Interleukin-6 Signaling via Four Transcription Factors Binding Palindromic Enhancers of Different Genes*

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Interferons (IFNs), as well as some interleukins, growth factors, and hormones, all induce tyrosine phosphorylation of STAT1 and additional transcription factors of similar sizes. These factors are activated to translocate to nucleus and bind to enhancers of consensus sequence TTnCnnnAA (γ-IFN activated sequence-like enhancers). In mammary cells or hybridoma B9 cells, four distinct tyrosine-phosphorylated transcription complexes activated by interleukin-6 (IL-6) and IFN-β were observed: pIRFA and complexes I, II, and III (of increasing electrophoretic mobility). The factors have unequal affinities for enhancers of different genes: they are activated with distinct kinetics and to different extents by IL-6 and IFNs. The pIRFA band isolated from IL-6-stimulated B9 hybridoma cells revealed three DNA-interacting components: two large subunits of 91 and 98 kDa, as well as a small component of 46 kDa not seen in other complexes analyzed. One of the large pIRFA subunits may be APRFBTAT3, since pIRFA reacted with antibodies to STAT1, indicating STAT1 is not the other large component of pIRFA. Complex II, which reacted to anti-acute phase response factor antibodies, also reacted to anti-STAT1 antibodies, whereas complex III reacted only to anti-STAT1 and was the only complex resistant to N-ethylmaleimide. By its multimeric subunit structure and cytokine and enhancer sequence specificities, the slowly migrating pIRFA band appears as a novel tyrosine-phosphorylated transcription complex acting on a subset of γ-IFN activated sequence-like enhancers.

GAS1 enhancers confer interferon-γ (IFN-γ) responsiveness through binding of the signal transducer and activator of transcription-1 (STAT1) also called ISGF3s91, or STAT91. Such enhancers are present in diverse cellular genes (1–3). A number of cytokines, growth factors, and hormones activate tyrosine kinases of the Jak1, Jak2, and Tyk2 family (4–10) and trigger tyrosine phosphorylation of STAT1 or related proteins that bind GAS-like enhancers (3, 11–16). IL-6 induction in the liver of the expression of acute phase protein (APP) genes correlates, at least in the case of human or rat αM, with binding of a p89 protein (16, 17). A protein of 93 kDa, APRF, isolated from livers of IL-6-treated rats by its affinity to α,M sequences, is structurally related to STAT1 and is tyrosine-phosphorylated in response to IL-6 (18). The same factor, called also STAT3, is tyrosine-phosphorylated in response to EGF (19). We have studied an effect of IL-6 seen in various cell types of lymphoid, myeloid, or epithelial origin, which is the rapid induction of the gene encoding transcription factor IRF-1 (20–22). The IRF-1 gene is controlled by a palindromic IFN-γ-responsive enhancer, pIRE (23), which also mediates the effects of IL-6 (22). The main DNA-protein complex observed in IFN-γ-treated mammary cells using this sequence contains STAT1, while an additional pIRFA complex is the major one in IL-6-treated cells (22). Here we show that the pIRFA complex differs in its subunit structure and antibody reaction from the three complexes (A, B, and C) reported previously on GAS sequences (19). Enhancer sequences, as found in the IRF-1 (23), ICSBP (24), α,M (17), and FcγR genes (25–27), display a TTTC...GAAA palindrome. We compared these DNA sequences with consensus GAS sequences (TTnCnnnAA) for their capacity to bind IL-6- and IFN-activated factors.

MATERIALS AND METHODS

Mobility Shift Assays—Mobility shift assays were done as detailed (22). Briefly, human breast carcinoma T47D-07 cells were subcultured and 1 day later were treated by human rIL-6 (20 ng = 100 units/ml), rIFN-β, or rIFN-γ (500 IU/ml) (all Chinese hamster ovary-produced). B9 hybridoma cells were grown in an incubator as described. Alternatively B9 hybridoma cells were injected into BALB/C mice together with 50 units/ml IL-6, and ascitic fluid cells obtained every 3–4 days were either frozen (untreated) or concentrated to 15 × 10^6 cells/ml and treated for 45 min in a 5% CO_2 incubator with 200 units/ml IL-6. From frozen cell pellets, cytosol was extracted in the low salt buffer W (which has antiproteases, and antiphosphatases 50 mM NaF, 0.1 mM sodium vanadate, 10 mM sodium molybdate) and then nuclear extracts made with 0.4 M NaCl, buffer W (22).

