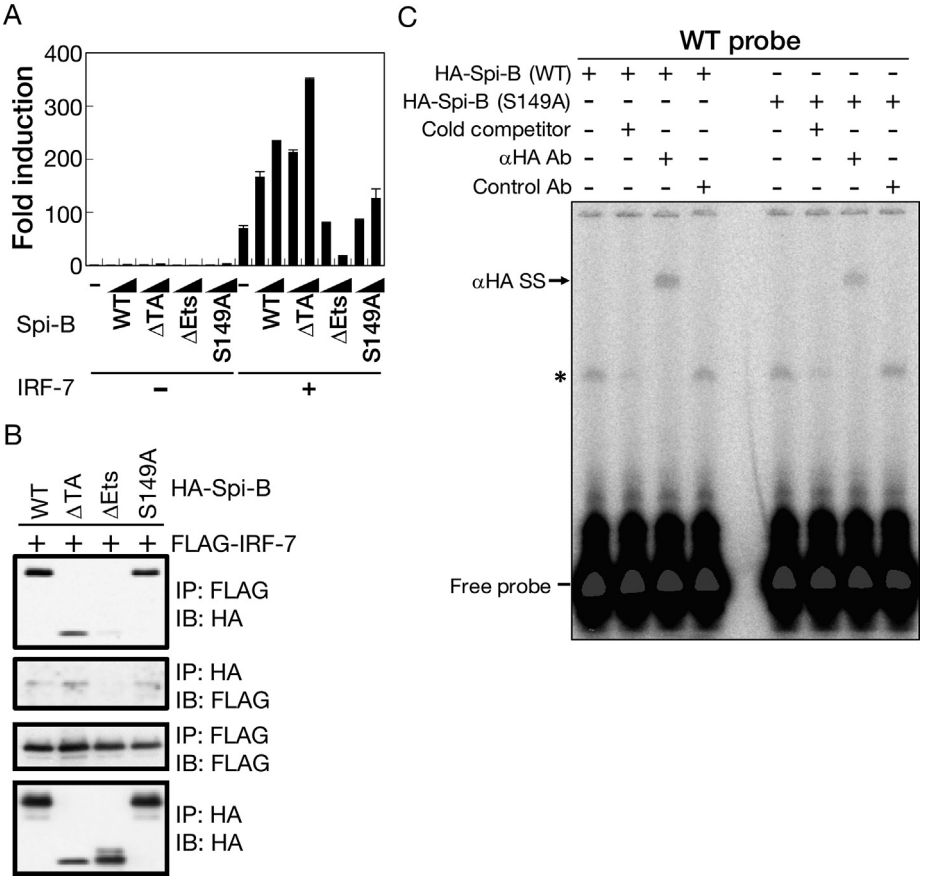

Fig. 3. Analysis of the molecular mechanisms underlying the Spi-B-mediated transactivation of the *Ifna4* promoter. The following Spi-B mutants were used. WT: wild-type Spi-B, ΔTA: a deletion mutant lacking transactivation domain of Spi-B, ΔEts: a deletion mutant lacking the Ets domain of Spi-B, S149A: Spi-B mutant carrying an Ser149Ala amino acid substitution. (A) 293T cells were transiently transfected with an *Ifna4* promoter-driven luciferase reporter plasmid together with a combination of expression vectors for Spi-B (0, 21, or 84 ng/well) and IRF-7 (0 or 8.4 ng/well). After 20 h, cell lysates were prepared and subjected to the luciferase assay. Data are representative of three independent experiments (mean ± SD). (B) Interaction of Spi-B mutants with IRF-7 in 293T cells. IP, immunoprecipitation; IB, immunoblot. A representative western blot from three independent experiments is shown. (C) An EMSA was performed the same way as Fig. 2 (A). The wild-type Spi-B or S149A mutant was used. A representative autoradiogram from three independent experiments is shown.

