BRCA1 Regulates GADD45 through Its Interactions with the OCT-1 and CAAT Motifs*

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BRCA1, a breast and ovarian cancer susceptibility gene, has been implicated in gene regulation. Previous studies demonstrate that BRCA1 induces GADD45, a p53-regulated and stress-inducible gene that plays an important role in cellular response to DNA damage. However, the mechanism(s) by which BRCA1 regulates GADD45 remains unclear. In this report, we have shown that BRCA1 activation of the GADD45 promoter is mediated through the OCT-1 and CAAT motifs located at the GADD45 promoter region. Site-directed mutations of both OCT-1 and CAAT motifs abrogate induction of the GADD45 promoter by BRCA1. Both OCT-1 and CAAT motifs are able to confer BRCA1 inducibility in a nonrelated minimal promoter. Physical associations of BRCA1 protein with transcription factors Oct-1 and NF-YA, which directly bind to the OCT-1 and CAAT motifs, are established by biotin-streptavidin pull-down and coinmunoprecipitation assays. Such protein interactions are required for interaction of BRCA1 with the GADD45 promoter because either immunodepletion of Oct-1 and NF-YA proteins or mutations in the OCT-1 and CAAT motifs disrupt BRCA1 binding to the GADD45 promoter. These findings indicate that BRCA1 can up-regulate its targeted genes through protein-protein interactions and provide a novel mechanism by which BRCA1 participates in transcriptional regulation.

Mutations of the breast cancer susceptibility gene, BRCA1, are associated with more than half the cases of hereditary breast cancer (1–3). The human BRCA1 gene encodes a nuclear protein of 1863 amino acids and is expressed in a variety of human tissues (3, 4). Neoplastic development in BRCA1 mutation carriers is generally accompanied by loss of the wild-type allele, suggesting BRCA1 protein may function as a tumor suppressor. A number of observations have implicated BRCA1 in cellular response to DNA damage. BRCA1 associates and colocalizes with Rad51 protein and may be involved in DNA recombinogenic repair. Following DNA damage, BRCA1 becomes hyperphosphorylated by ATM (5) and hCDC2/Chk2 (6) and relocates to complexes containing proliferating cell nuclear antigen (7). Additionally, BRCA1 plays an important role in the transcription-coupled repair (8) and in the control of cell cycle arrest following DNA damage (9, 10). Recently, multiple reports (11–13) have suggested that BRCA1 might also play a role in apoptosis. Therefore, through its functions in DNA repair process, apoptosis, and cell cycle arrest, BRCA1 plays an important role in the maintenance of genomic integrity. This is strongly supported by the demonstration that murine embryos carrying a BRCA1 null mutation exhibit hypersensitivity to DNA damage and chromosomal abnormalities, probably due to defective G1/M checkpoint control and improper centrosome duplication (14).

GADD45 is a DNA damage-responsive gene and is induced by a wide spectrum of genotoxic stress agents, including ionizing radiation, UV radiation, methyl methanesulfonate (MMS), and medium starvation (15–17). It has been shown that induction of GADD45 after DNA damage is mediated via both p53-dependent (18, 19) and -independent pathways (20). Expression of Gadd45 protein suppresses cell growth (21, 22). Gadd45 protein is able to associate with multiple important cellular proteins, including proliferating cell nuclear antigen (23), p21 (24, 25), Cdc2 (26), core histone (27), and MTK1/MEKK4 (28). Recent findings suggest that GADD45 is involved in the control of cell cycle checkpoint (29) and apoptosis (28, 30). This argument is further supported by the finding that GADD45-null mice exhibit significant genomic instability, which is exemplified by aneuploidy, chromosomal aberrations, and gene amplification, and increased carcinogenesis following treatment with DNA damage (31). Therefore, GADD45 appears to be an important player in maintenance of genomic stability.

