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Diverse functions of BRCA1 in the DNA damage response

Jong-Soo Lee and Jay H. Chung

Breast cancer is one of the most common causes of cancer-related mortality in women. It affects more than one in nine women over their lifetime. Although most breast cancers are sporadic, the genetics and molecular biology of the heritable forms of breast cancer have provided valuable insights into not only breast cancer but also cancers in general. Among the mutations linked to heritable breast cancers, the mutations in the breast cancer 1 (*BRCA1*) gene are the best characterised. The *BRCA1* gene encodes a nuclear protein that is important for maintaining genome integrity. However, a growing list of BRCA1-associated proteins suggests that BRCA1 has diverse and unexpected functions.

Most breast cancers are sporadic. Indeed, only 5–10% of all breast cancers are considered to be familial. Among these, germline mutations in the breast cancer 1 (*BRCA1*) gene are found in almost all of the families with inherited breast and ovarian cancers and about half of the families with only breast cancer (Ref. 1; reviewed in Ref. 2). Cancer cells from carriers of the *BRCA1* mutation contain 'loss of heterozygosity' (LOH) at the wild-type chromosome; this indicates that the loss of function predisposes to tumourigenesis and the wild-type BRCA1 is therefore considered to be a tumour suppressor (Ref. 3).

The *BRCA1* gene is found on chromosome 17q12-21 in humans and encodes a 1863 amino acid polypeptide (Ref. 4). The protein contains two notable types of domains: a RING finger in the N-terminal region and two BRCT domains in the C-terminal region (Fig. 1). The RING finger is a zinc-binding domain that interacts with BRCA1-associated RING domain protein (BARD1), which also contains an N-terminal RING finger and two C-terminal BRCT domains (Ref. 5). The BRCA1–BARD1 interaction is abolished by tumourigenic missense mutations in the RING finger of BRCA1, raising the possibility that tumour suppression is mediated by a heteromeric complex of BRCA1 and BARD1 (Ref. 5). The RING finger of BRCA1 also interacts with BAP1 (BRCA1-associated protein 1), a ubiquitin C-terminal hydrolase (see below). The BRCT domains in BRCA1 can activate transcription and are frequently found in proteins involved in DNA repair and cell cycle regulation (Refs 6, 7, 8, 9, 10).