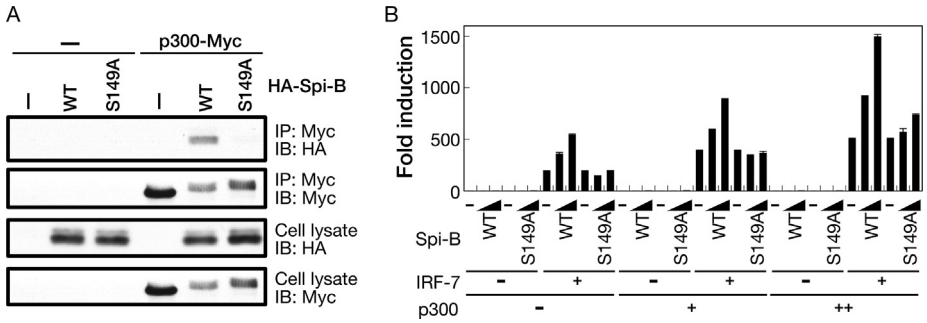

Fig. 4. The requirement of p300 for the synergistic activation of the *Ifna4* promoter activity by Spi-B. (A) The interaction of the Spi-B mutant with p300 in 293T cells. A representative western blot from three independent experiments is shown. (B) 293T cells were transiently transfected with an *Ifna4* promoter-driven luciferase reporter plasmid together with a combination of expression vectors for Spi-B (0, 1, or 42 ng/well), IRF-7 (0 or 8.4 ng/well), and p300 (0, 3, or 15 ng/well). After 20 h, cell lysates were prepared and subjected to the luciferase assay. Data are representative of three independent experiments (mean ± SD).

kinase α and then translocates from the cytosol to the nucleus [10,13,18,19]. We speculate that Spi-B, which is constitutively localized in the nucleus, assists the binding of IRF-7 to the promoter region of the type I IFN genes. The activation state of intranuclear Spi-B following TLR7/9 stimulation remains unknown.

To further investigate the mechanism of the transcriptional activation of type I IFN genes by Spi-B, we used structural variants of Spi-B. Spi-B is composed of three domains. We reported that the C-terminal Ets domain is involved in DNA binding and is essential for the association with IRF-7 [9]. The PEST domain of PU.1, which is a closely related Ets family transcription factor, is indispensable for the interaction with Pip/IRF-4 [20,21]. Ser144 in human Spi-B, which is equivalent to Ser149 in murine Spi-B, is located in the PEST domain. This Ser144 is essential for the association with Pip/IRF-4 and plays an important role in the transactivation of the λB DNA element with Pip/IRF-4 [21].

We therefore used the Spi-B (S149A) mutant to examine the mode of action of Spi-B during the transactivation of the *Ifna4* promoter. Our luciferase assay data showed that the Spi-B (S149A) mutant failed to augment the transactivation of the *Ifna4* promoter. However, the results of our coimmunoprecipitation and EMSA analyses indicated that the Spi-B (S149A) mutant could associate with IRF-7 and bind to the *Ifna4* promoter in the same manner as the WT Spi-B. We thus searched for Spi-B-binding partner(s) which could potentiate the transcriptional activation of the *Ifna4* promoter.

CREB binding protein (CBP) and p300 (CBP/p300) were originally identified as targets of the cyclic AMP response element binding protein (CREB) and act as a bridging factor between sequence-specific transcription factors and components of the basal transcription machinery [22,23]. CBP/p300 is a histone acetyltransferase (HAT) that is thought to play an important role in the regulation of chromatin assembly and is thereby responsible for enhanced transcription by increasing the accessibility of RNA polymerase II holoenzyme to the transcription machinery [24–26]. Although Spi-B interacts with p300 [16], it was not known how Spi-B augmented the transactivation of the type I IFN genes. Here we have shown that p300 is recruited to the complex composed of Spi-B and IRF-7 on the *Ifna4* promoter by interacting with Spi-B, and that p300 supports the maximal transactivation of the *Ifna4* promoter. We speculate that p300 bound to Spi-B on the *Ifna4* promoter might contribute to chromatin loosening and to the recruitment of the general transcription factors in order to maximally transactivate the *Ifna4* gene.

Type I IFN is composed of multiple IFN-α subtypes and one IFN-β. Murine IFN-α consists of 14 subtypes, and each of them might exert qualitatively distinct biological functions [27]. Murine IFN-α4 plays a specific role among the IFN-α subtypes. IFN-α4 is rapidly produced after viral infection and gives rise to the induction of other IFN-α subtypes in fibroblasts through an autocrine or paracrine feedback loop [28,29]. IFN-α4 gene is also rapidly expressed following TLR7/9 stimulation in pDCs. We thus analyzed the transactivation mechanism of the *Ifna4* promoter as a model for understanding the mechanism underlying the transcriptional activation of type I IFN genes in pDCs.

Our present findings clarify the mechanism of how Spi-B transactivates type I IFN promoter. Type I IFN produced by pDCs is involved not only in antiviral immunity but also in the pathogenesis of autoimmune diseases [6,30,31]. Our findings thus contribute to a fuller understanding of the mechanisms of type I IFN production by pDCs and may contribute to the management of virus infections or autoimmune disorders in which pDCs are critically involved.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrc.2020.02.101.

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