Journal of Cellular Biochemistry 88:1084–1091 (2003)

PROSPECT

Breast Cancer Gene 1 (BRCA1): Role in Cell Cycle Regulation and DNA Repair—Perhaps Through Transcription

Kumaravel Somasundaram*

Department of Microbiology and Cell Biology, Indian Institute of Science, Bangalore 560 012, India

Abstract Mutations of BRCA1 gene are associated with more than half the cases of hereditary breast cancer. Breast cancer formation in BRCA1 mutation carriers is generally accompanied by loss of the wild-type allele, suggesting that BRCA1 protein may function as a tumor suppressor. The human BRCA1 gene encodes a nuclear protein of 1863 amino acids. Although several lines of evidences suggest that BRCA1 protein may have a role to play in cell cycle regulation, DNA repair, and other processes, the exact mechanism of functioning by BRCA1 protein is not clear. Recent evidences from several laboratories suggest that BRCA1 may regulate the expression of many genes like $p21^{WAF1/CIP1}$, Gadd45, Cyclin B1, DBB2, XPC, 14-3-3ó and others at the level of transcription. These BRCA1-regulated gene products have been implicated directly or indirectly in cell cycle regulation and DNA repair. Thus a plausible model is proposed in which BRCA1 protein may bring its effects on cell cycle and DNA repair through its ability to modulate gene expression at the level of transcription. J. Cell. Biochem. 88: 1084–1091, 2003. © 2003 Wiley-Liss, Inc.

Key words: breast cancer; BRCA1; transcription; DNA repair; cell cycle regulation

Breast cancer is one of the most common cancers affecting women worldwide. It is estimated that approximately one in eight to ten women living in western countries will develop breast cancer during their lifetime [Casey, 1997]. Most of the breast cancers are sporadic. About 5–10% of breast cancers are considered to be familial. Of the breast cancer susceptibility gene identified so far, BRCA1 and BRCA2 are the most important "high risk" genes accounting for majority of families with multiple cases of breast and ovarian cancer [Antoniou et al., 2002]. Women who inherit a mutant allele of either of these two tumor suppressors genes have a significantly increased lifetime breast cancer risk compared to the general population. Increased risk to develop breast cancer is due to the inheritance of mutant copy of the gene and the cancer occurs when the second copy of the gene is lost or mutated [Smith et al., 1992; Nauhausen and Marshal, 1994]. Surprisingly, even though the inherited mutations of BRCA1 and BRCA2 are responsible for most of the familial breast cancer cases, neither gene is clearly involved in the development of sporadic breast cancer. Even though the majority of breast cancers are of sporadic type, the study of hereditary breast cancer has provided valuable information about breast cancer in general.

Several lines of approach have been attempted by different laboratories to define the biochemical function of BRCA1 protein. BRCA1 has thus far implicated in regulation of cell cycle checkpoints, apoptosis, DNA-damage repair, transcription-coupled repair and ubiquitin ligase activity. Although the participation of BRCA1 in these functions has been clearly demonstrated, the exact mechanism of BRCA1 function remains unclear. The presence of functional motifs on BRCA1 protein and the identification of many BRCA1 interacting cellular proteins linked to those functions shed some light about the possible mode of function by BRCA1. Involvement in DNA repair and cell cycle regulation by far seem to be the two most

Grant sponsor: Department of Science and Technology, Government of India.

*Correspondence to: Kumaravel Somasundaram, Department of Microbiology and Cell Biology, Indian Institute of Science, Bangalore 560012, India.
E-mail: skumar@mcbl.iisc.ernet.in

Received 5 December 2002; Accepted 6 December 2002
DOI 10.1002/jcb.10469.

important well-studied functions of BRCA1. After the initial report on the identification of transcription activation domain in the C-terminus of BRCA1 [Chapman and Verma, 1996; Monterio et al., 1996], several transcriptional targets of BRCA1 have been identified. The functions carried out by the many of the genes isolated as BRCA1-transcriptional targets, either induced or repressed, adequately explain a possible mechanism in which BRCA1 would participate in DNA repair and cell cycle regulation through its ability to regulate gene expression at the level of transcription. The main focus of this review will be the various BRCA1 transcriptional targets so far identified and how BRCA1 could be linked to its functions, particularly to DNA repair and cell cycle regulation, through these targets.

STRUCTURE OF BRCA1 PROTEIN

The first breast cancer susceptibility gene (BRCA1) was found on chromosome 17q12–21 in humans and encodes an 1863 amino acid polypeptide (Fig. 1) [Miki et al., 1994]. BRCA1 is a large and complex gene about 100 kb long with a transcript size of 7.8 kb. The N-terminal end of BRCA1 contains a zinc-finger domain with a conserved pattern of cysteine and histidine residues, which are found in variety of proteins that interact with DNA either directly or indirectly [Miki et al., 1994]. The N-terminus of BRCA1 also interacts with BARD1 [Wu et al., 1996], BAP-1 [Jensen et al., 1998], E2F-1 [Wang et al., 1997]. Exon 11 of BRCA1 is the largest exon, encoding over 60% of the protein, and contains two nuclear localization signals [Thakur et al., 1997]. Cellular proteins that interact with exon 11 of BRCA1 either directly or indirectly are RAD51 [Scully et al., 1997c], RAD50 [Zhong et al., 1999], p53 [Zhang et al., 1998], RB [Aprelikova et al., 1999], c-Myc [Wang et al., 1998]. The C-terminus of BRCA1, which contains transcription activation domain [Chapman and Verma, 1996, Monterio et al., 1996] and two BRCT (BRCA1 C-Terminal domain) domains [Koonin et al., 1996], interacts with RNA Polymerase II [Scully et al., 1997a], p300/CBP [Cui et al., 1998; Neish et al., 1998], BRCA2 [Chen et al., 1998], RNA helicase [Anderson et al., 1998], and CtIP [Yu et al., 1998; Li et al., 1999].

