Promoter Structures and Differential Responses to Viral and Nonviral Inducers of Chicken Type I Interferon Genes*

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Two serologically distinct type I interferons (IFNs), designated ChIFN1 and ChIFN2, are known in the chicken. ChIFN1 is encoded by a family of 10 or more genes, whereas ChIFN2 is encoded by a single gene. We show here that ChIFN1 and ChIFN2 transcripts are both strongly induced by Newcastle disease virus in primary chicken macrophages. By contrast, oral administration of the imidazooxquinoline S-28463, which selectively induces IFN-α in mammals, led to a rapid accumulation of ChIFN1 (but not ChIFN2) transcripts in adult chicken spleen and thymus. The 5'-upstream region of the ChIFN2 gene contains a NF-κB consensus motif flanked by a sequence element that could serve as a binding site for transcription factor IRF-1, reminiscent of mammalian IFN-β promoters, and it mediated powerful virus inducibility in a duck fibroblast cell line when cloned in front of a promoterless luciferase reporter gene. The 5'-upstream region of the cloned ChIFN1 gene contains two putative binding sites for IRF-1, but lacks NF-κB-binding sites, and it did not respond well to virus in transfected cells. Thus, the promoters of ChIFN1 and ChIFN2 genes not only exhibited differential responses to nonviral inducers in vivo, but also differed in structure and response to virus in transfected cells. These findings indicate that ChIFN2 represents the avian homolog of mammalian IFN-β, whereas ChIFN1 seems to correspond to mammalian IFN-α.

Interferons (IFNs) are cytokines that exhibit antiviral activity. IFN-α, IFN-β, IFN-δ, IFN-ω, and IFN-τ, which all signal through the same cell-surface receptor complex, are collectively designated type I IFNs. IFN-γ, which employs a different receptor complex for signaling, is referred to as type II IFN. In probably all mammals, it is coded for by a single intron-containing gene whose expression is induced by antigens and mitogens (1). A typical feature of type I IFN genes is that they lack introns (2). IFN-α, IFN-β, and IFN-ω genes are induced in response to virus in many cell types (3), whereas IFN-δ and IFN-τ genes are induced in response to developmental signals in trophoblasts of pigs and ruminants, respectively (4, 5). IFN-α is encoded by a gene family in mammals (6), whereas IFN-β is encoded by a single gene in humans and several other species (2), but by a small gene family in cattle (7). Based on amino acid comparisons, it was calculated that IFN-α and IFN-β have arisen by a gene duplication event that occurred at least 250 million years ago (2), probably before the mammals-birds/reptiles divergence. Genes for IFN-ω are found in humans and several other mammals, but not, for example, in dog and rodents (8), indicating that IFN-ω is phylogenetically much younger than IFN-α and IFN-β.

The IFN system of birds has only recently been characterized at the molecular level. A cDNA for a virus-induced chicken IFN was first described by Sekellick et al. (9). Recombinant protein generated from this cDNA exhibited some biochemical features that are typical for type I IFN (10, 11). Genomic DNA analysis revealed that the chicken contains several genes that code for two serologically distinct forms of type I IFN, designated ChIFN1 and ChIFN2 (12). ChIFN1 is encoded by a family of 10 or more intronless genes, whereas ChIFN2 is encoded by a single gene that also lacks introns. The various ChIFN1 gene products are >98% identical, whereas ChIFN2 is only ~57% identical to ChIFN1 (12). Although type I IFNs of chicken and mammals appear to have related structures, their primary sequences show <30% similarity. Consequently, it could not be decided on this basis which of the two chicken IFNs represents the avian equivalent of mammalian IFN-α and IFN-β. A cDNA for chicken IFN-γ has been cloned only recently (13, 14).

The mechanisms that lead to transcriptional activation of mammalian IFN-α and IFN-β genes in response to virus have been studied in great detail, and the important regulatory sequences and transcription factors were characterized (15–17). The virus response elements in the promoters of the human IFN-α1 gene (18) and the mouse IFN-α4 gene (19) have binding sites for IRF-1 and a virus-induced DNA-binding protein designated TG factor (18) or αF1-binding protein (20). Cooperation of these two factors seems to be required for efficient virus-mediated induction of IFN-α genes (18, 20). The promoter of the human IFN-β gene contains two distinct positive and one negative regulatory domains (21). Virus induction requires cooperative interaction between the two positive regulatory domains, which represent binding sites for IRF-1 or a related transcription factor and NF-κB, respectively (22). Thus, although some aspects of the regulation of mammalian IFN-α and IFN-β genes are conserved, the selective binding of unique transcription factors seems to determine specificity. The involvement of either NF-κB or the TG factor appears to be responsible for the cell type-specific selective induction of IFN-α and IFN-β genes in response to different viruses.

