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p53 Down-Regulates Human Bradykinin B1 Receptor Gene Expression

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Abstract The tumor suppressor, p53, has been shown to transcriptionally activate or silence a number of target genes. As an activator, p53 relies on its specific consensus sequence within the promoter. It is not clear whether p53 requires a specific DNA binding site in its action as a gene repressor. This report demonstrates that the human BKB1R gene is a p53 target. Expression of p53 in transiently transfected SV40-transformed IMR90 cells strongly suppressed luciferase reporter activity driven by a 1.8 kb BKB1R promoter as well as its minigene. These down-regulations were p53 dose-dependent. p53 reduced both basal and induced promoter activities of the minigene. Expression of p53 abolished the inducibility of the minigene. Induction of endogenous p53 expression by etoposide also inhibited promoter activity and minigene inducibility. Replacing the region containing both the putative p53 binding site and the TATA-box with a basal adenovirus promoter in the 1.8 kb promoter construct did not prevent p53 from inhibiting BKB1R promoter activity. Thus suppression by p53 is not mediated by competition with the TATA-binding protein and is not through interaction with the putative p53-binding site. p53 also does not appear to suppress BKB1R gene expression through interaction with c-Jun which functions in the inducibility of this gene [Yang et al., 2001]. J. Cell. Biochem. 82: 38–45, 2001.

Key words: tumor suppressor; AP-1; etoposide; minigene; inducible expression; p53 dominant negative

p53 has been defined as a tumor suppressor gene and has been studied extensively in cancer research [Oren, 1999]. The protein has four important structural domains, a transactivation motif at the N-terminus which is essential for regulating p53 target genes, a DNA sequence specific motif in the middle of the protein which is responsible for its binding to p53 consensus DNA sites, a tetramerization motif close to C-terminus which is critical for p53 tetramerization, and a C-terminal regulatory motif which may regulate the capacity of the p53 DNA binding domain to bind to its consensus DNA sequence [Somasundaram, 2000]. Mutations in the DNA binding domain of p53 occur in about 50% of all known tumors [Oren, 1999; Somasundaram, 2000]. Additionally, p53 functions in many physiological and pathological processes, such as normal cell growth, DNA repair, genetic stability, angiogenesis, and apoptosis [Oren, 1999].

p53 activates many target genes by binding to a specific consensus DNA sequence in the promoter region. The sequence consists of two palindromic decamers of 5′-RRRCWWGYYY-3′ (R: purine, W: adenine or thymine, and Y: pyrimidine) separated by 0 to 13 bp, forming four repeats of pentamer 5′-RRRCW-3′ alternating between the sense and antisense strands of the DNA duplex [Oren, 1999]. There are more than 30 p53 target genes, which are activated by p53 [Tang et al., 1998; Elkeles et al., 1999; Thornborrow and Manfredi, 1999; Yu et al., 1999]. Among these, bax, p21, mdm2, gadd45, IGF-BP3, cyclin G, c-fos, and human type IV collagenase genes are activated through the binding of p53 to its consensus DNA binding domain in the promoter region [Bian and Sun, 1997; Tang et al., 1998; Elkeles et al., 1999;

Abbreviations used: BKB1R, bradykinin B1 receptor; BK, bradykinin; LPS, lipopolysaccharide; DAK, des-arg^{10} kallidin; IMRSV, SV40 transformed IMR90 cells; TK, thymidine kinase; adv, adenovirus; SRE, serum response element; TBP, TATA box binding protein; p53^{DN}, p53 dominant negative.

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Thornborrow and Manfredi, 1999; Yu et al., 1999]. The mechanisms of activation of other p53 target genes remain to be defined.

p53 also suppresses many target genes, including cdc2, collagenase-1, cyclooxygenase-2, bcl-2, insulin receptor, presenilin 1, topoisomerase I alpha, map4, hsp70, IL-6, multidrug resistance-associated protein (MRP) gene, and other viral and cellular promoters [Wang et al., 1997; Roperch et al., 1998; Asschert et al., 1999; Subbaramaiah et al., 1999; Sun et al., 1999]. However, no p53 consensus DNA binding site has been defined in the promoters of these genes.

