Isolation and Characterization of the Hamster gadd153 Gene

ACTIVATION OF PROMOTER ACTIVITY BY AGENTS THAT DAMAGE DNA*

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A group of five cDNA clones, representing the gadd genes, were recently isolated from Chinese hamster ovary (CHO) cells as genes induced upon growth arrest and after DNA damage (Fornace, A. J., Jr., Nebert, D. W., Holland, M. C., Luethy, J. D., Pappas, M., Fargnoli, J., and Holbrook, N. J. (1989) Mol. Cell. Biol. 9, 4196-4203). We have isolated and characterized one of these genes, gadd153. The gene spans five kilobases and contains four exons. The 5'-flanking region of the gene, within 420 base pairs of the transcription initiation site, contains a number of cis elements associated with transcriptional regulation in other genes. These include a Hoggness box, ATAAAA, an inverted GCCAAT box; seven SP1 transcription factor binding sites, and an AP-1 site. This region is rich in G+C content (>70%) and contains an unusually long stretch of alternating CpG residues. The 800-base pair region immediately upstream of the transcription start site can drive expression of the bacterial chloramphenicol acetyltransferase (CAT) gene, but only in its endogenous orientation, in three different cell lines: HeLa, CHO, and Jurkat. The gadd153 promoter is strongly activated by methyl methanesulfonate, hydrogen peroxide, and UV irradiation, but not by growth arrest signals. This suggests that separate and very different regulatory pathways are involved in the induction of the gadd153 gene by growth cessation and DNA damage.

Treatment of bacteria with agents that damage DNA or inhibit its replication invokes a series of phenotypic alterations referred to as the SOS response (2). The response is presumed to be necessary to overcome the initial effects of the stress as well as to repair the potentially lethal damage. In Escherichia coli, some 20 different genes in metabolically diverse pathways are coordinately activated by DNA damage. While the precise functions of many of the activated genes have not been determined, it is clear from studies with various mutants that they are critical for growth control and survival. Eukaryotic cells also respond to DNA damage with the induction of numerous genes (3-9), but much less is known about the mechanism(s) controlling the DNA damage response in higher organisms. A protein kinase, presumably protein kinase C, is involved in mediating the induction of mammalian genes by UV. First, many of the known UV-responsive genes are also highly induced by phorbol esters which activate protein kinase C (3, 5, 7-9). Secondly, UV induction of several of these genes has been shown to be blocked by treatment with inhibitors of protein kinase C (7, 8). Finally, for three different UV-inducible genes, c-fos, human immunodeficiency virus type 1 (HIV-1), and collagenase, the UV-responsive elements have been shown to coincide with the enhancer regions of these genes which are also responsive to TPA (9). Since protein kinase C plays a central role in cellular signal transduction in many different circumstances, its activation by UV may represent a general cellular response to stressful external stimuli.

Recently, Fornace et al. (1) described a unique class of genes cloned from Chinese hamster ovary (CHO) cells whose expression was induced by both growth arrest and DNA damage (designated gadd). In contrast to the genes described above, the gadd genes are not induced by TPA. Their unique pattern of expression is of particular interest as a well known effect of DNA damage in both bacteria and eukaryotes is a transient inhibition of DNA synthesis and delay in cell cycle progression (10, 11). For example, the suda SOS gene in bacteria codes for a protein associated with growth arrest (12), and the RAD9 gene is responsible, at least in part, for the delay of cell cycle progression following DNA damage in yeast (13). It is possible that the gadd genes have a similar role in mammalian cells. As a step toward understanding more about their regulation, we have begun to isolate several of these genes. Here we report the isolation and characterization of the gene corresponding to gadd153. Sequence analysis of the region upstream of the gene revealed potential binding sites for several general transcription factors. The 5'-flanking region was linked to the bacterial reporter gene, chloramphenicol acetyltransferase (CAT), and used in transient assays to identify an 800-bp sequence which exhibits monodirectional basal promoter activity and which can be further activated by treatment with DNA damaging agents.

