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REVIEW

BRCA1 and BRCA2: breast/ovarian cancer susceptibility gene products and participants in DNA double-strand break repair

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***BRCA1* and *BRCA2* are tumor suppressor genes, familial mutations in which account for ∼5% of breast cancer cases in the USA annually. Germ line mutations in *BRCA1* that truncate or inactivate the protein lead to a cumulative risk of breast cancer, by age 70, of up to 80%, whereas the risk of ovarian cancer is 30–40%. For germ line *BRCA2* mutations, the breast cancer cumulative risk approaches 50%, whereas for ovarian cancers, it is between 10 and 15%. Both BRCA1 and BRCA2 are involved in maintaining genome integrity at least in part by engaging in DNA repair, cell cycle checkpoint control and even the regulation of key mitotic or cell division steps. Unsurprisingly, the complete loss of function of either protein leads to a dramatic increase in genomic instability. How they function in maintaining genome integrity after the onset of DNA damage will be the focus of this review.**

Introduction

BRCA1 and *BRCA2* are tumor suppressor genes, familial mutations in which account for ∼5% of breast cancer cases in the USA annually (1). Germ line mutations in *BRCA1* that truncate or inactivate the protein lead to a cumulative risk of breast cancer, by age 70, of up to 80%, whereas the risk of ovarian cancer is 30–40%. For germ line *BRCA2* mutations, the breast cancer cumulative risk approaches 50%, whereas for ovarian cancers, it is between 10 and 15% (2). Like *BRCA1* mutations, which almost exclusively result in female breast and ovarian cancers, *BRCA2* families also show a marked increase in breast and ovarian cancer. However, unlike *BRCA1* families, they exhibit an increased risk of male breast, pancreas and prostate cancers (3,4). Tumors of patients from *BRCA1* and *2* families typically exhibit a loss of heterozygosity or other somatic alterations of *BRCA1* and *2*, respectively, with the wild-type copy being lost (5). Both BRCA1 and BRCA2 are involved in maintaining genome integrity at least in part by engaging in DNA repair, cell cycle checkpoint control and even the regulation of key mitotic or cell division steps (6). Not surprisingly, the complete loss of function of either protein leads to a dramatic increase in genomic instability (7–10). How they function in maintaining genome integrity after the onset of DNA damage will be the focus of this review.

DNA double-strand break repair

The eukaryotic genome is under constant stress, one result of which is the constant generation of DNA damage (11). DNA damage can result from both endogenous (e.g. reactive oxygen species and cytosine deamination) and exogenous (e.g. ultraviolet radiation, ionizing radiation and chemicals) sources. One of the most toxic DNA lesions to a cell is the DNA double-strand break (DSB). This is because it affects both strands of the duplex, thus no intact complimentary strand is available as a template for repair (12). DSBs normally occur during DNA replication, during the generation of antibody diversity and in meiosis. DSBs can be induced exogenously by agents such as ionizing and ultraviolet radiation (reviewed in ref. 13). Failure to repair a DSB can result in apoptosis, whereas misrepair may lead to mutations or gross chromosomal rearrangements such as translocations and deletions. Repeated instances of these alterations can over time promote carcinogenesis and a number of genes involved in double-strand break repair (DSBR) are known tumor suppressors (reviewed in ref. 14). In order to prevent such pathological outcomes, cells have evolved two major pathways for the repair of DSBs: non-homologous end-joining (NHEJ) and homologous recombination (HR) (reviewed in ref. 15).

