FEBS Letters 441 (1998) 106–110 FEBS 21263

Positive feedback regulation of type I *IFN* genes by the IFN-inducible transcription factor IRF-7

Mitsuharu Sato, Naoki Hata, Masataka Asagiri, Takeo Nakaya, Tadatsugu Taniguchi*, Nobuyuki Tanaka

Department of Immunology, Graduate School of Medicine and Faculty of Medicine, University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-0033, Japan

Received 9 November 1998

Abstract The interferon regulatory factor (IRF) family of transcription factors regulate the interferon (IFN) system, among which IRF-3 is involved in the virus-induced *IFN*-β gene expression. Here we show that another member IRF-7 is critical for the *IFN*-α gene induction. Unlike the *IRF-3* gene, the *IRF-7* gene is induced by IFNs through activation of the ISGF3 transcription factor, and IRF-7 undergoes virus-induced nuclear translocation. In cells lacking p48, an essential component of IFN stimulated gene factor 3 (ISGF3), ectopic expression of IRF-7 but not IRF-3 can rescue the deficiency to induce *IFN*-α genes. These results indicate that IRF-7 is a key factor in the positive feedback regulation of IFN-α/β production.

Key words: Interferon-α; Interferon-β; Interferon-3; Interferon regulatory factor-7; p48; Transcriptional regulation

1. Introduction

Induction of type I interferon (IFN-αs and -β) gene transcription in virally infected cells is essential for the host defense [1,2]. The interferon regulatory factor (IRF) family of transcription factors was originally identified as regulators of the IFN system [3–5]. It has been shown that IRF-1 and p48, essential components of ISGF3 (IFN-stimulated gene factor 3), are critical for the IFN-mediated antiviral response [6,7]. Recent studies have suggested that another member of the IRF family, IRF-3, plays a critical role in the virus-induced *IFN*-β gene activation [8–13]. In fact, in normally growing cells IRF-3 resides in the cytoplasm and, upon virus infection of the cells, it is phosphorylated and translocates into the nucleus. The 'activated' IRF-3 associates with the co-activators CBP/p300 and enhances transcription of the *IFN*-β promoter. These results strongly suggest that IRF-3 is the bona fide transcriptional activator acting on the IRF binding elements within the virus-inducible *IFN*-β promoter (IRF-Es [14]; also referred to as PRDI and III [15,16]). Although the *IFN*-α promoters also contain sequences characteristic for IRF-E, it appears that the induction of *IFN*-α genes is controlled by a mechanism(s) distinct from that for the *IFN*-β gene. In this regard, we originally proposed a two-step induction model for the *IFN* genes, in which a positive feedback regulation mechanism of IFN production is operational to ensure an efficient production of IFN-α/β [17]. This model can be elaborated further by incorporating recent findings on IRF-3 as follows: *IFN*-β gene is primarily induced through virus-induced activation of IRF-3, which is followed by the inductions of IFN-α genes which are dependent on the IFN-activated transcription factor ISGF3. Consistent with this model are the observations that the induction of *IFN*-α genes, but not *IFN*-β gene, by Newcastle disease virus (NDV) is compromised in mouse embryonic fibroblasts lacking either functional IFN-α/β receptor or p48, the DNA binding subunit of ISGF3, indicating the critical role of IFN-activated ISGF3 in the positive feedback regulation of IFN production [17]. In this context, ISGF3 binding to the *IFN* gene promoters has been demonstrated [17–19]. However, the question remained as to whether or not it is ISGF3 per se or a factor(s) induced by ISGF3 which directly mediates the *IFN*-α gene induction. In fact, the kinetics of the ISGF3 activation is not in strict correlation with the kinetics of the *IFN*-α gene induction in virally infected cells [17,19], raising the possibility that the effect of ISGF3 may be indirect, that is, ISGF3 may induce as yet another transcription factor which, when activated by viruses, functions directly on the *IFN*-α promoters.