Some nonviral IFN inducers were reported to be effective in...
cells of various mammals (23) and chicken (24), of which the imidazoquinoline S-28463 is the most powerful agent known to date (23). Oral as well as parenteral applications of imidazoquinolines are effective in vivo (23). Imidazoquinolines were found to strongly induce the synthesis of IFN-α, but not IFN-β or IFN-ω, as evident from the fact that the antiviral activity induced by this drug could be neutralized very effectively with antisera against IFN-α (25). In human peripheral blood mononuclear cells, monocytes are mainly responsible for IFN synthesis in response to imidazoquinolines (26). An antiviral activity was present in the serum and spleen cell supernatants of chickens treated with an imidazoquinoline that was neutralized by antisera raised against recombinant ChIFN1 (24). No information is available on the signaling pathways leading to IFN gene activation in mammalian or avian cells after treatment with imidazoquinolines.

In this study, we examined the expression of the ChIFN1 and ChIFN2 genes in response to viral and nonviral inducers and characterized their promoters. Both IFNs were induced equally genes in response to viral and nonviral inducers and the 5′-noncoding region immediately upstream of the reading frame was used as template for PCR. PCR was performed with oligonucleotide primer 2 (5′-AGAGGAGCTTCCACTCCATGC-3′), which corresponds to nucleotides -687 to -676 (see Fig. 3B) and which carries a new SacI restriction site, and primer 3 (5′-GACTTGGATCTACAGGATTG-3′), which is complementary to nucleotides +60 to +71 and which carries a new BglII restriction site. To generate the Δ687ChIFN2 promoter construct, the PCR product was digested with SacI and BglII and ligated between the SacI and BglII sites of pGL-2basic. For creating the Δ149ChIFN2 construct, the PCR product was digested with RsaI, blunted, and digested with BglII, and the resulting 220-bp fragment was ligated between the SacI and BglIII sites of pGL-2basic. The same PCR product was digested with EcoRI, blunted, digested with BglII, and ligated between the SacI and BglIII sites of pGL-2basic, resulting in the construct Δ60-ChIFN2. A fragment obtained after PCR using primer 3 and primer 4 (5′-TAGACTGGACCTCAAGGGAATTCTC-3′), which corresponds to positions -65 to -53 of the ChIFN2 gene (see Fig. 3B) and which carries a new SacI restriction site, was digested with SacI and BglII before the resulting 135-bp fragment was cloned between the SacI site and BglIII sites of pGL-2basic to construct Δ687-ChIFN2. To generate the DNA template for in vitro synthesis of RNA complementary to the ChIFN2 promoter region, the 220-bp RsaI-BglII fragment of the ChIFN2 promoter described above was ligated between the SacI and BglII sites of vector pSP72, generating construct pcIFN2-RPA.

RNA Isolation and Northern Blot Analysis—Total RNA from cultured cells was prepared by the acid/guanidinium thiocyanate/isothiocyanate/phenol/chloroform method (31). For extraction of total RNA from organs, the tissues were snap-frozen in liquid nitrogen and stored at −70 °C. Frozen tissue (samples of 1 g) were thawed and homogenized in guanidium isothiocyanate buffer before RNA was extracted as described above. RNAs were separated by electrophoresis through 1.2% agarose gels containing 4% formaldehyde, transferred onto nitrocellulose membranes, and hybridized to radiolabeled DNA probes as described above.

RESULTS

Virus Infection Induces ChIFN1 and ChIFN2 Genes in Primary Macrophages—To determine whether the two previously described families of chicken type I IFN genes (12) could both be induced in response to virus infection, we exposed the fibroblast cell line CEC-32, primary blood monocyte-derived macrophages, and the macrophage cell line HD-11 to UV-inactivated NDV. Total RNA was extracted from the various cell cultures at 6 h post-infection and analyzed by Northern blotting for the presence of IFN transcripts. Under the high stringency washing conditions used, hybridization of ChIFN1 and ChIFN2 cDNA probes was mainly to their respective transcripts, and cross-hybridization was minimal (data not shown). High concentration of ChIFN1 and ChIFN2 RNAs was present in the virus-induced primary macrophages (Fig. 1). By contrast, neither ChIFN1 nor ChIFN2 transcripts could be detected in the two permanent cell lines under these conditions. We further failed to detect ChIFN1 or ChIFN2 transcripts in NDV-treated pared cells, chicken embryo cells (not shown).