The pIRE/IRF-1 oligonucleotides 5'-gatcCTGATTTCCCCGAAATGACG, pIRE/α,M oligonucleotides, 5'-gatcCTGATTTCTGGGAAATGACCG (in bold, the sequence found in the rat α,M enhancer or in the FcγR enhancer (opposite orientation)), and ICSBP oligoasides 5'-gatcCTGATTTCTGGGAAATGACCG, and their complements, were synthesized and end-labeled by [γ-32P]ATP with T4 polynucleotide kinase to 2 × 10^5 cpm/μl. Competitors are shown in Table I. Mobility shift reaction mixtures of 20 μl (22) with equal amounts of extract proteins (5–10 μg) and 2 × 10^5 cpm of DNA probes were incubated 15 min at 25 °C before gel electrophoresis 2–3 h at 175 V, subject to either autoradiography or exposure in a Fuji BAS1000 Phospho-Imager.

Anti-STAT1 antibodies were obtained from rabbits immunized with an Escherichia coli-produced fused protein containing amino acids 598–705 of p91 ISGFs (28) cloned in pGEX-3X vector (Pharmacia Biotech Inc.) and purified on glutathione columns (22). Ammonium sulfate-precipitated immunoglobulins from control and immune sera (1 μl) were preincubated with 5 μg of extract protein in 5 μl for 30 min at 0 °C before adding the [γ-32P]-labeled probe. Rabbit anti-STAT91N from Transduction Laboratories (Lexington, KY), anti-APRF from Dr T. Kishimoto (Osaka, Japan), anti-ISGF3γ p48 produced as above, and monoclonal anti-phosphotyrosine antibodies PT-66 (Bioyeda, Kiryat Weizmann, Israel) were used similarly. For N-ethylmaleimide (NEM) reaction, nuclear extracts were preincubated in 10 mM NEM (Sigma) for 10 min at 25 °C in a mixture containing 0.4 mM dithiothreitol, which
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**RESULTS**

**Binding of Four IL-6-Activated Factors to pIRE Sequences**

The pIRE sequences of two members of the IRF gene family, IRF-1 and ICsBP, differ by 2 bases in the central trinucleotide spacer separating the palindrome (Table I). A sequence that deviates from IRF-1 by only 1 of these bases was chosen so as to be similar to the FcγR gene enhancer but also to the core of the acute phase response element found in the rat (but not the human) α2M gene (17) and has been designated pIRE/α2M (Table I). Nuclear extracts from human mammary carcinoma (human) a,M gene (17) and has been designated pIRE/a,M were evident (Fig. 1A, lane 10). The DNA binding activity of ISGF3, the IFN-α/β-activated factor (29) that contains STAT1, STAT2, and an ISGF3γ p48 component, is also NEM-sensitive, but the STAT1 proteins of ISGF3αs (p91 and p84) were not reported to be NEM-sensitive (22).

The appearance of complexes III and pIRPA is rapid, within 5 min in T47D cells (22), and does not require protein synthesis (Fig. 1C, lanes 7–10). In line with activation of STAT1 binding to GAS elements by IFN-γ through tyrosine phosphorylation (2, 11), anti-phosphotyrosine antibodies blocked the binding of complex III to the IRF-1 probe when added to extracts of cells stimulated either with IL-6 or with IFN-γ (Fig. 1C, compare lanes 2 and 3 with lanes 5 and 6). The pIRPA activity induced by IL-6 was likewise eliminated by anti-Tyr(P) addition (Fig. 1C, compare lanes 2 with lane 5), indicating that pIRPA contains tyrosine-phosphorylated protein(s). Treatment of mammary cells by the tyrosine kinase inhibitor genistein (30) before IL-6 addition prevented the appearance of the STAT1 and pIRPA complexes (Fig. 1C, compare lanes 11–14 with lanes 15–18 or compare lanes 19 and 20 with 23 and 24), indicating that such kinase activity is also needed for IL-6 to trigger pIRPA binding. At 10 min after IL-6, pIRPA was localized in the nuclear fraction, whereas the IL-6-induced complex III (STAT1) was still present in the cytosolic fraction (Fig. 1C, lanes 11–14 and 19–22).

