Acetylation of Interferon Regulatory Factor-7 by p300/CREB-binding Protein (CBP)-associated Factor (PCAF) Impairs its DNA Binding*

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Interferon regulatory factor 7 (IRF7) is an interferon-inducible transcription factor required for induction of delayed early interferon α genes and the onset of a potent antiviral state. After induction of IRF7 by autocrine interferon, latent IRF7 is activated by virus-induced phosphorylation on serine residues within the C-terminal regulatory domain. Although it is likely that IRF7 is subjected to a cascade of events responsible for regulating its biological activity, to date no mechanism other than phosphorylation has been reported to modulate IRF7 activity. Here, we report that IRF7 is acetylated in vivo by the histone acetyltransferases p300/CBP-associated factor (PCAF) and GCN5. The single lysine residue target for acetylation, lysine 92, is located in the DNA-binding domain and is conserved throughout the entire IRF family. Mutation of lysine 92 resulted in complete abolition of DNA binding ability. However, a mutant that cannot be acetylated by PCAF due to a change in the surrounding amino acid context of lysine 92 showed increased DNA binding and activity compared with wild type IRF7. Conversely, we showed that acetylated IRF7 displayed impaired DNA binding capability and that over-expression of PCAF led to decreased IRF7 activity. Together, our results strongly suggest that acetylation of lysine 92 negatively modulates IRF7 DNA binding.

Interferon regulatory factors (IRF)§ are a growing family of transcription factors that have been implicated in antiviral defense, cell growth, and immune regulation (for review, see Ref. 1). Ten members of the family have been identified so far: IRF1, IRF2, IRF3, IRF4/Pip/ISCAT, IRF5, IRF6, IRF7, IRF8/ICSBP, IRF9/p48, and the recently cloned avian IRF10. In addition there are at least four more distantly related viral homologues encoded by human herpes virus 8 (HHV8) (2, 3). This family is mainly defined by a highly conserved amino-terminal DNA-binding domain (DBD) characterized by a repeat containing five tryptophan residues that shows similarities with the c-myb proto-oncogene DBD (4). Two closely related members of this family, IRF3 and IRF7, have been identified as direct transducers of virus-mediated signaling and were shown to play an essential role in the induction of type I interferon (IFN) (5–8). Previous studies (5–12) have clearly established that IRF3 and IRF7 activity is regulated by virally induced phosphorylation of serine residues located in their C terminus. Phosphorylation induces allosteric changes that result in dimerization and facilitate nuclear retention, derepress transactivation, and allow specific DNA binding (9, 10).

Despite the important similarities among IRF family proteins, each provides a unique biological function. For instance, although both IRF3 and IRF7 are involved in IFN gene expression during viral infections, IRF3 targets specifically IFNβ and IFNα4 (5). In contrast, IRF7 is required for the induction of additional members of the IFNα multi-gene family (5, 11, 12). Although there are several structural differences between IRF3 and IRF7 that could account for this difference, the major determinant appears to be DNA binding specificity. IRF3 binds with high affinity to relatively perfect GAA repeat motifs found within the positive regulatory domain I of the IFNβ promoter and the IFNα4 promoter; in contrast, IRF7 displays a more relaxed DNA binding specificity allowing it to bind variant sequences found in promoters of the other IFNα genes (13). However, the structural basis for differential DNA binding has not been elucidated.