These observations led us to investigate an ISGF3-dependent, IFN-inducible factor involved in the *IFN*-α gene transcription. It has been shown that the IRF-E sequence is indeed essential for the activation of *IFN*-α promoter [20,21]. In view of the wide-range involvement of the IRF members in the IFN system regulation, we investigated other IRF-family members which would fit into the above criteria. In particular, we focused our attention on IRF-7, since it shows high homology to IRF-3 at the amino acid level [10] and the *IRF-7* gene is induced by IFN-α in lymphoid cells [22]. In the present study, we show that the *IRF-7* gene is induced by IFN-α/β in fibroblast cells in an ISGF3-dependent manner. The induced IRF-7 resides in the cytoplasm, but undergoes nuclear translocation following NDV infection of the cells. The ectopic expression of IRF-7, but not IRF-3, in fibroblast cells lacking p48 resulted in the induction of a similar set of *IFN*-α genes as that induced in the wild-type fibroblasts, following NDV infection. Our results will be discussed in the context of the positive feedback regulation of *IFN*-β and *IFN*-α genes by two distinct IRF-family members, which may be important in understanding the efficient operation of the host defense mechanism against viruses.

*Corresponding author. Fax: (81) (3) 5689 7214.
E-mail: tada@m.u-tokyo.ac.jp

Abbreviations: IFN, interferon; IRF, IFN regulatory factor; IRF-E, IRF-element; ISRE, IFN stimulated response element; NDV, Newcastle disease virus; ISGF3, IFN stimulated gene factor 3; EF, embryonic fibroblast; EMSA, electrophoretic mobility shift assay

PII: S0014-5793(98)01514-2

2. Materials and methods

2.1. Construction of expression vectors

HA/IRF-7/pBabe, the retrovirus expression vector for HA-tagged IRF-7 was constructed as follows. To obtain the mouse IRF-7 cDNA, total RNA was prepared from mouse embryonic fibroblasts after IFN-β stimulation. The RNA was subjected to RT-PCR using sense (5′-CCTGTGTAGACGGAGCAATG) and antisense (5′-TCAAGGCCACTGACCCAGGT) primers, and the resulting 1.4-kb cDNA fragment was cloned into the *Sal*I site of pEF/HA [8] and generated pEF/HA-IRF-7. The cloned cDNA was sequenced to confirm its identity to the published sequence (GenBank accession no. U73037). The pEF/HA-IRF-7 was digested with *Xba*I and treated with T4 DNA polymerase, and the product was digested by *Eco*RI to obtain the HA-tagged IRF-7 cDNA. The HA-tagged cDNA was then cloned into the retrovirus vector, pBabe-puro [23].

To make the vector expressing the deletion mutant HA-IRF-7d, 1.3 kb of the *Eco*RI-*Bst*XI fragment and 77 bp of the *Bst*XI-*Nco*I fragment were first isolated from IRF-7 cDNA and then ligated with the backbone DNA of HA-IRF-7/pBabe pre-digested by *Eco*RI and *Psh*I (HA-IRF-7d/pBabe).

2.2. Cell culture and retrovirus infection

The $p48^{-/-}$ and $IFNAR1^{-/-}$ mice used in the study have been described [7,24]. Wild-type and $p48^{-/-}$ EFs were prepared from 13-day mouse embryos and maintained as monolayer cultures in Dulbecco's modified Eagle's medium supplemented with 10% FCS and 0.06% L-glutamine [7]. NIH/3T3 cells were also cultured in this medium. Retrovirus packaging was performed by cotransfection of pPAMpsi2 (kindly provided by Dr. Charles L. Sawyers, University of California, Los Angeles, CA, USA) and HA-IRF-7/pBabe, HA-IRF-7d/pBabe, HA-IRF-3/pBabe [8] or control pBabe-puro into 293T cells, and infection of the viruses to the cells was done as described previously [8].

2.3. RNA blotting analysis

The RNA blotting analysis and preparation of the probe DNAs for *IFN*-α and *IFN*-β have been described [17]. The 750 bp of the *Hin*dIII fragment from pIRF-3 was used as the *IRF-3* probe [8]. As for the IRF-7 mRNA detection, the 1.4-kb *Eco*RI fragment from pIRF-7 containing the IRF-7 cDNA was used as a probe. Five micrograms of total RNA was loaded on each lane.

2.4. Immunofluorescent staining and immunoblotting analysis

The NIH-3T3-derived cells, 3T3/IRF-7 and 3T3/IRF-7d, were first cultured for 8 h on chamber plate. After NDV infection (12 h), the cells were fixed and the HA-tagged IRF-7 was visualized as described [8]. Immunoblotting using anti-HA antibody was carried out as described [8].

