Sublocalization of the Human Interferon-γ Receptor Accessory Factor Gene and Characterization of Accessory Factor Activity by Yeast Artificial Chromosomal Fragmentation*

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A chromosomal fragmentation procedure was employed to produce a deletion set of yeast artificial chromosomes (YACs) from a parental YAC, GART D142H8, known to map to human chromosome 21q and to encode the human interferon-γ receptor (Hu-IFN-γR) accessory factor gene as well as the phosphoribosylpyrophosphamide formyltransferase (GART) gene. When expressed in Chinese hamster ovary cells, these deleted YACs retain accessory factor activity, as judged by major histocompatibility complex class I antigen inducibility, until the deletions from the acentric end exceed 390 kilobases (kb). Therefore, the accessory factor (AF-1) gene can be localized to a 150-kb region at the left (centric) end of the parental 540-kb GART YAC. Cells containing functional YACs are also able to induce the ISGF3γ and γ-activated factor (GAF) transcription factors, but were not protected against encephalomyocarditis virus (EMCV) upon treatment with Hu-IFN-γ. Therefore, the Hu-IFN-γR and the AF-1 are sufficient for some, but not all, of the actions of Hu-IFN-γ. We postulate that an additional accessory factor (AF-2) required for antiviral activity against EMCV is encoded on chromosome 21q.

The human and mouse interferon-γ receptors (IFN-γR)1 have been shown to be homologous to a considerable degree at the amino acid level (1). Nevertheless, these receptors are very species-specific in terms of binding human and mouse IFN-γ (1, 3). A second level of species specificity involves the IFN-γ accessory factor which is required for MHC class I induction. The existence of this IFN-γ accessory factor was first postulated because experiments with somatic cell hybrids indicated that the chromosome encoding the gene for the human IFN-γR (chromosome 6) is itself not sufficient for biological activity even though human IFN-γ can bind to the receptor (3-6). Only when human chromosome 6 is complemented by human chromosomal 21 in somatic cell hamster x human hybrids does Hu-IFN-γ signal transduction occur (5, 6). Similarly, only when the Mu-IFN-γR encoded on mouse chromosome 10 (7) is accompanied by mouse chromosome 16 (encoding the mouse accessory factor) does the Mu-IFN-γR become biologically active in hamster x murine somatic cell hybrids (8).

The human chromosome 21 accessory factor is likely to be a membrane-associated protein as several studies have shown that the accessory factor and the extracellular domain of the IFN-γR must be from the same species for signal transduction to occur (9-11). Although interactions with the transmembrane and intracellular domains have not been ruled out, these interactions, if they exist, are not species-specific. Use of radiolabel-purified somatic cell hybrids has enabled further mapping of the accessory factor gene on human chromosome 21 to a region proximal to dinucleotide repeat polymorphisms D21S58 and D21S223, as well as D21S224 and D21S235 (12-14). More recent data from this laboratory indicate that accessory factor activity is encoded by the yeast artificial chromosome (YAC) whose address on chromosome 21 is D142H8 (15). This YAC, designated GART D142H8 because it also encodes the GART gene, is 540 kb in length and is located proximal to the YAC which encodes the human IFN-α/β receptor (15).

The present study was initiated to localize the accessory factor gene on the GART D142H8 YAC. In addition, it was anticipated that mapping the location of the accessory factor gene would facilitate isolation of the gene and coding sequence from cosmid and cDNA libraries, as experiments with cosmid and cDNA expression libraries to complement accessory factor activity have to this point been unsuccessful. In a separate report (16) we have described a procedure for fragmenting the parental GART D142H8 YAC which is, in principle, applicable to any YAC carried in a Ura+ host. Application of this procedure to the GART D142H8 YAC yielded a number of fragmented YACs which have enabled us to determine the location of the accessory factor gene. Production of CHO cell lines containing a small segment of the human DNA containing the accessory factor has, in addition, enabled us to define further the properties of the accessory factor. The results of these studies are described in this communication.