Several lines of evidence support a role for BRCA1 in transcriptional regulation. BRCA1 has an N-terminal ring finger domain and a C-terminal transcription activation domain that activates transcription when fused to a DNA-binding domain (32). It has been shown that BRCA1 interacts with transcriptional regulators, including p53 (33, 34), c-Myc (35), STAT1 (36), and estrogen receptor (37), and proteins involved in chromatin remodeling including p300/CBP (38) and RBAP46/HDAC (39). Expression of BRCA1 activates or suppresses expression of several important cellular proteins, such as p21WAF1/CIP1 (10) and cyclin B1 (40). Most recently, studies from our group and others (30, 40, 41) have demonstrated that BRCA1 strongly activates GADD45 in a p53-independent manner. Activation of the GADD45 promoter requires normal transcription-activating function of BRCA1 because the tumor-derived BRCA1 mutants (1749R and Y1853insA), which lack transcription activity, are unable to activate the GADD45 pro-

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† The abbreviations used are: MMS, methyl methanesulfonate; CAT, chloramphenicol acetyltransferase; PBS, phosphate-buffered saline; GFP, green fluorescence protein; wt, wild type; mut, mutant.
OCT-1 and CAAT Motifs Mediate the BRCA1 Activation of GADD45

In this article, we identify OCT-1 and CAAT as the BRCA1-regulatory elements required for BRCA1 activation of the GADD45 promoter. Disruptions of the OCT-1 and CAAT motifs abolish activation of the GADD45 promoter by BRCA1. Moreover, BRCA1 physically associates with OCT-1 and NF-YA transcription factors. These results characterize an important molecular mechanism by which BRCA1 regulates GADD45.

**EXPERIMENTAL PROCEDURES**

**Plasmid Clones**—The following GADD45 promoter reporter constructs were used: pH45-CAT1, pH45-CAT2, pH45-CAT5, pH45-CAT7, pH45-CAT11, pH45-CAT12, and pH45-CAT13 (53, 54). GADD45 promoter reporters that contain mutations in either OCT-1 or CAAT box motifs, which are found in 30% of eukaryotic promoters (50, 51). Recently, both OCT-1 and NF-YA, but not NF-YB and NF-YC, were found to be induced following treatment with 51). NF-Y specifically binds CAAT AGTCAAAA consensus sequence through its DNA-binding domain family, is ubiquitously expressed and binds to the GADD45 factors may participate in cellular response to DNA damage (52). OCT-1 and CAAT Motifs Mediate the BRCA1 Activation of GADD45. More-
of the GADD45 promoter region, was cotransfected with either pCMV.neo (Neo) or pCR3.BRCA1 (BRCA1) into the human breast carcinoma MCF-7 cell line (wt p53), human colorectal carcinoma HCT116 cell line (wt p53), or HCT116 p53−/− cell line (where p53 alleles were deleted via homologue recombination), the GADD45 promoter reporter was strongly activated in all cell lines regardless of p53 status. To determine transfection efficiency, GFP expression vector was cotransfected with each tested plasmid, and the expression of GFP protein detected by immunoblotting analysis indicated that transfection efficiency was similar among different samples with variations less than 20%. To map the BRCA1-responsive elements in the GADD45 promoter, a series of the CAT reporters that spanned promoter region, was cotransfected with either pCR3.BRCA1 (BRCA1), pCMV.neo (Neo), or pC53-SN3 (p53). The CAT assays were performed, and the CAT activities were measured as described under “Experimental Procedures.” In some cases, the cells transfected with PG-CAT−107−57 alone were treated with UV radiation or MMS and followed by CAT assay. All experiments presented in A and C were repeated at least three times, but only a representative experiment of CAT assay is shown here. D, DNA sequence analysis indicates that there are two OCT-1 sites and one CAAT box located at the region of the GADD45 promoter from −107 to −62.

BRCA1 Activation of the GADD45 Promoter Is Mediated through Both OCT-1 and CAAT Motifs—To determine whether the OCT-1 and CAAT box motifs play roles in activating the GADD45 promoter following expression of BRCA1, we mutated the OCT-1 or CAAT motifs in GADD45 promoter (Fig. 1D). It should be noted here that our previous work (54) has demonstrated that there are certain regulatory elements located more upstream of the GADD45 promoter, such as EGR1/WT1. Therefore, to exclude the influence of such regulatory elements, we choose pHG45-CAT11, which only contains the region from −121 to +144 of the GADD45 promoter. Following cotransfection of these mutants of the GADD45 promoter reporters into both HCT116 (wt p53) and H1299 cells, PG-CAT−107−57 exhibited induction (Fig. 1C). In contrast, both pCMV.neo (Neo) and pC53-SN3 (p53) had no effect on this reporter, indicating that the region between −107 and −57 is capable of conferring the BRCA1 inducibility to a non-related promoter reporter. Interestingly, PG-CAT−107−57 was also shown to be strongly induced by UV radiation and MMS, suggesting that activation of the GADD45 promoter by BRCA1 and DNA damage might share some common regulatory elements. Inspection of DNA sequence exhibits two OCT-1 motifs and one CAAT box located at this region of the human GADD45 promoter (Fig. 1D).

