The Human Papillomavirus Oncoprotein E7 Attenuates NF-κB Activation by Targeting the IκB Kinase Complex*

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Infection with high-risk human papillomaviruses (HPV) can lead to the development of cervical carcinomas. This process critically depends on the virus-encoded E6 and E7 oncoproteins, which stimulate proliferation by manipulating the function of a variety of host key regulatory proteins. Here we show that both viral proteins dose-dependently interfere with the transcriptional activity of NF-κB. A variety of experimental approaches revealed that a fraction of the E7 proteins is found in association with the IκB kinase complex and attenuates induced kinase activity of IκB kinase α (IKKα) and IκKB, thus resulting in impaired IκBo phosphorylation and degradation. Indirect immunofluorescence shows that E7 impairs TNFα-induced nuclear translocation of NF-κB, thus preventing NF-κB from binding to its cognate DNA. While E7 obviates IKK activation in the cytoplasm, the E6 protein reduces NF-κB p65-dependent transcriptional activity within the nucleus. We suggest that HPV oncogene-mediated suppression of NF-κB activity contributes to HPV escape from the immune system.

HPVs1 are small DNA viruses, and specific high-risk types such as the HPV type 16 (HPV16) or HPV18 are causative agents of some forms of anogenital and oral cancers (1). HPV16 encodes six early proteins including the major oncoproteins E6 and E7. Both proteins play a central role in the induction of benign proliferation and malignant transformation (2), and at least the persistence of E7 is necessary to maintain the transformed phenotype (3). These two oncoproteins are selectively and continuously expressed in HPV-induced tumors and manipulate cell proliferation upon physical and functional interaction with several master cell cycle regulators (4). E6 binds to p53 (5) and causes its ubiquitin-dependent degradation (6), thereby interfering with p53 functions in cell cycle control and apoptosis. In addition, the E6 protein binds to the protein kinase PKN (7) and other regulators including interferon regulatory factor 3 (8) and the proapoptotic Bak protein (9). The E7 protein interacts with so-called "pocket proteins" such as the retinoblastoma protein pRb, p107, and p130 (10), resulting in their enhanced phosphorylation and degradation (11). pRb destruction results in the release of E2F family transcription factors and subsequent activation of genes promoting cell proliferation (12). But the stimulatory effects of E7 on cell proliferation depends not only on its association with pRb (13, 14), because E7 targets the function of a plethora of regulators including cyclin E (15), acid alpha-glucosidase (16), and M2 pyruvate kinase (17). E7 also interferes with the activity of a variety of transcription factors such as AP-1 (18), interferon regulatory factor-1 (19), fork head domain transcription factor MPP2 (20), and TATA-box-binding protein (21). This multiplicity of interaction partners and additional levels of functional E7 regulation by phosphorylations (22), protein stability (23), and the oligomerization state (24) allow a highly complex and sophisticated manipulation of the expression program by E7 oncoproteins (1, 25). Most of the E6/E7-regulated genes allow the virus to interfere either with cell proliferation and apoptosis or enable viral escape from the immune system. Immunological tolerance is induced by various mechanisms including transcriptional down-regulation of the major histocompatibility complex (MHC) class I gene (26) and selected proinflammatory cytokines (4, 27).

Some E6/E7-regulated gene products are target genes of NF-κB, a dimeric transcription factor involved in the expression of proteins necessary for innate immunity (28), apoptosis, and cell proliferation (29). NF-κB is typically a heterodimer between the p50 and p65 (RelA) subunits and is mainly regulated by intracellular compartmentalization. The inactive form of NF-κB is kept in the cytoplasm upon association with an inhibitory IκB protein (30). Triggering cells with a variety of stimuli including TNFα, IL-1, or phorbol ester induces phosphorylation of IκB, which allows subsequent ubiquitinylation and degradation of the inhibitor, thus leading to nuclear entry and DNA binding of NF-κB (31). The inducible phosphorylation of IκBo at serines 32 and 36 is mediated by the IκB kinase complex (IKC), which contains the IκB kinases IKKα and IKKB and the regulatory subunit IKKy/NEMO (30). The IKKs are activated by direct phosphorylation mediated by upstream kinases. Alternatively, IKKs can be recruited to intracellular domains of cell surface receptors that lead to an increased local concentration of the IKKs and allow their auto- and cross-phosphorylation (28).
A

![Graph](image)

B

![Graph](image)