2.5. Luciferase assay

NIH/3T3 cells (8×10^4 cells) were cultured on a 12-well plate. 0.4 μg of reporter plasmid and 1.6 μg of expression vector were cotransfected by DEAE-dextran method. After 32 h, the cells were infected with NDV for 12 h and the cellular extracts were prepared for the luciferase assay, as described previously [8].

3. Results

3.1. The p48-dependent induction of IRF-7 gene by IFN

We first examined the virus-induced expression of *IRF-3* and *IRF-7* genes in mouse embryonic fibroblasts (EFs). As shown in Fig. 1A, RNA blotting analysis revealed that the IRF-7 mRNA expression is strongly induced in NDV-infected EFs, whereas IRF-3 mRNA, which is expressed before NDV infection, remained unchanged during the course of infection. In fact, the IRF-7 mRNA becomes detectable at the time of IFN-α and -β mRNA induction, and its level increased thereafter. Interestingly, the IRF-7 mRNA induction by NDV is not observed in EFs lacking either the type I IFN receptor 1 (IFNAR1) or p48. In these cells, the induction of *IFN*-α gene, but not *IFN*-β gene, is also compromised. These observations indicate that the *IRF-7* gene induction by NDV is not direct, rather the gene is induced by ISGF3 following the IFN receptor stimulation by IFN-β. In fact, we found that the IRF-7 mRNA is strongly induced also by IFN-β in the wild-type EFs, reaching a peak earlier than the NDV-infected cells. Furthermore, this induction was again abolished in EFs lacking p48 (Fig. 1B). In contrast, the IRF-3 mRNA expression is not affected by the IFN stimulation. Taken together, we conclude that the *IRF-7* gene induction by IFN-β (and by IFN-α; data not shown) is mediated by ISGF3. Although the ISGF3 binding site ISRE (IFN Stimulated Response Element) [25] was not found in the putative *IRF-7* promoter region (spanning up to 500 nucleotides from the putative transcription initiation site; M.S., unpublished data), two such elements, GGTTTCATTTTCC and CAGTTTCGTTTTAC, were detected within the first intron (M.S., unpublished data). It remains to be clarified whether or not these two elements are involved in the ISGF3-mediated gene induction.

3.2. Activation of IFN-α genes by ectopic expression of IRF-7 in cells lacking p48

The above results suggest that the IFN-induced IRF-7 may play a critical role in the *IFN*-α gene induction by NDV. To test this possibility, we next constructed a retrovirus expressing an HA-tagged mouse IRF-7 (HA-IRF-7) and infected it into EFs lacking p48. Similarly, the retrovirus expressing an HA-tagged mouse IRF-3 (HA-IRF-3) was infected to the cells. The NDV-induced expression of IFN-α and IFN-β mRNAs was examined in these cells by RNA blotting (Fig. 2). The IFN-α mRNA expression was undetectable before NDV infection, but it was strongly induced 12 h after infection in the p48 null EFs expressing HA-IRF-7. In fact, the kinetics and levels of the mRNA induction were almost the same as in the wild-type EFs (Fig. 2). Moreover, when we compared the subtypes of the induced IFN-α mRNAs between the IRF-7 expressing EFs and the wild-type EFs, no notable differences were observed; the most abundant mRNA was that of IFN-α4 mRNA, followed by IFN-α1, 2, 5, in both cells (data not shown). In contrast, the expression of

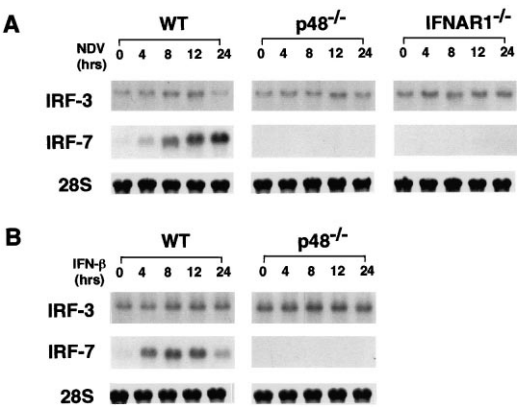

Fig. 1. Induction of IRF-7 and IRF-3 mRNAs in mouse EFs. A: NDV induction of IRF-7 mRNA in EFs. Wild-type, $p48^{-/-}$ and $IFNAR1^{-/-}$ EFs were infected with NDV, and total RNA was prepared at each time point indicated and subjected to RNA blotting analysis. B: Induction of IRF-7 mRNA by IFN-β. Wild-type and $p48^{-/-}$ EFS were treated with mouse IFN-β at the concentration of 250 U/ml. At each time point indicated, total RNA was extracted from the cells for RNA blotting analysis. Membranes were stained with methylene blue to visualize 28S ribosomal RNA.