BRCA1 and CAAT Motifs Mediate the BRCA1 Activation of GADD45

FIG. 1. Mapping of the BRCA1-regulatory elements in the GADD45 promoter. A, 4 μg of the GADD45 promoter CAT reporter constructs pHG45-CAT2 was cotransfected with 4 μg of either pCR3.BRCA1 (BRCA1) or pCMV.neo (Neo) expression vectors into MCF-7, HCT116, or HCT116p53−/− cells using calcium phosphate precipitation. 48 h later, cells were collected, and CAT activity was assayed (see “Experimental Procedures”). To determine transfection efficiency, 4 μg of GFP expression vector was cotransfected with each measured, and the expression of GFP protein detected by immunoblotting analysis indicates that transfection efficiency was similar among different samples with variations less than 20%. To map the BRCA1-responsive elements in the GADD45 promoter, a series of the CAT reporters that spanned promoter region, was cotransfected with either pCR3.BRCA1 (BRCA1), pCMV.neo (Neo), or pC53-SN3 (p53). The CAT assays were performed, and the CAT activities were measured as described under “Experimental Procedures.” In some cases, the cells transfected with PG-CAT−107−57 alone were treated with UV radiation or MMS and followed by CAT assay. All experiments presented in A and C were repeated at least three times, but only a representative experiment of CAT assay is shown here. D, DNA sequence analysis indicates that there are two OCT-1 sites and one CAAT box located at the region of the GADD45 promoter from −107 to −62.

BRCA1 Activation of the GADD45 Promoter Is Mediated through Both OCT-1 and CAAT Motifs—To determine whether the OCT-1 and CAAT box motifs play roles in activating the GADD45 promoter following expression of BRCA1, we mutated the OCT-1 or CAAT motifs in GADD45 promoter CAT reporter constructs (53). It should be noted here that our previous work (54) has demonstrated that there are certain regulatory elements located more upstream of the GADD45 promoter, such as EGR1/WT1. Therefore, to exclude the influence of such regulatory elements, we choose pHG45-CAT11, which only contains the region from −121 to +144 of the GADD45 promoter. Following cotransfection of these mutants of the GADD45 promoter reporters into both HCT116 (wt p53) and H1299 cells, where the p53 gene is deleted, induction of CAT activity was determined. As shown in Fig. 2, pHG45-CAT11 exhibited the strongest activation by BRCA1. Single mutation in either OCT-1 or CAAT1 motifs (pHG45-CAT11 m1, pHG45-CAT11 m2, and pHG45-CAT11 m3) had little effect on BRCA1-induced
activation of the GADD45 promoter. However, double mutations in OCT-1 and CAAT sites (pHG45-CAT11 m4, pHG45-CAT11 m5, and pHG45-CAT11 m6) inhibited activation of the GADD45 promoter by BRCA1, reducing induction of these reporters by 60%. When all three sites were mutated (pHG45-CAT11 m7), the GADD45 promoter reporter did not exhibit any activation following expression of BRCA1. The responsiveness of the pHG45-CAT11 m7 to BRCA1 expression was observed to be similar to that seen in pHG45-CAT13 (Fig. 1B), which only contains the GADD45 promoter region from −62 to +144. In addition to HCT116 and H1299, we have also examined the activity of the GADD45 promoter reporters in MCF-7 (wt 53) and HCT116 p53+/− and obtained similar results (data not shown), suggesting that the OCT-1 and CAAT-mediated BRCA1 activation of the GADD45 promoter does not require p53. These results indicate that both the OCT-1 and CAAT motifs play an important role in BRCA1 activation of the GADD45 promoter in a p53-independent manner.

