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Genetics

Human chromosomes 6 and 21 are required for sensitivity to human interferon γ

(receptor/class I major histocompatibility complex antigens)

VINCENT JUNG*, ABBAS RASHIDBAIGI*, CAROL JONES†, JAY A. TISCHFIELD‡, THOMAS B. SHOWS§, AND SIDNEY PESTKA*

*Department of Molecular Genetics and Microbiology, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway, NJ 08854; †Eleanor Roosevelt Institute for Cancer Research, Inc., Department of Biochemistry, Biophysics and Genetics, School of Medicine, University of Colorado, Denver, CO 80262; ‡Department of Anatomy, Medical College of Georgia, Augusta, GA 30912; and §Department of Human Genetics, Roswell Park Memorial Institute, New York State Department of Health, Buffalo, NY 14263

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ABSTRACT **The human interferon γ receptor has previously been assigned to chromosome 6. Chromosome 6 also encodes HLA, the human class I major histocompatibility antigens. However, the presence of chromosome 6 in hamster–human hybrids is by itself insufficient to confer sensitivity to human immune interferon as measured by the induction of human HLA. Human chromosome 21 was found to be the second chromosome essential for HLA inducibility. Similar results were found with mouse–human somatic cell hybrids. Thus, at least two steps are involved in the action of human interferon γ: the binding of interferon γ to its receptor coded by chromosome 6 and the linkage of this binding event through a factor coded by chromosome 21 to trigger biological action. Both of these steps are species-specific.**

The antiviral action of interferon γ (IFN-γ) is overshadowed by its ability to mediate a multitude of other biological effects. IFN-γ, by itself or synergizing with lymphotoxins, has much greater cytostatic and cytotoxic effects than IFN-α/β (1–3). The major histocompatability complex (MHC) antigens are greatly enhanced with IFN-γ: the class I human HLA-A, B, C and β-microglobulin (4–6), or the mouse H-2 antigens (7), the class II human HLA-DR, -SB and -DC (8–10), or the mouse Ia antigens (11), and the class III complement and factor B antigens expressed by mononuclear phagocytes (12). Other immunoregulatory effects of IFN-γ include its ability to potentiate macrophage cytotoxicity or phagocytosis, possibly through the stimulation of IgG Fc fragment receptors (13–15). IFN-γ can also induce the differentiation of myeloid cells into the monocytic pathway (16). The pleiotropic response to IFN-γ suggests complex interactions beyond the ligand–receptor binding.

We previously reported the localization of the human interferon γ (Hu-IFN-γ) receptor to chromosome 6 (17–19). Here we report a genetic approach that has begun to unravel this complex system of signal transduction. Initial experiments had indicated that chromosome 6, unlike chromosome 21 and its Hu-IFN-α/β receptor (20), is by itself incapable of conferring biological sensitivity to Hu-IFN-γ. The long and short arms of chromosome 6 encode the Hu-IFN-γ receptor (17) and the HLA antigens (21), respectively. The presence of human chromosome 6 in a heterologous host, therefore, provides a convenient system to determine whether other chromosomes are necessary to modulate the expression of MHC antigens. Through the use of somatic cell hybrids we have delineated the human chromosomes essential for induction of class I MHC antigens by Hu-IFN-γ.

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EXPERIMENTAL PROCEDURES

IFNs, Radiolabeling and Covalent Crosslinking. Recombinant Hu-IFN-αA/D(Bgl) and Hu-IFN-γ, with respective specific activities of 1.9×10^8 units/mg and 1×10^7 units/mg were purified from *Escherichia coli* as described (22–24) by R. Ning, S. J. Tarnowski, C. J. Chen, F. Khan, and J. Langer. Mouse interferon γ (Mu-IFN-γ) with a specific activity of about 1×10^7 units/mg was a gift from M. Sheppard of Genentech. Antiviral titers of these interferons were measured by a standard cytopathic inhibition assay with vesicular stomatitis virus (25), on human WISH cells or mouse L cells. The radiolabeling of Hu-IFN-γ and its binding and covalent cross-linking to cells were previously described (17–19). Protein concentration was determined by the method of Lowry *et al.* (26).