NHEJ involves the direct religation of the ends of a DSB. It is highly efficient and is the primary DSB repair mechanism used in the G_0-, G_1- and early S-phases of the cell cycle (16,17). Upon generation of a DSB, a Ku70/Ku80 heterodimer is recruited to the DSB ends (18,19). The Ku heterodimer then recruits DNA-dependent protein kinase, catalytic subunit (DNA-PK_{cs}) (20–22) and, together with the DNA ends, activates the DNA-PK_{cs} kinase activity, which is required for its DNA repair function (21). DNA-PK_{cs} molecules on either side of the break interact, thus linking both ends (23). The MRN complex (Mre11–Rad50–Nbs1) was recently demonstrated to be involved in these early steps of NHEJ (24–26). DSB ends may require some processing in order for repair to be possible, due to the presence of damaged bases, and the Artemis protein is recruited to a DSB following its interaction with DNA-PK_{cs}, to perform this role (27). Artemis itself exhibits both a DNA-PK_{cs}-independent 5′-to-3′-exonuclease activity and a DNA-PKcs-dependent endonuclease activity toward hairpins and double-stranded to single-stranded DNA transitions (28,29). In the absence of Artemis, cells exhibit radiosensitivity, but do not have a major DSB repair defect, suggesting that not all DSBs need processing by Artemis to be repaired (30). The processing of complex lesions at the ends of a DSB may result in asymmetric termini that need to be religated. Such termini may contain gaps that need to be filled in, and the X-family of DNA polymerases (such as Polμ, Polλ and tdT) are involved in this (reviewed in ref. 31). The final step in NHEJ involves the religation of the DNA ends by DNA ligase IV, which is recruited in a complex with X-ray repair complementing defective repair in Chinese hamster cells 4 (XRCC4) and XRCC4-like factor (32,33).

NHEJ can be error-free or error-prone depending on the nature of the sequence at a DSB, because the termini at some but not all DSBs are processed before ligation, and removal of bases can result in loss of DNA sequence at the break. An alternative end-joining pathway has been described which can function in the absence of factors including Ku, XRCC4 and DNA ligase IV (34–37). Such repair frequently relies upon short regions of homology (microhomology) and results in small deletions. This error-prone microhomology-mediated end-joining is not the only form of alternative end-joining, however, since in the absence of XRCC4–DNA ligase IV, error-free end-joining can still take place (38).

The second major pathway for DSB repair is HR, generally regarded as being error-free (Figure 1). HR relies on the presence of an intact sister chromatid to act as template for correct repair of the break without loss of sequence information. As such, HR can only take place in the S- and G_2-phases of the cell cycle. After DSB recognition by the MRN complex (39), 3′-overhanging single-stranded DNA (ssDNA) is generated. While the role of the MRN

Abbreviations: dHJ, double Holiday junction; DNA-PKcs, DNA-dependent protein kinase, catalytic subunit; DSB, double-strand break; DSBR, double-strand break repair; FA, Fanconi anemia; HR, homologous recombination; NHEJ, non-homologous end-joining; PARP, poly(adenosine diphosphate-ribose) polymerase; RPA, replication protein A; ssDNA, single-stranded DNA; XRCC4, X-ray repair complementing defective repair in Chinese hamster cells 4.

