Type I interferon (IFN) subtypes α and β share a common multicomponent, cell surface receptor and elicit a similar range of biological responses, including antiviral, antiproliferative, and immunomodulatory activities. However, α and β IFNs exhibit key differences in several biological properties. For example, IFN-β, but not IFN-α, induces the association of tyrosine-phosphorylated receptor components ifnar1 and ifnar2, and has activity in cells lacking the IFN-receptor-associated, Janus kinase tyk2. To define the structural basis for these functional differences we produced human IFN-β with point mutations and compared them to wild-type IFN-β in assays that distinguish α and β IFN subtypes. IFN-β mutants with charged residues (N86K, N86E, or Y92D) introduced at two positions in the C helix lost the ability to induce the association of tyrosine-phosphorylated receptor chains and had reduced activity on tyk2-deficient cells. The combination of negatively charged residues N86E and Y92D (homologous with IFN-α) increased the cross-species activity of the mutant IFN-βs on bovine cells to a level comparable to that of human IFN-α. In contrast, point mutations in the AB loop and D helix had no significant effect on these subtype-specific activities. A subset of these latter mutations did, however, reduce activity in a manner analogous to IFN-α mutations. The effects of these mutations on IFN-β activity are discussed in the context of a family of related ligands acting through a common receptor and signaling pathway.

The mammalian type I IFNs, produced in response to viral infection and other inducers, are divided into α and β subtypes on the basis of their reactivity with antisera raised against IFNs derived, respectively, from leukocytes and fibroblasts (1). The human IFN-αs are encoded by a family of at least 15 different genes, while IFN-βs, in potency and cell type specific activities were inactivated, with both subtypes eliciting a similar range of biological activities (3), differences between α subtypes, and between IFN-α and -βs, in potency and cell type specific activities were noted (4). In particular, IFN-β elicits a markedly higher anti-proliferation response in some cell types such as (5), embryonal carcinoma, melanoma and melanocytes than do IFN-αs (6, 7, and references therein). Higher potency of IFN-β in treatment of multiple sclerosis and certain cancers has been observed (7).

The entire class of type I IFNs elicit their biological activities through engagement of a common cell surface receptor (8–10). Two chains of the receptor, ifnar1 and ifnar2, both members of the type two cytokine receptor family, have been identified (11–15). Both components are necessary for function and in the absence of either there is neither high affinity binding nor biological effect (14, 16, 17). The intracellular portions of the receptor subunits are bound by tyrosine kinases, jak1 (12, 18) and tyk2 (19, 20), members of the Janus kinase family. Upon ligand binding these kinases are activated and phosphorylate members of the STAT family of transcription factors (21), as well as ifnar1 and 2. A further property that distinguishes these IFN subtypes is that IFN-β, but not IFN-α, induces association of tyrosine phosphorylated ifnar1 and 2, detectable by precipitation with anti-ifnar1 antibodies (22–25). In addition, tyk2-deficient cells retain partial responsiveness to IFN-β, but are completely unresponsive to IFN-α (26). Complementation of the tyk2 deficiency by expression of a kinase-inactive tyk2 partially restores IFN-α binding and activity, but has no effect on the IFN-β binding to these cells although it augments IFN-β-induced signaling (27). Thus, potency and specificity differences between IFN-αs and -βs may reflect differences in receptor interaction.

The type I IFNs are closely related members of the helical cytokine family (28). Resolution of the three-dimensional structures for crystals of murine IFN-β (29, 30) and human IFN-α2b (31) revealed that their overall structure is very similar, and that these IFNs are composed of 5 helices joined by loops of various lengths. Inspection of the crystal structures in light of previous extensive IFN-α mutational analyses (reviewed in Refs. 15 and 32) allows identification of putative domains likely to be involved in receptor interactions. Examination of structural models in regions of mutational hotspots, such as the AB loop, D helix, DE loop (32), and the C helix (33, 34), directed us to exposed residues available for receptor binding.

In this study we describe the functional consequences of site-directed mutations of human IFN-β. Our results reveal the importance of C helix residues in conferring subtype specific activities on IFN-β as judged from activity and biochemical assays. Mutation of AB loop (Arg27 and Arg30) and D helix
Mutational Analysis of Type I IFNs

Experimenal Procedures

Notation for IFN Amino Acid Sequences—We use the single letter code for amino acids. Substitutions are given as XnY, where X is the amino acid replaced, n, its number in the sequence and Y, the replacement. To facilitate discussion, we number the IFN-α amino acid sequence from the NH₂ terminus according to the estimation that counts the deletion at position 44 of IFN-α2 (29, 30, 32). Human IFN-β is numbered from the NH₂ terminus without deletion. This alignment leaves all α positions, n, with homologous β positions at n + 2, up to the COOH terminus of IFN-β. The five α helices of IFN are labeled from the NH₂ terminus: ABCDE, the loops are labeled with the letters of the helices at their NH₂-terminal and COOH-terminal ends.