**STAT Family Proteins Involved in Formation of the Four pIRE Complexes**—We have shown before (22), using anti-STAT1 antibodies (domain 598–705), that of the two main factors binding to pIRE/IRF-1, the fastest migrating one or complex III in this report, contains STAT1, while pIRPA does not react with these antibodies. Using ICsBP probes, antibodies to STAT1 (598–705) eliminated all of band III resulting from IFN-γ action and also the IL-6- and IFN-β-dependent complexes II (Fig. 1A, lanes 14–16). In contrast, complex I was resistant to these anti-STAT1 antibodies (Fig. 1A, lanes 14 and 15). Since factors recognized only by antibodies to the N-terminal domain of the 91-kDa protein STAT1 have been observed in IL-6- or TNF-stimulated cells (10, 31), we tested such anti-STAT1 (Fig. 1B, lanes 6–8). Of the four complexes formed on pIRE/α2M, only complex III was eliminated (shifted), but neither the slowly migrating pIRPA nor complexes I and II were perturbed by anti-STAT1. This identifies pIRE/α2M complex III as formed by STAT1, in line with its being the major complex after IFN-γ. Complex II, which reacts to anti-STAT1 but not to anti-STAT1, might contain the p91/STAT1 factor in another conformation or in association with another subunit, as suggested by NEM sensitivity of complex II as opposed to complex III (Fig. 1B, lanes 9 and 10). In nuclear extracts of mouse hybridoma B9 cells, the concentration in IL-6-activated factors is higher than in T47 cells, and four

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**Table I**

| Palindromic sequences of various GAS-like enhancers |
|----------------------------------------------------|
| Sequences are shown from strand with best fit to the GAS consensus. TT(N)AA is essential for IL-6 response (22). |
| **Enhancer** | **Sequence** | **Ref.** |
|-------------|-------------|---------|
| GAS consensus | TTTCNNAAA | 23 |
| pIRE/IRF-1 | TTTCCCAGAAA | 26 |
| FcγR | TTTCCCAGAAA | 27 |
| ICsBP | TTTCCCAGAAA | 24 |
| Ly6E | TTTCCCAGAAA | 2 |
| α2M (human) | ATTCCCTTAG | 17 |
| α2M (rat) | ATTCCCTAG | 17 |
| GBP | ATTCCCTAG | 1 |
| SiEm67 | TTTCCCAGAAA | 3 |
| SiFHos | TTTCCCAGAAA | 3 |

**Table II**

| Competitor titration |
|----------------------|
| **Competitor** | **Molar excess** | **pIRPA** | **Complex I** | **Complex II** | **Complex III** |
|-------------------|-----------------|----------|--------------|--------------|----------------|
| Ly6E | 25 | 108 | 41 | 33 | 23 |
| pIRE/α2M | 50 | 62 | 21 | 18 | 21 |
| pIRE/IRF-1 | 25 | 14 | 11 | 7 | 11 |
| pIRE/IRF-1 | 50 | 6 | 5 | 4 | 11 |

was adjusted to 10 mM dithiothreitol before addition to the mobility shift reaction mixtures.

UV Cross-linking—For UV cross-linking, nuclear proteins were extracted from murine hybridoma B9 cells first starved of IL-6 by resuspension at 2 x 10⁵ cells/ml for 3 h in fresh medium (22) and then treated for 1 h with IL-6 (20 ng/ml). The mobility shift assay was done with 15 μg of protein from B9 nuclear extracts and 10³ cpm of pIRE/α2M probe (core FcγR) or pIRE/IRF-1 probe, and the part of the gel corresponding to the pIRPA complex was exposed to UV light (302 nm) for 30 min. Analysis of the DNA-linked proteins was done by electrophoresis on a 7.5% SDS-polyacrylamide gel.