TRANSCRIPTIONAL REGULATION BY BRCA1

The first line of evidence implicating BRCA1 in transcription control came from an observation that the C-terminus of BRCA1 (amino acids 1528–1863), when fused to the GAL4 DNA-binding domain and tranfected into cells, activates transcription of GAL4-dependent promoters [Chapman and Verma, 1996; Monterio et al., 1996]. Furthermore, some of the BRCA1 mutations found in BRCA1-associated tumors abolish transcriptional activity in this assay, implying that the loss of transcriptional activation by BRCA1 may be involved in tumorigenesis. Subsequent to this observation, many BRCA1 targets genes have been identified. Induction of

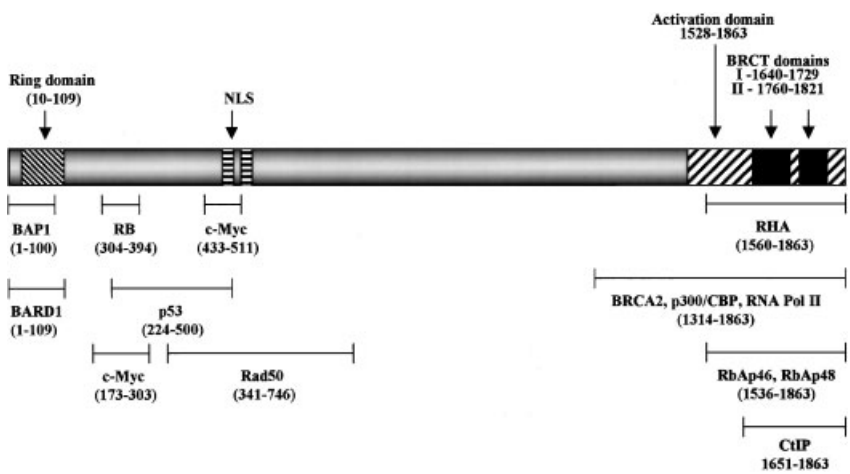

Fig. 1. A schematic diagram of BRCA1 protein is shown in the middle. Shown below are names and the interacting regions (with BRCA1 protein) of BRCA1 interacting proteins. Various functional domains of BRCA1 are shown above the BRCA1 protein.

$p21^{WAF1/CIP1}$ either dependent or independent of p53 by BRCA1 has been shown by several groups [Somasundaram et al., 1997, 1999; Ouchi et al., 1998; Zhang et al., 1998; Li et al., 1999; Maclachlan et al., 2000; Welcsh et al., 2002]. Similarly transcriptional activation of Gadd45 [Harkin et al., 1999; Maclachlan et al., 2000; Mullan et al., 2001; Fan et al., 2002; Hartman and Ford, 2002], 14-3-3ó [Aprelikova et al., 2001], p27(Kip1) [Williamson et al., 2002], DDB2 [Takimoto et al., 2002; El-Deiry, 2002; Hartman and Ford, 2002], XPC [Hartman and Ford, 2002] and TNF-α [Houvras et al., 2000] has been shown. BRCA1 has also been shown to repress the expression of certain genes at the level of transcription. Cyclin B1 [Maclachlan et al., 2000], estrogen receptor α (ERα)-responsive genes [Fan et al., 1999] and insulin growth factor 1 (IGF1) [Maor et al., 2000] are repressed by BRCA1.

Although the transcriptional regulation by BRCA1 has been shown to be specific, many in the field have questioned the physiological relevance of the transcriptional activity of BRCA1. DNA damage induced phosphorylation of BRCA1 protein is well documented [Scully et al., 1997b; Thomas et al., 1997]. So far three kinases—ATM [Cortez et al., 1999], ATM-related kinase (ATR) [Tibbetts et al., 2000], and hCds1 (CHK2) [Lee et al., 2000] have been shown to phosphorylate BRCA1 after DNA damage. The link between transcriptional regulation by BRCA1 and DNA damage was provided by the following observation. The activation potential of BRCA1 is partially suppressed by the CtIP-CtBP complex, which binds to the BRCT domain of BRCA1 [Li et al., 1999, 2000]. The association between BRCA1 with CtIP is abrogated by DNA damage induced ATM-dependent phosphorylation of CtIP, thus relieving the repression of transactivation by BRCA1. Thus the DNA damage mediated activation of BRCA1 transcription function suggests that transcriptional activation BRCA1 is indeed physiological.