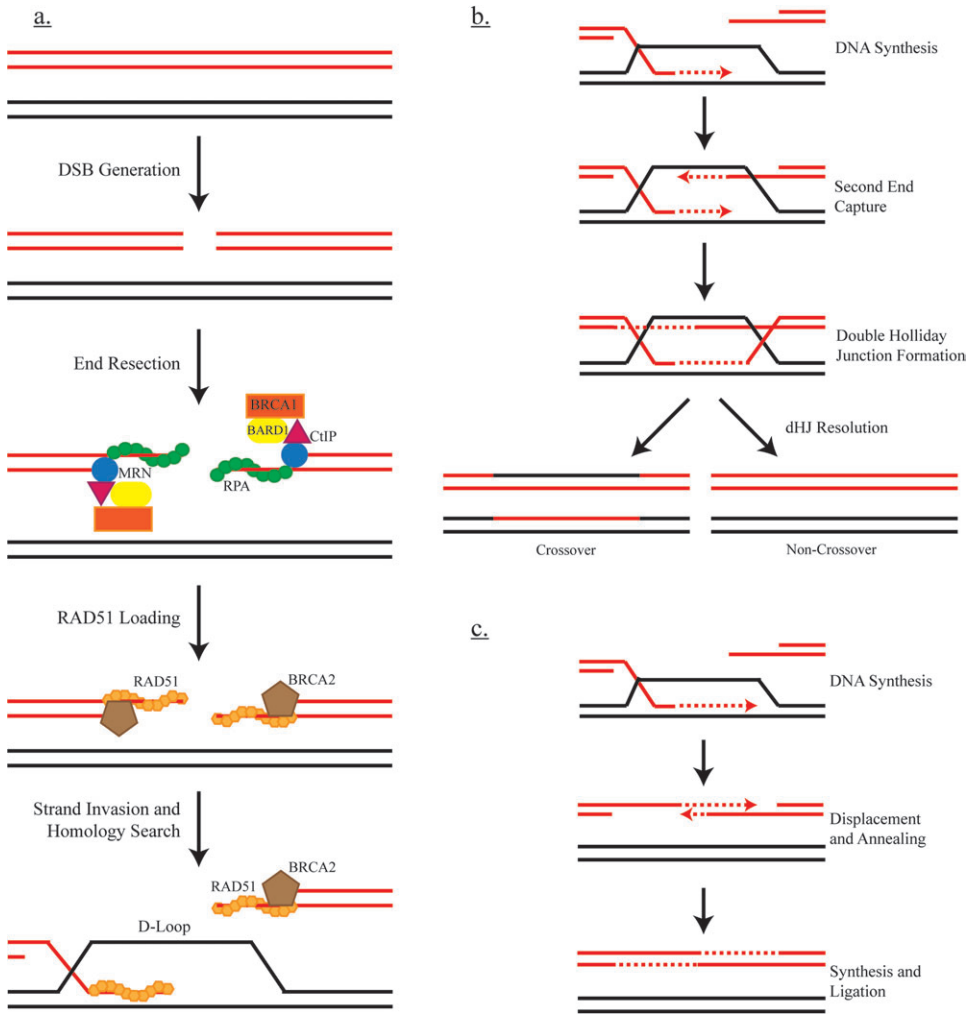

Fig. 1. (**a**) Upon generation of a DSB, the MRN complex recognizes the lesion. The MRN complex recruits CtIP and BRCA1/BARD1. MRN nuclease activity is stimulated following its interaction with CtIP. This nuclease activity, together with other unconfirmed factors, generates 3′-ssDNA overhangs on either side of the break that rapidly bind RPA. Through its interaction with PALB2, BRCA1 leads to the recruitment of BRCA2, which, in turn, recruits and loads the Rad51 recombinase, displacing RPA. This RAD51 nucleoprotein filament catalyzes strand invasion and initiates the homology search on the intact sister chromatid. (**b**) Classical HR model. Once homology is established, the invading strand primes DNA synthesis using the sister chromatid as a template. The second 3′-overhang is 'captured' by the displaced strand of the sister chromatid, and this also primes DNA synthesis. After repair is complete, the two sister chromatids are linked by a dHJ. Holliday junction resolving enzymes can resolve this structure in a crossover-generating manner or non-crossover-generating manner. (**c**) Synthesis dependent strand annealing. In synthesis dependent strand annealing repair, once DNA synthesis has generated a sequence complementary to the other side of the DSB, the invading strand is displaced from the sister chromatid and anneals to the opposing 3′-overhang. Gaps are filled in by further DNA synthesis. Repair can only generate a non-crossover product since the second 3′-end never anneals to the displaced strand of the sister chromatid.