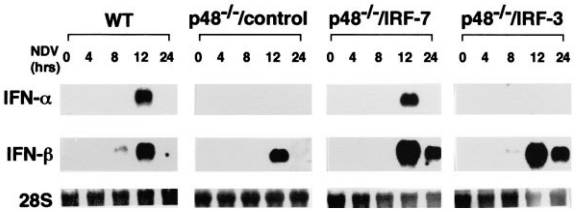

Fig. 2. Induction of *IFN*-α and -β genes by IRF-7. HA-tagged IRF-7 or IRF-3 cDNA was introduced into $p48^{-/-}$ EFs by retrovirus-mediated gene transfer ($p48^{-/-}$/IRF-7 and $p48^{-/-}$/IRF-3, respectively). After puromycin selection, the cells were infected with NDV for the time indicated and total RNA was extracted at the indicated time for RNA blotting analysis. Membranes were stained with methylene blue and stained 28S ribosomal RNA was indicated.

HA-IRF-3 had no effect on the IFN-α mRNA induction, although the IFN-β mRNA induction level was augmented about 3-fold compared to the wild-type EFs, an observation consistent with the previous findings in NIH/3T3 cells (Fig. 2 and [8]). Interestingly, the retrovirus-mediated IRF-7 expression resulted also in the upregulation of the IFN-β mRNA induction (Fig. 2). These results thus suggest that IRF-7 can act on both *IFN*-α and -β genes, whereas IRF-3 acts only on the *IFN*-β gene. Similar observations were also made in NIH/3T3 fibroblasts (data not shown).

3.3. Nuclear translocation of IRF-7 in NDV-infected cells

It is interesting to note that the forced expression of IRF-7 per se does not result in the induction of *IFN*-α genes, unless the IRF-7-expressing cells are infected by NDV (Fig. 2), suggesting an activation mechanism of IRF-7 in virally infected cells. To gain further insights into this mechanism, the retrovirus expressing HA-tagged IRF-7 was infected into NIH/3T3 cells (referred to as 3T3/IRF-7 cells thereafter) and its fate before and after NDV infection was examined by immunofluorescence staining. As shown in Fig. 3A, the HA-tagged IRF-7 protein is predominantly found in the cytoplasm in normally growing state. Upon NDV infection, the IRF-7 protein is accumulated in the nucleus, an observation similar to IRF-3 [8–13]. We also expressed a deletion mutant of IRF-7 which lacks the carboxyl terminal region, 411–453 amino acids, that contains several serine residues. This region is homologous to IRF-3, and the phosphorylation of these serines in IRF-3 critical for the virus-induced activation/nuclear translocation (Fig. 3A; see [9,11]). As shown in Fig. 3A, the mutant IRF-7 is incapable of translocation upon NDV infection of the cells. This result indicates an essential role of this region in nuclear translocation, and suggests a mechanism similar to that for IRF-3, in which virus-induced serine phosphorylation of this region is critical for its activation.

To examine further the status of the 'activated' IRF-7, we prepared nuclear extracts from 3T3/IRF-7 cells before and after NDV infection, and subjected to immunoblotting analysis using anti-HA antibody. A new band which migrates slower than that found already in uninfected cells was prominent 12 h after virus infection (data not shown), the time at which IFN-α mRNA accumulation peaks. As shown in Fig. 3B, the induction-specific band disappeared by treating the nuclear extract with calf intestinal alkaline phosphatase (CIAP), suggesting that IRF-7 is indeed phosphorylated after virus infection.