EXPERIMENTAL PROCEDURES

Cells—The hamster/human somatic cell hybrid 16-9 which contains human chromosome 6q was maintained in F-12 medium containing 10% fetal bovine serum. These cells had been transfected with a genomic clone for the class I HLA-B7 antigen (6, 15). The cell lines which were transformed by fragmented YACs were maintained in the same medium plus 450 μg/ml antibiotic G418 (Life Technologies, Inc.). The 153B7-8 cell line is a Chinese hamster ovary (CHO-K1) cell line which contains human chromosome 21q and the HLA-B7 antigen gene (6); 153B7-8HHH refers to the same cell line which was transfected with the Hu-IFN-γR cDNA. Both of these cell lines were maintained in

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F-12D containing 10% fetal bovine serum as described earlier (9, 17). The 3x1S cell line is a CHO-K1 cell line which contains 1–3 Mb of human chromosome 21 (12, 18). Reagents, Restriction Endonucleases, and Other Enzymes—Human IFN-γ, with a specific activity of 1.5 x 10^7 units/mg, was isolated from Escherichia coli as described (19). Human IFN-α/β (Bgl) was prepared as reported (20) and had a specific activity of 6.0 x 10^7 units/mg. Human IFN-β was isolated as described (21, 22) and had a specific activity of 3.5 x 10^7 units/mg. Restriction endonucleases were obtained from New England Biolabs and Boehringer Mannheim. Yeast DNA and a ladder pulsed-field gel markers were from Life Technologies, Inc. and New England Biolabs, respectively.

Construction of Fragmented YACs—The parental GART YAC (GART D142H8) was obtained through the “chromosome 21 joint YAC screening” (directed by Dr. David Patterson, Eleanor Roosevelt Institute, Denver, CO). The plasmids pSE1 and pSE2 (with Alu sequences in opposite orientations) were constructed such that BamHI and EcoRI digestion releases an 8.4-kb fragment containing an Alu sequence, an SV2neo gene, a URA3 gene, and a tetrahydronal RNA telomere, in that order (16, 23). The mixture of plasmids pSE1 and pSE2 (12.5 µg each) was so digested, and the 8.4-kb fragment was isolated and used to transform the yeast strain GART D142H8;ura.2 which contains the parental GART YAC and had been converted to a Ura− phenotype by 5-fluoro-orotic acid selection (16). Transformations were performed as described (23), and Ura+ transformants were obtained on uracil-deficient plates.

Fusion of Fragmented YACs to Mammalian Cells—Approximately 2 x 10^6 16-9 cells were fused to 10 ml of 5% confluent yeast culture with polyethylene glycol (23). After incubation for 24–36 h in F-12 medium plus 10% fetal bovine serum and 50 µg/ml gentamicin, the cells were washed twice with phosphate-buffered saline, and the transformants were selected in the same medium containing 400 µg/ml antibiotic G418.

Cytofluorography—Induction of MHC class I antigens by IFN was assayed as reported (9, 24). For each sample, 10,000 cells were analyzed with a Coulter Epics Profile cytofluorograph and Cytologic software.

Antiviral Assays—The cell lines 16-9, J18/16-9, J29/16-9 and 153B7-6 were assayed for resistance to encephalomyocarditis virus with a Coulter Epics Profile cytofluorograph and Cytologic software. Without order (16, 23). The mixture of plasmids pSE1 and pSE2 (12.5 µg each) was so digested, and the 8.4-kb fragment was isolated and used to transform the yeast strain GART D142H8;ura.2 which contains the parental GART YAC and had been converted to a Ura− phenotype by 5-fluoro-orotic acid selection (16). Transformations were performed as described (23), and Ura+ transformants were obtained on uracil-deficient plates.

RESULTS

Gene Mapping—Using hamster x human somatic cell hybrids, we determined that accessory factor activity is located on human chromosome 21q (5, 6) and on mouse chromosome 16 (8). Further cytogenetic evidence indicated that the chromosome 21 accessory factor gene resides within the 1–3 Mb of chromosome 21q which is contained in the 3x1S somatic cell hybrid (12, 16). In addition, the chromosome 21 accessory factor gene co-segregates with the IFN-α/β receptor gene and is also located near the GART gene (12, 15). To map more precisely the location of the human chromosome 21 accessory factor gene, we obtained a series of YACs specific to chromosome 21 into which we introduced a neomycin resistance gene in order to determine their biological activity by fusion to mammalian cells (15). These experiments indicated that the gene encoding the chromosome 21 accessory factor activity is located within a 540-kb YAC which also encodes the GART gene and whose address is D142H8. A second YAC, which is 160 kb in length and may partially overlap the GART YAC (Fig. 1), encodes a human IFN-α/β receptor gene (28) and is located at address B49P1 (15). These relationships are diagrammed in Fig. 1.