Somatic Cell Hybrids. The human–hamster hybrids were prepared by fusions between both human fibroblast and lymphocyte lines with several auxotrophic mutants of Chinese hamster ovary-(CHO)-K_1 (27–29). The human–mouse hybrids were fusions of human primary fibroblasts to adenine phosphoribosyltransferase-deficient L cells (30, 31) and contain chromosome 16, with the exception of cell lines TSL-2 and WIL-6, which were selected by use of a thymidine kinase-deficient mouse LM cell, maintained in selective hypoxanthine/aminopterin/thymidine media (32), and thus contain chromosome 17 (33, 34). Hamster–human hybrids were grown in Ham's F-12 medium (GIBCO) with 5% fetal calf serum (FCS), and mouse–human hybrids were grown in Dulbecco's modified Eagle's medium (GIBCO) with 10% FCS.

Plasmids and Transformation. Genomic clone pJY150R1.1 encoding the human MHC antigen HLA-B7 (35, 36) was from S. Weissman. Transformation was according to the procedure of Corsaro and Pearson (37) with the antibiotic G418 resistance plasmid pSV2-neo (38) as a cotransforming selectable marker. The parent hamster line CHO-K_1 and hybrid line 836-3A containing the human 6q translocation (17) were transformed with 20 μg of plasmid PJY150R1.1 and 0.1 μg of plasmid pSV2-neo per 10^6 cells. The RIA was carried out on mass cultures of transformants as described.

Cell Surface Radioimmunoassay. Supernatant from hybridoma cells producing W6/32, a mouse monoclonal antibody specific for a common determinant of human HLA-A, B, and C antigens (39) was used at a dilution to provide maximal binding to Hu-IFN-γ (100 units/ml)-induced HLA antigens on hamster–human hybrid cell line Q72-18. Rat monoclonal antibodies, K204 and 42.3.9.8, specific for the mouse H-2

Abbreviations: IFN, interferon; Hu-IFN, human interferon; Mu-IFN, mouse interferon; CHO, chinese hamster ovary; MHC, major histocompatibility complex (HLA for human and H-2 for mouse); Ab, antibody; FCS, fetal calf serum.

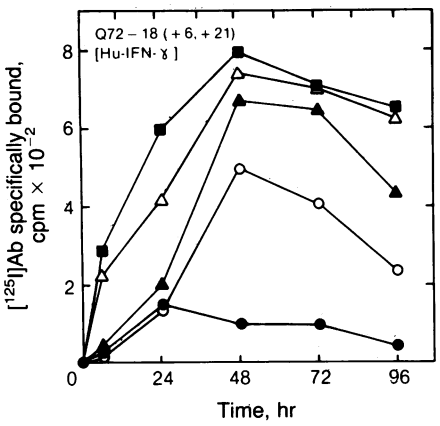

FIG. 1. Time course for the induction of HLA by Hu-IFN-γ on hamster–human hybrid Q72-18. A confluent monolayer for the cell surface RIA was provided by seeding the 6-, 24-, 48-, 72- and 96-hr points with ≈10,000, 5000, 2500, 2500, and 1250 cells per well, respectively. Measurement of HLA with W6/32 followed by ^{125}I-labeled anti-mouse immunoglobulin is as described. Protein determinations at each time point showed no significant variation in protein concentration, indicating that Hu-IFN-γ has no growth inhibitory effects on these cells at the concentrations tested. The specifically bound radioactivity was determined by the subtraction of radioactivity bound to untreated cells. ■, 1000 units/ml; △, 100 units/ml; ▲, 10 units/ml; ○, 1 unit/ml; and ●, 0.1 unit/ml.

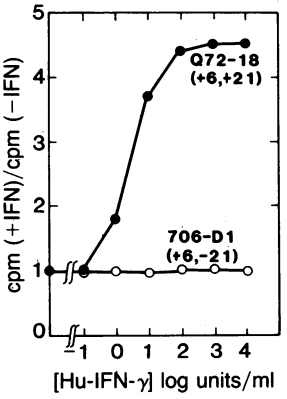

FIG. 2. Induction of HLA antigens on hamster–human hybrids Q72-18 and 706-D1 as a function of Hu-IFN-γ concentration. About 5000 cells were seeded per well. Assays for HLA were performed 72 hr after IFN addition as described. The noninduced expression of HLA, cpm(−IFN), for Q72-18 and 706-D1, were 591 ± 22 and 1318 ± 22, respectively. ±, SD for triplicate assays.

antigens (40, 41) were used as a 1:1 mixture for Mu-IFN-γ (1000 units/ml)-induced H-2 antigens on L cells. Antibodies to both human and mouse MHC antigens were provided by K. Ozato.