We also made mutations in all OCT1 and CAAT motifs in pHG45-CAT2, which covers a longer promoter region between −909 and +144 and determined the BRCA1 activation on this construct. BRCA1 activation of this mutated promoter (pHG45-CAT2ma) was reduced by 70% compared with the pHG45-CAT2 that contains the intact GADD45 promoter (results not shown). In contrast, BRCA1 activation of the pHG45-CAT11 m7 was completely abolished (Fig. 2). This result is in agreement with our previous finding (54) that there are certain regulatory elements (such as EGR1/WT1) at the upstream region of the GADD45 promoter. These upstream-responsive elements might also play a role in activation of the GADD45 promoter by BRCA1, even when mutations were made in OCT1 and CAAT1 motifs.

To determine further the roles of the OCT-1 and CAAT1 motifs in the BRCA1-mediated transcriptional activation, we constructed both OCT-1 and CAAT reporter plasmids, where the multiple repeats of either OCT-1 or CAAT motifs were placed upstream of a polyomavirus minimal promoter that is linked to a chloramphenicol acetyltransferase (CAT) gene. In Fig. 3A, PG-OCT-1wt that contains 5 repeats of intact OCT-1 motifs was transfected with expression vectors for BRCA1, Neo, and Oct-1 into HCT116 cells. PG-OCT-1wt was activated following expression of BRCA1. As an OCT-1 reporter, this construct was also strongly induced by Oct-1 expression. Interestingly, the OCT-1 reporter was responsive to MMS treatment. In contrast, the PG-OCT-1mut that contains 5 repeats of the mutated OCT-1 sites did not exhibit any responsiveness to expression of BRCA1 and Oct-1 protein or to MMS treatment. Similarly, the PG-CAATwt with 3 repeats of the CAAT motifs demonstrated a clear induction following expression of either BRCA1 or NF-YA, which is one of the subunits of NF-Y transcription factor and binds to CAAT box. PG-CAAT
also exhibited strong activation by MMS. However, PG-CAT-mut with mutated CAT motifs did not respond to expression of BRCA1 and NF-Y or MMS treatment. Collectively, the results presented above further indicate that the BRCA1 activation of the GADD45 promoter is mediated through the OCT-1 and CAAT motifs.

**BRCA1 Physically Interacts with OCT-1 and CAAT Motifs Via Its Physical Association with Both OCT-1 and NF-YA Proteins**—Because the OCT-1 and CAAT motifs mediate the transcriptional activation of the GADD45 promoter by BRCA1, effort was made to determine whether BRCA1 directly binds to the GADD45 promoter region containing both OCT-1 and CAAT sites. An approach called “biotin-streptavidin pull-down assay” was employed to identify the proteins bound to the BRCA1-responsive region of the GADD45 promoter. The biotin-labeled 51-bp double-stranded oligonucleotides corresponding to −107 to −57 of the GADD45 promoter were incubated with nuclear extracts from HCT116 cells and pulled down by streptavidin (see “Experimental Procedures”). The protein complex bound to the oligonucleotides were loaded onto SDS-PAGE gel and analyzed by immunoblotting assay with antibodies against BRCA1, Oct-1, and NF-YA. In Fig. 4A, the Oligo-wt that contains the intact OCT-1 and CAAT motifs was able to pull down the Oct-1, NF-YA, and BRCA1 proteins, indicating that all three proteins physically associate with this BRCA1-regulatory region. In Oligo-mut1, where the CAT box was mutated, both the Oct-1 and BRCA1 proteins but not NF-YA were detected in the precipitated complexes. In the case of Oligo-mut3, where two OCT-1 sites were disrupted, BRCA1, Oct-1, and NF-YA proteins were detected. These results strongly suggest the following two interpretations: (a) BRCA1 physically associates with the region of the GADD45 promoter between −107 and −57 through its interaction with both OCT-1 and CAAT motifs; and (b) BRCA1 interacts with OCT-1 or CAAT motifs independently because single mutation of either motif did not disrupt BRCA1 interaction with the BRCA1-responsive region of the GADD45 promoter.