One mechanism for p53 inhibition of target gene expression is its interaction with TBP (TATA-box binding protein) to inhibit the binding of TBP to the TATA box, thus inhibiting efficient initiation of transcription [Seto et al., 1992; Horikoshi et al., 1995; Farmer et al., 1996; Subbaramaiah et al., 1999]. This suppression occurs through direct protein–protein interaction [Subbaramaiah et al., 1999]. However the molecular mechanism of p53 interaction with TBP is unclear.

Evidence is converging to support another inhibitory mechanism of p53, which is repression of target gene transcription through direct interaction with transcription factors. For example, p53 interacts with a CCAAT-binding protein (CBP) in the promoter of hsp70 to inhibit hsp70 expression [Agoff et al., 1993]. An NF-Y transcription factor is required for p53-mediated suppression of cdc2 gene expression [Yun et al., 1999]. p53 inhibits MRP gene expression by diminishing the effect of a powerful transcription activator, Sp1 [Wang and Beck, 1998]. There is a potential interaction between p53 and AP-1 in the suppression of human matrix metalloproteinase-1 gene expression [Sun et al., 1999]. Moreover, other transcription factors, such as cAMP response element-binding protein (ATF/CREB) interact with p53 [Borellini and Glazer, 1993]. These reports suggest that p53 interacts directly with transcription factors to suppress target gene expression.

The bradykinin B1 Receptor (BKB1R) is inducible and G-protein coupled [Marceau et al., 1997; Ahluwalia and Perretti, 1999]. It is rapidly induced by inflammatory mediators, such as interleukin-1β (IL-1β), bradykinin (BK), desArg^{10}- kallidin (DAK), and lipopolysaccharide (LPS) [Marceau et al., 1997; Ahluwalia and Perretti, 1999]. The cDNA of the gene was identified by Menke et al. [1994]. Since then, much progress has been made in deciphering the regulatory mechanisms of this gene, such as the identification of a classic enhancer and exploring the roles of NF-κB, AP-1, and c-Jun in its inducible expression [Ni et al., 1998; Schanstra et al., 1998; Yang et al., 1998, 2001].

While characterizing the promoter of this gene, we found a putative p53 binding site, 5′-GGGCAAGTT*G*gcgatgtcaAAAC ATGTTT-3′, located at −271 to −234 upstream of the transcription start site. This site contains two copies of the p53 consensus binding motif separated by 9 bp with only one mismatch at the first motif. We speculated that p53 binds to the putative p53 binding site to regulate BKB1R expression. We cotransfected p53 with promoter constructs and also a minigene construct, which either contained or lacked the p53 binding motifs, into SV40 transformed IMR90 cells (IMRSV). We found that p53 down-regulates B1 receptor gene expression. Results suggest that p53 does not need to bind to the putative p53 binding site to suppress this gene's expression.

EXPERIMENTAL PROCEDURES

Materials

pcDNA3/c-Jun was a gift from Dr. Michael J. Birrer (NIH). pRSV/p53 and pRSV/p53^{DN} were obtained from Dr. Jim Xiao (Department of Biochemistry, Boston University School of Medicine). p53-Luc and p^{SRE}Luc were purchased from Stratagene. Bradykinin, desArg^{10}-kallidin, lipopolysaccharide (LPS), and etoposide were purchased from Sigma.

Plasmid Constructs

pGl3-BKA, pGl3-BKD, pGl3-BKE, pGl3-BKG, pGL3-TK, and pGL3-E-TK were described in detail in a previous study [Yang et al., 1998]. The minigene design and construction is described in detail in the accompanying communication [Yang et al., 2001]. In brief, this minigene construct, which mimics the genomic structure of human BKB1R gene, contains a 1.8 kb promoter, entire exon I and II, 1.5 kb intron I, entire intron II, and the luciferase coding region.