The cell surface RIA was as follows: cells were trypsinized and resuspended to 2.5 × 10^4 cells/ml. A volume of 200 μl (5000 cells) was pipetted into each well of a 96-well microtiter plate; each point was assayed in triplicate, and the assay was repeated at least twice. After overnight incubation IFN was added as indicated. The medium was removed after 72-hr incubation with IFN, and the wells were filled with cold (4°C) 10% FCS-supplemented medium and placed on ice for 10 min. The plates and solutions were kept chilled throughout subsequent procedures. The medium was removed, and 40 μl of the solution containing class I MHC specific monoclonal antibody was pipetted into each well. After having been gently shaken at 4°C for 1 hr, the wells were washed with 100 μl of medium and then twice again with 200 μl of medium. After the wells were drained, 50 μl containing 10^5 cpm in 10% FCS medium of ^{125}I-labeled anti-mouse immunoglobulin for the mouse anti-human HLA, or ^{125}I-labeled anti-rat immunoglobulin, for the rat anti-murine H-2 antigen, was added (Amersham). The plate was shaken gently at 4°C for 1 hr, and the washing procedure described above was repeated. To solubilize the cells, 75 μl of 2.0 M NaOH was pipetted into each well, and the plate was shaken gently at room temperature for 10 min. Each well was swabbed twice with two Q-tips that were then transferred into polystyrene tubes. Radioactivity was quantitated with a Beckman model 300 γ counter.

RESULTS

Both hamster CHO-K_1 cells and mouse L cells become sensitive to Hu-IFN-γ induction of the MHC antigen when containing a specific set of human chromosomes. Induction of human HLA antigen on hamster–human hybrid Q72-18 plateaus at 48 hr and exhibits a dose-dependent induction (Fig. 1); after 72 hr, a maximal 4.5-fold induction of HLA antigen is achieved with 100 units/ml of Hu-IFN-γ (Fig. 2). Hybrid Q72-18 is one of many lines containing the Hu-IFN-γ receptor and HLA antigen-coding chromosome 6 that responds to Hu-IFN-γ (Tables 1 and 2). Hybrids 706-D1 and 822-48A also contain chromosome 6, but these hybrids are completely unresponsive to Hu-IFN-γ induction of HLA antigen; no response could be elicited with exposure at various times and concentrations of IFN-γ (data not shown).

Table 1. Correlation of the Hu-IFN-γ receptor and HLA induction with human chromosomes in hamster–human somatic cell hybrids

Hamster–human hybrid	Hu-IFN-γ receptor	HLA	Human chromosome 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	X	Y
640-12	−	−	−	−	−	−	+	−	−	−	−	+	−	−	+	−	−	−	−	−	−	−	−	−	−	−
640-77A	−	−	−	−	−	+	−	−	−	−	+	−	−	−	+	+	−	−	−	−	−	−	−	+	+	−
Q72-18	+	+	+	−	−	+	+	+	−	+	+	+	+	+	−	+	+	+	−	+	+	+	+	−	−	−
805-32	+	+	−	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	−	−
822-19CL5	+	+	+	+	+	−	+	+	−	−	−	+	+	−	−	+	+	−	+	−	+	+	+	−	−	−
706-D1	+	−	−	+	−	+	−	+	−	−	−	−	−	+	+	−	−	+	+	+	−	−	−	+	−	−
640-34	+	+	−	−	−	+	−	+	−	−	+	+	−	+	−	−	−	−	−	+	+	−	+	−	−	−
822-48A	+	−	−	+	−	−	+	+	−	−	−	−	+	+	−	−	+	−	−	−	−	−	−	+	−	−
879-1b	+	+	−	−	−	−	+	+	−	−	+	−	−	+	−	−	−	−	−	−	+	−	+	−	−	−
640-34A5	+	+	−	−	−	−	−	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Receptor concordancy, %			40	60	40	50	50	100	30	40	40	60	60	70	30	40	60	50	50	50	70	50	80	40	10	0
MHC concordancy, %			50	25	50	50	50	75	38	50	75	75	50	50	25	63	50	38	38	38	88	63	100	13	0	0

+ and − designate the presence and absence of the chromosomes, respectively. The receptor concordancy is the percent of cell lines tested in which the presence (or absence) of the Hu-IFN-γ receptor correlates with the presence (or absence) or the specified chromosome. The MHC concordancy is the percent of cell lines containing chromosome 6 in which the inducibility (or noninducibility) of HLA by Hu-IFN-γ correlates with the presence (or absence) of the specified chromosome.