EXPERIMENTAL PROCEDURES

Screening of the Genomic Library—A CHO genomic DNA library was custom-synthesized in bacteriophage EMBl-3 for us by Clontech (Palo Alto, CA). The DNA was partially digested with the restriction endonuclease Mbol and fractionated on a sucrose gradient to yield 80-kb fragments which were pooled and cloned into the BamHI site of pUC13.

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The nucleotide sequence(s) reported in this paper has been submitted to the GenBank™/EMBL Data Bank with accession number(s) J05613.

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1 Abbreviations used are: TPA, 12-O-tetradecanoyl phorbol-13-acetate; bp, base pair(s); CHO, Chinese hamster ovary; CAT, chloramphenicol acetyltransferase; kb, kilobase(s); MMS, methyl methanesulfonate; PGA, prostaglandin A2; RNR2, ribonucleotide reductase 2; DMEM, Dulbecco's Modified Eagle's Medium.
and 70 bp of 5' coding sequence; the 3' probe is a 275-bp sequence corresponding to the 5' coding and untranslated region of the gadd153 cDNA (1). Genomic fragments of interest were subcloned into pUC19. Either Sequenase (U.S. Biochemical Corp.), T7 DNA polymerase (Pharmacia LKB Biotechnology Inc.), or avian myeloblastosis virus reverse transcriptase (Promega) as recommended by the manufacturers. Multiple synthetic oligonucleotide primers (Midland Certified Reagents Co.) were made for both strands.

**Primer Extension Analysis**—Total RNA was prepared from untreated or methyl methanesulfonate (MMS)-treated CHO cells by lysis in situ with guanidine thiocyanate and centrifugation through CaCl2. The primer extension was performed essentially as described byDean et al. (14). A 35-mer oligonucleotide primer spanning bases +43 to +77 of the gadd153 cDNA was radiolabeled at the 5' end with [α-32P]ATP (Du &t-New England Nuclear) and T, polynucleotide kinase (Pharmacia). The labeled primer (0.2 pmol) was annealed to extended DNA products, the 35-mer primer annealed to subcloned genomic 5' gadd153 sequences and with a 3' probe encompassing most of the remaining cDNA. While all three isolates contained the 3' end of the gene, only the A5 clone contained the 5' end of the gene and its flanking sequences (evidenced by the 1.9-kb Smal fragment in Fig. 1A). The 13-kb insert of A5 was further mapped, subcloned, and sequenced to identify the mRNA coding as a single copy in the CHO genome.

**Construction of CAT Recombinant Plasmids**—The gadd153-CAT fusion plasmid was generated first by digestion of the gadd153 5' flanking DNA (Fig. 1A) at the EcoRI site (−778) followed by a blunt end/fill-in reaction and Clal linker ligation. Oligonucleotides were synthesized for each strand from the endogenous Psdl site at −10 to 21 bases downstream of the major cap site where a HindIII site was added at the 3' end. These oligonucleotides were annealed and then ligated to the genomic DNA at the −10 Psdl site. The entire fragmentation from −778 to +221 was then directionally cloned into and sequenced with the 0.4-kb weakly hybridizing band (data not shown).

**RESULTS**

**Isolation and Characterization of the gadd153 Gene**—An EMBL-3 library prepared from size-fractionated genomic CHO DNA was screened for the gadd153 gene using gadd153 cDNA sequences as probes. Three positive phage clones obtained in the initial screen (Fig. 1C) were rescreened with a 251-bp Psdl fragment containing the 5' gadd153 cDNA sequences and with a 3' probe encompassing most of the remaining cDNA. While all three isolates contained the 3' end of the gene, only the A5 clone contained the 5' end of the gene and its flanking sequences (evidenced by the 1.9-kb Smal fragment in Fig. 1A). The 13-kb insert of A5 was further mapped, subcloned, and sequenced to identify the mRNA coding as a single copy in the CHO genome.

