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# Target cell specificity of two species of human interferon-α produced in *Escherichia coli* and of hybrid molecules derived from them

(active site/receptor/genetic engineering/gene expression/antiviral activity)

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**ABSTRACT** **Plasmids containing cDNAs for human interferon (IFN) α-1, IFN α-2, and several hybrids of the two cDNAs, all joined identically to an *Escherichia coli* lac promoter fragment gave rise, in *E. coli*, to fused interferons (fIFNs) that had very different target-cell specificities. fIFN α-1 had a lower specific activity on human WISH cells than on bovine MDBK cells, while fIFN α-2 showed the opposite behavior. fIFN hybrids with the *$NH_2$-proximal* half of fIFN α-1 behaved qualitatively like fIFN α-1, and those with the *$NH_2$-proximal* half of fIFN α-2, behaved like fIFN α-2. On mouse L929 cells, fIFN α-2 was almost inactive, while fIFN α-1 showed relatively high activity. In this case, the fIFN hybrids with the *COOH-proximal* half of IFN α-1 showed activity on mouse cells, while the reciprocal hybrid did not. In many cases, the activity spectrum of the hybrids was very different from that of either parent. We propose that the IFN molecule has either two binding sites or two regions constituting the binding site, one in the COOH- and the other in the $NH_2$-proximal half. The experimental findings can be accounted for if the fits of the two sites to their receptor counterparts on different cell lines are independent of one another.**

We have recently characterized 10 distinct leukocyte interferon (IFN-α) genes in man (1, 2). The genes encoding IFN α-1 and IFN α-2 differ in ≈20% of their nucleotide positions and the cognate IFNs have distinct target specificities: although IFN α-2 is slightly more active on human HEp-2 cells than on bovine BEK cells in regard to its antiviral activity, IFN α-1 is 10–20 times more active on BEK cells than on HEp-2 cells (3, 4).

To determine which part of the molecule is responsible for the target specificity, we prepared plasmids containing the cDNAs of IFN α-1, IFN α-2, and hybrids of the two, all joined identically to an *Escherichia coli* lac promoter fragment and determined the antiviral activities of these IFNs on a variety of cells. We found that the specificity for human cells appeared to be transmitted with the $NH_2$-proximal half of the IFN molecule but that that for mouse cells appeared to be transmitted with the COOH-proximal half. Moreover, the properties of several hybrids differed quantitatively from those of either parent. We propose that the IFN molecule has either two binding sites or two regions (idiotopes) constituting the binding site, one in the COOH-proximal and one in the $NH_2$-proximal half. Our experimental findings can be explained if the fit of the two idiotopes to their receptor counterparts on different cell lines vary independently.

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## MATERIALS AND METHODS

**Plasmids.** The isolation of the cDNA plasmids Z-pBR322(*Pst*)/HcIF-SN35 (SN35) and Z-pBR322 (*Pst*)/HcIF-SN206 (SN206) has been reported (5). The sequence of SN-206 cDNA (IFN α-2) was described (3). The cDNA for IFN α-1 in SN-35 is similar to that in Z-pBR322(*Pst*)/HcIF-2h (2h) (6); however, there is no *Pst* I site at the 3′ end of the sequence, and the signal sequence is missing up to nucleotide −50 (3). Moreover, a *Bsp* I replaces an *Ava* II site at position −42 and the *Ava* II site in position 508 is missing, suggesting that the cDNA in SN-35 is a polymorphic variant of that in 2h.

The plasmid HS-pBR322(*Eco*)/lac UV5-150 (lac plasmid, from H. Schaller) contains the lac promoter *Hae*III-203-base-pair (bp) fragment (7) flanked by an *Eco*RI linker at its 3′ end.