Table 2. Induction of human HLA by Hu-IFN on hamster–human somatic cell hybrids

Hamster–human hybrid	Chromosome 6/21	Induction of human HLA		
		− IFN	Hu-IFN-αA/D(Bgl)	Hu-IFN-γ
K1	−/−	96 ± 2	84 ± 9	69 ± 6
Q72-18	+/+	879 ± 21	4074 ± 288	4210 ± 33
805-32	+/+	2075 ± 14	3541 ± 128	4815 ± 86
822-19CL5	+/+	2435 ± 48	5286 ± 207	5318 ± 100
706-D1	+/−	1257 ± 6	3490 ± 109	1296 ± 59
640-34	+/+	385 ± 10	806 ± 19	854 ± 44
822-48A	+/−	337 ± 24	803 ± 42	371 ± 18
		(1291 ± 74)	(2786 ± 13)	(1246 ± 49)
879-1b	+/+	120 ± 9	233 ± 16	247 ± 13
		(195 ± 8)	(769 ± 95)	(762 ± 7)
640-34A5	+/+	1508 ± 57	3699 ± 131	2024 ± 43
		(321 ± 18)	(972 ± 40)	(839 ± 44)

The cell surface RIA for HLA induction was done with Hu-IFN-αA/D(Bgl) and Hu-IFN-γ at 10,000 units/ml and 1000 units/ml, respectively. See Table 1 for chromosome assignments. ±, SD for triplicate assays. Data in parentheses are from a different experiment. Hybrid 640-34A5 contains only chromosomes 6, 10, and 21 and responds in a dose-dependent fashion to both types of IFN. The antigen induced was also shown to be human HLA by an antibody-dilution curve (data not shown). Hu-IFN-αA/D(Bgl) exhibits antiviral activity on CHO-K_1 cells equivalent to that on human cells (data not shown).

In addition to karyotyping and isozyme measurement, we ascertained the presence of chromosome 6 in the hybrid cells by two assays: first, by the direct binding and crosslinking of [^{32}P]Hu-IFN-γ (18, 19; data not shown); secondly, by the sensitivity of the hybrids to Hu-IFN-αA/D(Bgl), which induces HLA antigens through the hamster IFN-α/β receptor. The ability to induce human HLA antigens on these hybrids by Hu-IFN-αA/D(Bgl), besides marking the presence of human chromosome 6, also affirms the integrity of the genes comprising the HLA antigens. The lack of response to Hu-IFN-γ is therefore not due to the lack of expression of the Hu-IFN-γ receptor or to the presence of defective *HLA* genes. Both 706-D1 and 822-48A are responsive only to Hu-IFN-αA/D(Bgl), whereas the other chromosome 6-containing hybrids respond to both Hu-IFN-αA/D(Bgl) and Hu-IFN-γ (Tables 1 and 2). These data demonstrate that the presence of human chromosome 6 and the receptor that it encodes is insufficient to confer biological sensitivity to Hu-IFN-γ as measured by HLA induction.

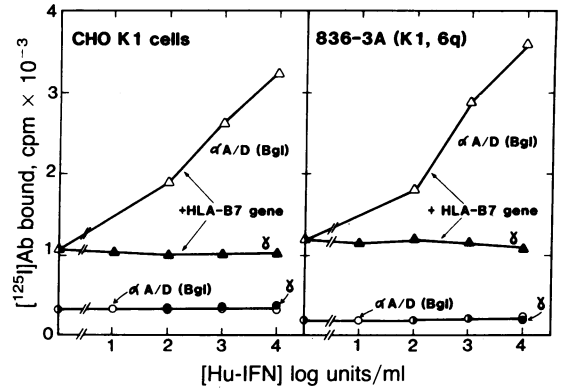

FIG. 3. Induction of HLA on hamster cells transformed with a plasmid encoding HLA-B7 antigen as a function of Hu-IFN-αA/D(Bgl) and Hu-IFN-γ concentration. About 5000 transformants were seeded per well, and the assays for HLA were performed as described. Hybrid 836-3A contains the translocated arm of human chromosome 6 and expresses the receptor. The deleted short arm encodes the HLA antigens that are consequently not expressed in untransformed 836-3A cells.

