Adenovirus E1A Down-regulates LMP2 Transcription by Interfering with the Binding of Stat1 to IRF1*

The LMP2 gene, which encodes a protein required for efficient presentation of viral antigens, requires both unphosphorylated Stat1 and IRF1 for basal expression. LMP2 expression is down-regulated by the adenovirus protein E1A, which binds to Stat1 and CBP/p300, and by the mutant E1A protein RG2, which binds to Stat1 but not to CBP/p300, but not by the mutant protein A2–36, which does not bind to either Stat1 or CBP/p300. Stat1 and IRF1 associate in untreated cells and bind as a complex to the overlapping ICS-2/GAS element of the LMP2 promoter. E1A interferes with the formation of this complex by occupying domains of Stat1 that bind to IRF1. These results reveal how adenovirus infection attenuates LMP2 expression, thereby interfering with the presentation of viral antigens.

Viruses have devised many methods to block host defenses. For example, infection of cells with adenovirus 12 down-regulates the cell surface expression of major histocompatibility complex class I antigens, which allows the infected cell to be recognized by the immune system. The attenuation of major histocompatibility complex class I expression involves down-regulation of the class I promoter (1), defects in β2-microglobulin synthesis (2), and abnormal function of the cellular antigen processing and transport machinery (3). Two proteins involved in antigen processing, LMP2 (low molecular mass polypeptide 2) and TAP1 (transporter associated with antigen processing), are encoded by closely linked genes within the major histocompatibility complex class II subregion that are transcribed in opposite directions from a common promoter region (4). Transcription of the TAP1 gene requires that either Stat1 dimer or IRF1 binds to an overlapping interferon consensus sequence (ICS) 2/γ interferon-activated sequence (GAS)1 motif in the LMP2/TAP1 promoter, whereas both constitutive and interferon (IFN)-induced expression of the LMP2 gene requires that both Stat1 and IRF1 bind to the ICS-2/GAS element (5). Adenovirus 12 infection down-regulates transcription of the LMP2 and TAP1 genes by interfering with the function of this bidirectional promoter (6).

The adenovirus early protein E1A alters host cell cycle pathways and also interferes with host anti-viral defenses by binding to the histone acetyltransferases and coactivators CBP and p300 (7–9). E1A interferes with DNA-protein interactions at certain IFN-responsive promoters (10) and also abrogates the binding of Stat1 to CBP/p300, because E1A and Stat1 utilize the same binding sites on CBP/p300 (11). Therefore, one way for E1A to affect Stat1-mediated gene expression would be through competition for CBP/p300. A recent study shows that E1A also binds to Stat1 directly and thus can affect Stat1-mediated gene expression (12). The involvement of CBP/p300 in DNA-protein interactions at the LMP2 promoter has not been studied. However, we do know that Stat1 must bind to the LMP2 ICS-2/GAS to support constitutive transcription of the LMP2 gene (5). Therefore, we attempted to analyze the involvement of CBP/p300 in LMP2 transcription and to evaluate whether down-regulation of constitutive LMP2 transcription by E1A is mediated by its direct binding to Stat1 or by interference with the Stat1-CBP/p300 interaction.

We find that the LMP2 gene is expressed at normal constitutive levels in cells that express a mutant of Stat1 (Y701F) that is incapable of forming homodimers in response to ligand stimulation. Stat1 and IRF1 bind to each other directly, and the resulting complex binds to the LMP2 ICS-2/GAS element. E1A down-regulates LMP2 transcription by interfering with the Stat1-IRF1 interaction, which is essential for the constitutive expression of LMP2.

MATERIALS AND METHODS
cDNAs and Cells—The following cDNA reagents were kind gifts: E1A 12S from M. L. Harter and E1A 12S mutants RG2 and A2–36 from G. C. Sen (Cleveland Clinic Foundation); IRF1 C-terminal mutants from J. Hiscott (McGill University); Stat1 ΔN135 from R. Schreiber (Washington University, St. Louis, MO); Stat1 ΔN200 from R. Ransohoff (Cleveland Clinic Foundation); and Stat5/1 chimera from C. Schindler (Columbia University). U3A, U3A-IRF1(H), U3A-701, and 2fTGH cells (13) were grown in Dulbecco’s modified Eagle’s medium, supplemented with 10% fetal calf serum, and 100 μg/ml from penicillin and streptomycin at 37 °C under 10% CO2.

