Cloning and Characterization of Soluble and Transmembrane Isoforms of a Novel Component of the Murine Type I Interferon Receptor, IFNAR 2*

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This report describes the cloning of cDNAs encoding transmembrane and soluble isoforms of a novel chain of the murine type I interferon (IFN) receptor and characterization of its capability to bind ligand and transduce signals. The transmembrane receptor (murine IFNAR 2c) has an extracellular domain of 215 amino acids and an intracellular domain of 256 amino acids, with 48% amino acid identity and 71% nucleotide identity with human IFNAR 2c. The cDNA for the soluble murine receptor (IFNAR 2a) encodes a 221-amino acid polypeptide identical to the first 210 amino acids of IFNAR 2c plus a novel 11 amino acids. Northern blot analyses show that murine IFNAR 2 is expressed as two transcripts of 4 kilobases encoding the transmembrane isoform and 1.5 kilobases encoding the more abundant soluble isoform. Studies using primary murine cells that lack IFNAR 1 show that IFNAR 2 is expressed, and cells bind type I IFN ligand, but do not transduce signals as detected by electrophoretic mobility shift assays of ISGF3 or GAF complexes binding to their cognate oligonucleotides. These cells show no effects on the ability of IFNγ to activate these complexes. These studies demonstrate that the IFNAR 2 transmembrane (2c) and soluble (2a) isoforms are conserved between the human and mouse and that IFNAR 2c has intrinsic ligand binding activity, but no intrinsic signal transducing activity as measured in this study.

The type I interferons (IFNs) are pleiotropic cytokines which, in all vertebrate species, can impart important signals to cells to protect against viral infection, inhibit proliferation, and activate immune effector cells (1). The human type I IFNs include multiple subtypes of IFNα, a single IFNβ, and in some species IFNγ and -r(2, 3). The structure of type I IFNs is highly conserved, ranging from 70–98% amino acid identity between IFNα subtypes to 35% identity between IFNα and IFNβ (2). Not only are type I IFNs structurally and functionally related, but they also compete with each other for receptor binding and therefore share one or more common receptor component(s) (4). Although two components of the human type I IFN receptor have been cloned, their role in ligand binding and signal transduction remains unclear.

The first component of the type I IFN receptor to be cloned was human IFNAR 1 (5) which was shown to mediate response to one human IFN subtype α8, but not α2, nor β when its cDNA was expressed in murine TG 9A cells (5). Subsequent studies demonstrated binding of type I IFNs to IFNAR 1 when expressed in Xenopus laevis oocytes (6) or in simian COS cells (7). By contrast, no binding of type I IFNs to IFNAR 1 was detected when IFNAR 1 was expressed in murine L929 cells (8) or hamster CHO cells (9, 10). Thus, in view of these contradictory data, the role of IFNAR 1 in ligand binding remains uncertain.

One possible explanation for the discrepancy between these studies may be that the human IFNAR 1 receptor component was expressed in various heterologous cell backgrounds which may either process human IFNAR 1 differently or may interact with the transfected component differently via its endogenous IFNAR chains. To define the function of receptor components clearly it would be an advantage to study the receptor function in a homologous background and without interference from other heterologous receptor components.

The cDNA encoding a second component of the human type I IFN receptor complex was cloned (11) and is now designated IFNAR 2. Subsequent studies have identified that the human IFNAR 2 gene encodes multiple mRNA transcripts which are translated into several isoforms: a soluble form designated as IFNAR 2a (11, 12), a “short” transmembrane form designated as huIFNAR 2b (11, 12) and a “long” transmembrane form designated as huIFNAR 2c (12, 13). Although the original report proposed IFNAR 2b to be the signaling subunit (11), subsequent studies proposed that IFNAR 2c possessed signaling activity not present in IFNAR 2b (12). The reason for the existence of two transmembrane isoforms of IFNAR 2 remains unknown. Indeed the extent to which any isoforms of IFNAR 2 are expressed other than in a few cell lines derived from human tumors also remains unknown. Co-expression of human cDNAs encoding IFNAR 1 and IFNAR 2 in murine 3T3 cells gives higher binding of ligand than when either chain alone is expressed (14), but the contribution of endogenous receptor chains from the host cell as discussed above complicates interpretation of these experiments. Thus the importance of the
multiple isoforms of human IFNAR 2 and their roles in ligand binding and signal transduction is still unclear.