complex in NHEJ is still poorly defined, it is known to play a pivotal role in HR. MRN keeps the DNA ends in close proximity to each other (40,41), recruits and activates the Ataxia Telangiectasia mutated protein kinase, which is a key mediator of the DNA damage response signaling pathways (42,43), and is required for end resection to generate the long 3′-ssDNA overhangs (44) required for HR. In yeast, it has been proposed that the MRX complex (an analog of MRN) together with Sae2 initiates the resection of the 5′-strand on each side of a DSB (45). In mammalian cells, the ortholog of Sae2, CtIP, has been implicated in DSB resection, through its stimulation of MRN nuclease activity (46–48). The 3′-ssDNA is rapidly bound by replication protein A (RPA), and through the action of BRCA1, BRCA2 and PALB2, the Rad51 protein is recruited and coats this ssDNA segment displacing RPA and forming a RAD51 nucleoprotein filament (49). Error-free HR repair involves invasion of the RAD51 nucleoprotein filament into the intact sister chromatid. After strand invasion, a search for a homologous sequence is initiated (50). Once homology is found, the invading ssDNA acts as a primer for DNA synthesis by an as yet unidentified DNA polymerase(s). DNA polymerase η can perform this synthesis *in vitro* (51), but whether this occurs *in vivo* has not yet been determined. Strand invasion results in the displacement of the second strand of the sister chromatid, thus forming a D-loop structure. In the classical homologous recombination model (Figure 1b), the displaced strand from the sister chromatid anneals to the 3′-overhang from the other end of the DSB. The displaced strand can now act as template for DNA synthesis primed by this second end of the DSB. Completion of DNA replication from the 3′-overhangs generates a joint molecule, with both sister chromatids connected via a double Holliday junction (dHJ). The dHJ must then be resolved in order to generate an intact repaired DNA molecule. The exact proteins required for Holliday junction resolution remain unclear, but recently the GEN1 Holliday junction resolvase was discovered in human cells (52) and SLX4 has been shown to play a role in resolution in higher eukaryotes (53–56). Resolution of dHJs may result in a crossover or non-crossover event. It should be noted, however, that crossing-over is a rare event during HR in somatic cells (57–60). While crossing-over is essential for generation of allelic diversity during meiosis, it may also have negative consequences. For example, if a mismatched base pair is present

on the sister chromatid template then it will generate a mutation in one of the duplexes during 3′-overhang-initiated DNA synthesis. If the resulting dHJ is resolved in a crossover manner, this mutation will become fixed in the repaired chromatid.

An alternative model was proposed to potentially explain the non-crossover repair bias in HR, namely synthesis-dependent strand annealing (Figure 1c). In the synthesis-dependent strand annealing model, the initial steps of strand invasion and DNA synthesis from the invading 3′-strand occurs just as in the classical HR model. However, there is no capture of the second 3′-overhang by the displaced sister chromatid strand. Instead, after synthesis from the invading 3′-overhang, the newly synthesized product becomes displaced and anneals to the processed 3′-overhang on the opposite side of the DSB. Further DNA synthesis can then fill in the gaps on both strands.

BRCA1 in DSB repair

The *BRCA1* gene is located on chromosome 17q21, and its primary product is a 1863 residue protein (Figure 2a(i)). The BRCA1 protein (a.k.a. p220) contains a RING domain in its N-terminal region and a coiled-coil domain together with tandem BRCT repeats in its C-terminal region. These domains are critical in the known DNA repair and DNA damage response signaling functions of BRCA1. BRCA1 is a component of a number of supercomplexes, each of which plays a role in DNA damage response activation, cell cycle checkpoint activation and/or DSB repair (all are functions elicited by DSBs) (Figure 2b). BRCA1 normally exists as a heterodimer with another RING/BRCT domain-containing protein, BARD1. In the absence of BARD1, BRCA1 is unstable and is rapidly degraded and vice versa (61). The interaction between these two proteins is mediated by alpha-helical units adjacent to their RING domains (62). The RING domain is highly conserved among BRCA1 and BARD1 gene products of multiple species and is a core component of many E3 ubiquitin ligases. *In vitro*, the BRCA1–BARD1 heterodimer serves as an ubiquitin ligase (63–65), although its *in vivo*, physiological substrates are as yet largely unknown. This E3 ligase activity is essential for BRCA1-mediated suppression of genomic instability (64,65). Recently, however, there has been some controversy regarding the