The Synthetic Cytokine Inducer S-28463 Activates ChIFN1 (But Not ChIFN2) Genes in Vivo—Oral administration of the imidazoquinoline S-28463 induces IFN-α and other cytokines in mammals (23). We therefore tested whether administration of this substance would induce both gene families that encode type I IFN in chickens. High levels of ChIFN1 transcripts were detected in the spleens and thymuses of two chickens treated...
for 2 h with 2 mg of S-28463/kg of body weight, whereas the corresponding organs of the untreated control chicken did not contain detectable amounts of this RNA (Fig. 2). ChIFN1 RNA was also found in the liver of one drug-treated animal, whereas a second treated animal and the control animal did not contain detectable amounts of ChIFN1 transcripts in this organ. The bursae of all three chickens lacked ChIFN1 RNA. A time course experiment showed that the response to S-28463 was very rapid and transient: ChIFN1 transcripts appeared in the spleens of treated animals within 1 h, reached a maximum after ~2 h, and were no longer detectable at 4 h post drug application (data not shown). Interestingly, we failed to detect transcripts for ChIFN2 in the various organs of drug-treated chickens (Fig. 2), indicating that at least one member of the ChIFN1 gene family responded much better to stimulation with S-28463 than the ChIFN2 gene. Neither ChIFN1 nor ChIFN2 transcripts were detected in primary blood monocyte-derived macrophages that were treated with 3 μg/ml S-28463 for 3 or 6 h (data not shown). Since the IFN-α genes are selectively induced by imidazoquinolines in mammals (25), this result suggested that the ChIFN1 genes, rather than the ChIFN2 gene, might represent the avian counterparts of mammalian IFN-α.

The Upstream Region of the ChIFN2 Gene Contains a Powerful Virus Response Element—To further study the regulation of the chicken IFN genes, we sequenced the upstream regions of one member of the ChIFN1 gene family (ChIFN1-2) (Fig. 3A) and of the single ChIFN2 gene (Fig. 3B). Both upstream sequences lacked classical TATA boxes and most other regulatory elements frequently found in promoters of mammalian genes. About 160 and 120 bp upstream of the beginning of the ChIFN1 open reading frame, we identified two sequence elements that might represent binding sites for transcription factor IRF-1 (Fig. 3A and Ref. 34), previously found to be part of the virus response elements of the mammalian IFN-α and IFN-β gene promoters (18). About 130 bp upstream of the beginning of the ChIFN2 open reading frame, we identified a consensus binding motif for the transcription factor NF-κB (Fig. 3B), which plays a critical role in the virus response of mammalian IFN-β genes, but not IFN-α genes (22). Immediately upstream of the putative NF-κB-binding site of the ChIFN2 promoter, we found a sequence element that resembles the binding site for mammalian transcription factors of the IRF family (Fig. 3B).

To test for promoter activity, the upstream regions of the ChIFN1-2 and ChIFN2 genes were cloned in the correct orientation in front of a promoterless luciferase reporter gene. The resulting constructs were then transfected into DEC141 cells, a permanent fibroblast duck cell line that readily synthesizes IFN in response to infection with NDV. The DEC141 cells were incubated with UV-inactivated NDV for either 6 or 15 h before the cells were lysed and assayed for luciferase activity. A DNA fragment derived from the ChIFN1-2 gene that included the 699 nucleotides immediately upstream of the ATG initiation codon conferred significant but rather poor inducibility to virus in this system (see Fig. 5): its expression increased not more than 5-fold in response to virus infection. The performance of the ChIFN1 promoter was not improved when a larger fragment was used that included ~1.8 kb of upstream sequence (construct Δ-1.8kbChIFN1-2 in Fig. 5). By contrast, the ~750 nucleotides located upstream of the ChIFN2 open reading frame conferred very strong inducibility to virus: the activity of this promoter was some 40-fold higher in NDV-infected cells than in uninfected control cells (see Fig. 5). It thus appeared that the upstream region of the ChIFN2 gene harbored a very potent virus response element.