Construction, Production, and Evaluation of Mutant IFNs—Substitutions introduced into human IFN-β are given in Fig. 1. The mutations were introduced into the human IFN-β gene carried on plasmid pJC017, a COS cell expression vector (Biogen, Inc, Cambridge, MA), using the transformer site-directed mutagenesis kit from CLONTECH Laboratories (Palo Alto, CA). Mutagenesis of the wild-type IFN-β, and the supernatants from cultures (3 days posttransfection) were screened for the presence of immunoreactive IFN-β and then for biological activity on human HL116 cells, which carry a luciferase reporter under control of an IFN-α-β-inducible promoter (33). Quantitation of IFN expression levels was performed by enzyme-linked immunosorbent assay utilizing rabbit polyclonal anti-IFN-β1a serum to coat plates, biotinylated rabbit polyclonal antibodies as a secondary reagent, followed by streptavidin-coupled horseradish peroxidase (Jackson Immunochemical, West Grove, PA). Enzyme-linked immunosorbent assay values were confirmed by Western blot analyses using a second rabbit monoclonal antibody (AB.B7.2, Biogen Inc.), or control mouse sera. Immunoprecipitations were obtained by site-directed mutations introduced into the cDNA encoding the IFN hybrid α8β[60]α192α8 (35). This hybrid, in which part of the B helix, the BC loop, and part of the C helix are derived from human IFN-α1, is labeled P. Construction, expression, purification, and characterization of the P mutants have been described in detail elsewhere (33).

Immunoprecipitations—Receptor chain immunoprecipitations were performed essentially as described previously (24). For each experimental point 2 × 10⁶ human Daudi B cells (ATCC no. CCL 213) were treated with wild-type or mutant IFN-β (2,500 units/mL, 10 min, 37 °C). Receptor proteins were immunoprecipitated from extracts using either anti-Ifnar1 monoclonal antibody (BA3, Biogen Inc.), anti-Ifnar2 monoclonal antibody (AB.B7.2, Biogen Inc.), or control mouse sera. Immune complexes were analyzed by Western blotting of SDS-polyacrylamide gel electrophoresis, 7.5% gels, probed with anti-phosphotyrosine monoclonal AB-2 antibodies (Oncogene Research Products, Cambridge, MA) followed by anti-mouse IgG coupled with horseradish peroxidase (Amersham Corp.). Blots were developed using enhanced chemiluminescence (ECL, Amersham). The blots were stripped and reblotted with anti-Ifnar1 monoclonal antibody to verify that equal amounts of protein were loaded in each lane.

Cells and IFN Assays—The recombinant IFNs, human IFN-β was from Biogen Inc.; human IFN-α2 (2c) was a gift from Dr. G. Adolf, Ernst Boehringer Institute, Vienna, Austria; human IFN-α8 and -α1 and hybrids of these were a gift from Ciba-Geigy, Basel, Switzerland. Concentrations of the IFNs were estimated against IFN reference prepara-
Mutational Analysis of Type I IFNs

Table I

Differences in activities induced by human α and β IFNs in the various assay systems used

| Assay system induced activity | Level of responsiveness | β/α difference |
|------------------------------|-------------------------|---------------|
|                             | IFN-β                   | IFN-α         |         |
| Equine cells, antiviral      | ~2 nm                   | ~1 pm         | 2000    |
| Bovine MDBK cells            | ~3 pm                   | ~0.2 pm       | 15      |
| Human WISH cells, antiviral  | ~0.4 pm                 | ~1.0 pm       | 0.4     |
| Human tyk2 cells, antiviral  | ~100 pm                 | >100 pm       | <0.001  |
| Human Daudi cells (ifnar1/ifnar2 co-IP) | Yes | No |         |

*Antiviral activities were expressed as average (±) concentrations giving a 50% response; fiducial limits at 95% in parentheses.

Ligand-induced coimmunoprecipitation (co-IP) of phosphorylated ifnar1 and ifnar2.