Although the GART YAC is known to be oriented as shown in Fig. 1, the orientation of the IFN-α receptor YAC has not been established. In addition, the overlap (if any) between the IFN-α

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determined to be Ura^*, neo^*, Trp^*. The transformants were next fused to recipient 16-9 somatic cell hybrids, which contained the human IFN-γ receptor as well as the HLA-B7 gene. These fusions produced variable numbers of antibiotic G418-resistant colonies. Certain YACs did not produce any viable cells. However, for the cell lines reported here, all fusions resulted in at least 100 antibiotic G418-resistant colonies. In one instance, a limiting dilution procedure was used to produce a clonal J29/16-9 cell line. Antibiotic G418-resistant cells were assayed for chromosome 21 accessory factor activity as described previously (24). As is shown in Figs. 2 and 3, cell lines J29/16-9, J28/16-9, J16/16-9, and J18/16-9 were responsive to Hu-IFN-γ as seen by induction of MHC class I antigen expression. However, cell lines J20/16-9 and J6/16-9 did not respond to Hu-IFN-γ. These results indicate that the chromosome 21 accessory factor gene is located within 150 kb from the centric end of the GART YAC. Restriction mapping of the YACS J20 and J18, both approximately 150 kb in size, indicated that these YACs are virtually identical. However, two additional fusions of yeast cells containing YAC J20 have not produced IFN-γ-responsive cells. We therefore conclude that YAC J20 contains a small deletion relative to YAC J18 which inactivates the accessory factor gene. Yeast cells containing YAC J6 have been fused twice to 16-9 cells without isolation of any Hu-IFN-γ-responsive cells. In addition, another 80-kb YAC was found to be inactive (data not shown). YACs less than 150 kb in size (i.e., with more than 390 kb of the acentric end deleted) were inactive. YAC J18 is the smallest YAC that retained accessory factor activity.

Although the magnitude of MHC class I antigen induction in cell lines J29/16-9 and J28/16-9 does appear somewhat greater than that of J18/16-9 in Fig. 3, subsequent assays showed that all cell lines responding to IFN-γ seemed to do so to approximately the same extent (Fig. 4). Therefore, it is unlikely that fragmentation has deleted a relevant gene at the acentric end of the GART YAC. In addition, it is significant to note that the MHC class I antigen response of the J16/16-9, J18/16-9, J28/16-9, and J29/16-9 cell lines as a function of Hu-IFN-γ concentration are comparable with that of certain human cell lines and hamster × human somatic cell hybrids containing human chromosomes 21 (or 21q) and 6 (or 6q) or the cloned Hu-IFN-γR; Refs. 5, 6, 17, and 18). Typically, a human cell line treated with 10–1,000 units/ml of IFN-γ for 2–3 days will exhibit 1.5–3-fold higher fluorescence as a population when analyzed by cytofluorography. The quantification of fluorescence for the individual cell lines produced by YAC fusion are all within this range (Fig. 4).

MHC class I antigen induction as a function of IFN-γ concentration with the cell lines produced by the fusions was examined. As shown in Fig. 4, half-maximal induction of MHC class I gene expression was elicited at IFN-γ concentrations between 1 and 10 units/ml. Significant increases in MHC class I antigen expression were detected at 1 unit/ml. Again, these sensitivities are similar to those observed in human cells and
Transcriptional Activation—We examined the induction of two transcription factors in these hamster cells. The transcriptional activation of interferon-inducible genes has been shown to be stimulated by transcription factors which accumulate in the cytoplasm and migrate to the nucleus (25, 32, 33). Levels of transcription factor ISGF3γ have been shown to increase in the cytoplasm after IFN-γ treatment (34). To determine how much of the IFN-γ pathway is functional in the YAC cell lines, we measured ISGF3γ in IFN-γ-treated and untreated cells by gel retardation assays with labeled interferon-stimulated response element (ISRE) (25). For GAF, cells were treated with Hu-IFN-γ at 100 units/ml for 30 min and assayed as described (26). C represents control cells, and γ represents Hu-IFN-γ-treated cells. GART refers to the 16-9 cell line which was transformed by the parental GART YAC.