To further substantiate this point we introduced the HLA-B7 genomic clone into both the parent CHO-K_1 line and hybrid 836-3A by DNA-mediated gene transfer. Hybrid 836-3A contains only 6q, the translocated long arm of chromosome 6 and expresses the receptor (17), but not HLA antigens. The resulting transformants are phenotypically identical to each other and to lines 706-D1 and 822-48A; they respond to Hu-IFN-αA/D(Bgl), but not to Hu-IFN-γ in the induction of the HLA-B7 antigen (Fig. 3).

By assaying a panel of human–hamster hybrids, we determined which human chromosome complements chromosome 6 in reconstituting HLA inducibility. Of those hybrids containing chromosome 6, only those containing chromosome 21 as well exhibited sensitivity to Hu-IFN-γ (Table 1).

The lack of antibodies against hamster MHC prevented us from answering the question of whether Hu-IFN-γ can also modulate the expression of hamster MHC. However, with mouse–human hybrids, the induction of both human HLA and mouse H-2 antigens by both Hu- and Mu-IFN-γ can be studied. The kinetics of induction of mouse and human class I MHC by Hu- and Mu-IFN-γ, respectively, are almost identical for the mouse–human hybrid p25b (Figs. 4 and 5). Like the hamster–human hybrid Q72-18, MHC antigen on the mouse–human hybrid p25b plateaus at 48 hr; saturation for MHC expression occurs at ≈10^4 units of Hu-IFN-γ per ml or 10 units of Mu-IFN-γ per ml. Hu-IFN-γ induces both human and murine MHC, albeit less efficiently than Mu-IFN-γ.

There were insufficient numbers of mouse–human hybrids with appropriate combinations of human chromosomes to exclude all the possible second chromosomes that might serve to couple the ligand–receptor binding to the induction of MHC (Tables 3 and 4). Chromosome 21 is one of three chromosomes not excluded by analysis of the mouse–human hybrids. The other chromosomes are either 6 by itself or 17. We had unequivocally excluded the ability of 6 to act by itself in the hamster–human hybrids. Chromosome 17 exhibits a low 38% "MHC concordancy" in the hamster–human hybrids and is inevitably present in the mouse–human hybrids to complement the thymidine kinase-deficient auxotroph on which the hybrid selection was based (hybrids TSL-2 and WIL-6). It is therefore very likely that chromosome 21 is the essential second chromosome in these mouse–human hybrid

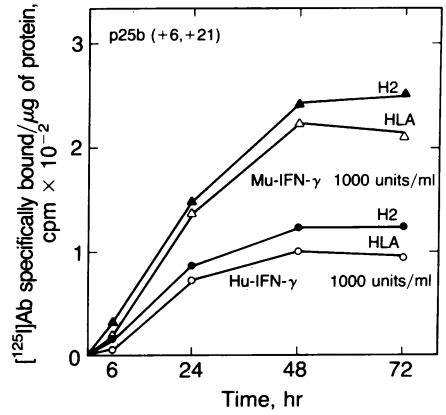

FIG. 4. Time course for the induction of HLA and H-2 by Hu- and Mu-IFN-γ on mouse–human hybrid p25b. A confluent monolayer was provided by seeding the 6-, 24-, 48- and 72-hr points with about 20,000, 15,000, 10,000, and 5000 cells per well, respectively. MHC surface antigens were measured as described. The radioactivity was normalized by protein concentration because of an observed antigrowth effect with high concentrations of Mu-IFN-γ. Specifically bound radioactivity was determined by the subtraction of radioactivity bound to untreated cells. Hu-IFN-γ had no antigrowth effect.

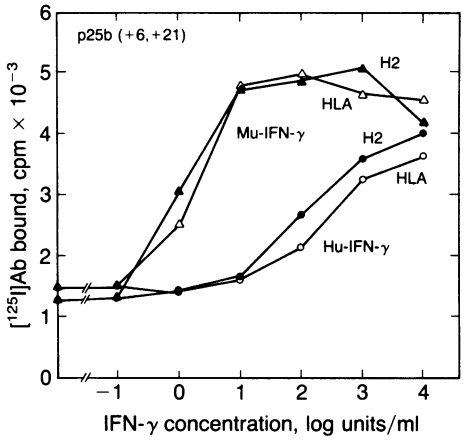

FIG. 5. Induction of HLA and H-2 on mouse–human hybrid p25b as a function of Hu- and Mu-IFN-γ concentrations. Approximately 5000 cells were seeded per well. Assays for HLA and H-2 antigens were done 72 hr after IFN addition as described.

cells. Two of the mouse–human hybrids, JBAIa and WAIa (Table 4), contain chromosome 21 without chromosome 6 and are insensitive to Hu-IFN-γ induction of mouse H-2.