The relative potencies of the IFN-β mutants that we determined in these assays are shown in Table I and are expressed as a percentage of wild-type IFN-β activity. We have used human HL116 cells, which carry a luciferase reporter gene under control of an IFN-inducible promoter, as the reference assay for human IFNs (33). Relative activities of mutant IFNs, estimated by luciferase induction, were confirmed by both antiviral assay on WISH cells and by antiproliferative assay on Daudi cells. All mutations at solvent exposed residues were found to result in an activity comparable to wild type in at least one of the assay systems used, suggesting that when functional differences were detected that they indeed reflect involvement of the mutated side chain. Expression of the Y125A mutant could not be detected at wild-type levels using two polyclonal sera, suggesting that either the substitution had collapsed a major epitope or that mutant protein could not be stably produced.

Substitutions in the C Helix—Substitution of the charged residues at IFN-β positions 86 and 92, either individually (N86E, N86K, and Y92D) or together (N86E, Y92D and N86K, Y92D), did not alter the specific activity as measured by luciferase induction on human HL116 cells, antiviral potency on equine NBL6 cells (Table II), or antiproliferative activity on human Daudi B cells (data not shown). However, in several assays where IFN-α and -β properties are distinctly different, the double substitutions were shown to result in biological activities different from wild-type IFN-β.

Table II shows the relative specific activities of IFN-β mutants on tyk2-deficient cells. The C helix double mutants showed a reduction in specific activity on these cells, suggesting a more IFN-α-like activity of these double mutants. While these differences (3-fold for N86E,Y92D and 2-fold for N86K,Y92D) were relatively small, they were seen consistently with different production batches. The tyk2-deficient cells carry an IFN-inducible construct that permits a bypass of an aminopterin block on purine synthesis (36). Consequently, IFN can be assayed for its capacity to induce cellular growth in HAT-containing medium or cell mortality in medium containing 6TG. Using this assay we confirmed that the C helix double mutants, N86E,Y92D and N86K,Y92D, were reduced in their activity on tyk2-deficient cells. Mutations in other regions of IFN-β did not alter activities on tyk2-deficient cells with the exception of Y30R, which reproducibly showed a slightly increased activity (2–3-fold) on these cells (Table II).

The mutants were analyzed on human Daudi Burkitt’s lymphoma cells for their capacity to induce the IFN-β-specific association of tyrosine-phosphorylated ifnar1 and ifnar2 chains, detectable following immunoprecipitations with antifnar1 antibodies. Fig. 2B shows that all mutants, except the

FIG. 1. Point mutations in human IFN-β. Sequence alignment of human (hu) and equine (eq) IFN-βs, showing substitutions introduced into the former. Vertical bars, identities; #, amino acid substitutions in human IFN-β (1, N86: K or E); *, groupings in equine IFN-β having distinct differences from the human with respect to size and hydrophobicity of amino acid side chains; —, position of α helices in murine IFN-β (30, 31, 37).
double C helix mutants (N86E,Y92D and N86K,Y92D) retained the IFN-β-specific capacity to induce association of tyrosine-phosphorylated receptor chains. It is important to note that, although C helix double mutants failed to induce this association, those mutants, as well as IFN-α (22, 23, 24), stimulate the tyrosine phosphorylation of both receptor chains, as shown in anti-ifnar2 (Fig. 2A) or anti-ifnar1 immunoprecipitates (Fig. 2, B1–3). The results from three different anti-ifnar1 immunoprecipitation assays are shown in panels B1–3 (Fig. 2).

Table II shows that all C helix mutants, whether single or double, exhibited enhanced antiviral potencies on bovine cells when compared with wild-type IFN-β, while mutations in the AB loop and D helix had no effect on this cross-species activity. Fig. 3 compares the effect of C helix substitutions on the antiviral activity of IFN-β in bovine MDBK cells with that of similar substitutions in IFN-α. The IFN-αs and their derivatives were all uniformly active on bovine cells, which are 15-fold more sensitive to human IFN-αs than IFN-β. The chimeric IFN-αs, labeled P in Fig. 3, was constructed from α8, with the relevant part of the C helix derived from α1 (point mutations at α1 sequences are K84E,Y90D). This chimeric IFN-α was used in previous studies to demonstrate that these residues participate to confer subtype specific activity on the chimera (33). Fig. 3 shows that in contrast to IFN-α the specific activity of IFN-β is increased by introduction of negatively charged side chains of low pK at positions 86 and 92; thus, in descending order of IFN-β activity on bovine cells: E > N > K at position 86, and D > Y at position 92. The cross-species activity of C helix IFN-β mutants N86E,Y92D, N86E, and Y92D on bovine cells was increased to levels comparable to that of human IFN-αs.

These data demonstrate that C helix residues 86 and 92 contribute to activities distinctive for IFN-β and implicate early events in receptor engagement as key to initiating subtype specific signals. In addition, the cross-species activity of IFN-β mutants on bovine cells was altered by introduction of charged residues in the C helix.