**Plasmid Constructions.** Restriction enzymes (from New England BioLabs, except for *Bsp* I, a gift of A. Kiss) were used essentially as recommended by the suppliers. When required, cleaved DNA was dephosphorylated (8) with calf intestine alkaline phosphatase (Boehringer Mannheim, 1 unit/μg of DNA) for 30 min at 37°C and extracted with phenol and ether. DNA fragments were separated on 0.8% low-gel-temperature agarose (Bio-Rad) in Tris acetate buffer (6). For ligation, fragment-containing gel pieces (about 5 μl each) were melted at 65°C and mixed, and the mixtures were cooled to 37°C, adjusted to 66 mM Tris·HCl, pH 7.2/6.6 mM $MgCl_2$/10 mM dithiothreitol/1 mM ATP, and treated with T4 DNA ligase (20 units/μl; New England BioLabs). Ligation was for 16 hr at 15°C in the solidified gel (9); 100 mM Tris·HCl, pH 7.5/100 mM $CaCl_2$/100 mM $MgCl_2$ (1:10 vol) was added, and the sample was heated 5 min at 65°C, cooled to 37°C, and used to transform $Ca^{2+}$-treated *E. coli* HB101 (5). Plasmid DNA was prepared as described (10).

## RESULTS

**Construction of Plasmids for Expression of Fused IFN (fIFN) α-1, fIFN α-2, and Their Hybrids.** cDNA coding for part of the signal sequence and the entire coding region of IFN α-1 was joined to the trimmed 3′ end of a UV5 lac promoter fragment extending to the beginning of the β-galactosidase gene (7) (Fig. 1). The best producer clone, C8, had an initiator triplet followed by the codons for the first six amino acids of β-galactosidase, a proline codon generated by the fusion, 13 codons of the signal sequence, and the IFN α-1 sequence. This IFN will be referred to as fIFN α-1, the "f" indicating that it is a fusion product.

Abbreviations: IFN, interferon; fIFN, fused interferon; bp, base pair(s).