**FIG. 1. Impact of E6 and E7 proteins on NF-κB-dependent transcription.** A, U2OS cells were transfected with a NF-κB luciferase reporter construct together with increasing amounts (1–5 μg) of eukaryotic expression vectors for E6 and E7 or E1A 12S at the indicated combinations. One day later, cells were stimulated for 10 h with TNFα, and luciferase activity was determined. Results shown are averages of three independent experiments, bars indicate S.D. B, U2OS cells were transfected with a NF-κB-dependent reporter gene and E6/E7 expression vectors as shown. Cells were stimulated for 10 h either with IL-1β (1 ng/ml) or 25 ng/ml phenylmethylsulfonylfluoride phorbol 12-myristate 13-acetate (PMA), and luciferase activity was determined. Maximal luciferase activity was arbitrarily set as 100%. Mean values from two independent experiments and S.D. are displayed.

Given the overlapping set of genes regulated by E6/E7 and NF-κB, we analyzed the effects of HPV E6 and E7 proteins on NF-κB activity. These experiments revealed a dose-dependent interference of these HPV oncoproteins with NF-κB functions.

**EXPERIMENTAL PROCEDURES**

**Cell Culture and Transfections—**Human U2OS and H1299 cells were grown in Dulbecco’s modified Eagle medium supplemented with 10% (v/v) fetal calf serum and 1% (v/v) penicillin/streptomycin (all from Invitrogen). These cell lines were transfected using Superfect (Qiagen) according to the instructions of the manufacturer. Primary embryonic fibroblasts stably transfected with the E6 or E7 gene under the control of the mouse mammary tumor virus (MMTV) promoter (32) were grown in the presence of 1 μM dexamethasone.

**Plasmids and Antibodies—**The reporter plasmids (κB)3-Luc (33) and (Gal4)2-Luc (34) as well as the expression vectors encoding E6 and E7 (35), E1A12S (36), Gal4-VP16, Gal4-p65 and Gal4 (34), GST-IκBα, Myc-IκBα/β, and NIK (33) were described. The vector encoding the FLAG-tagged E7 protein was constructed upon insertion of an appropriate PCR fragment into the vector pEF-BOS (37). The following antibodies were obtained from the indicated suppliers: αFLAG (M2), Sigma; αHA (12CA5), Roche Molecular Biochemicals; αIKKα/β (B7.1), BD Pharmingen; αp65 (sc-372X) and αIκBα, Santa Cruz Biotechnology; a phosho-IκBα, New England Biolabs.

**Luciferase Assays—**Luciferase activity in cell extracts was measured in a luminometer (Duo Lumat LB 9507, Berthold) by automatically injecting 50 μl of assay buffer and measuring light emission for 10 s after injection according to the instructions of the manufacturer (Promega). To ensure comparable transfection efficiencies, results were normalized to β-galactosidase expression produced by a cotransfected RSV-β-galactosidase expression vector.

**Electrophoretic Mobility Shift Assays (EMSAs)—**Cells stably transfected with MMTV-E6/E7 were washed twice with phosphate-buffered saline. Nuclear extracts were prepared by resuspending the cell pellet in 200 μl of cold buffer A (10 mM Hepes/ KOH (pH 7.9), 10 mM KCl, 0.1 mM EDTA, 0.1 mM EGTA, 1 mM dithiothreitol, and 0.5 mM phenylmethylsulfonyl fluoride). After incubation for 10 min on ice, 5 μl of 10% (v/v) Nonidet P-40 was added, and cells were lysed by vortexing. Cell nuclei were isolated by short centrifugation and dissolved in 30 μl of buffer C (20 mM Hepes/KOH (pH 7.9), 0.4 mM NaCl, 1 mM EDTA, 1 mM EGTA, 1 mM dithiothreitol, 0.5 mM phenylmethylsulfonyl fluoride, and 10 μg/ml aprotinin). After incubation on ice, the extract was centrifuged for 5 min in a microcentrifuge at 4 °C, and the supernatant was used for EMSAs essentially as described (33). The supershift experiments were performed by preincubating the nuclear extracts with 2 μg of αp65 antibodies for 15 min at 4 °C.

**Immunofluorescence—**H1299 cells were grown on cover slips and analyzed 1 day post-transfection by immunofluorescence. 20 min after TNFα stimulation, cells were fixed with 3.5% (v/v) paraformaldehyde for 15 min at room temperature. After permeabilization with 0.02% (v/v) Triton X-100, the primary antibodies were diluted to 1 μg/ml and added for 1 h at 22 °C. After further washing steps, the following secondary antibodies were added: Alexa-488-coupled goat α-rabbit (Molecular Probes) and Cy3-coupled goat α-mouse (Dianova). Chromosomal DNA was visualized by 4’,6-diamidino-2-phenylindole (DAPI), and stained cells were mounted on glass slides and examined using a Zeiss Axiohot microscope. The stained cells were further analyzed using Axiovision software.