Another lacuna is that there is no evidence that BRCA1 is able to bind to promoter regions of the target genes. BRCA1 binds to DNA without any sequence specificity, which may be an important part of its role in DNA repair transcription [Paull et al., 2001]. Mondal and Parvin [1999] have proposed that BRCA1 functionally links certain upstream enhancer-binding factors to the basal transcription machinery in the holoenzyme and that BRCA1 may act as a transcriptional coactivator. In fact, a number of observations, as listed below, confirm the above hypothesis. BRCA1 protein is a component of the RNA polymerase II holoenzyme, and a deletion of the C-terminal 11 amino acids of BRCA1 reduces its association with the RNA polymerase II holoenzyme [Scully et al., 1997a; Neish et al., 1998]. BRCA1 also interacts with RNA polymerase II via a linkage with RNA helicase [Anderson et al., 1998]. Thus it is possible that BRCA1 interact with DNA-bound transcription factors to mediate signal to RNA polymerase II. In fact, transcriptional activation by BRCA1 has been shown to occur in many examples by its ability to associate with sequence-specific DNA-binding transcription factors. BRCA1 binds to p53 resulting in the activation of $p21^{WAF1/CIP1}$ [Ouchi et al., 1998; Zhang et al., 1998], 14-3-3ó [Aprelikova et al., 2001], and DDB2 [Takimoto et al., 2002]. Interaction between ATF1 and BRCA1 results in the activation of TNF-α [Houvras et al., 2000]. BRCA1 interacts with Oct-1 and NF-YA, which results in the activation of Gadd45 [Fan et al., 2002]. BRCA1 also binds to ZBRK1, which is a transcription factor binding specifically to a DNA sequence, GGGxxxCAGxxxTTT [Zheng et al., 2000]. ZBRK1 binding sequence motif is present in the promoter regions of many transcriptional targets of BRCA1 like $p21^{WAF1/CIP1}$ (3 sites), Gadd45, and EGR1. Coexpression of ZBRK1 and BRCA1 were found to actually repress the Gadd45 promoter, contrary to what one would expect given previous findings of activation of Gadd45 expression by BRCA1. Thus far, it is hypothesized that overexpression of BRCA1 may titrate ZBRK1 away from the promoter, allowing transcription to occur. In addition, DNA damage induced phosphorylation of BRCA1 and binding of BRCA1 to other repressors like CtIP etc. may actually modify this regulation [Maclachlan and El-Deiry, 2000]. Thus it appears that BRCA1 may regulate transcription as a coactivator by binding to sequence-specific DNA-binding transcription factors.

LINK BETWEEN TRANSCRIPTIONAL REGULATION BY BRCA1 AND ITS FUNCTIONS

Although, BRCA1 has been implicated in a variety of functions, its role in cell cycle regulation and DNA repair has been very well

documented [MacLachlan and El-Deiry, 2002; Venkitaraman, 2002]. An attempt is made below to link the developments with regard to BRCA1-mediated transcriptional regulation to its functions, particularly cell cycle regulation and DNA repair (Fig. 2).

Cell Cycle Regulation by BRCA1

The regulation of cell cycle by BRCA1 has been demonstrated by several observations. The initial findings, which include the expression pattern of BRCA1 mRNA and protein and the association of BRCA1 with cell cycle regulatory proteins, suggested the possible role of BRCA1 in cell cycle regulation. The expression of BRCA1 mRNA and protein during different stages of cell cycle is highly specific, occurring late in the G1 phase and peaking in the S-phase [Chen et al., 1996; Gudas et al., 1996; Vaughn et al., 1996]. Western blot analysis of BRCA1 interacting protein (BIP) complex revealed binding of antibodies specific for cdc2, cdk2, cdk4, cyclin A, cyclin B1, cyclin D1, cyclin E, and E2F-4, suggesting an association between BRCA1 with these proteins [Wang et al., 1997]. BRCA1 is phosphorylated by kinases associated with cyclin D and cyclin A as well as by CDK2 in vitro [Chen et al., 1996]. The phosphorylation of BRCA1 continued throughout S and onto the G2/M phases, after which it was progressively dephosphorylated. It is likely that phosphorylation of BRCA1 may have some functional significance as it occurs in a cycle dependent manner.

The direct link between BRCA1 and its role in the cell cycle checkpoints came from the following observations. Overexpression of BRCA1 activated $p21^{WAF1/CIP1}$ in a p53-independent manner and inhibited cell cycle progression into