Functional Characterization of the ChIFN2 Promoter—To characterize the ChIFN2 promoter in more detail, we first determined the transcriptional start site of this gene. An RNase protection experiment was performed with RNA from virus-induced primary chicken macrophages and radiolabeled in vitro synthesized antisense RNA derived from a DNA fragment carrying the ChIFN2 upstream region (see “Materials and Methods”). We found that ChIFN2 transcripts have heterogeneous 5′-ends (Fig. 4). From their lengths, we calculated that transcription from the ChIFN2 gene initiates at six major sites located 71, 67, 63, 47, 44, and 41 nucleotides upstream of the open reading frame, the most upstream of which was defined as position +1 (Figs. 3B and 4).

By determining the activity of constructs containing shortened fragments of the ChIFN2 upstream region, we tried to define the minimal promoter sequence capable of mediating strong virus inducibility to the luciferase reporter gene. A DNA fragment comprising the ChIFN2 sequences between positions −149 and +70 mediated full-scale virus inducibility (Fig. 5), indicating that it contained all major regulatory elements. Further truncations of this fragment at the 5′-end to positions −60 (destroying the NF-κB and IRF motifs) and to position −65 (destroying the IRF motif, but sparing the NF-κB motif) abolished the virus response almost completely (Fig. 5).

**DISCUSSION**

Based on coding sequence comparisons, it could previously not be decided which of the two serologically distinct type I IFNs of chickens was the true homolog of IFN-α, IFN-β, or

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2 U. Schultz, unpublished results.
IFN-ω (12). It was also unclear whether the ChIFN2 gene was inducible by virus or whether it would not respond to this stimulus, like IFN-τ of ruminants (5) and IFN-δ of pigs (4). The fact that ChIFN2 is encoded by a single gene like human and murine IFN-β was not sufficient evidence for a final assignment, as IFN-β is encoded by a family of genes in bovines and other species (7).

We now found that both ChIFN1 and ChIFN2 gene families are strongly induced by NDV in primary macrophages, indicating that they are important viral response genes in chickens.

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**Figure 3.** Nucleotide sequences of the upstream regions of a ChIFN1 gene and the ChIFN2 gene. **A.** ChIFN1-2. As no information is available on the transcriptional start site of this gene, the numbering of nucleotides is given relative to the ATG initiation codon, which was defined as position +1. The arrow marks the upstream boundary of a sequence that was tested for virus-inducible promoter activity. The shaded sequences highlight two putative binding sites for IRF-like transcription factors. **B.** ChIFN2. Arrowheads mark the six major transcriptional start sites of the ChIFN2 gene as determined by the experiment shown in Fig. 4. The most upstream of these sites was defined as position +1. Arrows mark the upstream boundaries of fragments that were tested for virus-inducible promoter activity. The shaded sequence highlights a putative binding site for IRF-like transcription factors.

**Figure 4.** Mapping the transcriptional start sites of the ChIFN2 gene by RNase protection. RNAs from NDV-induced (lane 1) and uninduced (lane 2) primary macrophages were analyzed. tRNA (lane 3) served as negative control. The various RNAs were hybridized to suitable radiolabeled in vitro synthesized antisense transcripts before excessive treatment with RNase. The reaction products were separated on a sequencing gel together with appropriate molecular weight standards and visualized by autoradiography. The identity of the six major signals is indicated. The nomenclature refers to the numbering shown in Fig. 3B.

**Figure 5.** Virus inducibility of various ChIFN promoter-luciferase constructs. Constructs containing the indicated fragments of a ChIFN1 gene (ChIFN1-2) and the single ChIFN2 gene were transiently transfected into two parallel cultures of DEC141 cells. About 30 h post-transfection, one culture was treated with UV-inactivated NDV for 6 h (white bars) or 15 h (hatched bars), whereas the other culture was untreated (black bars). Cell lysates were prepared, and luciferase activities were determined. Virus inducibility of the various constructs was calculated by dividing the luciferase values of the virus-induced cultures by the values of the corresponding uninduced cultures.
ing that they cannot be the chicken homologs of mammalian IFN-α or IFN-β. High levels of ChIFN1 (but not ChIFN2) transcripts were present in lymphoid organs of chickens treated with the imidazoquinoline S-28463. In human peripheral blood mononuclear cells, this drug induces an antiviral activity that can be neutralized almost completely with antiserum to IFN-α (25). Since such antisera are usually highly specific and do not cross-react with IFN-ω or IFN-β (35), it appears that imidazo-quinolines selectively induce IFN-α. Our results therefore suggest that ChIFN1 is the chicken homolog of mammalian IFN-α. We further found that the promoter of the ChIFN2 gene contains a NF-κB consensus motif, whereas the ChIFN1 promoter lacks such a motif. This difference in promoter structure is reminiscent of mammalian IFN genes, where NF-κB motifs are exclusively found in IFN-β promoters (21). Taken together, these observations provide strong evidence that ChIFN2 represents the avian IFN-β homolog, whereas ChIFN1 seems to be the homolog of mammalian IFN-α. This conclusion is compatible with phylogenetic analyses of mammalian type I IFN genes, which suggested that the gene duplication event that gave rise to IFN-α and IFN-β occurred before the mammals-birds/reptiles divergence (2).