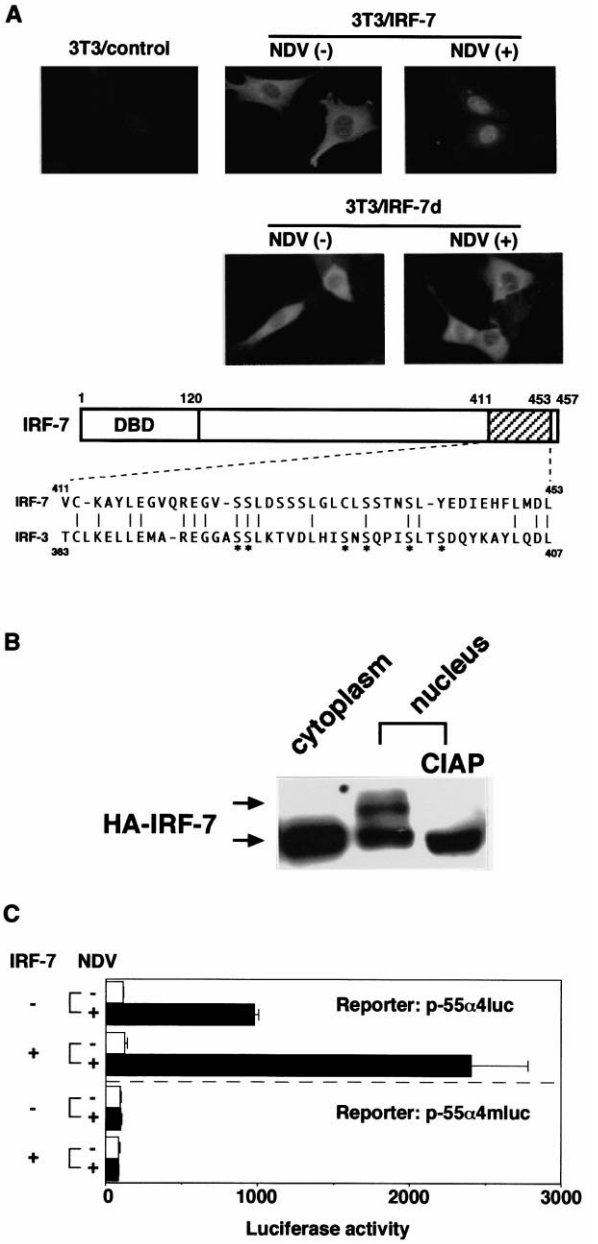

Fig. 3. Status of the ectopically expressed IRF-7 before and after NDV infection. A: Cellular localization of IRF-7. HA-tagged IRF-7 was visualized with an anti-HA monoclonal antibody and FITC conjugated anti-mouse IgG antibody. HA-IRF-7d is the mutant of HA-tagged IRF-7 with a deletion at the carboxyl-terminal region containing the potential phosphorylation sites. Six serine residues within IRF-3 which are critical for nuclear translocation [9,11], are asterisked. DBD represents the DNA binding domain. B: Evidence for the virus-induced phosphorylation of IRF-7. Nuclear extracts were prepared from NDV infected or uninfected 3T3/HA-IRF-7. The extract from NDV infected cells was treated with 18 units of CIAP. The extracts were resolved by SDS-PAGE and HA-IRF-7 was detected by immunoblotting using anti-HA antibody. C: Enhancement of the virus-induced *IFN*-α4 promoter activation by IRF-7. Cell lysates for the luciferase assay were prepared 12 h after NDV infection. The histogram shows the mean value of three samples and error bars show standard deviation. The experiment was repeated and essentially the same conclusion was reached.