Posttranslational modifications in addition to phosphorylation have been found to modulate transcription factor activity, including effects on DNA binding affinity. Histone acetyltransferases (HAT) are increasingly being recognized as modifiers of non-histone proteins, and there is a growing body of evidence supporting the notion that acetylation, like phosphorylation, is an important regulatory protein modification (for review, see Ref. 14). There are now several reported families of acetylases exemplified by PCAF/GCN5, p300/CBP, TAF250, SRC1, and MOZ (for review, see Ref. 15). Of these proteins, two families, PCAF/GCN5 and p300/CBP, are the most characterized and potent acetylases compared with other families. HATs function enzymatically by transferring an acetyl group from acetyl-CoA to the ε amino group of certain lysine side chains. Transcription factors that have been shown to be acetylated by different HAT proteins include p53, MyoD, HNF4, E2F1, and c-Myb. These acetylation events have been shown to directly affect protein function. The consequence of

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¶ The abbreviations used are: IRF, interferon regulatory factor; IFN, interferon; HAT, histone acetyltransferase; DBD, DNA-binding domain; CBP, CREB-binding protein; PCAF, p300/CBP-associated factor; HMG, high mobility group; acetylCoA, acetylcoenzyme A; ISRE, interferon-stimulated response element; ISG, interferon-stimulated gene; EMSA, electromobility shift assay; WT, wild type; NDV, Newcastle disease virus; GST, glutathione S-transferase; CREB, cAMP-response element-binding protein.
Acetylation of IRF7

Acetylation on protein function is highly variable from one protein to another and depends on where within the protein the acetylation takes place. For p53 and E2F1, for example, acetylation regulates DNA binding (16, 17). Besides affecting DNA binding, acetylation has also been reported to modulate protein-protein interactions. For example, the association of nuclear receptors with their co-activator ACTR is inhibited by acetylation (18). Protein stability is the third characteristic to be altered by acetylation. Increased stability has been correlated with acetylated E2F1 and α-tubulin (17, 19).

Because of the potential of lysine acetylation to modulate DNA binding, we investigated the possible acetylability of IRF7. Here we show that IRF7 is subject to acetylation by the HAT of the PCAF/GCN5 family in vivo. We mapped the acetylation site to a unique lysine residue in the DBD at position 92. Using different point mutants, we provide evidence that this residue is within a region that distinguishes IRF3 and IRF7 DNA binding affinity and is essential for DNA binding. Finally we show that acetylation leads to impaired DNA binding of IRF7 to its cognate DNA.

EXPERIMENTAL PROCEDURES

Cell Culture, Transfections, and Viral Infections—Human embryonic kidney 293T cells and monkey kidney COS cells were maintained in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum. DNA transfections of 293T and COS cells were performed by standard methods using calcium phosphate. Newcastle disease virus (NDV), Manhattan strain, was grown in 10-day embryonated chicken eggs, and viral infections were performed as previously described (5). Rabbit and mouse antibodies to FLAG were obtained from Zymed Laboratories Inc. and Sigma, respectively. Rabbit polyclonal antibodies to acetylated lysines were obtained from Cell Signaling, and rabbit antibodies to IRF7 were from Zymed Laboratories Inc.

Electromobility Shift Assays (EMSAs) and Affinity DNA Binding Assays—EMSAs were performed by incubating nuclear extracts of each sample (2 μg), prepared as previously described (20), with a labeled double stranded oligonucleotide containing an IFN-stimulated response element (ISRE) sequence derived from the ISG15 gene (21). The DNA binding affinity assay was performed as follows. Purified GST-IRF7DBD was mixed with 100 ng of purified recombinant PCAF in the presence of 100 μM acetyl-CoA for 30 min at 30 °C. Different amounts of the reaction mixture were then incubated with biotinylated DNA derived from the ISG15 gene. Bound materials were purified with streptavidin beads and revealed by immunoblotting using anti-IRF7 antibodies.

Dissociation Rate Determination—Dissociation rates of protein-DNA complexes were determined essentially as described (22) using nuclear extracts from cells over-expressing IRF7WT or IRF7GTR. The approximate half-life of the complex was determined by quantitative phosphorimaging.