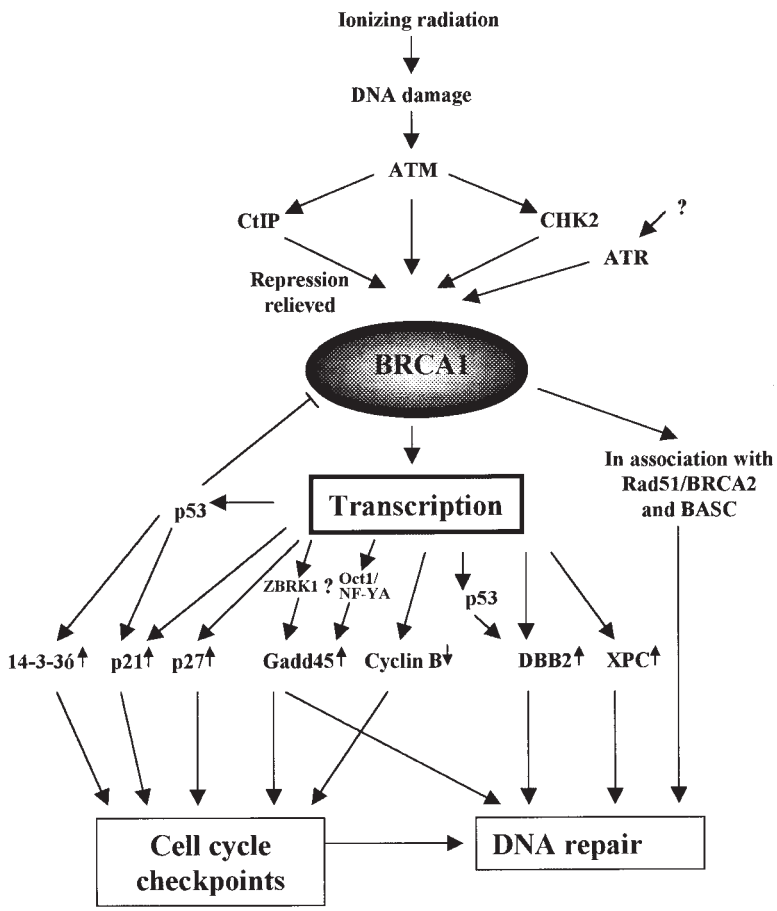

Fig. 2. Connection between BRCA1-mediated transcriptional regulation and its role in DNA repair and cell cycle regulation. The ability of BRCA1 to activate (shown by ↑) or repress (shown by ↓) transcription of certain genes specifically provides another mechanism by which BRCA1 carries out DNA repair functions either directly or indirectly by inducing cell cycle arrest.

S-phase [Somasundaram et al., 1997]. Moreover, this arrest in G1 phase is dependent on the presence of $p21^{WAF1/CIP1}$, as expression of BRCA1 in isogenic cell lines lacking $p21^{WAF1/CIP1}$ does not lead to G1 arrest [Maclachlan et al., 2000]. In another study, exogenous overexpression of BRCA1 has been shown to cause Rb-dependent cell cycle arrest in some cell lines [Aprelikova et al., 1999]. Exogenous overexpression of BRCA1 also activated p27(Kip1), which may also contribute to its ability to induce G1 arrest [Williamson et al., 2002]. BRCA1 overexpression also resulted in the transcriptional activation of Gadd45 [Harkin et al., 1999; Maclachlan et al., 2000]. Introduction of BRCA1 through a recombinant adenovirus in a variety of cell lines resulted in the increase of cells with G2/M phase DNA content [Maclachlan et al., 2000]. Gadd45 has been implicated in G2/M checkpoint, as Gadd45-knockout mice possess a defective G2/M checkpoint [Hollander et al., 1999]. A role for BRCA1 in G2-M checkpoint has been demonstrated by using mouse embryo fibroblasts carrying a homozygous deletion of BRCA1 exon 11 [Xu et al., 1999]. Therefore, it is possible that BRCA1 may in part induce the Gadd45 protein to activate G2/M checkpoint. BRCA1 also has been shown to transcriptionally activate 14-3-3ó in a p53-dependent manner [Aprelikova et al., 2001]. As 14-3-3ó has previously been shown to be a major G2/M checkpoint control gene, 14-3-3ó induction may also play an important role in the BRCA1-mediated G2/M checkpoint. Another target gene of BRCA1 identified was cyclin B1, which was actually repressed by exogenous expression of BRCA1 [Maclachlan et al., 2000]. Repression of cyclin B1 can easily be linked to BRCA1 regulated G2/M checkpoint because depletion of cyclin B1 would lead to inactivation of mitotic kinase cdc2. Indeed, the same study showed that exogenous expression of cyclin B1 abrogated the G2/M arrest induced by BRCA1 overexpression.

BRCA1 and DNA Repair

Studies from many laboratories suggested that BRCA1 is involved in DNA-damage repair. One set of evidences came from the findings that BRCA1 protein interacts with other cellular proteins involved in DNA repair and recombination. The DNA repair proteins with which BRCA1 has been shown to interact are Rad51 [Scully et al., 1997c], BRCA2 [Chen et al., 1998], hRad50-Hmre11-p95 complex [Zhong et al., 1999]. Immunoprecipiation studies also revealed that BRCA1 protein is associated with a large complex (>2 Mda), called BRCA1-associated genome surveillance complex (BASC) [Wang et al., 2000]. BASC is composed of many proteins involved with DNA repair either directly or indirectly like Mut S homologue (MSH2), Mut S homologue 6 (MSH6), Mut L homologue 1 (MLH1), ATM kinase, Bloom (BLM), and the hRad50-hMRE11-p95 complex [Wang et al., 2000].

The second set of evidences from the analysis of stem cells derived from BRCA1-deficient embryo. Mouse embryonic stem cells carrying homozygous deletion of BRCA1 are defective in their ability to carry out transcription-coupled repair and hypersensitive to ionization radiation and hydrogen peroxide [Gowen et al., 1998]. Another report showed that Brca1-deficient mouse embryonic stem cells have impaired the repair of chromosomal DNA double-strand breaks (DSBs) by homologous recombination [Moynahan et al., 1999]. Mouse embryo with a BRCA1-deficiencey was not only hypersensitive to γ-irradiation but also displayed numerical and structural chromosomal aberrations [Shen et al., 1998]. Consistent with this view, Abbott et al. [1999] showed that a human cancer cell line carrying a mutated BRCA1 allele is hypersensitive to ionizing radiation. More importantly, exogenous expression of certain regions of BRCA1 reversed the radiation sensitive phenotype.