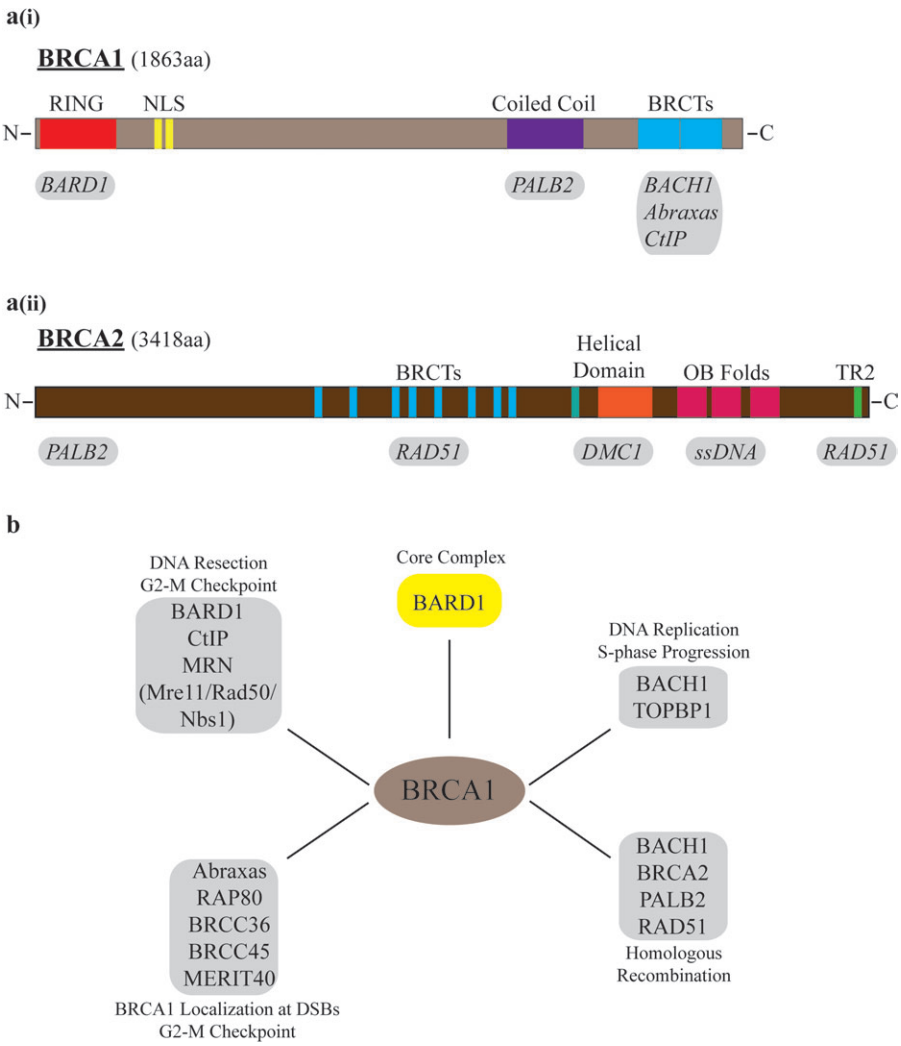

Fig. 2. **a(i)** Domain organization of BRCA1 and BRCA2. Sequences that abut the BRCA1 N-terminal RING domain are largely responsible for its interaction with BARD1. C-terminal to this domain is a nuclear localization signal. The central part of BRCA1 is devoid of established protein interaction or enzymatic function domains. Toward the C-terminus, there is a coiled-coil domain that interacts with a coiled-coil domain in PALB2. The C-terminal BRCT repeats are phosphoprotein interaction domains, responsible for multiple BRCA1/partner protein interactions. **a(ii)** BRCA2 is a protein of 3418 aa. The N-terminal 40 residues are necessary and sufficient for its interaction with PALB2. The BRC repeats and the TR2 region are required for interactions with RAD51 and its loading onto ssDNA. The a-helical domain interacts with DMC1 and contributes to BRCA2 function in meiosis. The OB folds bind to ssDNA and are likely involved in BRCA2 HR function. (**b**) Schematic of the various protein supercomplexes of which BRCA1 is known to be a major subunit. These structures play a role in maintaining genomic stability. These complexes do not appear to operate independently of one another but rather cooperate to promote physiological BRCA1 HR function.

involvement of the E3 ligase activity of BRCA1/BARD1 in DSBR. It was reported that in isogenic mouse ES cells, a BRCA1 mutant lacking its E3 ligase activity demonstrated near wild-type levels of BRCA1-mediated DNA repair (66). Subsequently, we have demonstrated that the BRCA1 mutant used in these experiments ($BRCA1^{I26A}$) retains some E3 ligase activity (6). This residual activity may be enough to allow BRCA1 to perform its DSB repair activities. Clinically relevant mutations occur within the RING domain that affect the BRCA1–BARD1 E3 activity, and the frequency, latency, histopathology and cytogenetic features of tumors from BRCA1-, BARD1- or BRCA1-ablated + BARD1-ablated mouse mammary glands are similar (67). This implies that the known tumor suppressor functions of BRCA1 require its interaction with BARD1. Whether this is due to the known E3 ligase activity of the heterodimer and/or the role of BARD1 in stabilizing the BRCA1 protein remains unclear.