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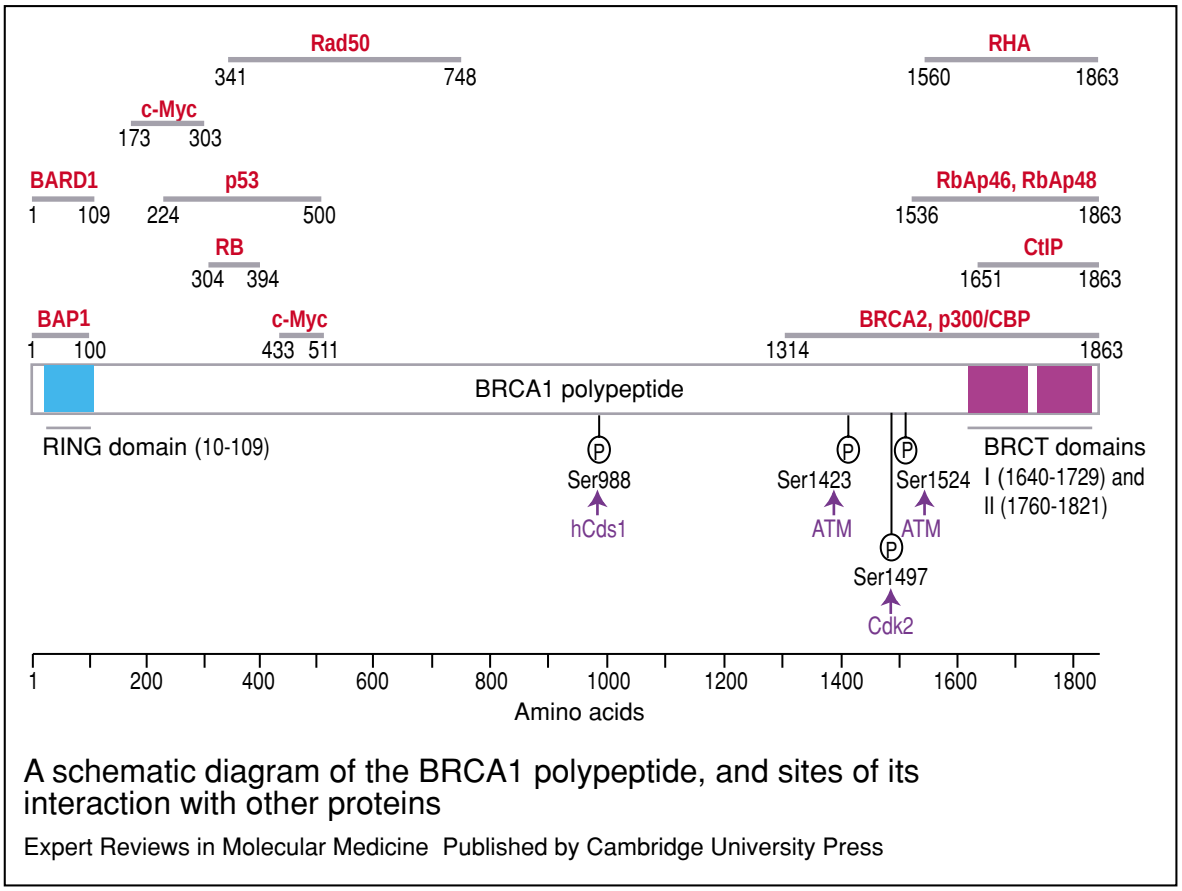
BRCA1 function

BRCA1 and regulation of cell proliferation

BRCA1 protein is localised to the nucleus (Refs 11, 12) and is expressed in a wide range of tissues in developing mouse embryos, particularly in proliferating and differentiating cells (Refs 13, 14). Its expression varies throughout the cell cycle, with a peak occurring in late G1 and S phase (Refs 15, 16, 17). Although *BRCA1*$^{+/-}$ mice are normal and fertile, the complete loss of BRCA1 expression causes embryonic death before day 7.5 of embryogenesis (E7.5) (Refs 18, 19, 20). *BRCA1*$^{-/-}$ embryos also demonstrate an early (~E7.5) cell-proliferation block accompanied by elevated expression of the cyclin-dependent kinase inhibitor p21 (Refs 19, 21), suggesting that BRCA1 protein plays an important role in cell proliferation. This is further supported by the observation that the mutation of *BRCA1* in mammary epithelial cells leads to blunted ductal morphogenesis and apoptosis (Ref. 22).

The apoptosis seen in *BRCA1*$^{-/-}$ cells might in part be a result of a disruption in the 'cell cycle checkpoint', which is a temporary halting of cell-cycle progression at G1, S, G2 or M phases of the cell cycle to allow cells to repair DNA damage



A schematic diagram of the BRCA1 polypeptide, and sites of its interaction with other proteins

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Figure 1. A schematic diagram of the BRCA1 polypeptide, and sites of its interaction with different proteins. The regions of BRCA1 that interact with other proteins are shown above the polypeptide. The phosphorylation sites (P) show the serine residues that are phosphorylated and the kinases responsible (in purple). Only the proteins that have been shown to interact with BRCA1 in vivo are given here. The RING domain is a zinc-binding domain that interacts with BARD1 (BRCA1-associated RING domain protein) (Ref. 5) and BAP1 (BRCA1-associated protein 1) (Ref. 72); the BRCT domains can activate transcription and interact with the transcription factors shown. The references for the BRCA1-interacting proteins are as follows: CtBP-interacting protein (CtIP) (Refs 57, 58), BRCA2 (Ref. 30), histone deacetylase complexes HDAC 1/2, retinoblastoma-associated proteins RbAP46 and RbAp48 (Ref. 59), Rad50 (Ref. 32), c-Myc (Ref. 60), p53 (Refs 8, 61, 62), retinoblastoma protein (RB) (Ref. 63), p300/CBP (CREB-binding protein) (Ref. 64) and RNA helicase A (RHA) (Ref. 65) **(fig001jcb)**.