RNA Preparations, Reverse Transcriptase-PCR, and S1 Nuclelease Analyses—Total RNA was prepared with the Trizol reagent (Life Technologies, Inc.), and mRNA was purified by using the Oligotex mRNA kit (Qiagen). Reverse transcriptase-PCR was performed by converting 1 μg of mRNA to cDNA using Moloney murine leukemia virus reverse transcriptase (Promega) and oligo(dT) primers (Life Technologies, Inc.). The LMP2 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) cDNAs were amplified from total cDNA by using specific primers (5). For S1 nuclease analysis, mRNAs were hybridized with end-labeled, PCR-derived LMP2 and GAPDH probes, using the Ambion S1 nuclease kit according to the manufacturer’s instructions. RNA-DNA hybrids were purified and then analyzed in a 6% PAGE gel containing 8 m urea. The sizes of the protected fragments were 677 base pairs for LMP2 and 450 base pairs for GAPDH. Signals were recorded using a Molecular Dynamics PhosphorImager.

Expression of Recombinant His-tagged Stat1—A vector for the expression of His-Stat1 was constructed by amplifying Stat1 cDNA by PCR and cloning the product downstream of a His6 tag. The forward
### RESULTS

**E1A Interferes with LMP2 Transcription in Both U3A-701 and 2TGH Cells**—To analyze the effect of E1A on LMP2 transcription and to evaluate the role of CBP/p300, U3A (lacking Stat1 expression), U3A-701 (expressing Stat1 Y701F), and 2TGH (expressing wild-type Stat1) cells were transfected transiently with constructs expressing the 12S splice variant of E1A, a mutant of E1A 12S lacking amino acids 2–36 (Δ2–36), which binds to neither CBP/p300 nor Stat1, and the RG2 mutant of E1A 12S, which does not bind to CBP/p300 but does bind to Stat1. LMP2 transcription was assessed in cells transfected with empty vector or the E1A variants after 48 h. LMP2 RNA is barely detectable in U3A cells. However, parental 2TGH and U3A-701 cells express this RNA well, at similar levels. LMP2 transcription is almost abolished in U3A-701 and 2TGH cells transfected with E1A (Fig. 1). This down-regulation is not seen in cells transfected with Δ2–36, but the effect of RG2 is similar to that of E1A. Therefore, E1A down-regulates constitutive LMP2 transcription mediated by unphosphorylated Stat1, and CBP/p300 is not involved in constitutive LMP2 transcription, because transcription with RG2, which binds to Stat1 and not to CBP/p300, also down-regulates LMP2 expression.

**Transcription Factor Binding to the ICS-2/GAS Site of the LMP2 Promoter in U3A-701 and 2TGH Cells**—To understand how unphosphorylated Stat1 regulates LMP2 transcription, we analyzed the binding of factors to the LMP2 promoter, which contains overlapping ICS-2 and GAS sites that bind to IRF1 and Stat1, respectively. EMSAs with an LMP2 GAS probe (ATTCGCTTTCCTCCATAAATG) reveal a novel complex with extracts of both 2TGH and U3A-701 cells (Fig. 2A). This oligonucleotide includes most of the ICS-2 site (ATTCGCTTTCCTCCATAAATG; shown in bold). The novel complex migrates more slowly than the complex containing tyrosine-phosphorylated Stat1 homodimer, formed in extracts of IFN-γ-treated 2TGH cells. Supershift analysis shows that the novel complex in both U3A-701 and 2TGH cells contains Stat1. Fig. 2B shows the supershift assay, using extracts from U3A-701 cells. U3A, U3A-701, and 2TGH cells were transfected transiently with E1A, Δ2–36, or RG2, and cell extracts were prepared 48 h later. The novel complex was almost totally absent in extracts of U3A-701 or 2TGH cells transfected with either E1A or RG2. However, Δ2–36 had no effect in either U3A-701 or 2TGH cells (Fig. 2C).
Analysis of Protein-Protein Interactions at the LMP2 Promoter in Vitro—The most likely secondary component of the novel binding activity observed in U3A-701 and 2fTGH cells is IRF1, because the GAS oligonucleotide used in gel shift assays contains part of the overlapping ICS-2 site from the LMP2 promoter. To confirm that a Stat1-IRF1 complex can bind to the LMP2 GAS element, we saturated biotinylated LMP2 GAS oligonucleotides bound to streptavidin agarose beads with either unphosphorylated His-Stat1 or in vitro translated IRF1. IRF1 does not bind to the LMP2 GAS alone, but bound His-Stat1 captured in vitro translated IRF1 (Fig. 3). To analyze whether His-Stat1 bound to the LMP2 GAS could also capture IRF1 from cell extracts, we used U3A cells expressing IRF1 from a transgene, because U3A cells express very low levels of endogenous IRF1 (13). The bound His-Stat1 did indeed capture IRF1 from U3A-IRF1(H) cell extracts (Fig. 3).