Cell Culture and Transfection

Log growing SV40-transformed IMR90 cells (IMRSV) cells were plated at a density of 40,000

cells/well in 24-well plates (Coster, Cambridge) in 0.5 ml of MEM with 10% FBS. After 24 h, the cells were cotransfected with 0.5 μg/well of target DNA and 25 ng/well of internal control plasmid (pRL-adv). We did not use the internal control plasmid, pRL-TK, from Promega because the luciferase activity of pRL-TK proved unstable under many conditions. Certain constructs such as enhancer constructs, or some effectors such as phorbol 12-myristate 13-acetate, LPS, and IL-1β increased the expression of pRL-TK. The pRL-adv is a plasmid designed and constructed in our laboratory. It is a very stable and reliable internal control plasmid. Cotransfection with our enhancer constructs, or cytokine stimulation did not affect the luciferase activity of pRL-adv. Transfections were performed using Profection Mammalian Transfection Systems Kit (Promega) following the manufacturer's instructions. After 16 h, the medium was replaced with fresh growth medium. After 6 h, the cells were treated with/without 100 nM BK, 100 nM DAK, or 10 μg/ml LPS. The cells were harvested 24 or 40 h later by lysis with passive lysis buffer (Promega), and dual luciferase activity was determined on TD-20/20 luminometer (Turner Designs, Sunnyvale, CA) and reported as relative luciferase activity. At least three transfections, each in triplicate or duplicate, were performed. Data were expressed as mean ± S.D.

RESULTS

Effect of p53 on Human BKB1R Gene Expression

To analyze the effect of p53 on human BKB1R expression, IMRSV cells were cotransfected with a minigene construct and increasing concentrations of the pRSV/p53 plasmid. The results are shown in Figure 1A. p53 suppressed the minigene activation in a dose dependent manner. Ninety four percent of the minigene promoter activity was lost when 100 ng/ml of p53 was cotransfected. To further verify the suppression of BKB1R gene expression by p53, the IMRSV were transfected with a 1.8 kb BKA promoter construct and the pRSV/p53^{DN} plasmid or increasing concentrations of pRSV/p53 plasmid. As shown in Figure 1B, expression of p53 down-regulated the promoter activity in a similar dose dependent manner as was seen with the minigene. Ninety four percent of the activity was lost when 100 ng/ml of p53 was

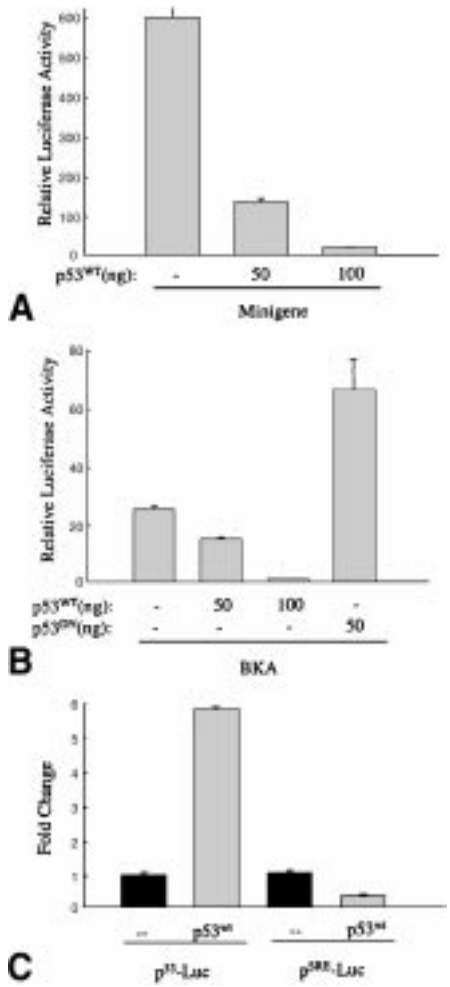


Fig. 1. **A:** Dose dependent suppression of the minigene activity by p53 plasmid. Values are shown as relative luciferase activity (minigene driven luciferase activity divided by second luciferase activity from the pRL-adv plasmid). The indicated values are from a representative experiment performed in triplicate. Each value is the mean±SD. Each experiment was repeated at least three times. p53 represents a pSV/p53 wild type plasmid. The amount of plasmid represent quantity of cotransfected plasmid per ml. **B:** Dose dependent suppression of human BKB1R gene promoter activity by p53 plasmid. Values are shown as relative luciferase activity, which is the BKB1R promoter driven luciferase activity divided by the second luciferase activity from the pRL-adv plasmid. The indicated values are from a representative experiment performed in triplicate. Each value is the mean±SD. Each experiment was repeated at least three times. p53 represents a pSV/p53 wild type plasmid. p53^{DN} represents a dominant negative mutant of p53. The amount of plasmid represents the amount of cotransfected plasmid/ml. The dash sign means that no plasmid was cotransfected with BKA promoter. **C:** Wild type p53 increases reporter activity of p53-Luc but not p^{RSE}-Luc. Values are shown as fold increase of the relative luciferase activity. The indicated values are from a representative experiment performed in triplicate. Each value is the mean±SD. Each experiment was repeated at least three times. p53 represents a pSV/p53 wild type plasmid. The amount of pSV/p53 used in the transient transfection is 100 ng/ml.