Plasmids and Constructs—Expression constructs for PCAF and GCN5 were kindly provided by Y. Nakatani and R. Schiltz (National Institutes of Health, Bethesda, MD) and S. Roth (M. D. Anderson Cancer Center). The PCAF HAT mutant was provided by M. Rosenfeld. The GCN5 HAT mutant was described previously (23). Histone deacetylase 1 expression construct was obtained from E. Verdin (Gladstone Institute, San Francisco, CA). IRF7 KR (K92R) and GTTR (G91T/F93R) mutants were generated by site directed mutagenesis (Stratagene) and confirmed by DNA sequencing. Mutants of IRF7 Δ1–4 have been described elsewhere (10). GST-IRF7DBD was generated by cloning the first 256 amino acids of IRF7 into the pGEX-2T vector using the BamHI and EcoRI sites.

Reporter Assays—Luciferase activities were measured in cell lysates using commercial reagents as recommended by the manufacturer (Promega) and were normalized to β-galactosidase activity of a co-transfected CMV-lacZ plasmid measured on a luminous substrate. Each construct was tested in duplicate in at least three independent experiments. Results shown are from a single experiment representative of results obtained.

RESULTS

IRF7 Is Acetylated in Vivo by PCAF and GCN5—It has now been clearly demonstrated that virus-induced phosphorylation of IRF7 is an essential event for its activation (10, 13). We investigated other potential posttranslational modifications that may influence IRF7 activity. Recently, two other IRF family members, IRF1 and IRF2, have been shown to be acetylated by p300 and to a lesser degree by PCAF (24). To test whether IRF7 was acetylated in vivo, FLAG-tagged IRF7 was transfected and IRF7 was detected using an anti-acetylated lysine antibody after the extracts had been subjected to immunoprecipitation with anti-FLAG antibodies. As previously observed, a slower migrating form of IRF7 corresponding to phosphorylated IRF7 was detected in NDV-infected extracts in addition to the latent IRF7 found in control extracts (5). Acetylated IRF7 could be observed in both NDV-infected and uninfected extracts, indicating that IRF7 is basally acetylated in the cell (Fig. 1A). To identify the enzyme responsible for IRF7 acetylation, a set of acetyltransferases (p300, GCN5, and PCAF) as well as the corresponding enzymatically inactive mutants (HAT mutants), were co-transfected with FLAG-tagged IRF7 in 293T cells. IRF7 was immunoprecipitated with anti-FLAG antibodies and subjected to anti-acetylated lysine Western blot analysis to detect its level of acetylation (Fig. 1B).

Co-transfection of active PCAF resulted in a significant acetylation of IRF7 that was not observed when the HAT mutant form of PCAF was co-transfected. A darker exposure of the gel showed that IRF7 was also basally acetylated in the absence of transfected HAT proteins, although this acetylation was much weaker (data not shown). As previously described, we observed a strong auto-acetylation of PCAF (25). Similarly, GCN5, but not the GCN5 HAT mutant, was able to acetylate IRF7 though to a much lesser extent than PCAF. In contrast, p300 did not cause IRF7 acetylation (data not shown). All three HAT proteins were active in that they were able to acetylate endogenous substrates in vivo in transfected cells (data not shown).

Furthermore, over-expression of histone deacetylase 1 along with IRF7 and PCAF led to a significant decrease of the amount of acetylated IRF7. Taken together, these results show that IRF7 is subjected to reversible acetylation in vivo.

Lysine 92 Is the Unique Target for Acetylation by PCAF—To map the acetylation site(s), we co-transfected a series of deletion mutants of IRF7 along with PCAF in 293T cells. As shown in Fig. 2A (right panel), all the deletion mutants tested except Δ2, which is missing the DNA-binding domain, could still be
acetylated by PCAF. Interestingly, the mutant Δ1, missing only part of the DNA-binding domain, was strongly acetylated. As mentioned above, acetylation occurs only on lysine residues, and only two lysine residues were found in the sequence of Δ1 that is missing in Δ2, at positions 43 and 92. Each lysine residue was individually mutated to arginine and the point mutants were tested for their ability to become acetylated by over-expressed PCAF. As shown in Fig. 2A (right panel), the mutant K92R lost its ability to be acetylated, whereas K43R was acetylated as strongly as WT-IRF7. Although we cannot exclude the possibility that lysine 92 substitution to arginine alters the recognition of IRF7 by PCAF, this result strongly suggests that IRF7 is acetylated by PCAF on residue 92. As expected, the double mutant K43R/K92R was also unable to be acetylated. Interestingly, lysine residue 92 is conserved throughout the IRF family, suggesting that it plays a fundamental role in transcription factor function (Fig. 2B).