Above studies involving BRCA1-interacting proteins and *BRCA1* knockout mice clearly demonstrate that BRCA1 has an important role to play in the DNA repair. The possible mechanism of action by BCRA 1 could be that BRCA1 may influence the DNA repair process through its association the proteins involved in DNA repair. On the other hand, there is enough evidence to functionally link the transcriptional regulation by BRCA1 to its DNA repair functions. For example, proteins encoded by many of the transcriptional targets of BRCA1 participate, either directly or indirectly, in the DNA damage response, including DNA repair. BRCA1 collaborates with p53 to induce DDB2 following UV- and cisplatin-induced damage via a p53 responsive element present in the human DDB2 promoter [Takimoto et al., 2002; El-Deiry, 2002]. Furthermore, the DNA repair activity is significantly increased by the

introduction of BRCA1 into WT as compared to DDB2-deficient cells. DDB2 is the smaller subunit of the DDB heterodimer, which binds to DNA damaged by UV or cisplatin and is mutated in a subset of patients with cancer-prone syndrome Xeroderma pigmentosum complementation group E [Chu and Chang, 1988]. Recent evidence suggests a role for DDB in enhancing global genomic repair (GGR) of cyclobutane pyrimidine dimers [Tang et al., 2000]. In another observation, Hartman and Ford [2002] showed that BRCA1 enhances GGR pathway by transcriptional induction of nucleotide excision repair (NER) genes XPC, DDB2 and GADD45 in a p53-independent manner. The important role played by GADD45, DDB2 and XPC gene products in NER pathway has been demonstrated previously [Tang et al., 2000; Emmert et al., 2000; Tran et al., 2002]. Thus the DNA repair functions of BRCA1 may also be attributed to its ability to induce NER genes.

Cell cycle checkpoints represent integral components of DNA repair that coordinate cooperation between the machinery of the cell cycle and several biochemical pathways that respond to damage and restore DNA structure. By delaying progression through the cell cycle, checkpoints provide more time for repair before the critical phases of DNA replication, when the genome is replicated, and of mitosis, when the genome is segregated. Loss or attenuation of checkpoint function may increase spontaneous and induced gene mutations and chromosomal aberrations by reducing the efficiency of DNA repair. In fact many BRCA1 target genes like $p21^{WAF1/CIP1}$ and Gadd45 would induce a robust cell cycle arrest thus allowing cells enough time to repair the damaged DNA. As discussed early, overexpression of BRCA1 can cause both G1/S and G2/M arrest. Several BRCA1 target genes, whose activation or repression by BRCA1 can bring about a clear G1/S or G2/M arrest. The details are given above in the previous sections. The ability of BRCA1 to induce G1/S arrest could be linked to BRCA1 targets $p21^{WAF1/CIP1}$ [Somasundaram et al., 1997; Ouchi et al., 1998; Zhang et al., 1998; Li et al., 1999; Maclachlan et al., 2000; Welcsh et al., 2002] and p27(Kip1) [Williamson et al., 2002]. BRCA1 induced G2/M arrest could be attributed to BRCA1 targets Gadd45 [Harkin et al., 1999; Maclachlan et al., 2000; Mullan et al., 2001; Fan et al., 2002], 14-3-3ó [Aprelikova et al., 2001], and Cyclin B1 [Maclachlan et al., 2000].

CONCLUSIONS

Involvement of BRCA1 in the development of hereditary breast cancer is very well established. Development of breast cancer among BRCA1 mutation carriers is accompanied by the loss of remaining WT BRCA1 allele, which suggests the importance of BRCA1 protein in the etiology of the disease. It is now becoming apparent that BRCA1 is a protein with complex and diverse set of functions. Several lines evidence implicates that BRCA1 is a protein with DNA repair function. Isolation of many BRCA1 interacting proteins, implicated in DNA repair processes, suggests that BRCA1 protein may be directly involved in the repair process. However, the identification of a handful of BRCA1 target genes, many of which either directly or indirectly by inducing cell cycle arrest involved in DNA repair process, suggest an additional model by which BRCA1 would participate in the DNA repair. That means a more elaborate study of transcriptional control by BRCA1 is required to understand better its role in DNA repair processes.

ACKNOWLEDGMENTS

The author apologizes to those whose work could not be cited directly due to limited space.

REFERENCES

Abbott DW, Thompson ME, Robinson-Benion C, Tomlison G, Jensen RA, Holt JT. 1999. BRCA1 expression restores radiation resistance in BRCA1-defective cancer cells through enhancement of transcription-coupled repair. J Biol Chem 274:18808–18812.

Anderson SF, Schiegal BP, Nakajima T, Wolpin ES, Parvin JD. 1998. BRCA1 protein is linked to the RNA polymerase II holoenzyme complex *via* RNA helicase A. Nat Genet 19:254–256.

Antoniou AC, Pharoah PDP, McMullan G, Day NE, Stratton MR, Peto J, Ponder BJ, Easton DF. 2002. A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. Br J Cancer 86: 76–83.