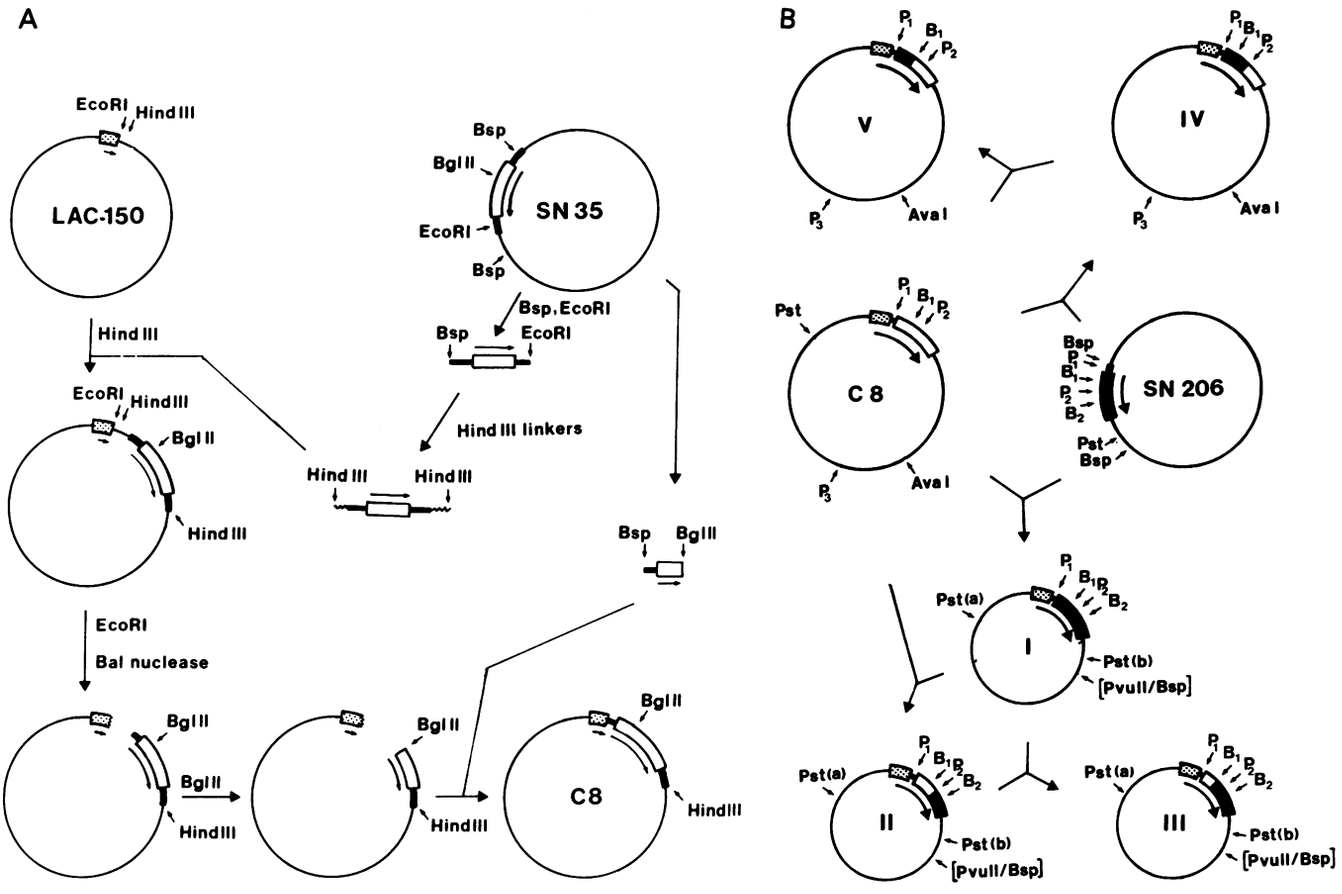


FIG. 1. Construction of plasmids for the expression of fIFN α-1, fIFN α-2, and hybrids of fIFN α-1 and fIFN α-2. (*A*) Expression plasmid for IFN α-1 (C8). SN35 was cleaved with *Bsp* I and *Eco* RI, the ends of the cDNA α-1-containing fragment were rendered flush with $T_4$ DNA polymerase, *Hin*dIII linkers were attached (11), and the fragment was joined to the *Hin*dIII-cleaved lac plasmid. The plasmid containing the insert with its 5′ end adjoining the lac fragment was identified by restriction analysis. It was cleaved with *Eco*RI and digested with exonuclease Bal-31 [0.06 units/ml; 2–4 min at 30°C (12)] to shorten the β-galactosidase coding segment. To ensure the presence of the complete IFN sequence, the plasmid was cleaved with *Bgl* II, the larger fragment was purified from a 2% agarose gel, and the 230-bp *Bsp/Bgl* II fragment from SN35 was joined to it. *E. coli* HB101 was transformed with the recombinants, and a clone (C8) containing a high level of IFN activity was selected. (*B*) Plasmid I—fIFN α-2 expression plasmid C8/206. SN206 (3) was cleaved totally with *Bsp* I and partially with *Pvu* II, and the 870-bp fragment (*Bsp* I to Pl) was isolated. C8 was totally cleaved with *Pvu* II and the 2590-bp fragment (P1 to P3) was isolated. The two fragments were joined. Plasmid II—α-1(P)α-2 hybrid. C8 was partially cleaved with *Pst* I, and the *Pst/Pvu* II(P2) fragment (≈1530 bp) was isolated. Plasmid I was cleaved totally with *Pvu* II and partially with *Pst* I, and the *Pst* I (a) *Pvu* II ($P_2$) 2130-bp fragment was isolated. The two fragments were joined. Plasmid III—α-1(B)α-2 hybrid. Plasmid II was cleaved with *Bgl* II and dephosphorylated, and the large *Bgl* II fragment was isolated. Plasmid I was cleaved with *Bgl* II, and the small *Bgl* II fragment was isolated. The two fragments were joined. The hybrid plasmid containing the correctly oriented small *Bgl* II fragment was identified by restriction analysis. Plasmid IV—α-2(P)α-1 hybrid. Plasmid C8 was partially cleaved with *Pvu* II, dephosphorylated, and cleaved with *Ava* I, and the 1630-bp *Pvu* II($P_2$) *Ava* I and 3150-bp *Pvu* II($P_1$) *Ava* I fragments were isolated. SN206 was digested with *Pvu* II, and the 300-bp *Pvu* II($P_1$) *Pvu* II($P_2$) fragment was isolated. The three fragments were joined, and the desired plasmid was identified by assaying transformed *E. coli* strains for IFN activity. Plasmid V—α-2(B)α-1 hybrid. C8 was cleaved with *Bgl* II and *Ava* I, and the 1770-bp fragment was isolated. Plasmid IV was cleaved with *Bgl* II and *Ava* I, and the 3360-bp fragment was isolated. The two fragments were joined with T4 DNA ligase. All plasmids were characterized by restriction analysis, and the sequences of plasmids III and V across the joint in the IFN sequence were determined.