For BRCA1 to carry out its DSBR functions, it must first become localized to a DSB-containing chromatin site. The BRCT repeats of BRCA1 are phosphopeptide-binding domains (68) essential for its targeting to sites of DNA damage (69–72). The Abraxas protein interacts with the BRCT repeats and links BRCA1 with the ubiquitin-binding protein RAP80. RAP80 contains two ubiquitin interacting motifs, and these bind one or more polyubiquitinated proteins at DSBs, helping to target BRCA1 in a timely manner (73,74). In the absence of RAP80, BRCA1 is still recruited to sites of damage, but to a much lesser extent. While one consequence of the absence of RAP80 or Abraxas is hypersensitivity to ionizing radiation, the physiological basis for this defect has, as yet, not been reported.

As briefly mentioned above, BRCA1 plays a major role in DSB repair by HR. After induction of DSBs by ionizing radiation, BRCA1/BARD1 heterodimers form a number of distinct protein supercomplexes with a variety of different binding partners. One of these complexes consists of BRCA1, CtIP and the MRN complex (47,75–77). As described above, it is thought that CtIP and the MRN complex function together in the generation of ssDNA at DSB ends. Depletion of CtIP leads to a marked reduction in ssDNA generation and RPA foci formation at DSBs. The BRCA1 interaction with CtIP only occurs after CtIP becomes phosphorylated in the S- and G_2-phases of the cell cycle, when HR is the prominent form of DSBR (78). In addition, the BRCA1 interaction with MRN components can be enhanced by genotoxic stress, and BRCA1 is itself required for efficient generation of ssDNA at DSBs, although whether this is a direct or indirect function of the protein is unclear (76,79). In this regard, in chicken DT40 cells, it was demonstrated that expression of a CtIP mutant, unable to be phosphorylated, and, thus unable to interact with BRCA1, led to a decreased level of ssDNA generation after DSB induction (47). However, CtIP still interacts with MRN in the presence of a mutant BRCA1 species that cannot interact with CtIP (46). Taken together, these data suggest that a direct role for BRCA1 in end resection is possible but has yet to be definitively shown.

In addition to a possible role in 5′-end resection, BRCA1 is also involved in a later stage of HR. This role is dependent on the interaction between BRCA1 and BRCA2 (80), which is necessary for the recruitment of RAD51 (77,81,82) and generation of the RAD51 nucleoprotein filament that mediates strand invasion. BRCA1 and BRCA2 interact through a mediator protein, PALB2 (83,84). BRCA1 and PALB2 interact via their respective coiled-coil domains and mutations in the BRCA1 coiled-coil domain that abolish its PALB2-binding activity result in compromised HR function (83). These mutations were found in BRCA1 tumors, implying that loss of this specific BRCA1 function in DSB repair is one source of the genomic instability and tumorigenesis observed in this subset of BRCA1 mutation carriers.

Other genome stability roles for BRCA1

In addition to a direct role in DSB repair, BRCA1 possesses other functions that promote genome stability and cell survival. Upon generation of DNA damage, cell cycle checkpoints are activated that arrest cells and allow them time to repair the damage before progressing. If the damage is not resolved, then the cells can remain arrested until an apoptotic pathway is activated. In the absence of such checkpoint responses, sufficient time may not be afforded for the DSB to be fully repaired prior to mitotic entry and may lead to genome instability, manifest by such abnormal developments as chromosomal loss and/or missegregation. The BRCA1–RAP80–Abraxas complex described above is not only directly involved in DSBR but also in the G_2–M checkpoint (69–72,74).