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before DNA replication or cell division. Cells that carry the deficient *BRCA1* exon 11 isoform are defective in the G2 checkpoint (Ref. 23). Some of these cells exhibit amplification of functional centrosomes (the primary site of nucleation of microtubules in animal cells), leading to unequal segregation of chromosomes (Ref. 23) and aneuploidy, a hallmark of many cancer types. Although the function of BRCA1 in centrosome amplification is not clear, hypophosphorylated BRCA1 interacts with γ-tubulin, a component of the centrosome, during mitosis (Ref. 24). Moreover, overexpression of wild-type BRCA1 induces G1–S arrest in tissue culture cells (Ref. 6), whereas expression of a mutant form attenuates the G2–M checkpoint (Ref. 25).

BRCA1 and DNA damage repair

BRCA1$^{-/-}$ cells are hypersensitive to ionising radiation, which causes double-stranded DNA damage (Ref. 26). This suggests that BRCA1 is important for DNA repair. Indeed, cells lacking BRCA1 are particularly deficient in transcription-coupled repair whereby DNA repair is linked to the transcriptional machinery such that the transcribed strand is preferentially repaired. Cells lacking BRCA1 are also deficient in homology-directed DNA repair, which uses the homologous sister chromatid as the repair template (Refs 27, 28, 29).

The role of BRCA1 in DNA damage repair is further suggested by its association with other proteins involved in DNA repair, including BRCA2 (Ref. 30), Rad51 (Ref. 31) and the hRad50–hMRE11–p95 complex (Ref. 32). The *BRCA2* gene, which was discovered soon after the *BRCA1* gene, is also mutated in some heritable breast cancers and pancreatic adenocarcinomas (Ref. 33), and encodes a large protein that is also important for maintaining genome integrity. More-recent work using immunoprecipitation indicates that BRCA1 is associated with a large complex (>2 MDa), named the BRCA1-associated genome surveillance complex (BASC), which is composed of several DNA repair proteins and tumour suppressors: Mut S homologue 2 (MSH2), Mut S homologue 6 (MSH6), Mut L homologue 1 (MLH1), the protein kinase ATM, Bloom (BLM) and the hRad50–hMRE11–p95 complex (Ref. 34). Although these associations do not prove functional interaction, they are consistent with the DNA-repair-defective phenotype of *BRCA1*-mutated cells.

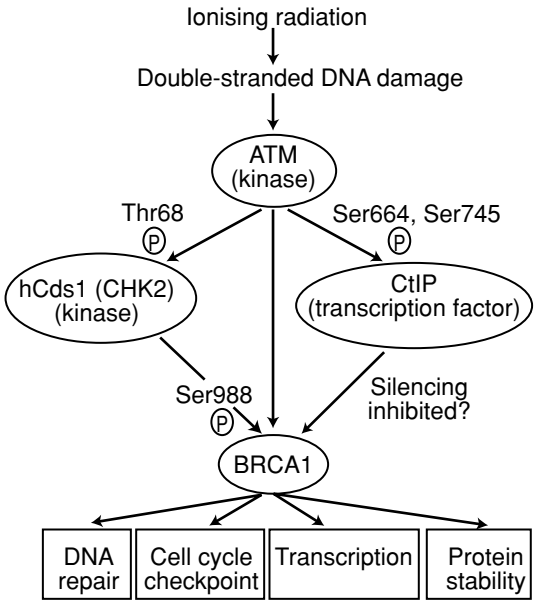

Figure 2. DNA-break-induced phosphorylation of BRCA1 and its possible consequences. Ionising radiation triggers ATM-dependent phosphorylation (P) of hCds1 (Thr68) and CtBP-interacting protein (CtIP) (Ser664 and Ser745). ATM and hCds1 are kinases and CtIP is a transcription factor. ATM phosphorylates Ser1423 and Ser1524 of BRCA1. CtIP binds to BRCA1 and silences the activation potential of BRCA1. hCds1 in turn phosphorylates BRCA1 (Ser988). Potential functions of BRCA1 that might be regulated by phosphorylation are shown. Therefore, wild-type BRCA1 might function as a coordinator of several activities that maintain genome integrity **(fig002jcb)**.