cotransfected. On the other hand, 50 ng/ml of the dominant negative p53 increased the promoter activity by more than two-fold. To eliminate a possible artifact caused by expression of p53, we cotransfected p53 cDNA with a p53-Luc plasmid. This plasmid has $15 \times$ p53 binding consensus sequences in the promoter region. This is a standard positive control plasmid used for testing p53 activation [Wang and Beck, 1998]. As a negative control, we cotransfected p53 with a p^{SRE}-Luc plasmid, which contains $5 \times$ SRE consensus sequences [Wang and Beck, 1998]. As results show in Figure 1C, p53 up-regulated the promoter activity of the p53-Luc plasmid by more than 5.6-fold. It did not up-regulate the promoter activity of the p^{RSE} -Luc.

p53 Effect on Inducibility of the Minigene

To determine whether p53 suppresses the inducibility of the minigene, a minigene construct was cotransfected with the pRSV/p53 plasmid into IMRSV treated with/without 100 nM DAK or 10 μg/ml LPS. As shown in Figure 2A, DAK and LPS both up-regulated the minigene activity by 2.6- and 4.0-fold respectively. However, when p53 was cotransfected with the minigene construct, it markedly lowered the basal minigene activity and abolished its induction as shown in Figure 2B.

Action of Endogenous p53 on Minigene Inducibility

To determine whether p53 suppression of BKB1R gene expression occurs naturally in the IMRSV, etoposide was used to induce endogenous p53 expression. Etoposide is a well characterized p53 inducer [Stefanelli et al., 1998; Sun et al., 1999; Yun et al., 1999]. It was added to the IMRSV 1 h before the transfection. As results show in Figure 3, etoposide markedly inhibited 90% of the minigene activity. It also abolished the induction of the minigene. The effect of induced endogenous p53 proved very similar to the effect caused by transfection with the p53 plasmid.

Mechanisms of BKB1R Gene Suppression by p53

To investigate the mechanism of p53 suppression of BKB1R gene expression, we generated a chimeric promoter construct by replacing the basal promoter containing the putative p53 binding site and TATA box with a 60 bp basal