DISCUSSION

Human chromosome 6 encodes both the Hu-IFN-γ receptor and the HLA antigens. In this report, we show that hamster–human hybrids containing chromosome 6 without chromosome 21 are insensitive to the induction of HLA by Hu-IFN-γ. The integrity of the *HLA* genes in these hybrids is shown by their response to Hu-IFN-αA/D(Bgl), which acts through the hamster IFN-α/β receptor. HLA antigen inducibility is only apparent when the hamster–human hybrids contain both chromosomes 6 and 21. The results with the mouse–human hybrids are consistent with this conclusion.

In contrast, chromosome 21, which encodes the human IFN-α/β receptor (42), is by itself capable of conferring biological sensitivity to human IFN-α/β as measured by antiviral activity (20). The presence of chromosome 21 without chromosome 6, however, is incapable of conferring biological sensitivity to Hu-IFN-γ in mouse–human hybrids, as shown by the failure of such hybrids to be induced for mouse H-2 by Hu-IFN-γ. Furthermore, hybrids containing only human chromosome 21 do not bind or exhibit antiviral sensitivity to Hu-IFN-γ (43).

The induction of MHC on the mouse–human hybrid p25b is particularly striking in that both Hu- and Mu-IFN-γ, respectively, induce both HLA and H-2 antigens simultaneously with identical kinetics, suggesting that the mechanism of receptor activation does not preferentially induce either HLA or H-2 (Figs. 4 and 5). There is, however, less sensitivity to Hu-IFN-γ than to Mu-IFN-γ. It can then be inferred that the difference in Hu- and Mu-IFN-γ sensitivity lies at either the receptor, or the signal transduction level. One of several possibilities might be that the contribution of chromosome 21 is not as efficient as the comparable mouse "transducer" in carrying out the induction of MHC. Tables 2 and 4 detail the MHC induction by Hu- and Mu-IFN-γ. It is apparent that there is great variation in the noninduced and induced levels of class I MHC. The variations are most likely due to differences in chromosome 6 and 21 content. It is also possible that other chromosomes are involved in the regulation of expression of the MHC genes themselves.

There is much overlap in the effects of IFN-α/β and IFN-γ. These two groups of structurally dissimilar molecules with their own unique receptors exhibit antiviral, antimitogenic, immunoregulatory, and cellular differentiation activities (44–46). Two-dimensional electrophoresis of polypeptides derived from IFN-α/β- or IFN-γ-treated cells (47) has revealed that the polypeptides induced by IFN-α/β are a subset of those induced by IFN-γ. Twelve proteins are unique to IFN-γ, and 12 common proteins exhibit slight quantitative variation. This suggests that other than the IFN-α/β-induced responses, there might be functions uniquely attributable but presently unassigned to IFN-γ. The common proteins may represent products of a similar transduction pathway in the cellular response to both classes of IFNs.

The observed chromosome 21 dose-dependent sensitivity for both Hu-IFN-α and Hu-IFN-γ activity (48) also suggests a common transduction pathway. This observation was the basis for the erroneous conclusion that the IFN-γ receptor resided on chromosome 21 (49). The complementation of the receptor-coding chromosome 6 with chromosome 21 for biological sensitivity to Hu-IFN-γ explains this controversial conclusion.

The above observations, coupled with the requirement of human chromosomes 6 and 21 for class I MHC inducibility by Hu-IFN-γ, might be explained by one of the following: (*i*) In the first model chromosome 21 encodes a signal transducing "coupler" to which both the IFN-α/β and IFN-γ receptor can directly or indirectly interact; this coupler might also be a common receptor subunit used by both classes of receptors. (*ii*) Alternatively, chromosome 21 may encode an IFN-γ

Table 3. Correlation of the Hu-IFN-γ receptor and class I MHC antigen induction with human chromosomes in mouse–human somatic cell hybrids