However, because BRCA1 is not a sequence-specific binding transcription factor, it is most likely that the association of BRCA1 protein with the GADD45 promoter is through its interaction with the Oct-1 and NF-Y factors, which directly bind to the GADD45 promoter via their motifs. To address this issue, the Oligo-wt was incubated with the nuclear extracts, which were immunodepleted with anti-Oct-1 or -NF-YA antibodies prior to the pull-down assay. As shown in Fig. 4B, depletion with single antibody to either Oct-1 or NF-YA proteins did not affect binding of BRCA1 to the GADD45 promoter region. However, immunodepletion of both the Oct-1 and NF-YA proteins completely abolished the association of BRCA1 with the GADD45 promoter, indicating that association of BRCA1 with the GADD45 promoter is through its interaction with the Oct-1 and NF-YA proteins, which directly bind to the GADD45 promoter.

Next, we further determined the physical interactions of BRCA1 with Oct-1 and NF-YA proteins. Nuclear extracts isolated from HCT116 cells were incubated with anti-Jun-D, anti-Oct-1, anti-NF-YA, or anti-BRCA1 antibodies and immunoprecipitated with protein A/G-agarose beads. The immunocomplexes were then analyzed by Western blotting assay, and the results are shown in Fig. 5. NF-YA protein was present in the immunocomplexes precipitated by the antibodies against Oct-1, NF-YA, and BRCA1, suggesting physical interactions of NF-YA with Oct-1 and BRCA1. Oct-1 protein was detected in
the immunocomplexes with both anti-Oct-1 and anti-BRCA1 antibodies. Similarly, BRCA1 protein was detected in the anti-Oct-1 and anti-BRCA1 immunocomplexes. In contrast, no NF-YA, Oct-1, or BRCA1 proteins were present in the anti-Jun-D-immunoprecipitated complex. However, it is somewhat surprising that we did not detect Oct-1 and BRCA1 proteins in the anti-NF-YA-immunocomplex. One likely interpretation is that the interacting domains of Oct-1 and BRCA1 in NF-YA protein might share the region with the epitopes to the antibody against NF-YA, which possibly lead to dissociation of the NF-YA-BRCA1 and NF-YA-Oct-1 protein complexes. Taken together, these results indicate an association of BRCA1 with Oct-1 and NF-YA and an interaction between Oct-1 and NF-YA as well.

**DISCUSSION**

Studies presented in this paper and our earlier report (41) have demonstrated that BRCA1 activates the GADD45 promoter. By using 5′-deletion analysis, the BRCA1-regulatory elements have been mapped at the GADD45 promoter region between −107 and −62, where there are two OCT-1 motifs and one CAAT motif. Disruption of the OCT-1 and CAAT motifs abrogates the activation of the GADD45 promoter by BRCA1 expression, indicating that both OCT-1 and CAAT sites are required for the BRCA1 activation of the GADD45 promoter. This finding is further supported by the observation that the OCT-1 and CAAT motifs are able to confer BRCA1 inducibility to a non-related minimal polyomavirus promoter, when multiple repeats of these motifs are cloned upstream of the minimal promoter linked to a CAT gene. In the biotin-streptavidin pull-down assay, BRCA1 protein exhibits an association with the oligonucleotides corresponding to the GADD45 promoter from −107 to −57. Mutations of all OCT-1 and CAAT sites in such oligonucleotides disrupt association of BRCA1 with the GADD45 promoter. Importantly, BRCA1 protein is demonstrated to interact physically with both Oct-1 and NF-YA proteins, and depletion of Oct-1 and NF-YA proteins results in abrogation of association of BRCA1 with the GADD45 promoter. We conclude that BRCA1 transactivation of the GADD45 promoter is mediated through BRCA1 interaction with Oct-1 and NF-YA proteins.