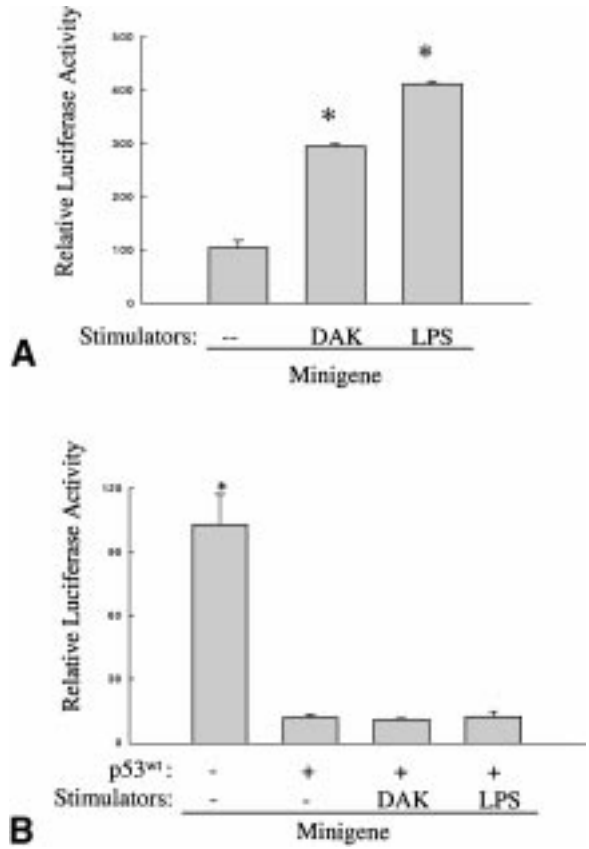


Fig. 2. **A:** Induction of minigene reporter activity by mediators. DAK, des-arg^{10}-kallidin; LPS, lipopolysaccharide. The detailed procedure is described in the methods section. $^*P < 0.01$, for each stimulated group vs. control. Statistical analysis was carried out by one factor analysis of variance (ANOVA) followed by Boferroni method. **B:** Transfection with p53 decreases minigene basal and induced reporter activity. Values are shown as relative luciferase activity. The indicated values are from a representative experiment performed in triplicate. Each value is the mean±SD. Each experiment was repeated at least three times. p53 represents a pSV/p53 wild type plasmid. There is no statistically significant difference in luciferase values between un-stimulated and stimulated groups when these cells were cotransfected with p53. However, there is a statistically significant difference in the luciferase values between no p53-cotransfected group with each of the p53 cotransfected groups. The statistical analysis procedure used is the same as in Figure 2A.

adenovirus promoter, as shown in Figure 4A. We then examined the effect of p53 on this chimeric promoter construct (BKA-adv) following a transient transfection. p53 still strongly inhibited the chimeric promoter activity in a dose dependent manner. 100 ng/ml of p53 plasmid inhibited 98% of the chimeric promoter activity as shown in Figure 4B. Removal of the putative p53 binding site and TATA box did not prevent p53 from inhibiting promoter activity.

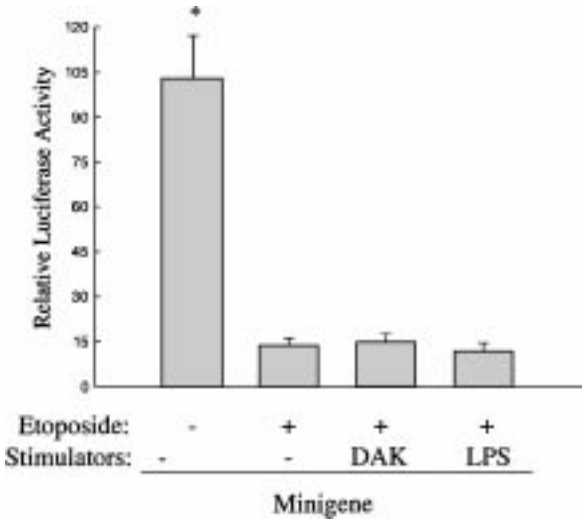


Fig. 3. Endogenous p53 induced by etoposide decreases minigene basal and induced reporter activity. Values are shown as relative luciferase activity. The indicated values are from a representative experiment performed in triplicate. Each value is the mean±SD. Each experiment was repeated at least three times. The + sign means the cells had been incubated with etoposide (10 μM) for 24 h. There is no statistically significant difference in the luciferase values between effector unstimulated and stimulated cells incubated with etoposide. There is a statistically significant difference in the luciferase values between the etoposide treated and untreated groups. The statistical analysis used is the same as in Figure 2A.

These results show that suppression by p53 of BKB1R gene expression is neither through p53 binding to the putative p53-binding site nor through inhibiting the binding of TBP to the TATA box.

p53 Effect on c-Jun Up-Regulation

To further define p53 suppression of BKB1R gene expression, we examined the effect of p53 on basal promoter activity and activity up-regulated by c-Jun. As shown in Figure 5, transfection with c-Jun plasmid up-regulated the activity of variously sized promoter constructs. However, cotransfection with p53 decreased basal as well as induced promoter activity to approximately the same degree. These data suggest that p53 does not inhibit BKB1R gene expression through interaction with c-Jun.