Gene sequences are shown from strand with best fit to the GAS consensus.
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A. DNA binding activities induced by IL-6 and IFNs on related pIRE sequences. A, nuclear extracts from human T47D cells were subjected to mobility shift assay (see "Materials and Methods") using pIRE sequences from the IRF-1 (lanes 1–4), FcγR (pIRE/a,M, lanes 5–8), or ICSBP genes (lanes 9–16). Cells were treated for 15 min by IL-6 (lanes 2 and 6), IFN-β (lanes 3 and 7), and IFN-γ (lanes 4 and 8), for 10 min by IL-6 (lanes 10 and 14), or for 1 h by IFN-β (lanes 11 and 15) or IFN-γ (lanes 12 and 16), or were left untreated (lanes 1, 5, 9, and 13). In lanes 13–16, anti-STAT91C (amino acids 598–705) antibodies were preincubated with the extracts before adding the ICSBP probe. N.S. indicates use of preimmune control rabbit immunoglobulins. Exposure to films was for 48 h. B, mobility shift assay with nuclear extracts of T47D cells after 45 min of treatment by IL-6 (lanes 2, 6, 9, 12, and 16), IFN-β (lanes 3, 7, 13, and 17), or IFN-γ (lanes 4, 8, 10, 14, and 18) or were left untreated (lanes 1, 5, 9, and 13). In lanes 13–16, anti-STAT91N (amino acids 1–194) antibodies were preincubated with the extracts. In lanes 9, 10, and 15–18, the extracts were pretreated with non-immune mouse IgG (NS) (lanes 13) or with anti-phosphotyrosine antibodies (lanes 4–6) before incubation with probe. In lanes 9 and 10, nuclear extracts of T47D cells were pretreated for 30 min with cycloheximide (50 μg/ml) or not treated (lanes 7 and 8). Cytosolic extracts (lanes 11–18) and nuclear extracts (lanes 19–24) from T47D cells treated for 10 min with IL-6, IFN-β, or IFN-γ, or left untreated. In lanes 15–18, 23, and 24, the cells were pretreated for 30 min with genistein (Sigma, 100 μg/ml) before cytokine addition. Exposure to films was for 48 h.
complexes could be visualized with the pIRE/IRF1 probe (Fig. 2A), STAT1 antibodies inhibited complexes III and II as above (Fig. 1A).

Antipeptide antibodies against APRF/STAT3 (18) were assayed using IL-6-treated extracts of the mouse hybridoma B9 cells (Fig. 2A) or of the T47 mammary cells (data not shown). B9 cell extracts show the same four complexes as T47 extracts with pIRE/αM probes, but much stronger signals are obtained with B9 cells. APRF antibodies eliminated (supershifted) complexes II, I, and pIRFA (Fig. 2A), indicating that APRF or a similar protein enters in the composition of these complexes. By contrast complex III was not displaced by APRF antibodies (Fig. 2A). The same effects are observed with T47 cell extracts and pIRE/αM probe (data not shown).

Among other antibodies to known factors tested, neither anti-NF-IL-6 (35) nor anti-ISGF3y p48 (36) had an effect on pIRFA or any of the other three complexes (data not shown).

Composition of pIRFA Factor—The protein composition of pIRFA formed on pIRE/IRF1 or pIRE/αM oligonucleotides was examined by UV cross-linking (see “Materials and Methods”) on preparative mobility shift assay with nuclear extracts of IL-6-stimulated hybridoma B9 cells (Fig. 2B). The pIRFA complex contained two large cross-linked components of about 91 and 98 kDa, as well as a smaller component at 46 kDa (Fig. 2B). In complex I, which forms efficiently on pIRE/αM probes, the 46-kDa component was not observed, whereas the 91–98-kDa bands were present (data not shown). In the IFN-γ-induced complex III, a 91-kDa protein was cross-linked to DNA, but no small component was detectable (data not shown). Thus pIRFA is another type of factor on the pathway of IL-6 or IFN action, since it has both large and small DNA-cross-linked proteins. Of the pIRFA components interacting with DNA, one may be APRF or a related protein. Among these or other subunits of pIRFA, at least one is NEM-sensitive and one or more is tyrosine-phosphorylated as shown above.

DISCUSSION

Our data show that the four protein complexes assembling on the pIRE/αM sequence in response to IL-6 have distinct properties. Functionally, they diverge in their affinities for individual GAS enhancers conserving the TThnCnnnA consensus and clearly discriminate between several pIRE sequences despite conservation of the TTTC...GAA palindrome. Comparison of the pIRE from IRF-1, ICSBP, and αM(FCyR) genes shows how single-base differences in the spacer can affect factor binding. The change between IRF-1 and pIRE/αM allows formation of the additional complexes I and II, and the additional single-base change to ICSBP prevents pIRFA formation while allowing complexes I and II to assemble. All the pIRE probes used here bind STAT1 in line with having GAS consensuses sequences. Among the four factors, pIRFA displays the lowest affinity for GAS consensus Ly6E and seems more specific for palindromic pIRE sequences, such as in the IRF-1 and αM(FCyR) gene enhancers. However, some base changes in the spacer greatly reduce its affinity, as seen with the ICSBP pIRE enhancer. The early and strong induction of pIRFA by IL-6 could correlate with activation of the IRF-1 gene, as observed in mammary and lymphoid cells (22) and also in myeloid cells, in which ICSBP was not induced (21, 22). The FCyR protein was induced by IL-6 in myeloid M1 cells (32).