Mouse–human hybrid	Hu-IFN-γ receptor	Class I MHC	Human chromosome 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	X	Y
WA-V	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−		+	−	−	−	+	+	+	−	−
JBAIa	−	−	−	−	+	+	−	−	−	−	−	−	+	−	−	−	−	+	+	+	−	+	+	−	+	
WAIa	−	−	+	+	−	+	−	−	+	−	−	+	−	+	−	−		+	−	+	+	+	+	+	+	−
p22b	+	+	+	−			±	+		−		+		+		+	+	+		+	+	−	+			−
p25b	+	+	+	+	−	−	±	+		−		+	−	+	−	+	+	+		+	+	+	+	−	−	−
TSL-2	+	+	−	+	3/17	−	+	+	−	−	−	+	−	+	−	−	−	−	17/3	+	−	+	+	−	−	−
WIL-6	+	+	−	+	−	+	+	+	+	+	−	−	+	−	−	+	−	−	+	−	+	+	+	−	+	−
Receptor concordancy, %			57	71	50	17	71	100	60	57	60	71	50	71	50	86	60	29	80	57	71	43	57	17	33	33
MHC concordancy, %			50	75	33	33	50	100	50	25	0	75	33	75	0	75	50	50	100	75	75	75	100	0	33	0

+ and − designate the presence and absence of chromosomes, respectively. ± indicates a low frequency (<10%) of the chromosome in the cell population, and a blank indicates that no analysis was done for the specified chromosome. 3/17 designates a translocation from 17 onto 3 and vice versa. The MHC concordancy is the percent of cell lines containing chromosome 6 in which the inducibility (or noninducibility) of human HLA and mouse H-2 by Hu-IFN-γ correlates with the presence (or absence) of the specified chromosome.

Table 4. Induction of human HLA and mouse H-2 by human and mouse IFN-γ on mouse–human somatic cell hybrids

Mouse–human hybrid	Chromosome 6/21	Induction of human HLA			Induction of mouse H-2		
		−IFN	Mu-IFN-γ	Hu-IFN-γ	−IFN	Mu-IFN-γ	Hu-IFN-γ
LM/tk⁻	−/−	273 ± 7	199 ± 5	256 ± 4	5013 ± 187	11,166 ± 197	4777 ± 67
WA-V	−/+	124 ± 33	121 ± 14	98 ± 8	—	—	—
JBAIa	−/+	221 ± 1	181 ± 5	222 ± 6	943 ± 1	3,027 ± 6	938 ± 7
WAIa	−/+	278 ± 50	255 ± 9	368 ± 45	1491 ± 24	2,747 ± 167	1557 ± 120
		(499 ± 7)	(441 ± 14)	(491 ± 15)	(4762 ± 394)	(5,395 ± 163)	(4414 ± 41)
p22b	+/+	779 ± 88	5065 ± 42	2489 ± 85	4114 ± 77	10,463 ± 186	8482 ± 29
p25b	+/+	1341 ± 139	4579 ± 56	3202 ± 89	1501 ± 39	4,175 ± 14	3262 ± 78
TSL-2	+/+	271 ± 29	1532 ± 27	1291 ± 34	4688 ± 14	7,615 ± 396	7177 ± 159
WIL-6	+/+	850 ± 24	3192 ± 82	1790 ± 68	5296 ± 464	11,009 ± 115	7509 ± 91

The cell surface RIA for HLA and H-2 was carried out with Hu- and Mu-IFN-γ concentrations of 1000 units per ml, as described. See Table 3 for chromosome assignments. ±, SD for triplicate assays. Data in parentheses are from a different experiment.

receptor-specific transducer that fortuitously activates similar biological effects as IFN-α/β. In the second model, the IFN-α/β receptor is the signal-transducing element. The IFN-γ receptor, upon binding Hu-IFN-γ, may modify the IFN-α/β receptor into an active conformation.

These models can explain the similar biological responses induced by the two groups of IFNs, the observed chromosome 21 dose-dependence of IFN-γ and IFN-α, and the chromosome 21 requirement for inducibility of MHC in chromosome 6-containing hybrids. The entire system for HLA inducibility by Hu-IFN-γ might not be entirely contained within chromosomes 6 and 21. These two chromosomes might provide human species-specific factors that are capable of meshing into a more complex network, the components of which are of hamster or mouse origin. We thus conclude that human cells utilize both of these chromosomes in response to Hu-IFN-γ.

Clearly, at least two steps provided by different chromosomes are required for Hu-IFN-γ action. Chromosome 6 provides the human species-specific Hu-IFN-γ receptor, and chromosome 21 provides a species-specific transducer that triggers the biological response by the occupied receptor.

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