To resolve these problems, we have undertaken to study the murine type I IFN system which is analogous to the human system in that it contains multiple IFNα subtypes and a single IFNβ (2), and murine IFNAR 1 is homologous to human IFNAR 1 (15). The study of the IFN system in the mouse has several advantages. In particular the availability of transgenic and gene knock-out technology will enable functional studies on receptor function in vivo in physiological and pathological conditions. For example earlier studies by us (16) and others (17) of IFNAR 1−/− mice demonstrated the importance of type I IFNs in antiviral defense and hemopoiesis. Furthermore the availability of cells from receptor knock-out mice will enable the study of one receptor component in cells where another component is absent. The comparison of data from the mouse and human system will also enable the identification of important isoforms or critical functional residues which are likely to be conserved across species.

In the present study we describe the cloning of two cDNAs encoding transmembrane and soluble isoforms of the second murine type I IFN receptor, IFNAR 2, which is highly homologous to the human IFNAR 2c and 2a isoforms, respectively. In addition, we report the conserved structural features of this receptor chain, demonstrate the expression of IFNAR 2 transcripts in normal adult mouse tissues, and demonstrate that when IFNAR 2 is expressed in primary cells in the absence of IFNAR 1 it has intrinsic binding activity, but alone does not transduce signals, as measured herein.

EXPERIMENTAL PROCEDURES

Cell Culture and Interferons—The murine interferons used in these studies were obtained from the following sources: recombinant murine IFNγ, Toray Industries, Tokyo, Japan; natural murine IFNβ and mixed IFNα subtypes, Lee Biomedical, Los Angeles, CA; recombinant murine IFNα, Life Technologies, Inc.

Murine L cells were grown in RPMI 1640 containing 10% fetal calf serum, 100 units/ml penicillin, and 100 mg/ml streptomycin. Embryo fibroblast cell lines were grown in Dulbecco’s modified Eagle’s medium containing 10% fetal calf serum, penicillin, and streptomycin. Embryo fibroblast cell lines were grown in Dulbecco’s modified Eagle’s medium supplemented with fetal calf serum, L-cell conditioned medium, and colony-stimulating factor 1 for 7–8 days as described previously (18).

Cloning of the MuIFN AR 2—A mouse testis cDNA library (CLON-TECH) was screened with a 757-bp huIFNAR 2 cDNA probe (nucleotides 410 to 1167 of published sequence (11). Two identical clones containing the insert were obtained after tertiary screening. The insert was sequenced using an automated sequencing machine (Applied Biosystems, 373A DNA sequencer). The sequence of the insert corresponds to the sequence from nucleotides 622 to 2220 of human IFNAR 2a (Fig. 1). To obtain the rest of the sequence a 544-bp fragment corresponding to nucleotides 622 to 1176 was generated by PCR and used to screen a mouse lung cDNA library (Stratagene). After three rounds of screening, a clone containing an approximately 3-kb insert was obtained, and both strands of the insert were sequenced as above. The sequence (Fig. 1) contains a full open reading frame (513 amino acids) which included 16 potential casein kinase II phosphorylation sites at Ser-29, 16 potential tyrosine kinase phosphorylation sites at Y-471, and Ser-448, Thr-463, Ser-500, Ser-502, and potential N-myristylation sites at Gly-233, -237, Ser-403, Ser-415, Ser-416, Ser-448, Thr-463, Ser-500, Ser-502, and potential N-myristylation sites at Gly-233, -237.

RESULTS

Sequence of Murine IFNAR 2 cDNA—The cDNA sequence of the approximately 3-kb clone obtained from the mouse lung library is shown in Fig. 1A. It comprises 108 nucleotides of 5′-untranslated sequence, a 1539-nucleotide open reading frame, 824 nucleotides of 3′-untranslated sequence, and a polyadenylation sequence at nucleotides 2340 to 2345. The 1.6-kb clones obtained from the testis library were identical in sequence from nucleotides 622 to nucleotide 2220, except A (lung)→G (testis) at 1124, C→T at 1163, and G→A at 1394.