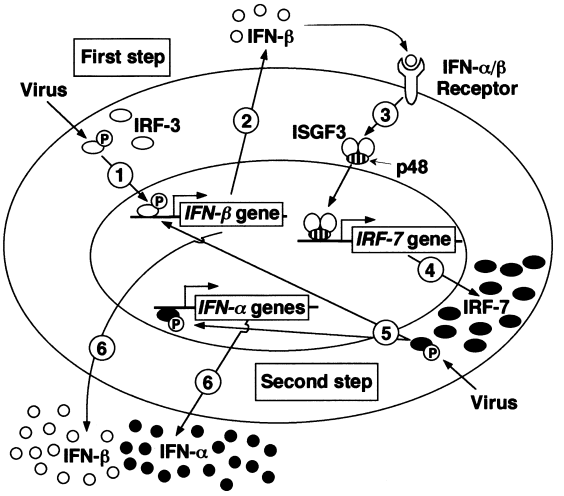

Fig. 4. The positive feedback regulation of the IFN-α/β production mediated by IRF-3 and IRF-7. In this two-step activation model, IRF-3, which is expressed in uninfected cells, is first activated by virus, translocates into nucleus to act on the *IFN*-β, but not *IFN*-α genes, resulting in the initial production of IFN-β. IFN-β signals through its receptor to induce *IRF-7* gene expression via activation of ISGF3, and IRF-7 then acts on *IFN*-α and *IFN*-β genes, provided that it undergoes virus-induced activation by phosphorylation. The sequential operation of the two steps was revealed in the present study for the mouse EFs, however, it is possible that they may operate simultaneously in cells where IRF-7 may be induced by other yet unknown stimuli. Numbers in circles indicate the sequence of the events.

3.4. Activation of the IFN-α promoter by IRF-7

In an electrophoretic mobility shift assay (EMSA) using the *IFN-α1* or *IFN-α4*-derived IRF-E, and the nuclear extracts from 3T3/IRF-7 cells, a low mobility band was detected in NDV-infected, but not in uninfected cells, and this band reacted with anti-HA antibody (data not shown). This prompted us to study the activation of the *IFN*-α promoter by IRF-7. We employed a transient assay using a reporter gene consisting of the *IFN-α4*-derived IRF-E (spanning −110 to −76 [21]) and luciferase gene (p-55α4luc [17]). As shown in Fig. 3C, luciferase activity was significantly augmented when p-55α4luc was cotransfected with an IRF-7 expression vector after NDV infection. On the other hand, this effect was not seen in the construct p-55α4mluc, in which the IRF-E element is mutated (GAAAGTGAAAAGA to GATCATGAAAAGA). Thus, IRF-7 can directly act on the *IFN-α4* promoter, provided that it is activated, probably by phosphorylation, following NDV infection.

4. Discussion

Both *IFN*-α and *IFN*-β genes are induced by viral infection of the cells, and induction of these genes constitutes an essential part in the innate immune response, i.e. the immediate host defense against viruses [1,2]. The mechanisms of regulation of these genes, which operate primarily at the transcriptional level, have been extensively studied. In particular, the IRF family of transcription factors has been known to regulate the IFN system in both IFN production and action [6,7,17,26,27]. Both *IFN*-α and -β genes contain within their respective promoters the binding element, IRF-E (also referred to as PRD-I and III for the *IFN*-β gene [15,16]). Recently, we and others have reported on the potential role of IRF-3, a factor normally found in the cytoplasm in uninfected cells, which gets activated upon viral infection to undergo nuclear translocation and acts on the *IFN*-β promoter in association with the co-activator CBP/p300 [8,13]. However, the question has remained unanswered on the role of IRF-3 in the IFN-α gene induction.

We have shown previously that in EFs lacking the IRF member p48, in which the IFN-induced activator of transcription ISGF3 cannot be formed, the *IFN*-α gene induction by NDV is severely compromised [17]. We then proposed two models of the ISGF3-mediated *IFN*-α gene induction; one model argued that ISGF3 acts directly on the *IFN*-α promoter, while the other predicted a factor, hereupon termed X [17], which is induced by ISGF3 and acts on the promoter. Our present study strongly supports the second model, in which the ISGF3-induced factor X is IRF-7 (Fig. 4). In fact, IRF-7 is induced in mouse EFs by IFNs in a ISGF3-dependent manner, and the deficiency of the p48 null EFs in the *IFN*-α gene induction can be rescued by an ectopic expression of IRF-7. In fact, the spectrum of the *IFN*-α gene family induced in IRF-7-expressing p48 null EFs is essentially the same as that of the wild-type EFs, further supporting the notion that IRF-7 is the bona fide transcription factor governing the *IFN*-α gene induction.

It is interesting to note that the expression of IRF-7 also affects the *IFN*-β gene. In this context, one may recall that in macrophages from p48 null mice, *IFN*-β m RNA induction by NDV is also decreased by 10 fold compared to wild-type macrophages [17]. We infer that in these cells the IRF-7 pathway is important for maximal *IFN*-β gene induction, possibly owing to the limitation of IRF-3 and/or its function in these cells. It is also possible that the IRF-7 gene can be induced not only by IFNs but also by other stimuli in an ISGF3-independent manner, so as to insure prompt induction of the *IFN*-α and -β genes in vivo. In this regard, it is interesting that a high level expression of IFN-α mRNAs was detected in the splenocytes isolated from NDV-infected, p48 null mice (M.S., unpublished data).