**Co-precipitation Experiments and Immunoblotting—**Cells were washed with phosphate-buffered saline, and pellets were resuspended on ice for 15 min in 250 μl of Nonidet P-40 lysis buffer (20 mM Tris/HCl (pH 7.5), 150 mM NaCl, 1 mM phenylmethylsulfonyl fluoride, 10 mM NaF, 0.5 mM sodium vanadate, leupeptin (10 μg/ml), aprotinin (10 μg/ml), 1% (v/v) Nonidet P-40, and 10% (v/v) glycerol). Cell debris was pelleted upon centrifugation, and extracts were precleared with protein A/G-Sepharose. Equal amounts of protein contained in the supernatants were mixed with 1–2 μg of antibodies and 25 μl of protein A/G-Sepharose and rotated for 4 h on a spinning wheel at 4 °C. The immunoprecipitates were washed five times in Nonidet P-40 lysis buffer and then boiled in 1× SDS sample buffer prior to SDS-PAGE and further analysis by semidry Western blotting.

**IκB Kinase Assays—**Cells were transfected and lysed in Nonidet P-40 lysis buffer. An aliquot of the cell extract was directly analyzed by immunoblotting. The tagged IKK proteins contained in the remaining cell lysate were immunoprecipitated using αHA antibodies. The precipitate was washed three times in lysis buffer and two times in kinase buffer (20 mM Hepes/KOH (pH 7.4), 25 mM β-glycerophosphate, 2 mM dithiothreitol, 20 mM MgCl2). The kinase assay was performed in a final volume of 20 μl of kinase buffer containing 2 μg of bacterially expressed GST-IκBα-(1–54), 20 μM ATP, and 5 μCi of [γ-32P]ATP. After incubation for 20 min at 30 °C, the reaction was stopped by the addition of 5×
RESULTS

HPV E6 and E7 Interfere with Transcriptional Activity of NF-κB—To investigate the impact of HPV E6 and E7 proteins on NF-κB activity, human U2OS cells were transfected with a NF-κB-dependent luciferase reporter gene and various combinations of expression vectors encoding the two HPV oncoproteins and the adenovirus-encoded control protein E1A 12S. TNFα-induced NF-κB activity was only mildly impaired by E6, whereas the inhibitory effect of E7 on NF-κB was more pronounced (Fig. 1A). Maximal NF-κB inhibition was achieved with intermediate amounts of expression vector, whereas NF-κB inhibition was diminished upon expression of higher levels of viral proteins. Also, E6 and E7 encoded by the HPV high-risk strain 18 were negatively interfering with NF-κB activity (data not shown), revealing that the inhibitory activity is not restricted to HPV16. To test whether E7 also inhibits NF-κB that is activated by further stimuli, we determined the effects of E6/E7 expression on NF-κB-dependent reporter gene activity that is induced by IL-1β or phorbol ester. The HPV oncoproteins inhibited NF-κB activity in response to both stimuli (Fig. 1B), indicating that the viral proteins interfere with one or more common steps during NF-κB activation rather than with a single event that is specific for an individual stimulus. Accordingly, E7 also inhibited NF-κB activity that

FIG. 2. Effect of E6 and E7 proteins on NF-κB DNA binding and transactivation. A, rat cells stably transfected with MMTV-E6 were cultured in the presence of dexamethasone (proliferating) or for 48 h in the absence of hormone (arrested). At various time points after the dexamethasone-induced expression of E6, TNFα (1000 units/ml) was added for 15 min to the cells as shown. Equal amounts of protein contained in nuclear extracts were tested for DNA binding activity of NF-κB by EMSAs. An autoradiogram is displayed. The arrow points to the complexes supershifted by αp65 antibodies. The filled arrowhead indicates the location of the DNA/NF-κB complex. The circle indicates the position of a constitutively DNA-binding protein, and the triangle highlights the location of the unbound oligonucleotide. B, the experiment was performed as in A with the exception that cells containing MMTV-E7 were used. C, U2OS cells were transfected with a Gal4-dependent luciferase reporter gene and Gal4, Gal4-p65, or Gal4-VP16 expression constructs. Gene expression was determined in the absence or presence of co-expressed E6 and E7 proteins. To facilitate comparison, maximal gene expression was arbitrarily set as 100%. Bars indicate S.D.
was induced by expression of MEKK1 (data not shown). The inhibitory effect occurred also in other human and murine cell lines (data not shown), excluding cell type-specific effects.