To express IFN α-2 as the same type of fusion protein, the IFN α-1 sequence in C8 was replaced by the IFN α-2 sequence, such that the junction between the lac fragment and the signal sequence was preserved [plasmid I (C8/206); Fig. 1*B*]. Hybrids between the IFN α-1 plasmid and its IFN α-2 counterpart were constructed as shown in Fig 1*B*, using as crossover points the *Pvu* II site at codon 92 and the *Bgl* II site at codon 63. The designation of the hybrids is 5′-proximal portion of cDNA (α-1 or α-2), crossover point (P, *Pvu* II site or B, *Bgl* II site), 3′-proximal portion of cDNA (α-1 or α-2). Restriction and sequence analysis supported the structures indicated in Fig. 1*B*.

To estimate the relative specific activities of the different IFN species, we introduced the plasmids into the mini-cell-forming strain *E. coli* DS410. Minicells produce almost exclusively plasmid-encoded polypeptides (13); by separating [$^{35}$S]methionine-labeled proteins on a polyacrylamide gel, the radioactivity in the IFN band can be determined. The IFN antiviral activity in the minicell extracts can be related to the labeled IFN, to yield a measure for the specific activity of the IFN.

Labeled minicells containing a complete IFN cDNA produced a major radioactive product having a mobility corresponding to about 19,000–20,000 daltons, which was absent in the control (Fig. 2). The control consisted of minicells with a cDNA similar to that in plasmid III (see Fig. 1*B*), except that the *Bgl* II fragment was inverted; this generated one new codon and a termination triplet after the first *Bgl* II site. The resulting polypeptide, with 86 amino acids, may be close to the front in lane 6 of Fig. 2.

As judged by mobility, fIFN α-2 should be nine amino acids shorter than fIFN α-1. However, as none of the hybrids containing either the 5′ or 3′ part of fIFN α-2 showed the mobility of fIFN α-2, it is unlikely that the increased mobility of fIFN