Aprelikova ON, Fang BS, Meissner EG, Cotter S, Campbell M, Kuthiala A, Bessho M, Jensen RA, Liu ET. 1999. BRCA1-associated growth arrest is RB-dependent. Proc Natl Acad Sci USA 96:11866–11871.

Aprelikova ON, Pace AJ, Fang B, Koller BH, Liu ET. 2001. BRCA1 is a selective co-activator of 14-3-3ó gene transcription in mouse embryonic stem cells. J Biol Chem 276: 25647–25650.

Casey G. 1997. The BRCA1 and BRCA2 breast cancer genes. Curr Opin Oncol 9:88–93.

Chapman MS, Verma IM. 1996. Transcriptional activation by BRCA1. Nature 382:678–679.

Chen Y, Farmer AA, Chen CF, Jones DC, Chen PL, Lee WH. 1996. BRCA1 is a 220-kDa nuclear phosphoprotein that is expressed and phosphorylated in a cell cycle-dependent manner. Cancer Res 56:3168–3172.

Chen J, Silver DP, Walpita D, Cantor SB, Gazdar AF, Tomlinson G, Couch FJ, Weber BL, Ashley T, Livingston DM, Scully R. 1998. Stable interaction between the products of the BRCA1 and BRCA2 tumor suppressor genes in mitotic and meiotic cells. Mol Cell 2:317–328.

Chu G, Chang E. 1988. Xeroderma pigmentosum group E cells lack a nuclear factor that binds to damaged DNA. Science 242:564–567.

Cortez D, Wang Y, Qin J, Elledge SJ. 1999. Requirement of ATM-dependent phosphorylation of BRCA1 in the DNA damage response to double-strand breaks. Science 286: 1162–1166.

Cui JQ, Shao N, Chai Y, Wang R, Reddy ES, Rao VN. 1998. BRCA1 splice variants BRCA1a and BRCA1b associate with CBP co-activator. Oncol Rep 5(3):591–595.

El-Deiry WS. 2002. Transactivation of repair genes by BRCA1. Cancer Biol Ther 5:490–491.

Emmert S, Kobayashi N, Khan SG, Kraemer KH. 2000. The xeroderma pigmentosum group C gene leads to selective repair of cyclobutane pyrimidine dimers rather than 6-4 photoproducts. Proc Natl Acad Sci USA 97:2151–2156.

Fan S, Wang J, Yuan R, Ma Y, Meng Q, Erdos MR, Pestell RG, Yuan F, Auborn KJ, Goldberg ID, Rosen EM. 1999. BRCA1 inhibition of estrogen receptor signaling in transfected cells. Science 284:1354–1356.

Fan W, Jin S, Tong T, Zhao H, Fan F, Antinore MJ, Rajasekaran B, Wu M, Zhan Q. 2002. BRCA1 regulates GADD45 through its interaction with the OCT-1 and CAAT motifs. J Biol Chem 277(10):8061–8067.

Gowen LC, Gowen LC, Avrutskaya AV, Latour AM, Koller BH, Leadon SA. 1998. BRCA1 is required for transcription-coupled repair of oxidative DNA damage. Science 281:1009–1012.

Gudas JM, Li T, Nguyen H, Gowen LC, Avrutskaya AV, Latour AM, Koller BH, Leadon SA. 1996. Cell cycle regulation of BRCA1 messenger RNA in human breast epithelial cells. Cell Growth Differ 7:717–723.

Harkin DP, Bean JM, Miklos D, Song YH, Truong VB, Englert C, Christians FC, Ellisen LW, Maheswaran S, Oliner JD, Haber DA. 1999. Induction of GADD45 and JNK/SAPK-dependent apoptosis following inducible expression of BRCA1. Cell 97:575–586.

Hartman A-R, Ford JM. 2002. BRCA1 induces DNA damage recognition factors and enhances nucleotide excision repair. Nat Genet 32:180–184.

Hollander MC, Sheikh MS, Bulavin DV, Lundgren K, Augeri-Henmueller L, Shehee R, Molinaro TA, Kim KE, Tolosa E, Ashwell JD, Rosenberg MP, Zhan Q, Fernandez-Salguero PM, Morgan WF, Deng CX, Fornace AJ, Jr. 1999. Genomic instability in Gadd45a-deficient mice. Nat Genet 23:176–184.

Houvras Y, Benezra M, Zhang H, Manfredi JJ, Weber BL, Licht JD. 2000. BRCA1 physically and functionally interacts with ATF1. J Biol Chem 275:36230–36237.

Jensen DE, Proctor M, Marquis ST, Gardner HP, Ha SI, Chodosh LA, Ishov AM, Tommerup N, Vissing H, Sekido Y, Minna J, Borodovsky A, Schultz DC, Wilkinson KD, Maul GG, Barlev N, Berger SL, Prendergast GC, Rauscher FJ, IIIrd. 1998. BAP1: A novel ubiquitin hydrolase which binds to the BRCA1 RING finger and enhances BRCA1-mediated cell growth suppression. Oncogene 15:1097–1112.

Koonin EV, Altschul SF, Bork P. 1996. BRCA1 products—Functional motifs. Nat Genet 13:266–267.