**Mapping of the Transcriptional Start Site and Analysis of 5' Flanking Sequences**—Primer extension analysis was used to map the transcriptional start site of the gadd153 gene. Total RNA from untreated or MMS-treated CHO cells was annealed to a 35-mer oligonucleotide synthesized to span bases +43 to +77 of the gadd153 cDNA, and transcripts were generated by reverse transcriptase. To demonstrate specificity of the oligomer for gadd153 and to accurately map the extended products, the 35-mer oligonucleotide was used as a primer to sequence the EH plasmid clone (Fig. 1B) containing 5' sequences of the gadd153 gene. As shown in Fig. 2, two major extension products were identified. The "A" residue, represented as nucleotide +1 in Fig. 3, corresponds to the smaller, more abundant transcript (Fig. 2) which confirmed the predicted genomic structure based on mapping analysis and suggest the gene is expressed as a single copy in the CHO genome.

**Cells, Media, and Transfections and Treatments**—All cell lines were maintained in medium supplemented with 10% fetal bovine serum (Hyclone) and 50 μg/ml gentamicin (Gibco). HeLa cells were grown in Dulbecco's modified Eagle's medium (DMEM, Gibco). CHO-K1 (CHO) cells were grown in Ham's F-12 medium (Gibco). Jurkat cells were maintained in suspension in RPMI 1640 medium (Gibco).

**All treatments to the transfected cells were performed 24 h after transfection.** Methyl methanesulfonate (MMS; Aldrich) and hydroperoxide were added at the 3' end. These oligonucleotides were annealed and then ligated to the genomic DNA at the −10 Psdl site. The entire fragmentation from −778 to +221 was then directionally cloned into and sequenced with the 0.4-kb weakly hybridizing band (data not shown).

**Inspection of the gadd153 5' flanking sequences, diagrammed in Fig. 3, shows that the promoter region from −420 to +1 is relatively (G + C)-rich (71%), a characteristic of many housekeeping genes. Seven putative SP1 factor binding sites are present within this region. A TATA-like sequence, ATAAA, is present 32 bp 5' of the cap site and an inverted GCCAT box is located at −76 to −80. A consensus AP-1 sequence, TGACTCA, resides at −246 to −240. Immediately
FIG. 1. Structure of the gadd153 gene and subclones. A, restriction map of the gadd153 gene and flanking sequences is shown. The four exons are designated as black boxes and are numbered. The lines subcloned into pUC19 vectors using the restriction sites shown in A. C, the three genomic clones isolated from a CHO genomic library as indicated under “Experimental Procedures.” The lines represent the genomic DNA sequences corresponding to the map in A which were flanked by the EMBL3 phage arms.

upstream of this site is an unusually long stretch of CpG sequences.

Inducible gadd153 Promoter Activity in the 5′ Flanking Region—To determine whether the genomic sequences located 5′ of the gadd153 mRNA start site exhibit promoter activity, we constructed a chimeric gene, gadd153-CAT, containing the 5′ flanking sequence from −778 through the transcriptional start site to +21 fused to the bacterial CAT reporter gene. The gadd153-CAT plasmid was transiently transfected into mammalian cells and assayed for CAT activity to test for functional promoter activity and to determine the effects of various DNA-damaging agents on promoter activity. A typical CAT assay, shown in Fig. 4A, demonstrates the high basal level transcriptional activity of gadd153-CAT relative to its promoterless parent vector, JymCATO, in HeLa cells. Treatment of the transfected cells with the alkylating agent MMS (100 μg/ml) for 4 h increased the gadd153 promoter activity more than 29-fold over basal levels. Placement of the promoter sequence in the antisense orientation relative to the CAT coding sequences resulted in no CAT activity, even with MMS treatment. As a point of reference, Fig. 4A includes the level of CAT expression observed in the same experiment from the SV40 early promoter plus enhancer sequences (pSV2CAT). The level of CAT activity obtained from the gadd153 promoter in the presence of MMS is similar to that seen with pSV2CAT. To demonstrate that the effect of MMS on the gadd153 promoter is not just a nonspecific effect due to a toxic effect of MMS to the cells, we also examined the effect of MMS on CAT expression driven by the β-actin promoter as previous studies showed that endogenous actin mRNA levels in mammalian cells were not elevated by MMS treatment (1). The results in Fig. 4B show that MMS treatment resulted in less than a 2-fold increase in β-actin promoter activity. A similar small increase in the activity of several other promoters (actin, β-tubulin, and CYC1) following MMS treatment has previously been reported in yeast and is believed to represent a nonspecific effect of the treatment (19). In contrast, the specific enhancement of gadd153 promoter activity is at least 15-20-fold higher than this general effect.