**E6 Interferes with NF-κB-dependent Transactivation, whereas E7 Impairs Induced DNA Binding**—The step within the NF-κB activation cascade affected by HPV E6/E7 expression was investigated by indirect immunofluorescence using αp65 antibodies. The E7 protein was detected with αFLAG antibodies. NF-κB p65 (green) and E7 (red) localization is shown. An overlay of both stains reveals areas of co-localization in yellow. Nuclear DNA was visualized with DAPI (4′,6-diamidino-2-phenylindole).

**FIG. 3.** HPV E7 interferes with TNFα-induced nuclear translocation of NF-κB. H1299 cells were transiently transfected with an expression vector encoding FLAG-tagged E7 and were either left untreated (A) or stimulated for 20 min with TNFα (B). Intracellular localization of p65 was investigated by indirect immunofluorescence using αp65 antibodies. The E7 protein was detected with αFLAG antibodies. NF-κB p65 (green) and E7 (red) localization is shown. An overlay of both stains reveals areas of co-localization in yellow. Nuclear DNA was visualized with DAPI (4′,6-diamidino-2-phenylindole).

**FIG. 4.** E7 is constitutively associated with the IKK. A, U2OS cells were transiently transfected with either empty expression vector or an expression vector for FLAG-tagged E7. One day later cells were lysed, and the E7 protein was immunoprecipitated (IP) from an aliquot of the lysates with αFLAG antibodies. The co-precipitating IKKα protein was detected by immunoblotting using αIKKα antibodies (upper). Aliquots of the whole cell extract (WCE) were tested by immunoblotting for the expression of IKKα and E7 (lower). The position of molecular mass markers is indicated at the left. B, expression vectors for Myc-tagged IKKα and IKKβ and FLAG-tagged E7 were transfected into U2OS cells at the indicated combinations. One day later cells were lysed, and an aliquot of the lysate was used to immunoprecipitate the E7 protein with αFLAG antibodies. The co-precipitating IKK proteins were detected by immunoblotting using αMyc antibodies. In a complementary experiment, another aliquot of the cell lysate was used to immunoprecipitate the IKKs with αMyc antibodies followed by detection of co-precipitating E7 protein with αFLAG antibodies (middle). Five percent of the WCE was analyzed by immunoblotting for the correct expression of the ectopically expressed proteins (lower). Representative results are shown.

was induced by expression of MEKK1 (data not shown). The inhibitory effect occurred also in other human and murine cell lines (data not shown), excluding cell type-specific effects.

**E6 Interferes with NF-κB-dependent Transactivation, whereas E7 Impairs Induced DNA Binding**—The step within the NF-κB activation cascade affected by HPV E6/E7 expression was further analyzed by testing the impact of both proteins on TNFα-induced DNA binding of NF-κB. Primary cells stably transfected with the E6 or E7 gene under the control of the glucocorticoid-inducible MMTV promoter were cultured in the absence or presence of the synthetic steroid dexamethasone. Because of the lack of E6/E7-recognizing antibodies, the hormone-inducible production of both oncoproteins was confirmed by cell proliferation assays (data not shown). TNFα stimulation induced DNA binding of nuclear NF-κB, as determined by EMSAs. Supershift assays showed that the NF-κB/DNA complex contained the transactivating p65 subunit. Whereas dexamethasone-triggered expression of E6 failed to interfere with DNA binding of NF-κB (Fig. 2A), the E7 protein strongly reduced DNA binding of NF-κB (Fig. 2B). The E6 protein interferes with NF-κB-dependent transcription without changing induced DNA binding, raising the possibility that E6 affects NF-κB-dependent transactivation. To test this hypothesis, a nuclear fusion protein between the transactivating NF-κB p65 subunit and the Gal4 DNA-binding domain was tested for its activity in the presence of HPV E6 and E7 proteins. Gal4-p65-induced transcription of a Gal4-dependent luciferase reporter gene was slightly but significantly impaired by E6, whereas E7 had no impact (Fig. 2C). In a control experiment, E6 expression did not interfere with transcription in-
NF-κB Inhibition by E7