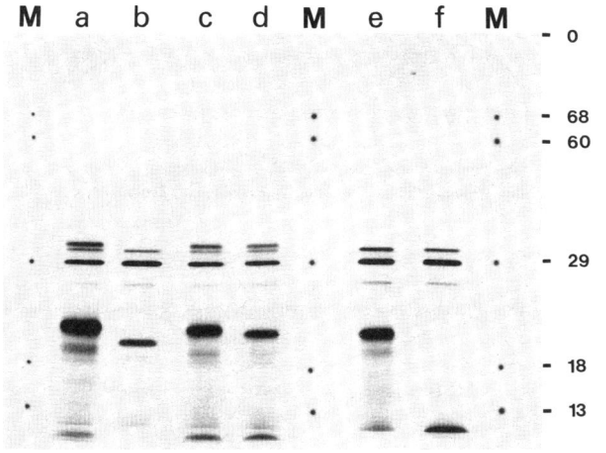


FIG. 2. Analysis of $^{35}$S-labeled proteins from minicells containing IFN cDNA plasmids. The plasmids described in Fig. 1 were introduced into the mini-cell-forming strain *E. coli* DS410 (obtained from Julian Davies). Minicells were purified essentially as described (13), and 2 × $10^9$ minicells (preincubated in 100 μl of M9 salt medium for 30 min at 37°C) were treated with methionine assay medium (Difco) containing 50 μCi (1 Ci = 3.7 × $10^{10}$ becquerels) of [$^{35}$S]methionine (10 μl; 500 Ci/mmol; NEN). After 90 min at 37°C, the harvested cells were heated to 100°C for 3 min in 50 μl of 200 mM Tris·HCl, pH 8.6/20% glycerol/2% $NaDodSO_4$/1 M 2-mercaptoethanol, and a 10-μl sample (equivalent to 4 × $10^8$ minicells) was analyzed on a 17% $NaDodSo_4$/polyacrylamide gel (14). The bands were located by fluorography (15), and the radioactivity was measured by scintillation counting. Lanes: a, fIFN α-1; b, fIFN α-2; c, fIFN α-2(B)α-1; d, fIFN α-2(P)α-1; e, fIFN α-1(P)α-2; f, $NH_2$-proximal fragment of fIFN α-1, derived from a plasmid such as III (see Fig. 1*B*), however, with the *Bgl* II fragment inverted. M, markers (from top to bottom: bovine serum albumin, catalase, β-lactamase (pBR322), β-lactoglobulin, cytochrome *c*) revealed by staining.

α-2 is due to a shorter protein. A single amino acid substitution may substantially change the mobility of a protein (16, 17), perhaps by modifying its conformation or its $NaDodSO_4$-binding capacity.

The amount of labeled IFN in the different strains varied considerably; for example, five times as much labeled fIFN α-1 as fIFN α-2 was found in minicells (Table 1). This is not due to variable plasmid copy number or unequal recoveries, because when the labeled β-lactamase (encoded by the ampicillinase gene of pBR322) is used as internal reference, the differences are even more pronounced. The different IFNs are either formed or turned over at different rates.

**Antiviral Activities of fIFN α-1, fIFN α-2, and Their Hybrids.** The antiviral activities were determined by the cytopathic effect reduction assay, which has a standard error of ≈50%. Overinterpretation of 2- to 3-fold variations in antiviral activities should therefore be avoided.

It is notable that fused IFN proteins carrying part or all of the signal sequence are biologically active (5, 18) and appear to have the same properties as natural IFNs (18). As all the IFNs discussed below carry the same extension, we assume that the differences among them cannot be ascribed to this feature.

Table 1 shows that all fIFNs had about the same specific activities on bovine cells (within a factor of four), whereas fIFN α-1 and the hybrid fIFNs with the $NH_2$-terminal moiety of fIFN α-1 had 1/40 to 1/1000 the activity on the human cells of fIFN α-2. fIFN α-2 and the hybrid fIFNs with the $NH_2$-terminal moiety of fIFN α-2, were 3–7 times as active on BEK as on HEp-2 cells. Thus, the high ratio of "bovine to human" activity reported previously (3) for IFN α-1 was due to low activity on HEp-2 cells. Moreover, the hybrid with the $NH_2$-proximal part of fIFN α-1 had less than 1/40 the activity on human cells of fIFN α-1 itself.

In Table 2, the relative activities of the different fIFNs were tested on bovine MDBK, murine L929, guinea pig, and a variety of human cell lines. The activities are in IFN units per $OD_{260}$ unit of *E. coli* extract, corrected for the different IFN-specific polypeptide contents of each strain, as given in Table 1. As the data obtained from minicells may not be strictly applicable to extracts from unfractionated *E. coli* DS410, the relative specific activities given Table 2 are only approximate.

The activities of all IFNs were the same on bovine MDBK cells but varied widely on any of the human cell lines. As above, the lowest values on human cells were found with fIFN α-1 and hybrids containing the $NH_2$-proximal moiety of fIFN α-1. The different human cell lines responded in different ways to one and the same IFN preparation; the ratio of the activities of fIFN α-1 on human FS4, WISH, FR48, GM2767, U amnion, GM28, and HeLa cells was 1:10:0.15:8:0.2:5:1.5, and similar values were found for fIFN α-2, the hybrid fIFNs, and IFN from leukocytes (preparation PIF), although the specific activities varied several hundred fold between, for example, fIFN α-2 and fIFN α-1(P)α-2.