The more detailed mechanism by which IRF-7 activates the IFN-α (and IFN-β) gene transcription remains to be clarified. It has been shown that IRF-3 interacts, when activated by virus, with the co-activator CBP/p300. In this regard, our EMSA data indicates that the NDV induction-specific band involving IRF-7 migrates as slowly as the previously identified IRF-3:CBP/p300 complex (data not shown), raising the possibility that IRF-7 also interacts with these co-activators. Unlike IRF-3 which apparently acts on *IFN*-β gene, but not *IFN*-α genes, IRF-7 seems to be active on both genes. One may envisage that IRF-3 functions only in combination with other factors, such as NF-κB, which is critical for the former but not the latter gene induction [28], whereas IRF-7 is more independent on other factors to activate these genes. The possibility also remains that IRF-7 can function only in the presence of IRF-3, by forming a complex [10]. These are interesting future issues to be addressed, and work is in progress to generate mice deficient in the *IRF-3* and/or *IRF-7* alleles.

Our present findings may have some implications regarding to how the type I IFN gene subtypes, i.e. *IFN*-α genes and *IFN*-β gene, have evolved, as well as to the biological significance of the regulation of this gene family. The results presented here reemphasize the presence of the positive feedback

regulation mechanism of IFN production during virus infection, i.e. a more elaborated, two-step induction model, as illustrated in Fig. 4. In this model, constitutively expressed IRF-3 is first activated by virus-induced phosphorylation, resulting in *IFN*-β gene induction. This initially produced IFN-β then signals target cells to activate ISGF3, which in turn induces the *IRF-7* gene. IRF-7 then acts on both *IFN*-α and *IFN*-β genes, provided once again that it has undergone virus-induced activation by phosphorylation. The operation of this regulatory mechanism is almost certainly critical for the immediate response (i.e. innate immune response [1,2,29]) of the host, potently limiting virus replication. One may also speculate that the *IFN*-β gene might represent the prototype *IFN* gene whose expression has come under the control of IRF-3, and that *IFN*-α genes, derived by gene duplication, have evolved to promote a rapid, efficient amplification mechanism for IFN production under the control of IRF-7.

After completion of this work, we learnt that D. Levy and colleagues obtained results similar to ours (Isabelle et al., EMBO J., in press), and that P. Pitha and colleagues obtained data for the potential role of IRF-7 in the *IFN*-α gene expression [30].

Acknowledgements: We thank Dr. E.L. Barsoumian for critical reading of the manuscript. This work was supported in part by the RFTF Program (96L00307) from JSPS, and by a special grant for Advanced Research on Cancer from the Ministry of Education, Science and Culture of Japan. M.S. is a JSPS fellow.