The ChIFN2 promoter contains a NF-κB-binding site located some 60 nucleotides upstream of the transcriptional start site, which is preceded by a sequence motif that resembles the binding site of mammalian transcription factors of the IRF family. A promoter fragment containing these putative regulatory elements was sufficient to mediate virus inducibility, whereas constructs lacking either the IRF motif or both motifs no longer responded to virus. NF-κB-binding sites are present at corresponding positions in the promoters of human and murine IFN-β genes, where they constitute the positive regulatory domain II (22, 36). Binding sites for IRF-1 or related transcription factors (21) are present immediately upstream of the NF-κB site, where they constitute the positive regulatory domain I in human and murine IFN-β promoters. Taken together, these observations suggest that conserved signal pathways are responsible for the activation of the ChIFN2 and mammalian IFN-β promoters. A more refined analysis of the ChIFN2 promoter and binding studies with purified transcription factors are required to confirm this concept.

Except for two IRF-binding sites, the promoter region of the cloned ChIFN1 gene contains no sequence motifs with obvious similarity to virus response elements of mammalian IFN genes. Although, as stated above, the lack of a NF-κB site indicates that this gene is not homologous to mammalian IFN-β, we have no clear evidence that the promoter of this gene is organized like that of mammalian IFN-α genes. In particular, we failed to detect a binding motif for the TG factor (18) or the αF1-B complex (19). As our experiments showed that the isolated ChIFN1-2 promoter responded rather poorly to virus in transfected cells, it was formally possible that we cloned the 5′-upstream region of a poorly expressed member of the ChIFN1 gene family that lacks an important regulatory element. This seems unlikely because the promoter region of another gene of the ChIFN1 family (ChIFN1-1 (12)) showed that the 400 nucleotides located upstream of the open reading frame were identical to the ChIFN1-2 sequence shown in Fig. 3A, except for two nucleotide exchanges. In particular, the two putative IRF-binding sites were present at corresponding positions in both promoters. Thus, the poor activity of the cloned ChIFN1 promoters might instead be explained by assuming that the duck cell line used for the transfection experiments lacks a transcription factor required for effective regulation of the ChIFN1 genes. In the mammalian system, it is well known that the response of the IFN-α and IFN-β promoters to virus is not uniform, but rather varies considerably between cell lines (37). Future experiments using other cell lines should allow optimal conditions to be defined for virus induction of the isolated ChIFN1 promoters.

In human peripheral blood mononuclear cells treated with S-28463, the monocyte population was found to be the principal producer of IFN-α (26). In a previous study (24), spleen cells and blood lymphocytes from imidazoquinoline-treated chickens were found to secrete high amounts of IFN. In agreement with these results, we now found that ChIFN1 transcripts were abundantly present in the spleens and thymuses of drug-treated chickens. Since S-28463 failed to induce ChIFN transcripts in primary macrophages, it seems that IFN present in the serum of imidazoquinoline-treated chickens mainly originates from lymphoid organs.

A surprising result of our study was that we failed to induce the chicken IFN genes by Newcastle disease virus in fibroblasts and in a macrophage cell line under conditions that strongly induced ChIFN1 and ChIFN2 transcripts in primary macrophages. Although the molecular basis for nonresponsiveness remains elusive, our findings might explain why efficient production of virus-induced chicken IFN in fibroblasts was successful in the hands of only a few experts after careful conditioning of the cell cultures (38, 39). The elaborate conditioning might have induced essential transcription factors that are not constitutively present in most chicken cells. Thus, in agreement with previous findings in the mammalian system (40), our results suggest that primary macrophages are the most effective producers of virus-induced IFNs. Our principal finding that mammalian IFN-α and IFN-β probably have their true counterparts in birds supports previous notions (41, 42) that most elements of the mammalian IFN system are conserved in birds, although the primary sequences of the critical protein components are quite dissimilar.

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