The gadd153 promoter was found to be active in a variety of cell types, and, as shown in Table II, expression of the transfected gadd153-CAT chimeric gene in three different cell lines was greatly enhanced following MMS treatment. Surprisingly, the promoter sequences were least responsive to MMS when transiently expressed in CHO cells, the cells from which the gene was isolated. Since the greatest MMS induction of gadd153-CAT was observed in HeLa cells, this cell line was used for further transient transfections and analyses.

Transcriptional activity from the gadd153 promoter was enhanced by various DNA-damaging agents in a dose-dependent manner (Table III). Treatment of transiently transfected HeLa cells with increasing MMS concentrations resulted in corresponding increased levels of CAT activity (Table III). This dose-responsive increase in gadd153 promoter-driven CAT expression is consistent with that seen for the induction of endogenous gadd153 mRNA expression in CHO cells (1). Hydrogen peroxide and UV irradiation, two other treatments which damage DNA and have been shown to increase gadd153 mRNA expression in CHO cells, also increased gadd153 promoter activity in a dose-dependent fashion (Table III).
FIG. 2. Primer extension analysis of endogenous gadd153 message. A gadd153-specific primer was annealed at various temperatures designated above the lanes to total RNA from CHO cells which had been treated with (+) or without (-) MMS as described under “Experimental Procedures.” The cDNA was extended and displayed on an 8% acrylamide gel. Arrows point to the extended products which can be mapped to specific nucleotides in the sequence shown to the right. The sequence was generated from the gadd153-specific primer annealed to the EH genomic subclone (Fig. 1B).

FIG. 3. Sequence of the gadd153 promoter region. The arrow marks the most 3’-transcriptional start site, of which the “A” nucleotide is designated as +1. The TATA-like box is underlined with a solid line; the inverted GCCAAT sequence is underlined with a boldfaced broken line. Consensus sequences for SP1 factor binding sites are boxed in solid borders; the consensus AP-1 site is boxed in broken borders. Restriction enzymes are labeled, and arrows mark their cutting sites.

FIG. 4. CAT activity of gadd153-CAT fusion gene. The constructs were transfected into HeLa cells, treated with (+) or without (-) MMS, and assayed for CAT activity as described under “Experimental Procedures.” A, CAT activities observed with 200 μg of protein per 2 h assay from the same transfection experiment. PSV represents the pSV2CAT plasmid; JYM designates the promoterless CAT vector, JYMCA; 153-S describes the gadd153-CAT construct with the promoter region in the sense orientation relative to the CAT gene; 153-A represents the gadd153 promoter in its antisense orientation fused to the CAT gene. B, a separate transfection experiment comparing the effects of MMS on CAT activity directed by gadd153 promoter (153-S) and the β-actin promoter (Actin).

TABLE II

| Cell type             | Relative fold induction by MMS | Relative fold induction by TPA |
|-----------------------|-------------------------------|-------------------------------|
| HeLa (human epithelial)| 27.12                         | 2.03                          |
| Jurkat (human T-cell) | 15.39                         | 3.41                          |
| CHO (Chinese hamster ovary) | 10.15                  | 0.97                          |

Stein et al. (9) reported that the UV response element in the human collagenase gene is identical with the cis-acting element, an AP-1 site, which is responsive to phorbol esters. Previous studies (1) showed that, in CHO cells, the endogenous gadd153 expression was not altered by TPA treatment, and we have observed that endogenous gadd153 mRNA levels in HeLa and Jurkat cells are not affected by TPA (not shown). However, since the gadd153 promoter region contains a perfect AP-1 consensus sequence, it was important to determine if gadd153 promoter activity would be affected by TPA. Results in Table II demonstrate that TPA had little or no effect on gadd153 promoter expression in either HeLa or CHO cells,
but did enhance the expression in Jurkat cells by about 3.5-fold. However, this is still much lower than the effect seen with MMS.