How is the presence of DNA damage signalled to BRCA1? One mechanism by which BRCA1 receives the DNA damage signal is through phosphorylation (Fig. 2) (Refs 35, 36). Thus far, three kinases – ATM (Ref. 37), ATM-related kinase (ATR) (Ref. 38) and hCds1 (CHK2) (Ref. 39) – have been shown to phosphorylate BRCA1 after DNA damage (see below). BRCA1 is also phosphorylated in late G1 and S phase (Refs 12, 35, 36, 40) by Cdk2 at the Ser1497 residue (Ref. 41), but the role of this phosphorylation in BRCA1 function is not known.

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Regulation of BRCA1 by ATM and ATR

The checkpoint protein kinase ATM is activated by double-stranded DNA breaks (Ref. 42). Mutations in the *ATM* gene cause ataxia telangiectasia (AT), which is a complex autosomal recessive disorder with a pleiotropic phenotype including neuronal degeneration (particularly in the cerebellum), oculocutaneous telangiectasias, cancer disposition, immunodeficiency, gonadal abnormalities, growth retardation and premature ageing (Ref. 43). Cells derived from patients with AT are characterised by reduced cell lifespan in culture, cytoskeletal abnormalities, chromosomal instability, hypersensitivity to ionising irradiation and radiomimetic agents, and defective radiation-induced checkpoints at G1, S and G2 phases of the cell cycle (Refs 44, 45).

ATM interacts with BRCA1 in vivo and phosphorylates Ser1423 and Ser1524 of BRCA1 in response to ionising radiation (Ref. 37). It is not known how phosphorylation of these residues affects BRCA1 at the molecular level. However, reconstituting *BRCA1*-mutated breast cancer cell line HCC1937 with wild-type BRCA1 increased their survival after ionising radiation, whereas reconstituting with BRCA1 containing mutations in the ATM-phosphorylated residues did not increase survival. These findings suggest that ATM phosphorylation of BRCA1 is important for BRCA1-mediated responses to double-stranded DNA breaks after ionising radiation.

ATR also phosphorylates Ser1423 of BRCA1 in response to DNA damage and replication block (Ref. 38). However, unlike ATM, the kinase activity of ATR is not enhanced by DNA damage and replication block; instead, under these conditions it relocalises to sites of stalled replication forks where it colocalises with BRCA1. More-recent work suggests that ATR might also phosphorylate sites other than those phosphorylated by ATM, indicating that ATM and ATR act in parallel but partially overlapping pathways of the DNA damage response [K.K. Khanna (University of Queensland, Queensland, Australia) and B-B. Zhou Zhou (Smith Kline Beecham, King of Prussia, PA, USA), pers. commun.].

Regulation of BRCA1 by hCds1

The ATM kinase phosphorylates Thr68 of another checkpoint kinase, hCds1 (Refs 46, 47, 48, 49, 50), and activates it in response to ionising radiation (Refs 46, 51, 52). *hCds1* is mutated in a variant form of Li-Fraumeni syndrome, a highly penetrant familial cancer associated with inherited mutations in the p53 gene (Ref. 53). The link with a syndrome classically associated with p53 mutation might indicate that hCds1 is a tumour suppressor that functions in the same pathway as p53. This notion is supported by the observation that hCds1 phosphorylates Ser20 of p53 and stabilises it in response to DNA damage (Refs 54, 55, 56). If hCds1 is indeed a tumour suppressor, it is surprising that the hCds1 mutation is so rare in cancers (one heterozygotic mutation in 49 cancers studied) (Ref. 53). One explanation might be that the high frequency of the p53 mutation or destabilisation obviates the need for the hCds1 mutation.