Stat1 and Stat1 Y701F both bind to IRF1 in vivo (Fig. 4A). Stat1 was co-immunoprecipitated from extracts of U3A-701 or 2fTGH cells but not from extracts of U3A cells, using an antibody against IRF1. Although the levels of IRF1 are low in 2fTGH, U3A, and U3A-701 cells, IRF1 could still be detected in immunoprecipitates of U3A-701 and 2fTGH cells with an antibody against Stat1 (Fig. 4A).

To investigate whether additional proteins are required for the Stat1-IRF1 interaction, IRF1, Stat1, and Stat1 Y701F were translated in vitro, using a T7-based coupled transcription/translation system in rabbit reticulocyte lysates, and the proteins alone or in pairwise combinations were immunoprecipitated with anti-Stat1 or anti-IRF1 (Fig. 4B). The results clearly show that Stat1 and Stat1 Y701F interact directly with IRF1.

E1A Inhibits the Stat1-IRF1 Interaction—The Stat1 binding capacity of E1A is required to down-regulate LMP2 transcription, and a complex of unphosphorylated Stat1 and IRF1 binds to the LMP2 GAS. To analyze the effect of E1A on the binding of Stat1 to IRF1, extracts were prepared from U3A, U3A-701, and 2fTGH cells transfected transiently with either E1A, Δ2–36, or RG2. Equal parts of each extract were immunoprecipitated with antibodies against E1A or IRF1, and the immunoprecipitates were analyzed with antibodies against Stat1. As observed before (12), Stat1 binds to E1A and RG2 but not to Δ2–36. Both Stat1 Y701F and Stat1 bound to E1A (Fig. 5, top panel). Stat1-IRF1 binding was markedly reduced in U3A-701 and 2fTGH cells transfected with either E1A or RG2 but not in cells expressing Δ2–36 (Fig. 5, bottom panel). Thus, E1A binds to unphosphorylated Stat1, interfering with Stat1-IRF1 binding directly.

E1A Binds to Two Domains of Stat1—To analyze the domains of Stat1 required for binding to E1A, E1A, Stat1, Stat2 Y701F, Stat1 ΔN135 (lacking the first 135 residues), Stat1 ΔN200, and Stat1-p84 (lacking the C-terminal transactivation domain, residues 712–750) were translated in vitro, alone or pairwise. Immunoprecipitations were performed with an antibody to E1A, and Stat1 was detected with antibodies directed against either the N or C terminus. Both Stat1 and Stat1 Y701F bind well to E1A (Fig. 6). The binding is barely detectable with Stat1 ΔN135, Stat1 ΔN200, and Stat1-p84. Thus, E1A binds to both ends of Stat1.

Regions of Stat1 and IRF1 Required for Mutual Binding—We employed a series of C-terminal deletion mutants of IRF1, translated in vitro, in co-immunoprecipitation assays with recombinant Stat1. IRF1, IRF1 1–300, IRF1 1–250, and IRF1 1–200 were all able to bind to recombinant Stat1 (Fig. 7A). The binding of IRF1 1–170 was very weak, and IRF1 1–150 and IRF1 1–120 did not bind detectably (Fig. 7A). Thus, the minimal region of IRF1 required for binding to Stat1 probably lies between residues 170 and 200.

Stat1 binds to another member of the IRF family, IRF9, through the N-terminal coiled-coil domain of Stat1 (15). To evaluate whether the same region is important for Stat1-IRF1 binding, two deletion mutants of Stat1, Stat1 ΔN135 (lacking the first 135 residues) and Stat1 ΔN200 (lacking the first 200 residues, which include most of the coiled-coil domain), were translated in vitro with IRF1 and used in co-immunoprecipitation assays using an antibody to IRF1. Both deletion mutants of Stat1 failed to bind to IRF1 (Fig. 7B). We have also observed that IRF1 does not interact with Stat5 in vitro (data not shown).