**Effect of PGA on gadd153 Promoter Activity**—In addition to DNA damage, gadd153 mRNA levels are greatly enhanced by treatments or culture conditions which result in the growth arrest of cells. In particular, we have found that the treatment of HeLa cells with PGA, a cyclopentenoone prostaglandin which arrests HeLa cells in the G1 phase of the cell cycle (20), increases levels of gadd153 mRNA by about 20-fold within 12 h of treatment. It was therefore of interest to determine if the gadd153 promoter activity would also be affected by treatment with PGA (Fig. 5). In contrast to its effect on endogenous gadd153 mRNA levels, PGA had no effect on the promoter activity of the gadd153 promoter construct transfected into HeLa cells. Twenty-four h later, the cells were treated overnight with 10 μg/ml PGA.

**DISCUSSION**

*gadd153* is one of a class of 5 genes which are induced in mammalian cells both by DNA damage and growth arrest. While the function of these genes is at present unknown, their pattern of expression following DNA damage and/or growth arrest suggests they play a role in the response or adaptation to adverse conditions.

The gadd153 gene has several characteristics of housekeeping genes. It is ubiquitously and constitutively expressed at low levels in mammalian cells, and the 5′ region of the gene is highly rich in G-C content with seven high affinity binding sites for the RNA polymerase II transcription factor SP1 (21, 22). However, unlike most housekeeping genes, the promoter region lacks multiple transcription initiation start sites, and has a putative TATA box, an ATAAAA sequence, 30–32 bp upstream from the two adjacent transcription start sites. This sequence is also present in at least two other mammalian genes, keratin (23) and skeletal β-actin (24). In addition, the promoter region contains an inverted GCCAAT sequence, a putative binding site for one or more CCAAT binding transcription factors (22, 25).

Previous studies indicated that both DNA damage-induced and growth-related increases in gadd153 mRNA levels were due at least in part to increased transcription of the gene (1). Here, functional promoter activity of the 5′ flanking region was examined using transient CAT expression assays. The genomic segment from −778 to +21 proved to be an active promoter in a variety of cell types. Furthermore, CAT-driven expression from the gadd153 promoter was greatly increased by three different DNA damaging agents, MMS, UV-irradiation, and hydrogen peroxide. Interestingly, the effect of MMS on promoter activity was least dramatic in CHO cells, the cells from which the gene was cloned, and in which the endogenous mRNA levels are increased in 40-fold by treatment with MMS. In addition, the effect of UV-irradiation on promoter activity (80-fold increase) was much greater than the effect seen on the endogenous gene mRNA levels (<10-fold increase) at similar UV dosage (14–15 J/m²). These apparent discrepancies are likely the result of additional factors involved in the regulation of gadd153 expression such as post-transcriptional mechanisms which are not addressed in these assays. In this regard, we have obtained preliminary evidence which indicates that gadd153 mRNA levels are much more stable in MMS-treated cells (data not shown). Further experiments are necessary to clarify the contributions of both transcriptional and post-transcriptional mechanisms in controlling expression of gadd153 with various DNA damage treatments.

It will be of interest to determine exactly which sequences in the 5′ region of the gadd153 gene mediate its response to DNA damage and whether these elements resemble those mediating the induction of other eukaryotic genes after DNA damage. The yeast ribonucleotide reductase 2 gene (RNR2) has recently been shown to contain a 42-bp region, designated the DNA damage response element, which mediates the induction of the gene in cells after MMS treatment (26). However, additional elements including three upstream activating sequences and a repressor element within 600 bp 5′ of the transcriptional start site also influence this expression (19, 26). The 5′ flanking region of the gadd153 gene shows no homology to the 42-bp DNA damage response element of RNR2.