**AB Loop and D Helix Mutations**—The substitutions R27A, Y30R, and R35T in the AB loop were made to mimic analogous residues of the equine IFN-β (Fig. 1). None of the mutant IFN-βs showed higher activity on equine cells than wild-type IFN-β (Table II), as would have been expected if these residues were an important site for equine receptor recognition. Substitution Y30R increased by nearly 3-fold the IFN-β activity on tyk2-deficient cells, but had neither effect on activity in bovine antiviral assays nor on the IFN-β-induced association of receptor chains (Table II). Mutations at two positions in the AB loop, R27A and R35T, caused a diminution in activity in assays on bovine and human cells. Residue Arg27 is not conserved between IFN-α and -β subtypes, while Arg35 is conserved in all human IFN-αs and -βs (2, 3). The IFN-α homologue Arg25 is particularly sensitive to mutational change, where even the charge conserved mutation R33K produces more than 100-fold loss in activity (33). The mutation R35T in IFN-β produced a modest 10–30-fold loss in antiviral potency in all assay systems, except on equine cells where it assay as wild-type activity.

The D helix was scanned by alanine substitutions at residues Lys123 and Arg124, which were previously shown to be sensitive to mutation in IFN-αs (32). Tandem charge reversal mutations in IFN-αs of the basic residue pair (Lys121, Arg121, or Arg122) produces a 3-log loss in activity, while apolar (leucine substitution) mutations resulted in a 1–2-log loss in antiviral activity (32). The individual substitution K123A in IFN-β produced a

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**Table II**

| IFN       | Specific activities of mutant human IFN-βs compared to the unmutated form (wt) in the assay systems described in Table 1 | Human tyk2− | Bovine MDBK | Equine NBL6 | Human tyk2− | Bovine MDBK | Equine NBL6 | Human tyk2− | Bovine MDBK | Equine NBL6 | Human tyk2− | Bovine MDBK | Equine NBL6 |
|-----------|-------------------------------------------------------------------------------------------------|------------|-------------|-------------|------------|-------------|-------------|------------|-------------|-------------|------------|-------------|-------------|
|           | Cell type for assay of specific activity as % of wt* IFN-β                                        |            |             |             |            |             |             |            |             |             |            |             |             |
| wt        | 100 100 100 100                                                                                  | 100        | 100         | 100         | 100        | 100         | 100         | 100        | 100         | 100         | 100        | 100         | 100         |
| AB loop   |                                                                                                 |            |             |             |            |             |             |            |             |             |            |             |             |
| R27A      | 30 10 100 100                                                                                   | 100        | 280         | 100         | 100        | 100         | 100         | 100        | 100         | 100         | 100        | 100         | 100         |
| R35T      | 10 <wt 3 10                                                                                     |            |             |             |            |             |             |            |             |             |            |             |             |
| C helix   |                                                                                                 |            |             |             |            |             |             |            |             |             |            |             |             |
| N86E      | 100 100 700                                                                                     | 300        | 500         | 100         | 100        | 100         | 100         | 100        | 100         | 100         | 100        | 100         | 100         |
| N86K      | 100 100 50                                                                                       | 100        | 300         | 500         | 100        | 100         | 100         | 100        | 100         | 100         | 100        | 100         | 100         |
| Y92D      | 100 <100                                                                                         | 100        | 450         | 100         | 100        | 100         | 100         | 100        | 100         | 100         | 100        | 100         | 100         |
| Y92D      | 100 100 30                                                                                       | 100        | 1200        | 300         | 100        | 100         | 100         | 100        | 100         | 100         | 100        | 100         | 100         |
| N86E,Y92D | 100 100 150                                                                                      | 100        | 180         | 100         | 100        | 100         | 100         | 100        | 100         | 100         | 100        | 100         | 100         |
| D helix   |                                                                                                 |            |             |             |            |             |             |            |             |             |            |             |             |
| K123A     | 40 <wt 20                                                                                       | 100        | 100         | 100         | 100        | 100         | 100         | 100        | 100         | 100         | 100        | 100         | 100         |
| K124A     | 100 <wt 100                                                                                     | 100        | 100         | 100         | 100        | 100         | 100         | 100        | 100         | 100         | 100        | 100         | 100         |

* Wild type: supernatants from COS cells transfected with cDNA for unmutated IFN-β. <wt means that no end point could be scored.