The results obtained in this study indicate that it is feasible to map eukaryotic genes by fragmentation of YACs followed by the expression of fragmented YACs in a host cell which is capable of providing a specific assay for the gene product. Although a number of fragmentation vectors have been developed (35-37), we are not aware of any studies in which yeast artificial chromosomal fragmentation has been used to map genes based on complementation of gene function. In principle, the same conclusions could be obtained by transfection of cosmide clones. However, given the size constraints of cosmide vectors, it may be difficult to obtain a single cosmide which contains a complete and functional gene. None of the cosmids which we have mapped to the region of chromosome 21 under consideration produced accessory factor activity (18). The localization of accessory factor activity on the GART YAC will enable us to identify the AF-1 gene.

To obtain fragmented derivatives of the parental GART YAC, we developed vectors (pSE1 and pSE2) which fragment from the acentric end of the YAC. Homologous recombination of vector DNA with the YAC results in the addition of a URA3 and a neo' gene to the acentric end. Yeast clones containing fragment YACs were then fused to 16-9 cells and transformants were selected with antibiotic G418. Although this procedure requires selection for Ura" mutants, the frequency of fragmentation is high, with 78% of the yeast transformants containing a YAC smaller than the parental GART YAC. The Ura" selection procedure has the further advantage that it can be used with YACs in both ypH252 and AB1380 yeast strains. The fragmented YACs obtained with this procedure were shown to be truncated from the acentric end only based upon hybridization to a probe (pGC8.10E6) which is specific for the left end of the parental YAC. Restriction mapping of the fragmented YACs indicated that some fragments are shared by all of the YACs, due presumably to their shared centric ends.

The present study localizes the human chromosome 21 accessory factor to a position which is within 310 kb of the human IFN-α/β receptor gene. This estimate is derived from the fact that the YAC containing the IFN-α/β receptor gene is 160 kb in size and the J18 fragmented YAC, which encodes accessory factor activity, is 150 kb in size. The distance between the accessory factor gene and the GART gene has not been established with precision. The GART gene is not encoded by J18 (data not shown), but mapping of cosmids derived from the GART and J18 YACs indicates that the acentric end of J18 and the GART gene are present in a single cosmide clone. Precise localization of the accessory factor gene is not yet possible, since we do not have any YACs which are larger than J6 (80 kb)

a J. Soh and S. Pestka, unpublished data.
Table 1

Antiviral (EMCV) activity of interferons in cell lines stably fused with YACs containing the human chromosome 21 accessory factor gene

Interferons were tested over the following concentration ranges: for 16-9 cells (the untransfected host) and J18/16-9 cells, all interferons were tested from 0.78 to 3,250 units/ml. For J29/16-9 cells, the interferons were tested from 3.1 to 13,000 units/ml. NP designates no protection observed at maximal Hu-IFN-γ concentration tested; ND, not done. HHH indicates that the Hu-IFN-γ receptor cDNA was transfected into these cells.

| Interferon        | IFN concentration (units/ml) providing half-maximal protection |
|-------------------|---------------------------------------------------------------|
|                   | 16-9 cells | J18/16-9 cells | J29/16-9 cells | 153B7-8 (HHH) |
| Hu-IFN-α/D(Bgl)   | 528        | 264           | 378           | ND            |
| Hu-IFN-γ          | 700        | 172           | 112           | ND            |
| Hu-IFN-γ (>3,250) |            |               |               | 3.2           |
|                   | NP         | NP            | NP            |               |

and smaller than J18 (150 kb). J20, which is also 150 kb in size, was negative for MHC class I antigen induction in several assays. If these data result from the fact that YAC J20 is actually slightly more truncated than YAC J18, the accessory factor gene would have to be bounded by the right end of YAC J18. On the other hand, we cannot exclude that the inactivity of YAC J20 is due to a small internal deletion, undetectable by our gross restriction mapping analyses. We have assayed an additional small YAC which is the same size as J6 (J9, 80 kb).

This YAC was also negative for MHC induction and ISGF3γ expression.

Since hamster interferons and hamster interferon-induced genes are not available, we chose to examine whether two transcription factors which have been shown to be induced by IFN-γ in human cells can be induced in a hamster cell background. ISGF3γ is a 48-kb protein which is the DNA binding component of the ISGF3 complex (32). Three other proteins associate with ISGF3γ to form ISGF3. The other transcription factor, γ-activated factor (or GAF), is rapidly induced by IFN-γ and binds to a DNA sequence different from that to which ISGF3γ binds (26). We found that there is a correlation between MHC class I antigen inducibility and induction of hamster ISGF3γ and GAF in the cell lines transformed by the fragmented YACs; the cell lines in which Hu-IFN-γ can induce MHC class I surface antigens are also inducible for ISGF3γ and GAF in response to Hu-IFN-γ (Fig. 5). This indicates that the chromosome 21 accessory factor is required and sufficient for ISGF3γ and GAF induction.