The activities of the IFNs on both mouse and guinea pig cells also varied greatly; however, in this case, the lowest values were found with fIFN α-2 and hybrids containing the *COOH-proximal* moiety of fIFN α-2. In many cases, the activity patterns of the hybrid IFNs were quite different from those of either

Table 1. Antiviral activity and amount of [$^{35}$S]-labeled IFN produced in *E. coli* DS410 minicells

| | α-1 | α-2 | α-1(P)α-2 | α-2(B)α-1 | α-2(P)α-1 | LeIFN* |
|---|---|---|---|---|---|---|
| cpm (× $10^{-3}$) in IFN band | 172 (172) | 35 (41) | 87 (101) | 96 | 49 | — |
| cpm (× $10^{-3}$) in β-lactamase band I | 48 | 76 | 85 | 35 | 33 | — |
| Activity on HEp2 cells | | | | | | |
| Units | 400 | 4,000 | <6 | 1,200 | 2,600 | 30 |
| Specific† | 2.3 | 98 | <0.06 | 12.5 | 53 | — |
| Activity on BEK cells | | | | | | |
| Units | 12,000 | 12,000 | 12,000 | 8,000 | 12,000 | 100 |
| Specific† | 70 | 293 | 119 | 83.3 | 245 | — |
| Specific activity ratio (BEK/HEp2) | 30 | 3 | >2,000 | 7 | 5 | 3 |

Ten microliters of each minicell preparation described in the legend to Fig. 2 was lysed as in the legend to Table 2, and the IFN titer was determined by the cytopathic effect assay, using Mengo virus (5). The results are in units (defined in the legend to Table 2) per 4 × $10^8$ minicells. The radioactive proteins (see Fig. 2) are from the same number of minicells. Values in parentheses are cpm multiplied by 7/6 to account for the presence of an additional (seventh) methionine residue in the COOH-proximal part of IFN α-2. HEp2 (human) and BEK (bovine) cells were from GIBCO and Flow Laboratories (McLean, VA), respectively.

* Leukocyte IFN, 100 international units/ml (preparation PIF, specific activity 1.2 × $10^6$ units/mg) was from K. Cantell.

† Expressed as units × $10^3$/cpm.

Table 2. Relative specific activities (approximate) of different IFNs on several cell lines

| fIFN | FS4 | WISH | FR48 | GM2767 | U amnion | GM258 | HeLa | MDBK | L929 | GPIG | Vero |
|---|---|---|---|---|---|---|---|---|---|---|---|
| α-1 | 350 | 3,500 | 50 | 2,700 | 80 | 1,700 | 500 | 17,000 | 1,800 | 1,000 | 2 |
| | (2) | (20) | (0.3) | (16) | (0.5) | (10) | (3) | (100) | (10) | (6) | (0.01) |
| α-2 | 3,000 | 25,000 | 1,100 | 63,000 | 600 | 46,000 | 2,500 | 13,000 | 60 | 200 | 12 |
| | (23) | (190) | (8.5) | (480) | (5) | (350) | (20) | (100) | (0.5) | (1.5) | (0.1) |
| α-1(P)α-2 | 5 | 70 | 4 | 100 | 1.5 | 50 | 6 | 6,000 | 30 | 40 | <0.5 |
| | (0.08) | (1) | (0.07) | (1.7) | (0.03) | (0.8) | (0.1) | (100) | (0.5) | (0.7) | (<0.01) |
| α-1(B)α-2 | 5 | 100 | 3 | 120 | 2.5 | 160 | 11 | 6,000 | 9 | 90 | <0.5 |
| | (0.08) | (1.7) | (0.05) | (2) | (0.04) | (3) | (0.2) | (100) | (0.15) | (1.5) | (<0.01) |
| α-2(P)α-1 | 2,800 | 36,000 | 2,300 | 60,000 | 900 | 30,000 | 2,300 | 6,000 | 6,000 | 500 | 40 |
| | (46) | (600) | (38) | (1,000) | (15) | (500) | (38) | (100) | (100) | (8) | (0.7) |
| α-2(B)α-1 | 500 | 7,000 | 800 | 9,000 | 800 | 10,000 | 1,000 | 7,000 | 12,000 | 500 | 10 |
| | (7) | (100) | (11) | (130) | (11) | (140) | (14) | (100) | (170) | (7) | (0.14) |
| LeIFN* | 100 | 630 | 60 | 630 | <10 | 630 | 20 | 63 | <10 | <10 | <10 |
| | (160) | (1,000) | (100) | (1,000) | (<16) | (1,000) | (32) | (100) | (<16) | (<16) | (<16) |