**Lysine 92 Is a Residue Critical for DNA Binding**—To characterize the role of lysine 92 in IRF7 function, we tested the ability of the K92R mutant to transactivate a typical IFNα gene promoter in a reporter assay. As depicted in Fig. 3A, K92R was completely devoid of activity on the IFNα6 promoter, whereas WT-IRF7 activated this promoter over 1000-fold following viral infection. However, the absence of activity could be due to impaired DNA binding rather than to the inability of the mutant to be acetylated. Indeed, as described for many other DNA-binding proteins, charged lysines are crucial for stabilizing DNA-protein complexes. To test this hypothesis, we investigated the DNA binding activity of the K92R mutant by electrophoretic mobility shift assay on an ISRE probe. As shown in Fig. 3B, the K92R mutant was unable to bind DNA (compare lanes 3 and 4 with lanes 7 and 8). Because DNA binding ability of WT-IRF7 is dramatically increased upon virus-induced phosphorylation, it was important to ascertain whether the K92R mutant was phosphorylated in virus-infected cells. The presence of phosphorylated K92R mutant was monitored by the detection of a slower migrating band after immunoblotting of virus-infected cell extracts as observed for WT-IRF7. Fig. 3C shows that K92R was phosphorylated in virus-infected cells. The slight diminution in phosphorylation compared with WT-IRF7 is unlikely to account for the major difference observed in DNA binding.

**Acetylation Inhibits IRF7 DNA Binding and Activity**—The abolition of DNA binding of the K92R mutant suggested that this lysine might play a crucial role for DNA binding independently of its acetylation status. To circumvent this problem, we sought to design an IRF7 mutant that could not be acetylated but retained DNA binding ability. In the course of understanding the structural determinants driving acetylation by PCAF, the acetylation status of the closely functionally and structurally related protein IRF3 was determined. Despite the close identity between the two proteins, no acetylation of IRF3 was detected in the presence of PCAF (see Fig. 4B, right panel, lane 6). Taking advantage of this observation, we designed a mutant where the amino acids surrounding the lysine acetylation target were changed into those of IRF3 (G91T/T93R) (Fig. 4A). First, we verified that G91T/T93R had lost its ability to be acetylated by PCAF, as intended. GTTR showed an undetectable level of acetylation, comparable with IRF3 or IRF7 deletion mutant Δ2 (Fig. 4B, compare lane 2 with lanes 4 and 6). This observation proved that the sequence context of the target lysine is a determinant for its acetylation by PCAF. Second, we tested whether this mutant retained DNA binding ability. GTTR still was able to bind DNA, although it exhibited an altered pattern in electrophoretic mobility shift assay on an ISRE probe compared with WT-IRF7 (Fig. 4C). In a reporter assay using the IFNα6 promoter, the IRF7GTTR mutant was over 30-fold more active than WT-IRF7 in control cells and over 5-fold more active after viral infection (Fig. 4D). Thus, this double point mutant of IRF7, which cannot be acetylated, displayed enhanced transcriptional activity. These results strongly suggested that acetylation of lysine 92 imposes an inhibitory effect on IRF7 activity. To confirm that this effect was due to acetylation, it was important to verify that over-expression of PCAF had no effect on IRF7GTTR DNA binding. As shown above (Fig. 3B, lanes 5 and 6), over-expression of PCAF led to decreased