**Fig. 2** Western blot analysis with anti-phosphotyrosine of immunoprecipitates from extracts of Daudi Burkitt’s lymphoma cells treated with mutant IFN-βs. A, immunoprecipitation with monoclonal antibody specific for the extracellular domain of ifnar2. B, immunoprecipitation with monoclonal antibody specific for the extracellular domain of ifnar1. Replicates are from different production batches. Wild-type (wt) and mutant IFNs were supernatants from COS cells transfected with the appropriate constructs; c, conditioned medium from mock transfected cells; beta, the purified reference IFN-β. Arrowheads indicate the position of receptor proteins; 97k is the size of the closest migration marker.
The aim of this study was to characterize the functional consequences of point mutations in IFN-β, which IFN-α mutational analyses and sequence comparisons had implicated as important for receptor interactions. We examined the biological activity of these mutant IFN-βs in assays that distinguish between IFN-α and -β subtypes, and in further assays that detect overall losses in activity (i.e. HL116 and WISH cells, which are equally sensitive to INF-α and -β subtypes). We primarily targeted solvent exposed residues of the AB loop, C helix and D helix, which are regions of the molecule shown to be important for IFN-α binding and function (32–34). We found that mutations in the NH$_2$-terminal AB loop and D helix had no effect on subtype-specific activities. Substitutions of residues highly conserved between IFN-α and -βs, R35T in the AB loop, and K123A in the D helix moderately reduced activity on human cells. By comparison with analogous mutations in IFN-α (32), these residues are relatively insensitive to mutation in IFN-β, suggesting quantitatively different contributions of these residues to IFN-β-receptor interactions. We cannot exclude the possibility, that since much of the structure/function studies were performed on bacterially produced IFN-αs, those mutants may have been misfolded or less quantitatively assayed due to technological limitations (38–44). The eukaryotic cell expressed IFN-β mutants described in this study were soluble, highly glycosylated, and retained full activity over many months in conditioned medium. The importance of glycosylation for IFN-β stability and solubility have been recently described (53).

Heterologous systems have been used to define important domains of IFN-α necessary for cross-species reactivities, presumably by creating hybrid IFNs that interact better than parental forms with receptor components (42–44). We sought to extend these studies for human IFN-β by substituting AB loop residues, Arg$^{27}$, Tyr$^{30}$, and Arg$^{35}$, for equine IFN-β residues, since these residues are not well conserved between equine and human IFN-βs (Fig. 1). Neither substitutions of the AB loop nor C helix mutants showed increased activity on equine cells. This result implicates other regions of the molecule, possibly in the A helix or proximal D helix (homology comparisons shown in Fig. 1), as important determinants for equine receptor binding.

The introduction of charged residues at two positions in the C helix (N86E, N86K, Y92D, N86E,Y92D, and N86K,Y92D) resulted in IFN-β mutants with altered activities in several assays that distinguish between α and β subtypes. The tandem substitutions (N86E,Y92D and N86K,Y92D) had the most striking effect on subtype-specific activities, eliminating the IFN-β-induced association of phosphorylated ifnar1 and ifnar2 receptor chains in human Daudi Burkitt’s lymphoma cells, increasing antiviral activity on bovine MDBK cells, and lowering activity on tyk2-deficient human cells. While these changes represent a loss or decrease of specifically IFN-β characteristics and a shift toward the properties of IFN-α, it is not clear that they represent an acquisition of α-like properties. In particular, recent results show that the 11.1, tyk2-deficient cells from which the A27 strain was derived, express low levels of ifnar1 (45), and the C helix mutation may represent simply a reduced functionality in a specifically IFN-β-type interaction.

Considering that the two chains of the IFN receptor provide binding sites for different jak kinases, (12, 18–20) and STAT transcription factors, STAT1, STAT2 (46–48), and STAT3 (49), whose activities are induced by type I IFN binding, it is interesting to consider how alternative geometries of ligand-receptor complexes may achieve distinct signals through a common receptor.

STAT proteins bind to distinct receptor cytoplasmic domains and considerable overlap exists in their activation profiles in response to a wide spectrum of cytokines (46). Specificity of cytokine action may be achieved through finely tuned activation events mediated through specific receptor associations with Janus kinases, interdependent STAT binding and phosphorylation events, and differential assembly of homo- and heteromeric STAT complexes (21, 47, 48, 50), which distinguish promoter elements on the basis of their distinctive binding properties (21, 47). The potential for IFN-αs and -βs to differentially activate different STAT complexes, or to induce other signaling events (51, 52), could result in distinctive gene activation events. Further studies to delineate putative distinctive signaling events and differentially inducible genes will be necessary to test these possibilities.

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Differences in Activity between α and β Type I Interferons Explored by Mutational Analysis
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