Lee JS, Collins KM, Brown AL, Lee CH, Chung JH. 2000. hCds1-mediated phosphorylation of BRCA1 regulates the DNA damage response. Nature 404:201–204.

Li S, Chen P-L, Subramanian T, Chinnadurai G, Tomlinson G, Osbornei CK, Sharp CD, Lee W-H. 1999. Binding of CtIP to the BRCT repeats of BRCA1 involved in the transcription regulation of p21 is disrupted upon DNA damage. J Biol Chem 274:11334–11384.

Li S, Ting NS, Zheng L, Chen PL, Ziv Y, Shiloh Y, Lee EY, Lee WH. 2000. Functional link of BRCA1 and ataxia telangiectasia gene product in DNA damage response. Nature 406:210–215.

Maclachlan TK, El-Deiry WS. 2000. Pointing (zinc) fingers at BRCA1 targets. Nat Med 6:1318–1319.

Maclachlan TK, El-Deiry WS. 2002. Functional interaction between BRCA1 and the cell cycle. In: Mikhail V. Blagosklonny editor: Cell cycle check points and Cana Landes Bioscience. p 126–134.

MacLachlan TK, Somasundaram K, Sgagias M, Shifman Y, Muschel RJ, Cowan KH, El-Deiry WS. 2000. BRCA1 effects on the cell cycle and the DNA damage response are linked to altered gene expression. J Biol Chem 275: 2777–2785.

Maor SB, Abramovitch S, Erdos MR, Brody LC, Werner H. 2000. BRCA1 suppresses insulin-like growth factor-1 receptor promoter activity: Potential interaction between BRCA1 and SP1. Mol Genet Metab 69:130–136.

Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W, Bell R, Rosenthal J, Hussey C, Tran T, McClure M, Frye C, Hattier T, Phelps R, Haugen-Strano A, Katcher H, Yakumo K, Gholami Z, Shaffer D, Stone S, Bayer S, Wray C, Bogden R, Dayananth P, Ward J, Tonin P, Narod S, Bristow PK, Norris FH, Helvering L, Morrison P, Rosteck P, Lai M, Barrett JC, Lewis C, Neuhausen S, Cannon-Albright L, Goldgar D, Wiseman R, Kamb A, Skolnick MH. 1994. A strong candidate for breast and ovarian susceptibility gene BRCA1. Science 266:66–71.

Mondal N, Parvin JD. 1999. BRCA1 function in transcription. Gene Ther Mol Biol 4:397–404.

Monterio ANA, August A, Hanafusa H. 1996. Evidence of a transcriptional activation function of BRCA1 C-terminal region. Proc Natl Acad Sci USA 93:13595–13599.

Moynahan ME, Chiu JW, Koller BH, Jasin M. 1999. BRCA1 controls homology directed DNA repair. Mol Cell 4:511–518.

Mullan PB, McWilliams S, Quinn J, Andrews H, Gilmore P, McCabe N, McKenna N, Harkin DP. 2001. Uncovering BRCA1-regulated signalling pathways by microarray-based expression profiling. Biochem Soc 29:678–683.

Nauhausen SL, Marshal CJ. 1994. Loss of heterozygosity in familial tumors from three BRCA1-linked kindreds. Cancer Res 54:6069–6072.

Neish AS, Anderson SF, Schlegel BP, Wel W, Parvin JD. 1998. Factors associated with the mammalian RNA polymerase II holoenzyme. Nuc Acids Res 26:847–853.

Ouchi T, Monteiro AN, August A, Aaronson SA, Hanafusa H. 1998. BRCA1 regulates p53-dependent gene expression. Proc Natl Acad Sci USA 95:2302–2306.

Paull TT, Cortez D, Bowers B, Elledge SJ, Gellert M. 2001. Direct DNA binding by BRCA1. Proc Natl Acad Sci USA 98:6086–6091.

Scully R, Anderson SF, Chao DM, Wei W, Ye L, Young RA, Livingston DM, Parvin JD. 1997a. BRCA1 is a component of RNA polymerase II holoenzyme. Proc Natl Acad Sci USA 94:5605–5610.

Scully RS, Chen J, Ochs RL, Keegan K, Hoekstra M, Feunteun J, Livingston DM. 1997b. Dynamic changes of BRCA1 subnuclear location and phosphorylation state are initiated by DNA damage. Cell 90:425–435.

Scully R, Chen J, Plug A, Xiao Y, Weaver D, Feunteun J, Ashley T, Livingston DM. 1997c. Association of BRCA1 with RAD51 in mitotic and meiotic cell. Cell 88:265–275.

Shen SX, Weaver Z, Xu X, Li C, Weinstein M, Chen L, Guan XY, Ried T, Deng CX. 1998. A targeted disruption of the murine BRCA1 gene causes gamma-irradiation hypersensitivity and genetic instability. Oncogene 17:3115–3124.

Smith SA, Easton DF, Evans DG, Ponder BA. 1992. Allele losses in the region 17q12-21 in familial breast and ovarian cancer involve the wild-type chromosome. Nat Genet 2:128–131.

Somasundaram K, Zhang H, Zeng YX, Houvras Y, Peng Y, Zhang H, Wu GS, Licht JD, Weber BL, El-Deiry WS. 1997. Arrest of cell cycle by the tumor-suppressor BRCA1 requires the CDK-inhibitor $p21^{WAF/CIP1}$. Nature 389: 187–190.