Expression of E7 impairs IKK activity and IκBα phosphorylation. A, U2OS cells transfected to express E7 were either left untreated or stimulated for 5 min with TNFα. Cell extracts were analyzed by immunoblotting for the abundance of IκBα (upper). In parallel, the extract was tested by Western blotting for the phosphorylation of IκBα as detected by phosphospecific antibodies (lower). The position of a nonspecific (ns) band is shown. B, HA-tagged IKKα was expressed either alone or in combination with NIK and increasing amounts of E7 in U2OS cells as shown. 24 h post-transfection, cell lysates were prepared, and IKKα was immunoprecipitated. Kinase activity was determined by immune complex kinase assays (KA) using purified GST-IκBα (1–54) as substrate. An autoradiogram from a reducing SDS gel shows IKKα phosphorylation (upper) and phosphorylation of the recombinant substrate protein and a quantitative evaluation obtained by phosphorimaging (middle). A fraction of the cell lysate was analyzed by Western blotting (WB) for expression of IKKα, NIK, and E7 (lower). C, the experiment was done and analyzed as in (B) with the exception that an expression vector encoding IKKβ instead of IKKα was used. Representative experiments are shown.

E7 Partially Co-localizes with NF-κB p65 and Prevents Its TNFα-induced Nuclear Translocation—To test whether impaired DNA binding of NF-κB in the presence of E7 may be caused by the effects on nuclear import of NF-κB, H1299 cells were transfected with an expression vector encodingFLAGtagged E7 or the empty expression vector as a control. The next day, cells were either left untreated or stimulated with TNFα. Double staining with αp65 and αFLAG antibodies was used to identify transfected cells by immunofluorescent staining (Fig. 3A). In unstimulated cells, the p65 subunit was found in the cytoplasm. In agreement with previous reports (38, 39), the E7 protein occurred in the nucleus and the cytoplasm. Double staining for NF-κB p65 and E7 revealed areas of overlapping localization in the cytoplasm, which are shown in yellow. In the absence of E7, TNFα treatment induced complete nuclear localization of p65, whereas expression of this viral oncoprotein strongly interfered with nuclear uptake of p65 (Fig. 3B).

E7 Is Constitutively Associated with the IκB Kinase Complex—The overlapping subcellular localization of E7 and NF-κB p65 raises the possibility of a physical association between this viral protein and the IKC, which was experimentally tested by co-immunoprecipitation experiments. In the absence of antibodies immunoprecipitating the endogenous E7 protein, a FLAG-tagged E7 protein was expressed in U2OS cells. Cells were lysed, and the viral protein was immunoprecipitated from the cell extracts with αFLAG antibodies. Subsequent immunoblotting revealed the occurrence of endogenous IKKα in E7 immunoprecipitates (Fig. 4A), showing an association between the endogenous IKC and the E7 protein. The association between the IKC and E7 was not modulated after TNFα stimulation (data not shown). This interaction was further characterized upon transfection of cells with Myc-tagged versions of IKKα and IKKβ either alone or together with a FLAG-E7 encoding vector. The E7 protein was immunoprecipitated from an aliquot of the cell lysates, and Western blotting showed its association with IKKα and IKKβ (Fig. 4B). In a complementary experimental approach, the IKKs were immunoprecipitated from another aliquot of the cell lysate followed by the detection of associated E7 proteins by Western blotting. These experiments confirmed the E7-IKK interaction by an independent experimental approach. Of note, these biochemical experiments and the co-localization studies revealed only a fraction of the total cellular E7 proteins in association with the IKC.

E7 Interferes with Induced IκBα Phosphorylation and IKK Kinase Activity—To test whether the IKK association of E7 has any consequences for induced IκBα phosphorylation and degradation, U2OS cells were transfected at high efficiency with an E7 expression vector or empty control vector. Cells were either left untreated or stimulated with TNFα, and extracts were tested by immunoblotting for the occurrence of IκBα. Expression of E7 impaired TNFα-induced degradation of IκBα (Fig. 5A). The incomplete protection of TNFα-induced IκBα proteolysis by E7 can be attributed to the limited transfection efficiency of cells. In parallel, determination of IκBα phosphorylation by Western blotting using phosphospecific antibodies...
revealed an impaired TNFα-triggered phosphorylation of IκBα in the presence of E7. To directly test the consequences of E7 expression on IKK activity, cells were transfected with vectors expressing the IKK activator NIK and increasing amounts of E7. The tagged IKKα protein was immunoprecipitated, and its activity was examined by measuring the phosphorylation of the exogenously added substrate protein (GST-IκBα-1 (54)) in immune complex kinase assays (Fig. 5B). NIK-induced kinase activity of IKKα was dose-dependently impaired upon coexpression of E7. The impact of E7 on IKKβ activity was assayed by an analogous experimental approach by ectopically expressing IKKβ instead of IKKα. As already seen for IKKα, the expression of E7 also inhibited NIK-activated IKKβ activity (Fig. 5C), showing that the viral protein can directly interfere with induced kinase activity.