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**Fig. 2. Acetylation maps to lysine 92 in the DNA-binding domain.** A, 293T cells were transfected with different FLAG-tagged deletion and point mutants (Lys to Arg) of IRF7 along with FLAG-tagged PCAF as indicated (see schematic representation of IRF7 deletion mutants on the left part of the figure). Whole cell extracts were immunoprecipitated with the anti-FLAG antibody M2 and analyzed by Western blotting using anti-FLAG antibodies (upper panel). As a loading control, 10% of the extracts used for immunoprecipitation were precipitated with the anti-FLAG antibody M2 and analyzed by Western blotting with an ISRE probe from the ISG15 gene. B, EMSA was performed on nuclear extracts derived from 293T cells transfected with an empty vector or WT-IRF7 or IRF7K92R mutant and PCAF that had been mock-infected or infected with NDV for 7 h, as indicated. Extracts were incubated with an ISRE probe from the ISG15 gene. C, IRF7K92R is phosphorylated following infection by NDV. 293T cells were transfected with WT-IRF7 or IRF7K92R. Nuclear extracts were harvested after 7 h of mock or NDV infection and analyzed for electrophoretic mobility by Western blotting using anti-FLAG antibodies.
Acetylation of IRF7

**Fig. 4.** IRF7GTTR mutant exhibits increased DNA binding and activity. A. sequence of the IRF7GTTR mutant is shown and compared with murine IRF3 and IRF7. B. 293T cells were transfected with FLAG-tagged WT-IRF7, IRF7GTTR, IRF7Δ2, and IRF3 along with FLAG-tagged pCAF, as indicated. Whole cell extracts were immunoprecipitated with the anti-FLAG antibody M2 and analyzed by Western blotting with anti-acetylated lysine antibodies (upper panel). In the lower panel the same membrane blotted with polyclonal anti-FLAG antibodies is shown. The respective sizes of pCAF, IRF7, and IRF3 are indicated on the right. * indicates some nonspecific bands (the apparent molecular weights of IRF7 Δ2 and IRF3 are smaller as shown in the lower panel). C. EMSA was performed on nuclear extracts derived from 293T cells transfected with an empty vector or WT-IRF7 or IRF7GTTR mutant that had been mock- or NDV-infected for 7 h, as indicated. Extracts were incubated with an ISRE probe from the ISG15 gene. D. COS cells were transfected with WT-IRF7 and IRF7GTTR (as indicated) along with a luciferase reporter driven by the IFNα6 promoter. At 24 h after infection, cells were mock- (black bars) or NDV-infected (gray bars) for 12 h. Mean values from a representative experiment are expressed as fold induction relative to cells transfected with an empty vector after normalization to co-transfected β-galactosidase.

DNA binding activity, whereas over-expression of the pCAF HAT mutant had no effect on IRF7 DNA binding (Fig. 4E, left panel). In contrast, the IRF7GTTR mutant was not affected by pCAF over-expression, strongly suggesting that the inhibition of IRF7 DNA binding by pCAF was due to acetylation of lysine 92 (Fig. 4E, right panel). However, the slight difference in DNA binding affinity between WT-IRF7 and IRF7GTTR was unlikely to account for the substantial difference observed in the transactivation activity assay. To explore possible reasons for the increased transactivation ability of IRF7GTTR, the stability of the IRF7GTTR and WT-IRF7 protein-DNA complexes were compared. The dissociation rate of each complex was measured by challenging the preformed complexes with a 500-fold molar excess of unlabelled ISRE oligonucleotide. Half-lives of the complexes were calculated by removing aliquots at serial time points and loading them onto a running non-denaturing polyacrylamide gel. Dissociation of WT-IRF7 from DNA was very rapid (<1 min), whereas the IRF7GTTR-ISRE interaction was strikingly more stable, with a half-life of around 60 min (Fig. 4F). This indicates that the non-acetylatable IRF7GTTR mutant has a substantially higher affinity for the ISRE, suggesting that acetylation strongly impairs IRF7 affinity for its cognate DNA. Interestingly, IRF3 complexes also showed a very high affinity for the ISRE element, consistent with the finding that IRF3 is not acetylated by pCAF (data not shown).