The open reading frame encodes a 513-amino acid polypeptide with a predicted 27-amino acid leader sequence (boxed, Fig. 1A) and hydrophobic transmembrane domain of 21 amino acids (boxed and shaded, Fig. 1A). Thus the murine IFNAR 2 would have an extracellular domain of 215 amino acids with 8 potential N-glycosylation sites (underlined, Fig. 1A), a fibronectin-like cell attachment sequence, RGD, at residues 115 to 117, and 7 cysteine residues. The long intracellular domain contains 250 amino acids with 6 tyrosine residues, a potential eAMP/GMP-dependent protein kinase phosphorylation site at Ser-403, 8 potential protein kinase C phosphorylation sites at Thr-44, Thr-88, Thr-96, Thr-158, Ser-180, Thr-306, Thr-341, Ser-194, 16 potential casein kinase II phosphorylation sites at Ser-29, Ser-74, Ser-91, Ser-293, Ser-321, Ser-323, Thr-336, Ser-354, Ser-364, Ser-403, Ser-415, Ser-416, Ser-448, Thr-463, Ser-500, Ser-502, and potential N-myristylation sites at Gly-233, -237, -245, -365, -373, -387, -394, and -471.

The murine IFNAR 2 shows 48% amino acid identity overall with the human IFNAR 2c and 71% nucleotide identity (Fig. 1B). A comparison of the murine and human IFNAR 2c amino acid sequences (Fig. 1B) shows that the cysteine residues are conserved between human and mouse except an extra C in murin IFNAR 2 at amino acid residue 121. Intracellular tyrosine residues Tyr-268, Tyr-315, Tyr-317, Tyr-335, and Tyr-510 are conserved, but Tyr-306 and Tyr-411 are present in human not mouse, and Tyr-398 is present in mouse not human. Since functionally important residues are more likely to be conserved across species, the former tyrosines are likely to be the important ones, for example in phosphorylation associated with sig-
nal transduction. The degree of amino acid sequence identity between the murine and human IFNAR 2 is similar to that between murine and human IFNAR 1, namely 48 and 46%, respectively.

Several cDNA clones encoding a soluble isoform of IFNAR 2 were isolated from the libraries (12 of 14 clones analyzed), the sequence of a 1045-bp clone is shown in Fig. 2. This isoform is designated muIFNAR 2a because of its similarity with the soluble human isoform, huIFNAR 2a. The predicted amino acid sequence derived from the coding cDNA sequence is identical to the sequence of muIFNAR 2c for the first 237 amino acids (including the signal sequence) and contains an additional 11 amino acids which are specific to this isoform (Fig. 2).

Murine IFNAR 2 Expression—Northern blot analysis of mRNA from normal mouse liver and placenta using a full-length murine IFNAR 2 cDNA probe indicates two major transcripts of approximately 4.0 and 1.5 kb in size (Fig. 3A), similar to the sizes reported for human IFNAR 2 transcripts. An identical filter was simultaneously hybridized with a probe encompassing nucleotides 917–1579 of the cDNA which encodes the cytoplasmic domain of murine IFNAR 2c. This cytoplasmic domain probe hybridized with only the larger 4.0-kb transcript. Hybridization with a probe that contained nucleotides 913 to 1012 of the IFNAR 2a cDNA detected only the 1.5-kb band. This probe contained nucleotide sequences that are absent in the IFNAR 2c cDNA, namely the 3'-untranslated region and the nucleotides encoding the soluble-specific amino acids. These data indicate that the 1.5-kb transcript contains mRNA encoding the soluble muIFNAR 2a, whereas the 4.0-kb transcript encodes the transmembrane IFNAR 2c. This situation appears to be different from the human in which the soluble receptor isoform is encoded by a 4-kb transcript, whereas the shorter transcript encodes the short C-terminally truncated transmembrane isoform, IFNAR 2b (12). Interestingly, we are yet to isolate any murine cDNA clones homologous to the short C-terminally truncated transmembrane human IFNAR 2b isoform (from more than 20 clones from three different cDNA libraries). Because the human IFNAR 2b is proposed to have arisen because of an Alu sequence in the gene (27), the existence of this isoform may be specific to human species.