BRCA1 has been implicated in DNA damage-induced cellular response, including apoptosis, cell cycle arrest, and DNA repair (7–13). Inactivation of BRCA1 correlates with genomic instability (14), indicating that one of the major roles for BRCA1 is to maintain genomic fidelity. In addition to direct interactions of BRCA1 with proteins involved in cell cycle control and DNA repair, BRCA1-mediated transcriptional regulation may also greatly contribute to its role in cellular response to DNA damage. For example, both p21and GADD45, which are important players in the control of cell cycle checkpoints (29, 57), are regulated by BRCA1 (10, 41). It has been well accepted that the roles of BRCA1 as a tumor suppressor might be at least in part mediated through its transcriptional properties, given the evidence that tumor-derived mutations within the C terminus of BRCA1 are defective in transcriptional activation (10, 32). In agreement with this point, the tumor-derived BRCA1 mutants (p1740R and Y1655insA) that lack transcriptional activity are unable to activate the GADD45 promoter (41). However, the regulation of GADD45 by BRCA1 appears to be complex and might involve differential mechanism(s). This complex regulation may be due to the following points. (a) BRCA1 activation of GADD45 has been shown to involve the BRCA1-responsive elements located at both the intronic or promoter regions of GADD45 (30, 41, 58). (b) Most likely, BRCA1 regulates GADD45 through its interaction with other transcription factors that directly bind to the GADD45 promoter or intronic regions instead of direct binding of BRCA1 to the regulatory regions. (c) BRCA1 protein might be subject to phosphorylation in the process of DNA damage-induced transcriptional activation (5, 6). (d) BRCA1-mediated transactivation might recruit transcriptional coactivators, such as p300/ CBP (38). Therefore, future work will further characterize the biochemical consequences of the interaction between BRCA1 and Oct-1 and NF-YA to determine whether Oct-1 and NF-YA are subject to protein stabilization, phosphorylation, or acetylation.

The GADD45 promoter is strongly activated following genotoxic stress, including UV radiation, MMS, and medium starvation (54). Most recently, we have demonstrated that the p53-independent UV induction of the GADD45 promoter is also regulated through both OCT-1 and CAAT motifs located at the same region between −107 and −62 of the GADD45 promoter. Mutations of all OCT-1 and CAAT motifs abolish the induction of the GADD45 promoter by UV radiation and MMS. In addition, protein levels of the Oct-1 and NF-YA transcription factors are elevated following DNA damage (53). Moreover, mitogen-activated protein kinases (c-Jun N-terminal kinase and extracellular signal-regulated kinase) also activate the GADD45 promoter through the OCT-1 and CAAT motifs. In the current study, we demonstrate that the OCT-1 and CAAT motifs mediate the BRCA1 activation of the GADD45 promoter. Therefore, it can be speculated that the OCT-1 and CAAT motifs are critical in the regulation of the p53-independent induction of GADD45 in response to growth arrest signals (such as BRCA1 expression) and a variety of DNA-damaging agents. It is worth noting that in the OCT-1 and CAAT motifs appear to function in an additive but independent manner because single mutation of either OCT-1 sites or the CAAT box only reduced induction of the GADD45 promoter by BRCA1, whereas mutations of all OCT-1 and CAAT motifs completely disrupted the BRCA1 activation of the GADD45 promoter (Fig. 2).

The finding that BRCA1 regulates the GADD45 through its interaction with transcription factors Oct-1 and NF-YA is of importance, given evidence that both the OCT-1 and CAAT motifs are widely present in the many gene promoters. Oct-1 and NF-YA are ubiquitous transcription factors involved in the development, cell cycle regulation, and cellular senescence (50, 51, 59, 60). Recently, we have found that OCT-1 and NF-YA proteins are induced after exposure of cells to multiple DNA-damaging agents and therapeutic agents in a p53-independent manner (52, 53). These observations indicate that both Oct-1 and NF-YA proteins are able to participate in cellular responses to genotoxic stress. In addition, our current study has shown a physical interaction of NF-YA with Oct-1 protein, suggesting that induction of GADD45 by BRCA1 might involve a functional interaction between these two proteins. In fact, Oct-1 and NF-YA proteins have been reported previously to synergistically regulate histone H2B gene transcription during Xenopus early development (61). In summary, the study presented here has demonstrated the biochemical mechanism by which BRCA1 regulates the GADD45 promoter and indicated that GADD45 is a BRCA1 downstream effector. Furthermore, identification of the OCT-1 and CAAT1 as BRCA1-responsive elements has broadened the biological roles for BRCA1 in transcriptional regulation.

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