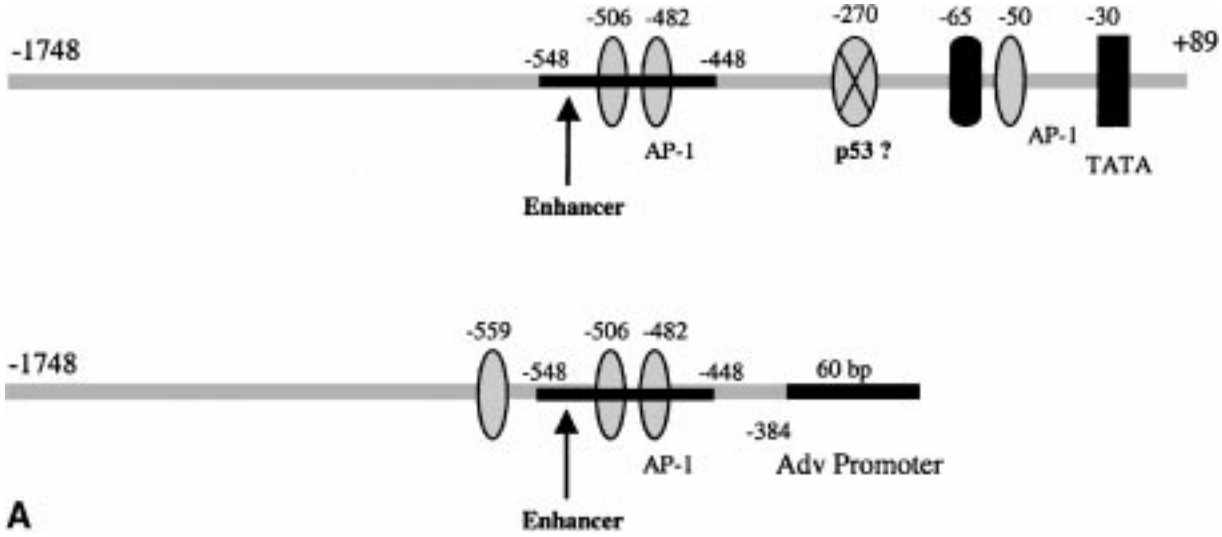
DISCUSSION

In this study, we demonstrate that the BKB1R gene is a p53 target. In the transient transfection assays, p53 markedly down-regulated not only the minigene promoter activity, but also the activity of the promoter constructs. To verify these findings, we designed several experiments. We examined the effect of a p53 dominant negative mutant. Whereas, p53 inhibited the action of the promoter, $p53^{DN}$ increased the promoter action by more than three fold. When $p53^{DN}$ is overexpressed in IMR90SV it should compete with the endogenous p53 to block its suppression of BKB1R gene expression. Thus under basal, non-induced conditions, endogenous p53 is inhibiting the expression of the BKB1R gene and therefore is contributing to its very low expression.

We tested the effect of p53 using p53-Luc and p^{SRE}-Luc plasmids. Expressing p53 should increase the luciferase reporter activity of this plasmid which contains $15 \times$ p53 consensus binding sequence repeats. It should not increase the reporter luciferase activity of the p^{SRE}-Luc plasmid which contains $5 \times$ SRE elements in the promoter region. Indeed, p53 only increased luciferase activity of the p53-Luc plasmid. It slightly decreased luciferase activity of the p^{SRE}-Luc plasmid. These data confirm that the inhibitory effect of p53 on BKB1R gene expression is a specific event.

Experiments with a minigene model of human BKB1R gene, which exhibits induction with mediators, such as DAK, and LPS, illustrated that p53 decreases not only the basal but also induced reporter gene activity. To confirm this as in vivo relevant, we examined the effect of endogenous p53 expression on the minigene activity. Etoposide is used widely to induce endogenous p53 gene expression [Stefanelli et al., 1998; Sun et al., 1999; Yun et al., 1999]. Consistent with these results, endogenous p53 induced by etoposide also markedly reduced basal and induced minigene activity. These results further support a key repressor role for p53 in BKB1R gene expression.

One proposed mechanism for the inhibition of gene expression by p53 is the prevention of TBP binding to the TATA box region [Seto et al., 1992; Horikoshi et al., 1995; Farmer et al., 1996; Subbaramaiah et al., 1999]. To determine whether p53 inhibits BKB1R gene expression through this mechanism, a chimeric promoter construct, modified from the pGL3-BKA plasmid, was generated. The chimeric construct contained a minimal (60 bp) adenovirus promoter replacing the 470 bp promoter fragment containing the classic TATA box. The 60 bp