Deletion studies are currently in progress to identify the specific sequences involved in the induction of gadd153 expression by DNA damaging agents. One possible element is the region comprising the consensus sequence for binding of the AP-1 family of proteins. An AP-1 consensus sequence is also present in the human collagenase gene where it was first described as a TPA response element, but has subsequently been shown to play a role in mediating UV-induced expression of the gene (9). Similarly, the TPA-responsive elements in the c-fos and HIV-1 genes (the serum response element and NFκB site, respectively) are also believed to mediate the induction of these genes by UV irradiation (9).

**TABLE III**

Enhancement of gadd153-CAT expression in HeLa cells after exposure to DNA-damaging agents

HeLa cells were transiently transfected with gadd153-CAT and treated with or without the indicated agents 24 h after transfection. Cells were harvested 48 h after transfection and assayed for CAT activity as described under “Experimental Procedures.” The relative activity of treated cells transfected and harvested at the same time.

| Treatment               | Condition | Relative fold induction |
|-------------------------|-----------|------------------------|
| MMS                     | None      | 1.00                   |
|                         | 10 μg/ml, 4 h | 1.14                   |
|                         | 50 μg/ml, 4 h | 6.42                   |
|                         | 100 μg/ml, 4 h | 26.20                  |
|                         | 200 μg/ml, 4 h | 36.31                  |
| Hydrogen peroxide       | None      | 1.00                   |
|                         | 100 μM, 1 h | 5.14                   |
|                         | 200 μM, 1 h | 9.60                   |
|                         | 400 μM, 1 h | 13.80                  |
| UV irradiation          | None      | 1.00                   |
|                         | 5 J/m²    | 3.70                   |
|                         | 15 J/m²   | 78.70                  |
|                         | 30 J/m²   | 122.60                 |

**Fig. 5.** Effect of PGA on gadd153 mRNA and promoter activity. Left, HeLa cells were treated with PGA overnight, after which RNA was isolated and analyzed by dot-blot analysis. Lane 1, control untreated cells; lane 2, 6 μg/ml PGA; lane 3, 12 μg/ml PGA. Right, the gadd153-CAT construct was transfected into HeLa cells. Twenty-four h later, the cells were treated overnight with 10 μg/ml PGA.
However, the gadd153 gene in HeLa and CHO cells is not induced by treatment with TPA and in Jurkat cells it is only modestly affected by TPA (Table II). More detailed studies will be necessary to determine whether this AP-1 site in gadd153 does in fact play any role in the regulation of the gene by DNA damage, and, if so, which members of the AP-1 family of transcriptional proteins are involved.

Arrest of the cell cycle is characteristic of both bacterial and mammalian cells’ response to DNA damage (10, 11). Arrest can occur anywhere between the G1/S border and G2 phase, depending on where the cell is in the cycle at the time of damage, and the type or degree of DNA damage. It is interesting therefore that gadd153 is also highly induced by treatments unrelated to DNA damage in which growth arrest is induced by PGA2. These facts suggested that there is a common signal pathway involved in the regulation of gadd153 expression by DNA damage and growth arrest. However, the results presented here indicate that the regulation of gadd153 by PGA2 and MMS are quite different. PGA2, which induces growth arrest and induces high levels of the gadd153 mRNA in both HeLa and CHO cells, has no effect on the activity of our gadd153 promoter-CAT construct. It is possible that the cis elements responsive to PGA2 lie outside of the genomic segment we have used in these studies, being further upstream or downstream, perhaps within an intron. We have, however, extended our promoter-CAT construct to include sequences up to −1300 bp 5’ of the cap site; this is still unaffected by PGA2 (not shown). Alternatively, the regulation may occur primarily at the post-transcriptional level. Preliminary studies suggest that like MMS, PGA2 does stabilize gadd153 mRNA levels.

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