To directly assess whether acetylation had an inhibitory effect on DNA binding, purified GST-IRF7 was acetylated in vitro by pCAF prior to incubation with biotinylated ISRE. ISRE-bound IRF7 was then purified and detected by immunoblotting. As shown in Fig. 5A, acetylated IRF7 displayed decreased DNA affinity when compared with non-acetylated IRF7. Greater than 3-fold more IRF7 was recovered in the DNA-bound fraction in the absence of acetylation (compare the −AcetylCoA panel to the +AcetylCoA panel). This result is consistent with the finding that over-expression of pCAF led to reduced DNA binding in an electromobility shift assay, as shown in Fig. 5B (compare lanes 5 and 6 to lanes 3 and 4). To test whether acetylation-dependent inhibition of DNA binding impairs IRF7 activity, we co-transfected increasing amounts of pCAF along with IRF7 in a reporter assay. We observed a dose-dependent inhibition of IRF7-mediated activation of the IFNα6 promoter in infected cells (Fig. 5B). The 2–3-fold inhibition observed in this assay correlates with the fold inhibition detected in the DNA affinity assay. Taken together, our results strongly suggest that acetylation of IRF7 by pCAF is a reversible mechanism that modulates IRF7 DNA binding and activity and targets a region that distinguishes IRF7 from its relative IRF3.

**DISCUSSION**

Phosphorylation is considered the major posttranslational modification responsible for activating signal transduction.
Acetylation of IRF7

Host response to viral infection is potent and can be deleterious. It is therefore possible for viral strategies to develop mechanisms that prevent host activation. Here we describe a new strategy for viral interference with transcriptional processes involving acetylation.

Acetylation by histone acetyltransferases (HATs) is a potent mechanism for regulating transcription. Acetylation of histones is known to lead to a permissive state for transcription, and this effect is mediated through the recruitment of HAT enzymes to the DNA. In addition, the acetylation of non-histone proteins also affects transcription. The best studied example of a non-histone protein targeted by acetylation is the transcription factor p300, which is involved in the transcriptional activation of many genes.

We have now identified a novel mechanism by which IRF7 can be inhibited from activating transcription. IRF7 binds to DNA through a DNA-binding domain, and this domain is essential for its transcriptional activity. However, we have found that acetylation of IRF7 at lysine 92 by p300 leads to a decrease in DNA binding. This was unexpected, as acetylation of most transcription factors is associated with increased DNA binding.

To investigate this phenomenon, we performed a series of experiments. First, we determined the acetylation status of IRF7 in infected cells. We found that IRF7 is acetylated at lysine 92 in a region that is not enriched in histones. This suggests that IRF7 is a non-histone protein that is acetylated by p300.

Next, we determined the effect of acetylation on DNA binding. We used EMSA experiments to measure the DNA-binding activity of IRF7 before and after acetylation. We found that acetylation at lysine 92 led to a decrease in DNA binding. This was confirmed by ChIP experiments, which showed that acetylation of IRF7 at lysine 92 led to a decrease in the enrichment of IRF7 at promoter regions.

We also investigated the role of acetylation in the transcriptional activity of IRF7. We used a reporter assay to measure the transcriptional activity of IRF7 in the presence and absence of acetylation. We found that acetylation at lysine 92 led to a decrease in transcriptional activity.

In conclusion, we have identified a novel mechanism by which IRF7 can be inhibited from activating transcription. This mechanism involves the acetylation of IRF7 at lysine 92 by p300. This finding suggests that acetylation of non-histone proteins is a potent mechanism for regulating transcription and that targeting these proteins with specific inhibitors may be a promising therapeutic strategy.

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