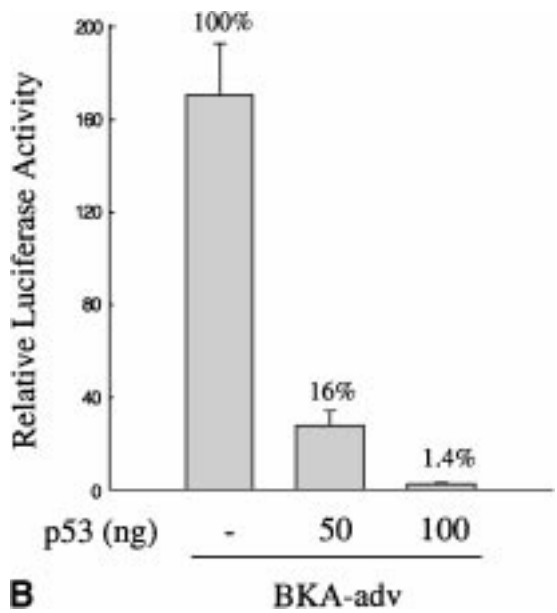


Fig. 4. **A:** Schematic representation of the 1.8 kb and a chimeric promoter. The AP-1, TATA box, p53 putative binding sites and the enhancer are illustrated within the promoter region by different shapes. A 60 bp adenovirus promoter was used to replace the fragment (−384 to +89) of the 1.8 kb promoter construct to generate the chimeric promoter construct BKA-adv. **B:** p53 plasmid decreases chimeric promoter activity in a dose dependent manner. Values are shown as relative luciferase activity. The indicated values are from a representative experiment performed in triplicate. Each value is the mean±SD. Each experiment was repeated at least three times. p53 represents the pcDNA3/c-Jun plasmid. BKA-adv represents the chimeric promoter construct.

promoter originated from the pRL-adv plasmid, a plasmid which is used as a standard internal control in our transfection experiments. This standard control is not affected by p53 overexpression. In addition, a putative p53 consensus binding site, located 270 bp upstream of the transcription start site, was also removed. p53 also inhibited this chimeric promoter activity in a dose dependent manner. Removal of the classic TATA box and the putative p53-binding site did not prevent the inhibitory action of p53. These results suggest, (1) the putative p53 binding site is not required for p53 to inhibit BKB1R gene expression and (2) p53 inhibits BKB1R gene expression through mechanisms other than through competition with TBP for binding to the TATA box.

Another proposed mechanism for p53 inhibition is through interaction with key transcription activators of the target gene [Agoff et al., 1993; Wang and Beck, 1998; Sun et al., 1999; Yun et al., 1999]. c-Jun is proving to be such a key activator of the BKB1R gene [Yang et al., 2001]. To determine whether p53 inhibits BKB1R gene expression through interaction with c-Jun, we examined its effect on c-Jun's activation. Results suggest that p53 does not interact directly with c-Jun. Taken together,

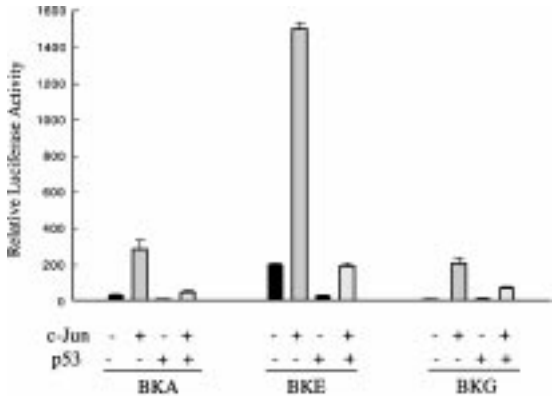


Fig. 5. Transfection with p53 plasmid decreases basal and c-Jun up-regulated minigene activity. c-Jun represents the pcDNA3/c-Jun plasmid. p53 represents the pSV/p53 plasmid. BKA is a 1.8 kb promoter construct. BKE is a 693 bp promoter construct. BKG is a 473 bp promoter construct. These promoter constructs were described in detail previously [Yang et al., 1998] Values are shown as relative luciferase activity. The indicated values are from a representative experiment performed in triplicate. Each value is the mean±SD. Each experiment was repeated at least three times.

these results suggest that p53 inhibits BKB1R gene expression but through interactions not directly related to the induction of this gene.

A recent publication [Saifudeen et al., 2000] reported that p53 activates the expression of the bradykinin B2 receptor gene expression. Up to now, bradykinin B1 and B2 receptors are the only two G-protein coupled receptors reported to be subject to p53 regulation. The opposite effects of p53 on BKB2R and BKB1R genes may ultimately prove physiologically relevant.

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