Cultures of *E. coli* DS410, transformed with the plasmids described in Fig. 1, were grown in tryptone medium (1 liter) to an $OD_{650}$ (Beckman DB) of 1. The bacteria were washed with and then suspended in phosphate-buffered saline (50 ml) and incubated 60 min with lysozyme at 1 mg/ml (Sigma) at 37°C; the mixture was adjusted to 10 mM EDTA, frozen, and thawed four times. The lysate was sheared and centrifuged 40 min at 13,000 × *g*. IFN was determined by the cytopathic-effect reduction assay (19) using vesicular stomatitis virus; one unit/ml is the concentration of IFN reducing the effect by one-half. Values are expressed as units per $OD_{260}$ unit of extract and corrected for the different levels of labeled IFN accumulated in the different strains as determined in Table 1 (except for those of LeIFN, which are in units): fIFN α-1 values were taken as reference, those for fIFNα-2 were multiplied by 172/41 (the ratio of labeled IFN in strain fIFNα-1 to that in strain fIFNα-2) and so forth. Values in parentheses are specific activities in percent of those on bovine cells. Cell lines: FS4, WISH, FR48, GM2757, U amnion, GM258, and HeLa are human; MDBK is bovine; L929 is mouse; GPIG is guinea pig; and Vero is monkey.

* Human leukocyte IFN (preparation PIF, specific activity $10^6$ units/mg) was from K. Cantell.

parental molecule. For example, the "bovine (MDBK)/human (WISH)" activity ratios of the hybrids fIFN α-2(P)α-1 and fIFN α-1(P)α-2 are 0.2 and 100, respectively, while those of the parental molecules are 0.5 (fIFN α-2) and 5 (fIFN α-1).

## DISCUSSION

The simplest hypothesis relating the exposure of cells to IFN with the appearance of an antiviral state postulates two distinct steps: (*i*) the triggering of the cellular response—triggering efficiency is assumed to depend on the fit between the IFN binding site and a receptor on the cell surface (for review, see ref. 20)—and (*ii*) the intensity and quality of the cellular response, which depends on the number of receptors, the amplification of the signal generated by the IFN–receptor interaction, and other biochemical peculiarities of the cell, including its susceptibility to the virus. The same triggering event may give rise also to the other effects ascribed to IFNs, such as killer cell activation and growth inhibition (21). In any event, it is clear that a single IFN α species can elicit many different effects (18).

The various human cell lines show different responses to a given IFN, but the response pattern is similar for all IFNs, albeit at different levels. This suggests that the intensity of response of the different cell lines to the same triggering event differs. In some instances, an IFN species shows what may be interpreted as a different triggering efficiency on the various human cell lines—i.e., a relatively low efficiency of IFN α-1 on FR48 and a high efficiency of α-2(B)α-1 on U amnion cells; however, these results are not definitive.

The specific activities of the different fIFNs vary many hundred fold on any given cell line; this we ascribe to different triggering efficiencies. The same effect is shown by the ratios of activities of different IFNs on bovine MDBK, human WISH, and murine L929 cells, which are 1:0.2:0.1 for IFN α-1, 1:1.9:0.005 for IFN α-2, and 1:1:1.7 for IFN α-2(B)α-1.