**DISCUSSION**

Given the important contribution of NF-κB to central biological processes, this transcription factor and its activation pathways are frequently targeted by viruses. Early evidence for viral appropriation of the NF-κB pathway came from the finding that the turkey retrovirus REV-T encodes the v-rel protein, an oncogenic homologue to the NF-κB-de-...
33. Hehner, S. P., Hofmann, T. G., Ushmorov, A., Dienz, O., Wing-Lan Leung, I., Lassam, N., Scheidereit, C., Droge, W., and Schmitz, M. L. (2000) Mol. Cell. Biol. 20, 2556–2568
34. De Bosscher, K., Schmitz, M. L., Vanden Berghe, W., Plaisance, S., Fiers, W., and Haegeman G. (1997) Proc. Natl. Acad. Sci. U. S. A. 94, 15504–15509
35. Spitzkovsky, K., Aengevyndt, F., Braspenninck, J., and Knebel Doeberitz, M. (1996) Oncogene 15, 1027–1035
36. Schmitz, M. L., Indorf, A., Limbourg, F. P., Stadtler, H., Traenckner, E. B., and Baeuerle, P. A. (1996) Mol. Cell. Biol. 16, 4052–4063
37. Mizushima, S., and Nagata, S. (1990) Nucleic Acids Res. 18, 5322
38. Mannhardt, B., Weinzierl, S. A., Wagner, M., Fiedler, M., Cohen, P., Jansen-Durr, P., and Zeerschke, W. (2000) Mol. Cell. Biol. 20, 6483–6485
39. Smith-McCune, K., Kalman, D., Robbins, C., Sharma, K., Yungyuen, K., and Bishop, J. M. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 6999–7004
40. Karin, M., and Delhase, M. (1998) Proc. Natl. Acad. Sci. U. S. A. 95, 9067–9069
41. Lee, F. S., Peters, R. T., Dang, L. C., and Maniatis, T. (1998) Proc. Natl. Acad. Sci. U. S. A. 95, 9319–9324
42. Gilmore, T. D. (1992) Cancer Surv. 15, 69–87
43. Hiscott, J., Kwon, H., and Genin, P. (2003) J. Clin. Invest. 107, 143–151
44. Tait, S. W., Reid, E. B., Greaves, D. R, Wileman, T. E., and Powell, P. P. (2000) J. Biol. Chem. 275, 34656–34664
45. Fontaine, V., van der Meijden, E., de Graaf, J., ter Schegget, J., and Struyk, L. (2000) Virology 272, 40–49
46. Kyo, S., Inoue, M., Hayashi, N., Inoue, T., Yutsudo, M., Tanizawa, O., and Hakura, A. (1994) Virology 200, 130–139
47. Malejczyk, J., Malejczyk, M., Majewski, S., Breitburd, F., Luger, T. A., Jablonski, S., and Orth, G. (1994) Int. J. Cancer 56, 589–598
48. Tarteur, E., Gev, A., Sastre-Garaus, X., Fannetier, C., Mosseri, V., Kourilsky, P., and Fridman, W. H. (1994) Cancer Res. 54, 6243–6248
49. Vancurova, I., Wu, R., Miskolci, V., and Sun, S. (2002) J. Virol. 76, 1533–1536
50. Schmitz, M. L., and Baeuerle, P. A. (1991) EMBO J. 10, 3805–3817
51. Viskhanskaya, F., Fabugi, C., Valente, P., and Russo, P. (2002) Int. J. Cancer 97, 732–739
52. Chinami, M., Sasaki, S., Hachiya, N., Yuge, K., Ohnishi, T., Maeda, H., and Shingu, M. (1994) J. Gen. Virol. 75, 277–281
53. Israel, A. (2000) Trends Cell Biol. 10, 129–133
54. Chu, W. M., Ostertag, D., Li, Z. W., Chang, L., Chen, Y., Hu, Y., Williams, B., Perrault, J., and Karin, M. (1999) Immunity 11, 721–731
55. Ryan, K. M., Ernst, M. K., Rice, N. R., and Vousden, K. H. (2000) Nature 404, 892–897.
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