It was reported (3, 19) that the high affinity SIEm67 sequence, a mutant of the c-fos SIE, forms three complexes, A, B, and C, with factors by EGF in A341 cells. Complex A has been found to contain the STAT3 factor, which is also activated to bind to the same sequence by EGF (19) and is identical to the APRF factor, related to the effect of IL-6 on certain APP genes (18). Differential binding of the EGF-dependent factors to SIE (m67) oligonucleotides, wild-type c-fos SIE and Ly6E were observed, indicating that the slower migrating complexes A and B form better on SIEm67 than on Ly6E sequences (3) and are only partially (complex B) or not at all (complex A) blocked by antibodies to STAT1, while the latter eliminated complex C (13). By their electrophoretic migration, reaction with antibodies, and preferential binding sequences, the SIEm67 A and B bands may be akin to the ICSBP and pIRE/αM(FCyR) complexes I and II, while complex III corresponds to complex C. STAT1 binds to DNA as a dimer (33), and it was proposed that STAT1 is able to dimerize with an EGF-inducible factor of the same family (STAT3) to form complex B, while complex A would
be a dimer of STAT3/APRF (3, 19). Although our antibodies to anti-STAT1 (598–705) also recognize the p84 ISGF3α protein, which is derived from the same gene as STAT1, by differential splicing (33), the p84/STAT1 is not detected on Western blots of our cell extracts at these times of treatment (data not shown). It is thus unlikely that either of the two small complexes III and II contains this protein.

The additional complex pIRFA forming on some of the palindromic pIRE enhancers, has a mobility lower than that of complex I and appears as a newly defined oligomeric factor. We show that pIRFA is composed of three proteins, one of 98 kDa, one of 91 kDa, and one of 46 kDa. These results were obtained with B9 cells, most sensitive to IL-6, and where the concentration of the factor pIRFA is much higher than in the mammary cell line T47 or hepatoma cell line HepG2 (data not shown). The composition of pIRFA suggests that a heterodimer of STAT3/APRF and another large component can associate with a small DNA-binding protein, which would explain why it migrates more slowly. Either of the two large proteins could be APRF since pIRFA is shifted by anti-APRF antibodies. The 91-kDa component of pIRFA is probably not ISGF3 p91/STAT1, and the 46-kDa component is distinct from p48 ISGF3γ because pIRFA remains to be tested. Akira et al. (12) mentioned the copurification of other large molecular mass components with pIRFA. In extracts of cells treated by IFN-γ, a 43-kDa protein, one of 91 kDa, and one of 46 kDa. These results were obtained in cell line T47 or hepatoma cell line HepG2 (data not shown). The expression of these cytokines is expected to be generated by what at first sight appears as a common mechanism of action through GAS enhancers. In addition to STAT1 and STATB/APRF, two other proteins of the same family were cloned (19, 34). Their participation to the action of these cytokines as compared to growth factors such as hormones can be expected to be generated by what at first sight appears as a common mechanism of action through GAS enhancers.

This pIRFA factor is intensely and rapidly activated by IL-6, as well as, although to a lesser extent and more slowly, by IFN-β. This factor could be of critical importance in generating the different patterns of gene activation resulting from the action of these cytokines as compared to growth factors such as EGF. As a consequence of activation of multiple factors with discrete target sequence affinities, cellular genes controlled by closely related but not identical pIRE or GAS enhancers have the possibility to respond specifically to stimulation by a given cytokine. For example, we have observed that in transfected mammary cells, IL-6 activates much less luciferase expression driven by GAS/GTP-binding protein than that driven by pIRE/IRF-1 or pRE/α,M, whereas this difference was not seen when the same cells were stimulated by IFN-γ (22). Such heterogeneous gene responses observable in a given cell stimulated by one cytokine are expected to be amplified when comparing different cell types. Indeed, comparison of various cells has shown that different combinations of Jak1, Jak2, and Tyk2 tyrosine kinases can associate with and may activate the IL-6/leukemia inhibitory factor/oncostatin M/ciliary neurotropic factor gp130 receptor component (9). Hence, a large diversity of transcriptional responses to individual cytokines, growth factors, and hormones can be expected to be generated by what at first sight appears as a common mechanism of action through GAS enhancers. In addition to cell- and receptor-specific variations, the enhancer sequence specificity of the multiple pIRE and GAS binding factors is obviously an important element in generating this diversity.

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