Through a still unknown mechanism, BRCA1 also regulates phosphorylation of the CHK1 kinase, a protein known to be involved in DNA damage-driven cell cycle checkpoint control (85). This regulation correlates with the ability of BRCA1 to accumulate at damage-induced foci (86–88), although how and why this is so is not understood. Activated CHK1 is also required for the phosphorylation of the FANCD2 and FANCE components of the Fanconi anemia (FA) pathway (89,90), which is involved in the repair of DNA interstrand cross-links, by a mechanism that, at least in part, involves HR. Thus, the influence of BRCA1 on CHK1 function might represent another means by which it contributes to the HR process.

BRCA1 has also been ascribed a role in those replication checkpoints that are activated in response to replicative stress such as stalled or collapsed replication forks (91,92). This appears to be via its interactions with BACH1 and TOPBP1. BACH1 is a helicase and binds to the BRCA1 BRCT repeats (93). This interaction occurs during S-phase and requires BACH1 phosphorylation (94). In the absence of BACH1 activation, cells fail to progress through S-phase in a timely manner (95). TOPBP1 is known to be involved in DNA replication and checkpoint control (96,97) and was found to be part of the BRCA1–BACH1 complex (77). Absence of any of these three proteins results in failure of cells to slow their progression through S-phase following ionizing radiation. Moreover, all three proteins are loaded onto replication origins after exposure to DNA-damaging agents and appear to facilitate the removal of, or prevent the loading of, the CDC45 origin-licensing factor (77).

The BRCA1/BARD1 heterodimer is also active in mitosis control. In *Xenopus laevis* cell-free extracts and human cells, the BRCA1–BARD1 complex is required for mitotic spindle pole assembly, and the absence of BRCA1 results in defective spindle pole formation (6). Defective spindle pole and spindle formation lead to genomic instability due to incorrect chromosomal segregation, and, thus can result in aneuploidy, a hallmark of BRCA1 tumors.

Finally, BRCA1 regulates the ubiquitination status of topoisomerase IIa (98), which is involved in the decatenation of sister chromatids after their replication. Failure to decatenate chromatids can also lead to aneuploidy, and lagging chromosomes are observed in BRCA1-deficient cells. Moreover, BRCA1 is also a centrosomal protein and in that setting may be engaged in the control of centrosome duplication, which also has the potential to elicit a defect in chromosomal segregation (99,100).

Therefore, through its ability to participate in error-free DSBR, checkpoint control, mitotic spindle assembly, sister-chromatid decatenation and centrosomal duplication, BRCA1 plays a critical role in maintaining genome stability. As such, failure of BRCA1 function leads to genomic instability by any of several pathways resulting in gross chromosomal rearrangements, chromosomal missegregation and aneuploidy. Since many of the mutations identified in *BRCA1* families have been demonstrated to affect these BRCA1 functions, one can surmise that these activities are required for BRCA1 tumor suppression.

BRCA2 in DSB repair

The *BRCA2* gene (located on chromosome 13q) encodes a protein of 3418 residues (Figure 2a(ii)). Its primary function is in HR and is based upon its ability to bind to the strand invasion recombinase, RAD51 (80,101–104). BRCA2 contains eight BRCT repeats, each of which can bind Rad51, and an ssDNA-binding domain, the exact role of which remains unclear. Recruitment of RAD51 to sites of DNA

damage requires BRCA2. Given the absolute requirement for RAD51 in HR, its not surprising that BRCA2-deficient cells exhibit genomic instability (8,105–107). As mentioned above, BRCA2 interacts with PALB2, through which it localizes to DSBs together with BRCA1. Once concentrated at a DSB, BRCA2 is able to load RAD51 onto the 3′-ssDNA overhangs, displacing RPA (108,109). After RAD51 loading, BRCA2 functions to stabilize the resulting nucleoprotein filament, through the TR2 domain at its C-terminus (110). BRCA2 also participates in meiotic recombination through its interaction with the DMC1 recombinase (111), and in BRCA2-deficient mice, there is persistence of Spo11-induced DSBs in the gonads (products of the early steps in meiotic recombination) and such animals are infertile (112).