Somasundaram K, MacLachlan TK, Burns TF, Sgagias M, Cowan KH, Weber BL, El-Deiry WS. 1999. BRCA1 signals ARF-dependent stabilization and coactivation of p53. Oncogene 18:6605–6614.

Takimoto R, Maclachlan TK, Dicket DT, Niitsu Y, Mori T, El-Deiry WS. 2002. BRCA1 transcriptionally regulates damaged DNA binding protein (DDB2) in the DNA repair response following UV-irradiation. Cancer Biol Ther 1: 177–186.

Tang JY, Hwang BJ, Ford JM, Hanawalt PC, Chu G. 2000. Xeroderma pigmentosum p48 gene enhances global genomic repair and suppresses UV-induced mutagenesis. Mol Cell 5:737–744.

Thakur S, Zhang H, Peng Y, Le H, Carroll B, Ward T, Yao J, Farid LM, Couch FJ, Wilson RB, Weber BL. 1997. Localization of BRCA1 and a splice variant identifies the nuclear localization signal. Mol Cell Biol 17:444–452.

Thomas JE, Smith M, Tonkinson JL, Rubinfeld B, Polakis P. 1997. Induction of phosphorylation on BRCA1 during the cell cycle and after DNA damage. Cell Grow Differ 8:801–809.

Tibbetts RS, Cortez D, Brumbaugh KM, Scully R, Livingston D, Elledge SJ, Abraham RT. 2000. Functional interactions between BRCA1 and the checkpoint kinase ATR during genotoxic stress. Genes Dev 14:2989–3002.

Tran H, Brunet A, Grenier JM, Datta SR, Fornace AJ, Jr., DiStefano PS, Chiang LW, Greenberg ME. 2002. DNA repair pathway stimulated by the forkhead transcription factor FOXO3a through the Gadd45 protein. Science 296: 530–534.

Vaughn JP, Davis PL, Jarboe MD, Huper G, Evans AC, Wiseman RW, Berchuck A, Lglehart JD, Futreal PA, Marks JR. 1996. BRCA1 expression is induced before DNA synthesis in both normal and tumor-derived breast cells. Cell Growth Differ 7:711–715.

Venkitaraman AR. 2002. Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell 108:171–182.

Wang H, Shao N, Ding QM, Cui J, Reddy ES, Rao VN. 1997. BRCA1 proteins are transported to the nucleus in the absence of serum and splice variants BRCA1a, BRCA1b are tyrosine phosphoproteins that associate with E2F, cyclins and cyclin dependent kinases. Oncogene 15:143–157.

Wang Q, Zhang H, Kajino K, Greene MI. 1998. BRCA1 binds c-Myc and inhibits its transcriptional and transforming activity in cells. Oncogene 17:1939–1948.

Wang Y, Cortez D, Yazdi P, Neff N, Elledge SJ, Qin J. 2000. BASC, a super complex of BRCA1-associated proteins involved in the recognition and repair of aberrant DNA structures. Genes Dev 14:927–939.

Welcsh PL, Lee MK, Gonzalez-Hernandez RM, Black DJ, Mahadevappa M, Swisher EM, Warringto JA, King MC. 2002. BRCA1 transcriptionally regulates gene involved in breast tumorigenesis. Proc Natl Acad Sci USA 99: 7560–7565.

Williamson E, Dadmanech F, Koeffler HP. 2002. BRCA1 transactivates the cyclin dependent kinase inhibitor p27(Kip1). Oncogene 21:3199–3206.

Wu LC, Wang ZW, Tsan JT, Spillman MA, Phung A, Xu XL, Yang MC, Huang LY, Bowcock AM, Baer R. 1996. Identification of a Ring protein that can interact in vivo with BRCA1 gene product. Nat Genet 14:430–440.

Xu X, Weaver Z, Linke SP, Li C, Gotay J, Wang X-W, Haris CC, Reid T, Deng C-X. 1999. Centrosome amplification and a defective G2-M cell cycle checkpoint induce genetic instability in BRCA1 exon 11 isoform-deficient cells. Mol Cell 3:389–395.

Yu X, Wu LC, Bowcock AM, Aronheim A, Baer R. 1998. The C-terminus BRCT domains of BRCA1 interact in vivo with CtIP, a protein implicated in the CtBP pathway of transcriptional repression. J Biol Chem 273:25388–25392.

Zhang H, Somasundaram K, Peng Y, Tian H, Zhang H, Bi D, Weber BL, El-Deiry WS. 1998. BRCA1 physically associates with p53 and stimulates its transcriptional activity. Oncogene 16:1713–1721.

Zheng L, Pan H, Li S, Wang Y, Cortez D, Yazdi P, Neff N, Elledge SJ, Qin J. 2000. Sequence-specific transcriptional corepressor function for BRCA1 through a Novel Zinc Finger Protein, ZBRK1. Mol Cell 6:757–764.

Zhong Q, Chen CF, Li S, Chen Y, Wang CC, Xiao J, Chen PL, Sharp ZD, Lee WH. 1999. Association of BRCA1 with the hRad50-hMre11-p95 complex and the DNA damage response. Science 285:747–750.