References

[1] DeMaeyer, E. and DeMaeyer-Guignard, J. (1988) Interferons and Other Regulatory Cytokines, Wiley, New York, NY.
[2] Vilcek, J. and Sen, G.S. (1996) in: Fields Virology, 3rd Edn. (Fields, D.M., Knipe, P.M. and Howley, P.M., Eds.) pp. 375–399, Lippincott-Raven, Philadelphia, PA.
[3] Bluyssen, A.R., Durbin, J.E. and Levy, D.E. (1996) Cytokine Growth Factor Rev. 7, 11–17.
[4] Taniguchi, T., Lamphier, M.S. and Tanaka, N. (1997) Biochim. Biophys. Acta 1333, M9–M17.
[5] Nguyen, H., Hiscott, J. and Pitha, P.M. (1997) Cytokine Growth Factor Rev. 8, 293–312.
[6] Kimura, T., Nakayama, K., Penninger, J., Kitagawa, M., Harada, H., Matsuyama, T., Tanaka, N., Kamijo, R., Vilcek, J., Mak, T.W. and Taniguchi, T. (1994) Science 264, 1921–1924.
[7] Kimura, T., Kadonaga, Y., Harada, H., Matsumoto, M., Sato, M., Kashiwazaki, Y., Tarutani, M., Tan, R.S.-P., Takasugi, T., Matsuyama, T., Mak, T.W., Noguchi, S. and Taniguchi, T. (1996) Genes Cells 1, 115–124.
[8] Sato, M., Tanaka, N., Hata, N., Oda, E. and Taniguchi, T. (1998) FEBS Lett. 425, 112–116.
[9] Yoneyama, M., Suhara, W., Fukuhara, Y., Fukuda, M., Nishida, E. and Fujita, T. (1998) EMBO J. 17, 1087–1095.
[10] Wathelet, M.G., Lin, C.H., Parekh, B.S., Ronco, L.V., Howley, P.M. and Maniatis, T. (1998) Mol. Cell. 1, 507–518.
[11] Lin, R., Heylbroeck, C., Pitha, P.M. and Hiscott, J. (1998) Mol. Cell. Biol. 18, 2986–2996.
[12] Schafer, S.L., Lin, R., Moore, P.A., Hiscott, J. and Pitha, P.M. (1998) J. Biol. Chem. 273, 2714–2720.
[13] Juang, Y., Lowther, W., Kellum, M., Au, W.C., Lin, R., Hiscott, J. and Pitha, P.M. (1998) Proc. Natl. Acad. Sci. USA 95, 9837–9842.
[14] Tanaka, N., Kawakami, T. and Taniguchi, T. (1993) Mol. Cell. Biol. 13, 4531–4538.
[15] Leblanc, J.F., Cohen, L., Rodrigues, M. and Hiscott, J. (1990) Mol. Cell. Biol. 10, 3987–3993.
[16] Thanos, D., Du, W. and Maniatis, T. (1993) Cold Spring Harbor Symp. Quant. Biol. 58, 73–81.
[17] Harada, H., Matsumoto, M., Sato, M., Kashiwazaki, Y., Kimura, T., Kitagawa, M., Yokochi, T., Tan, R.S.-P., Takasugi, T., Kadokawa, Y., Schindler, C., Schreiber, R.D., Noguchi, S. and Taniguchi, T. (1996) Genes Cells 1, 995–1005.
[18] Kawakami, T., Matsumoto, M., Sato, M., Harada, H., Taniguchi, T. and Kitagawa, M. (1995) FEBS Lett. 358, 225–229.
[19] Yoneyama, M., Suhara, W., Fukuhara, Y., Sato, M., Ozato, K. and Fujita, T. (1996) J. Biochem. 120, 160–169.
[20] Ryals, J., Dierks, P., Ragg, H. and Weissmann, C. (1985) Cell 41, 497–507.
[21] Raj, N.B., Au, W.C. and Pitha, P.M. (1991) J. Biol. Chem. 266, 11360–11365.
[22] Zhang, L. and Pagano, J.S. (1997) Mol. Cell. Biol. 17, 5748–5757.
[23] Morgenstern, J.P. and Land, H. (1990) Nucleic Acids Res. 18, 3587–3596.
[24] Müller, U., Steinhoff, U., Reis, L.F.L., Hemmi, S., Pavlovic, J., Zinkernagel, R.M. and Aguet, M. (1994) Science 264, 1918–1921.
[25] Darnell Jr., J.E., Kerr, I.M. and Stark, G.R. (1994) Science 264, 1415–1421.
[26] Matsuyama, T., Kimura, T., Kitagawa, M., Pfeffer, K., Kawakami, T., Watanabe, N., Kündig, T.M., Amakawa, R., Kishihara, K., Wakeham, A., Potter, J., Furlonger, C.L., Narendran, A., Suzuki, H., Ohashi, P.S., Paige, C.J., Taniguchi, T. and Mak, T.W. (1993) Cell 75, 83–97.
[27] Reis, L.F.L., Ruffner, H., Stark, G., Aguet, M. and Weissmann, C. (1994) EMBO J. 13, 4798–4806.
[28] Tjian, R. and Maniatis, T. (1994) Cell 77, 5–8.
[29] Medzhitov, R. and Janeway Jr., C.A. (1997) Cell 91, 295–298.
[30] Au, W.C., Moore, P.A., LaFleur, D.W., Tombal, B. and Pitha, P.M. (1998) J. Biol. Chem. 273, 29210–29217.