DISCUSSION

The LMP2 gene requires unphosphorylated Stat1 for basal transcription. Transcription was detected in U3A-701 cells (expressing Stat1 Y701F, which is incapable of participating in dimer formation through the interaction of tyrosine-phosphorylated Y701 with the SH2 domain of a Stat1 partner) but not in U3A cells (which lack Stat1). Previous work from our labo-
FIG. 3. The LMP2 GAS-Stat1 complex can recruit IRF1. Neutravidin-agarose was saturated with the LMP2 GAS oligonucleotide and allowed to bind to either His-Stat1, IRF1 from in vitro translations (IVT) or to extracts of U3A or U3A-IRF1(H) cells. His-Stat1 saturated beads were then incubated with either IRF1, extracts from U3A cells, or extracts from U3A-IRF1(H) cells. The beads were then washed five times, and the eluted proteins were separated by 12% SDS-PAGE. Proteins were transferred to PVDF membranes and detected with anti-IRF1.

FIG. 4. Stat1 interacts with IRF1 in vivo and in vitro. A, Stat1 associates with IRF1 in vivo. Total cell extracts prepared from U3A, U3A-701, or 2TGH cells were immunoprecipitated with anti-Stat1, anti-IRF1, or a nonspecific antibody (n.s. Ab). The immunoprecipitates were resolved in 12% SDS-PAGE gels, transferred to PVDF membranes, and analyzed by using either anti-Stat1 or anti-IRF1. B, Stat1 and Stat1 Y701F associate directly with IRF1 in vitro. Stat1, Stat1 Y701F, and IRF1 were expressed in vitro using a T7-coupled transcription-translation system. Stat1, Stat1 Y701F, IRF1, or mixtures of equal amounts of Stat1 and IRF1 or Stat1 Y701F and IRF1 were immunoprecipitated by using either anti-Stat1 or anti-IRF1. The immunoprecipitates were resolved by 12% SDS-PAGE, transferred to PVDF membranes, and analyzed by using either anti-IRF1 or anti-Stat1. I.P., immunoprecipitation; W.B., Western blot.

FIG. 5. E1A and RG2 inhibit Stat1-IRF1 interactions in vivo. U3A, U3A-701, or 2TGH cells were transfected transiently with E1A, Δ2–36, or RG2, and extracts were prepared 48 h later. Equal parts of each extract were immunoprecipitated with antibodies against E1A or IRF1. Immunoprecipitates were separated by 12% SDS-PAGE and detected with anti-Stat1. The top panel shows the interaction of Stat1 with E1A, and the bottom panel shows the inhibition of Stat1-IRF1 binding by E1A. I.P., immunoprecipitation.

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The laboratory has identified other genes that can be activated in U3A-701 cells (10). Transfection of U3A-701 or 2TGH cells with E1A abrogates LMP2 transcription. A mutant of E1A that binds to Stat1 but not to CBP/p300 also down-regulates LMP2 transcription, whereas Δ2–36, which binds to neither CBP/p300 nor Stat1, has no effect on the levels of LMP2 RNA in either U3A-701 or 2TGH cells. A novel DNA-binding complex containing Stat1 can be detected in extracts of untreated U3A-701 or 2TGH cells. The other protein component of this complex appears to be IRF1. Stat1 and IRF1 bind to each other directly through the N-terminal region of Stat1 and residues 170–200 of IRF1. The N-terminal region of Stat1, especially R161 within the coiled coil domain, is required for the binding of Stat1 to another member of the IRF1 family, IRF9 (previously called p48; Ref. 15). The N-terminal region of Stat1 might also be important for it to interact with accessory proteins that aid in its nuclear translocation and also with certain phosphatases (16). We have observed that E1A binds to both the N- and C-terminal regions of Stat1 and probably interferes with Stat1-IRF1 interactions directly by occupying the N terminus of Stat1.

E1A, essential for adenovirus replication, also activates the
host cell cycle by sequestering proteins important for cell cycle checkpoint control (17). E1A may also help to suppress host defenses against virus infection by binding to the cellular co-activator CBP and the highly homologous p300 protein. The activation of many genes requires the histone acetyl transferase activity associated with CBP/p300. E1A competes with transcription factors for CBP/p300 and thus alters the transcription of many genes (7, 9, 18). E1A competes with Stat1 (19), and both phosphorylated and unphosphorylated Stat1 bind to CBP/p300 (18).

The LMP2/TAP1 bi-directional promoter is down-regulated by adenovirus 12 (6). We show that the down-regulation of constitutive LMP2 transcription depends on the direct interaction of E1A with Stat1 and does not involve CBP/p300. A previous study identified the region of Stat1 required for binding to E1A to be the C-terminal transactivation domain (12).