FA is a rare genetic disorder characterized by a high cancer incidence and developmental disorders (reviewed extensively in ref. 113). A hallmark of FA cells is their hypersensitivity to DNA cross-linking agents. Three of the thirteen FA complementation groups result from mutations in BRCA2, PALB2 and BACH1. It has been proposed that repair of interstrand DNA cross-links may require HR, and thus, the role of BRCA2 in FA may be due to its contribution to HR. It is tempting to ascribe a role for BRCA1 in FA due to the involvement of multiple BRCA1-interacting proteins in FA disease prevention, but there is as yet no compelling evidence for such a role.

The known effects of BRCA2 loss on genome stability are also observed in tumors that arise in *BRCA2* mutation carrying families. As in the case of BRCA1, the gross chromosomal rearrangements and aneuploidy that develop in BRCA2-deficient cells may also be involved in BRCA2 tumorigenesis. It should be noted here that while *BRCA1* and *2* families both primarily develop breast and ovarian tumors, the breast tumors are often pathologically distinct form each other, with most BRCA1 cancers being basal-like, whereas most BRCA2 tumors are luminal (114–116).

Conclusion

BRCA1 and BRCA2 play a number of major roles in the maintenance of genome integrity. They are involved directly in a number of steps during DSBR; they control cell cycle checkpoint responses and they are involved in chromosomal segregation. Yet, the detailed mechanisms by which these large proteins operate *in vivo* are still not well understood. Recently, it has been shown that inactivating TP53BP1, a major player in NHEJ, could rescue the sensitivity of BRCA1-null cells to DNA-damaging agents (117), suggesting that, in the absence of BRCA1 and NHEJ, some form of HR is still able to function and repair DSBs (A.Nussensweig, personal communication). Such work illustrates well the complexity of the BRCA1 and 2 damage response, and the cross talk between various DNA repair and DNA damage response pathways.

In addition, it has been known for some time that chromatin state can affect the ability of a cell to repair DNA damage (118,119) and that the presence of DNA damage affects chromatin state ((118) reviewed in ref. 119,120). In this regard, in higher eukaryotes, repair of DNA DSBs in heterochromatin seems to occur less efficiently in heterochromatin than in euchromatin (121,122), and wild-type Ataxia Telangiectasia mutated protein is required for their repair in heterochromatin but not in euchromatin, at least in the G_0/G_1-phases of the cell cycle (121,122). Hence, there are different requirements for DSB repair in heterochromatin and in euchromatin. The fact that BRCA1 is known to interact with chromatin remodeling proteins *in vivo* (123) makes it an attractive protein to study in this regard, and we are currently trying to learn whether its DSBR function is differentially directed at DSB in heterochromatin versus euchromatin.

Clinically, the genomic instability phenotype of BRCA1- and 2-deficient cells may provide an opportunity for treatment. Recently much interest has been generated in poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors. PARP1 is involved in the repair of DNA single-strand breaks (124,125), and failure of their repair can lead to the generation of DSBs during DNA replication. Inhibition of PARP1 is suspected of leading to a large increase in DSBs that, in the absence of BRCA1 or 2, and hence a proper HR response, cannot be repaired and are suspected of leading to cell death (126). In HR-proficient cells, however, these breaks can be efficiently repaired, and this is hypothesized to suppress their potential lethality. In BRCA1- and BRCA2-deficient cell lines and in mouse BRCA1 breast cancer models, inhibition of PARP1 can lead to selective death of tumor cells (126,127), providing proof of the concept that induction of excessive DNA damage in repair deficient tumors may provide a novel strategy for cancer therapy, at least in women with BRCA1 and 2 cancers. Indeed, in a recent clinical trial, the PARP inhibitor olaparib was demonstrated to exhibit antitumor activity in BRCA1- and 2-associated cancers while exhibiting side effects far less severe than conventional chemotherapy (128).

While much more is known than was the case a decade ago, it would be naive to assume that a majority of the mysteries surrounding BRCA1 and BRCA2 function have been deciphered. In that context, there may well be much more to learn of the clinical impact of BRCA1 and BRCA2 misbehavior.

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