hCds1 and BRCA1 colocalise in nuclear foci (Ref. 39). However, after ionising radiation, the hCds1–BRCA1 interaction is completely disrupted. Exactly what regulates the hCds1–BRCA1 disruption is not known, but evidence indicates that phosphorylation of BRCA1 by hCds1 might play a role. In vitro, hCds1 phosphorylates Ser988 of BRCA1 most strongly; in vivo, Ser988 is phosphorylated after ionising radiation but is blocked in the presence of dominant-negative hCds1, suggesting that hCds1 can phosphorylate Ser988 in response to DNA damage. Dispersion of BRCA1 and its separation from hCds1 after ionising radiation are decreased if the hCds1-phosphorylated residue (Ser988) is mutated. The physiological significance of BRCA1 dispersion is not known, but if the DNA-damage-induced dispersion of BRCA1 is important for its function in the DNA damage response, Ser988 should also be important. Indeed, BRCA1 did not restore survival after DNA damage in HCC1937 cells if the hCds1-phosphorylated residue was mutated (Ref. 39).

Transcriptional and other activities of BRCA1

A group of BRCA1-interacting proteins belongs to the transcription factor family (Fig. 2). These include C-terminal binding protein (CtBP)-interacting protein (CtIP) (Refs 57, 58), histone deacetylase complexes HDAC 1/2, retinoblastoma-associated proteins RbAP46 and RbAp48 (Ref. 59), c-Myc (Ref. 60), p53 (Refs 8, 61, 62), retinoblastoma protein (RB) (Ref. 63), CBP (CREB-binding protein) (Ref. 64) and RNA helicase A (RHA) (Ref. 65). The BRCT domains at the C-terminus of BRCA1 have transcription-activating potential (Ref. 8). Indeed, BRCA1 has

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been shown to transactivate the GADD45 and p21 promoters (Refs 6, 57, 66). The tumourigenic missense mutations of the BRCT domains fail to activate transcription, suggesting that transcriptional activity of BRCA1 is important for tumour suppression (Ref. 7). In contrast, BRCA1 suppresses the estrogen receptor α (ERα)-responsive promoter (Ref. 67) (see below) and the insulin growth factor 1 (IGF1) receptor promoter (Ref. 68).

The physiological relevance of the transcriptional activity of BRCA1 has been questioned by many in the field. However, the following observations linking the DNA damage signal and the transcriptional activity of BRCA1 argue that it is physiological. In the absence of DNA damage, the activation potential of BRCA1 is partially suppressed by the CtIP–CtBP complex, which binds to the BRCT domain of BRCA1 (Refs 57, 69). After ionising radiation, Ser664 and Ser745 of CtIP are phosphorylated by ATM, and, as a result, BRCA1 and CtIP separate. However, it must be noted that in a paper by another group, radiation did not induce the separation of BRCA1 and CtIP (Ref. 70). It is not known why the two groups obtained contradicting results.

The physiological relevance of the role of BRCA1 in transcription was further strengthened by the observation that BRCA1 is a component of the human SWI–SNF complex, a large ATP-utilising complex that disrupts histone–DNA contact, helping transcription complexes gain access to DNA (Ref. 71). In light of the BRCA1–SWI–SNF association, it would be intriguing to test whether the genes encoding the components of the SWI–SNF complex are also mutated in breast cancers.

BRCA1 and ubiquitin metabolism

The diversity of BRCA1-associated proteins has increased with the recent discovery that the RING finger domain located near the N-terminus of BRCA1 interacts with BAP1, a nuclear ubiquitin C-terminal hydrolase (Ref. 72). In addition, the BRCA1 RING finger itself mediates ubiquitination in vitro (Ref. 73). There is no direct evidence that the ubiquitin-related activity of BRCA1 is a component of its function in the DNA damage response or tumour suppression. However, several tantalising observations support this possibility: the growth-suppressive effect of BRCA1 is enhanced by BAP1 and, in addition, point mutations in the RING domain that are associated with familial breast cancers abrogate BRCA1–BAP1 interaction. It would be interesting to test whether the ubiquitin-related activity of BRCA1 is also regulated by DNA damage.