We find that the N-terminal region is also important, because the binding of E1A to N-terminal deletion mutants of Stat1 is very low. The N-terminal region of Stat1 is also required for binding to IRF1; the C-terminal region of Stat1 is not important for this interaction since Stat1-p84 does bind to IRF1 (data not shown). Therefore inhibition of Stat1-IRF1 binding and thus of constitutive LMP2 transcription is probably mediated by a competition between E1A and IRF1 for the N-terminal region of Stat1.

The N-terminal region of IRF1 is involved in DNA binding (20) and perhaps homodimerization (21), whereas the C-terminal region is involved in interactions with other proteins (20). This demarcation is not absolute, because casein kinase II interacts with IRF1 through the N-terminal residues 1–120 (14). IRF1 mutants 1–170 and 1–200 can still bind to DNA but do not heterodimerize with IRF8 (also called ICSBP; Ref. 20). The in-

FIG. 6. E1A binds to two domains of Stat1. Immunoprecipitations were performed with mixtures of in vitro translation products of E1A with Stat1, Stat1 Y701F, Stat1 ΔN135, Stat1 ΔN200, or Stat1-p84 by using anti-E1A. The immunoprecipitates were analyzed in Western transfers with a mixture of Stat1 N-terminal and C-terminal antibodies. I.P., immunoprecipitation; W.B., Western blot.

FIG. 7. Domains of IRF1 and Stat1 required for their interaction. A, the domains of IRF1 that bind to Stat1. A series of C-terminal deletion mutants of IRF1 were translated in vitro, mixed with recombinant Stat1 and immunoprecipitated with anti-IRF1. The in vitro translation products were analyzed in parallel with the immunoprecipitates. The upper panel shows the expression of IRF1 C-terminal mutants. The lower panel shows the detection of Stat1 in the immunoprecipitates with anti-IRF1. B, domains of Stat1 required for binding to IRF1. Stat1, Stat1 Y701F, Stat1 ΔN135, and Stat1 ΔN200 were translated in vitro together with IRF1. The in vitro translation products were immunoprecipitated with anti-IRF1. Immunoprecipitates and the in vitro products were analyzed in Western transfers with anti-Stat1. The upper panel shows the in vitro translation products, and the lower panel shows Stat1 in the immunoprecipitates. C, Stat5/1 fails to bind to IRF1 in vivo. Extracts of U3A cells expressing Stat1 or Stat5/1 were used in immunoprecipitation reactions with anti-IRF1. Lysates from U3A, U3A-Stat1, and U3A Stat5/1 and the immunoprecipitates were analyzed on Western transfers with anti-Stat1. I.P., immunoprecipitation; W.B., Western blot.
teraction of Stat1, Stat2, and IRF9 to form ISGF3 already is well known, and the elucidation here of Stat1-IRF1 interactions reveals yet another way that members of the two interferon-inducible protein families can communicate. The region of IRF1 required for binding to Stat1 appears to be residues 170–200. Thus, IRF1 may interact with several proteins through different domains, allowing it to play a broad role in cellular signaling and transcription. In this regard, it is interesting that the IRF1-null mice used to analyze LMP2 gene transcription (22) actually express a truncated protein, generated by exon skipping (23). The deleted exons encode residues 63–182, and although the lack of this region abrogates the DNA binding activity of IRF1, the truncated protein may still bind to Stat1, and the complex may still bind to the ICS-2/GAS element through the DNA-binding domain of Stat1 and thus support the low level of LMP2 transcription observed in these mice.

IRF1 alone does not bind to the LMP2 GAS; however, the ICS-2 and GAS elements overlap in this promoter. Thus, Stat1, IRF1, or both could provide DNA binding. Complexes of Stat1 with IRF1 or with another transcription factor would bind very specifically to DNA sequences that recognize both factors, and GAS sequences are close to other transcription factor binding sites in several genes (24, 25).

E1A represses the transcription of major histocompatibility complex class I genes by interfering with the binding of NF-κB, AP-1, and COUP-TF to regulatory elements in the promoters (26–28). We show here that E1A also interferes with the formation of the Stat1-IRF1 complex and with its binding to the ICS-2/GAS element of the LMP2/TAP1 promoter. Thus, in cells infected with adenovirus 12, the host antigen presentation machinery is virtually shut down, allowing them to escape killing by cytotoxic T lymphocytes.

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