Let us consider the nature of the binding sites of IFN α-1 and IFN α-2. A binding site can be formed by a number of adjacent amino acids (single idiotope) or by two or more regions of the polypeptide chain (idiotopes) that are linearly distant but spatially close. Two spatially remote idiotopes would constitute two separate (possibly, but not necessarily, independent) binding sites, but intermediate situations may occur. A characteristic feature of fIFN α-1 is the high activity ratio on bovine and human (WISH) cells, respectively, and a characteristic feature of fIFN α-2 is the relatively low ratio on the same pair of cell lines. If IFN had a single idiotope (for example, in the $NH_2$-proximal part of the molecule), then hybrid IFNs with the $NH_2$-proximal half of fIFN α-1 should show the characteristic behavior of fIFN α-1, and the reciprocal construction, that of fIFN α-2. Tables 1 and 2 show that the characteristic high bovine/human ratio appears to be transmitted to the hybrid with the $NH_2$-proximal part of fIFN α-1 and, conversely, the characteristic of a relatively low bovine/human ratio is transmitted with the $NH_2$-proximal part of fIFN α-2. This is true whether the junction point of the hybrids is located at amino acid 63 or at amino acid 92. It is, however, striking that the specific activity of some hybrids is lower than that of either parent.

The ratios of activities on murine and bovine cells were 0.1 for fIFN α-1 and 0.005 for fIFN α-2. Surprisingly, the hybrid fIFN α-2(P)α-1 had the higher activity on murine cells (a ratio of 1) and the hybrid fIFN α-1(P)α-2 had the lower one (0.005), suggesting that the idiotope was transmitted with the COOH-proximal half of the molecule, in contradiction to the previous conclusion.

Clearly, a simple model involving a single idiotope located entirely within either the COOH- or the $NH_2$-proximal half of the molecule explains neither the apparently paradoxical "inheritance pattern" nor that hybrid IFNs can have specific activities higher or lower than those of either parent. We therefore propose that IFN possesses (at least) two distinct idiotopes, one located in the $NH_2$-proximal and the other located in the COOH-proximal part of the polypeptide chain; these could be spatially adjoining or remote. We postulate that each idiotope interacts with a cognate area on the receptor and that the efficiency of triggering is determined by the quality of the fit of the idiotope–receptor pairs. This model (Fig. 3) explains how either the $NH_2$- or the COOH-proximal half of the molecule can determine target specificity and how IFN hybrids may have spe-

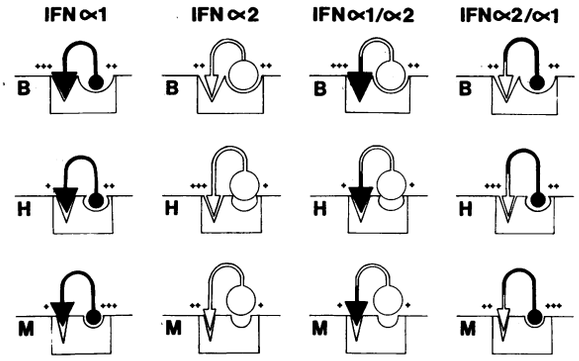


FIG. 3. A model for the interaction of interferon and its receptor. IFN is postulated to have either two binding sites or a single binding site consisting of two idiotopes, one located in the $NH_2$-proximal (triangles) and the other located in the COOH-proximal (circles) moiety of the polypeptide. Black, IFN $\alpha$-1; white, IFN $\alpha$-2. Thin black lines indicate the profiles of the receptors, which differ for different species. (H, human; M, mouse; B, bovine). The quality of the idiotope–receptor fit is indicated by the number of crosses. Triggering efficiency is some function (e.g., additive or multiplicative) of the two idiotope–receptor interactions.

cific activities higher or lower than those of either parent. IFN $\alpha$-1 and IFN-$\beta$ (fibroblast IFN) show two major blocks of sequence homology, between amino acids 28 to 80 and 115 to 151 (22), respectively. Perhaps these two regions correspond to the idiotopes described above, in which case the receptors for IFN-$\alpha$ and $\beta$ might be the same or closely related.

It has been proposed that the IFN receptor consists of a ganglioside and a glycoprotein moiety (20, 23, 24); it is possible that these bear a relationship to the postulated double idiotope nature of the IFN binding site.

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