Northern blot analyses of poly(A)+ mRNA obtained from several organs of adult mice show that both the 4.0- and 1.5-kb transcripts are present in all tissues (Fig. 3B), as is also the case in the murine cell lines examined (data not shown). Occasionally a weak, larger transcript was observed at about 9 kb in some organs (e.g. liver, thymus, lung, Fig. 3B); this may represent unprocessed mRNA or another, minor transcript. It is notable from the Northern blots that the 1.5-kb transcript was more intense relative to the 4-kb transcript in most tissues analyzed, implying that the soluble receptor encoded by this transcript may be functionally important.

Function of Murine IFNAR 2 in Ligand Binding and Signal Transduction—To perform functional studies on murine IFNAR 2, we have utilized the murine IFNAR 1−/− mice previ...
厂区内的工作人员正在全力保障生产。生产区域里，机器轰鸣声和流水线作业声交织在一起，呈现出一派繁忙的景象。工人们穿着统一的工作服，戴着防护口罩，熟练地操作着各种设备，将原材料加工成产品。

“今天的工作量有点大，”一位工友一边擦拭着机器上的汗水一边说道，“但是大家都没有抱怨，都尽力在保证生产。”

这是一家生产高科技产品的公司，员工们对于工作的认真态度和责任心让公司能够在激烈的市场竞争中脱颖而出。
Cloning and Characterization of Murine IFNAR 2

For many cytokine receptors it has been demonstrated that two or three chains constitute the functional receptor. These chains have been defined as primary ligand binding (or α) chains, accessory (non-binding or β), or signal transducing or co-binding chains (29). This definition has been an important step in understanding how the receptor works in ligand interaction and signal transduction and in defining the action of soluble receptors (e.g., whether they inhibit interaction with a functional receptor or facilitate interaction by presenting the ligand to an accessory or transducing chain). However, as yet there has been no convincing definition of the role of the receptor chains in the type I IFN system. The availability of IFNAR 1 −/− mice from our previous work provides an ideal opportunity to study the function of IFNAR 2 in primary cells lacking the other component. In this study we have shown that in primary bone marrow-derived macrophages which lack IFNAR 1, but express IFNAR 2, there is significant binding of ligand. These data indicate for the first time, unequivocally, the intrinsic ligand binding capability of IFNAR 2. The observation that binding is reduced in IFNAR 1 −/−/− cells relative to IFNAR 1+/+ cells indicates clearly that IFNAR 1 also contributes to signaling. This result also clarifies the contradictory data from human studies of the role of IFNAR 1 in ligand binding (see introduction).

Our studies show that despite this intrinsic ligand binding activity, IFNAR 2 cannot transduce signals in the absence of IFNAR 1. Co-expression of both receptor chains is therefore necessary for these signals to be transduced. We demonstrated that IFNα activated the formation of the classical ISGF3 complex as well as GAS-binding factors that contained STAT-1 and STAT-3. However none of these activated factors were observed in IFNAR 1 −/−/− cells relative to IFNAR 1+/+ cells indicates clearly that IFNAR 1 also contributes to binding. This result also clarifies the contradictory data from human studies of the role of IFNAR 1 in ligand binding (see introduction).

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...data also indicate that the shorter transcript is the more abundant of the two in most tissues analyzed. Confirmation of similar differences in expression for the different IFNAR 2 isoforms at the protein level would suggest an important role for the soluble receptor in regulating the IFN response. The likelihood that a soluble isoform has biological activity is strengthened by our finding that the transmembrane isoform of IFNAR 2 has intrinsic ligand binding activity, thereby enhancing the probability that the soluble isoform will also bind ligand.

Thus this study demonstrates the sequence and important characteristics of murine IFNAR 2 as having a major role in binding type I IFN ligand but requiring the cooperation of IFNAR 1 for complete binding and signal transduction. These results will form the basis for significant future studies on understanding the regulation of the type I IFN system in vivo.

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Fig. 6. Electrophoretic mobility shift assays of cell lysates prepared from PEF cells, before (−) and after (+) treatment with 1000 IU/ml of recombinant IFNs or IFNγ and incubated with GAS oligonucleotide as above. A, response of cells from IFNAR 1+/+ mice to treatment with IFNα or γ. B, response of cells from IFNAR 1−/− mice to treatment with IFNs. C, lysates of cells from IFNAR 1+/+ mice preincubated with antibodies as indicated. D, lysates of cells from IFNAR −/− mice preincubated with antibodies as indicated.
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