Clinical implications

An unsolved mystery is the discrepancy between the ubiquitous expression of BRCA1 and the restriction of the cancers caused by *BRCA1* mutations to the breast and ovary. Because the breast and ovarian tissues are responsive to the mitogenic stimulus of estrogen, and BRCA1 suppresses the activity of ERα, it has been speculated that BRCA1 acts as a tumour suppressor in breast and ovary by counteracting the mitogenic effect of estrogen (Ref. 67). Thus, when there is a loss of function of BRCA1, estrogen-induced growth might go unchecked, and estrogen-induced breast cancer might result. One argument against this theory is that most BRCA1 breast cancers do not express ERα. However, if the antagonistic relationship between BRCA1 and estrogen is physiological, it could have clinical implications. For example, chemopreventive therapies (Ref. 74) with antiestrogens such as tamoxifen and raloxifene might be particularly beneficial for carriers of the *BRCA1* mutation.

Mutations of the *BRCA1* gene are very rare in sporadic breast and ovarian cancers. However, the expression of BRCA1 is often suppressed in many sporadic breast cancers, particularly in those that are highly malignant (Refs 75, 76). In some cases, the BRCA1 promoter region is hypermethylated – a DNA modification that is usually associated with inactive genes (Refs 77, 78). ATM, which regulates hCds1 activity and also directly phosphorylates BRCA1 (Ref. 37), is frequently expressed at low levels in many sporadic breast cancers (Ref. 79); this might in effect block BRCA1 function in the DNA damage response. Moreover, LOH of the BRCA1 locus (over 30%) and the ATM locus (40%) is frequently seen in sporadic breast cancers (Ref. 80). Thus, BRCA1-mediated tumour suppression might be indirectly compromised in a significant proportion of breast cancers – heritable as well as sporadic. If this is the case, progress in the understanding of BRCA1-mediated tumour suppression should benefit not only the small number of families carrying the *BRCA1* mutation but also the >10% of women in the general population who will develop breast cancer.

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Concluding remarks

It is beginning to appear that BRCA1 is a protein with complex and seemingly unrelated functions. The future challenge is to understand how these diverse functions work together to suppress tumour development. Several groups are currently investigating the roles of the BRCA1-interacting proteins in DNA damage responses. Understanding exactly how the DNA damage signal pathways coordinate the functional and physical interactions between BRCA1 and the BRCA1-interacting proteins will be crucial as we move towards the next phase of BRCA1 and breast cancer research.

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Patient support groups in the USA

American Cancer Society (National; Tel: +1 800 ACS 2345)

Y-Me National Breast Cancer Organization

http://www.y-me.org

Susan G. Komen Breast Cancer Foundation

http://www.breastcancerinfo.com

National Coalition for Cancer Survivorship

http://www.cansearch.org/

Information resources for researchers, health professionals and patients

American Institute for Cancer Research (AICR) (focuses on diet and nutrition in cancer prevention and treatment)

http://www.aicr.org

National Alliance of Breast Cancer Organizations

http://www.nabco.org

National Action Plan on Breast Cancer (information on hereditary factors, ethical issues and genetic testing)

http://www.4woman.gov/napbc/

NCI (National Cancer Institute) Cancer Information Service (Tel: +1 800 4 CANCER)

NCI Cancer Trials

http://cancertrials.nci.nih.gov

NCI CancerNet

http://cancernet.nci.nih.gov

OncoLink (information on genetics and cancer)

http://cancer.med.upenn.edu/causeprevent/genetics

The Genetics of Cancer

http://www.cancergenetics.org

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Features associated with this article

Figures

Figure 1. A schematic diagram of the BRCA1 polypeptide, and sites of its interaction with different proteins (fig001jcb).

Figure 2. DNA-break-induced phosphorylation of BRCA1 and its possible consequences (fig002jcb).

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