The observation that cells J18/16-9 and J29/16-9 are not protected from EMCV infection even in the presence of very high (>3,000 units/ml) Hu-IFN-γ concentrations indicates that, although the accessory factor and the Hu-IFN-γR are adequate to induce MHC class I antigens and to activate the ISGF3γ and GAF pathways, an additional factor is required to generate resistance to EMCV. This factor is clearly not located within the J18 or J29 YACs. Examination of the parental GART YAC has also shown that this YAC is not sufficient to produce anti-EMCV activity when expressed in CHO cells (15). We have designated this chromosome 21 accessory factor that induces MHC class I antigens and transcription factors ISGF3γ and GAF as AF-1 (Fig. 6). The second factor, which is also encoded on chromosome 21q and is required for EMCV resistance, has been designated AF-2. We cannot exclude the possibility that the activity we ascribe to AF-2 is due to a dosage effect with respect to AF-1: that is, it is conceivable that what we have designated AF-2 may reflect quantitative differences in the expression of AF-1. We will examine this possibility with a cDNA encoding AF-1 and/or with antibodies to AF-1. However, the amount of AF-1 produced is clearly sufficient for ISGF3γ, GAF, and MHC class I antigen induction in J18/16-9 cells (Figs. 2–5). Furthermore, the magnitude of the inductions observed in J18/16-9 cells was similar to those in human cell lines: dose-response characteristics were comparable as well. Although AF-2 is required for the antiviral EMCV activity in response to Hu-IFN-γ, it may function alone or together with AF-1. The accessory factor designated AF-3 was defined in a previous study (24) in which it was shown that CHO cells containing chromosome 21q (and expressing both AF-1 and AF-2) are incapable of generating full VSV resistance in response to Hu-IFN-γ. AF-3 is therefore located on a chromosome other than 21q. As with AF-2, although AF-3 is required for the antiviral VSV activity in response to Hu-IFN-γ, AF-3 may function alone or together with AF-1 and/or AF-2. AF-1, AF-2, and AF-3 are species-specific in their activity.

The conclusions obtained in this study with fragmented YACs which map to human chromosome 21 should be compared with those recently reported by Kalina et al. (38) using human × mouse somatic cell hybrid fibroblasts. These chromosome 21-containing mouse fibroblasts transfected with the Hu-IFN-γR cDNA were found to be resistant to EMCV upon IFN-γ treatment; 2',5'-oligoadenylate-synthetase and MHC class I antigens were also induced by Hu-IFN-γ. However, when individual clones were examined, it was found that EMCV protection was absent in 67% of the clonal cell lines. Therefore, the genes present on human chromosome 21 may be insufficient to produce EMCV protection in all cases, parts of chromosome 21 may be missing in some clones, or there may be variable expression of the factor encoded on chromosome 21 responsible for EMCV protection. Our experiments with WA17 cells (a mouse × human somatic hybrid cell line which is trisomic for human chromosome 21; Refs. 39 and 37) transfected with the Hu-IFN-γR failed to show anti-EMCV activity in response to human IFN-γ. We have not yet introduced the fragmented YACs into mouse cells. Hence, we did not recreate the cellular

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assay systems employed in the present study in mouse cells. In any case, although the data of Kalina et al. (38) support the hypothesis that other species-specific proteins besides AF-1 are required for anti-EMCV activity, the present study indicates that a factor (AF-2) encoded by chromosome 21 complements AF-1 to produce EMCV resistance. In summary, the fact that a specific chromosomal fragment containing a gene for AF-1, which is functional in CHO cells (as judged by MHC class I antigen, ISGF3γ, and GAF induction), is not sufficient for either anti-EMCV or anti-HSV activities indicates that other factors are required in order to produce the full spectrum of IFN-γ activities. Taken as a whole, our results support the hypothesis that multiple accessory factors (AF-1, AF-2, and AF-3) are required for the full functional activity (including anti-EMCV and anti-HSV activity) of Hu-IFN-γ and its receptor. Further identification and characterization of these accessory factors will be necessary to understand the IFN-γR signal transduction mechanism.

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