BRCA2 functions: from DNA repair to replication fork stabilization

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Abstract

Maintaining genomic integrity is essential to preserve normal cellular physiology and to prevent the emergence of several human pathologies including cancer. The breast cancer susceptibility gene 2 (*BRCA2*, also known as the Fanconi anemia (FA) complementation group D1 (*FANCD1*)) is a potent tumor suppressor that has been extensively studied in DNA double-stranded break (DSB) repair by homologous recombination (HR). However, BRCA2 participates in numerous other processes central to maintaining genome stability, including DNA replication, telomere homeostasis and cell cycle progression. Consequently, inherited mutations in *BRCA2* are associated with an increased risk of breast, ovarian and pancreatic cancers. Furthermore, bi-allelic mutations in *BRCA2* are linked to FA, a rare chromosome instability syndrome characterized by aplastic anemia in children as well as susceptibility to leukemia and cancer. Here, we discuss the recent developments underlying the functions of BRCA2 in the maintenance of genomic integrity. The current model places BRCA2 as a central regulator of genome stability by repairing DSBs and limiting replication stress. These findings have direct implications for the development of novel anticancer therapeutic approaches.

Key Words
- BRCA2
- homologous recombination
- replication stress
- DNA double-stranded break repair
- genomic stability
- Fanconi anemia
- DNA replication
- cancer therapy

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Introduction

Our genome is continuously exposed to DNA-damaging agents such as ionizing radiation, ultraviolet light or DNA replication errors that can generate cytotoxic DNA lesions. The range of DNA lesions include single- (SSBs) and double-stranded DNA breaks (DSBs), inter- and intrastrand DNA crosslinks, base depurination and deamination as well as oxidative damage (reviewed in Goldstein & Kastan (2015)). These lesions interfere with basic cellular processes and can result in DNA replication errors, stalled transcription complexes or missegregation of chromosomes during mitosis. Ultimately, the mutagenic potential of DNA lesions may lead to genomic rearrangements, a hallmark of cancer cells. Persistent DNA damage is also linked to several human pathologies, including neurodegenerative diseases, infertility, developmental disorders, immunodeficiency syndromes and accelerated aging.

To circumvent the threat posed by DNA-damaging agents, cells have evolved highly complex and specific DNA damage responses that detect, signal and ultimately repair these lesions throughout the cell cycle (reviewed in Helleday *et al.* (2014)). Although each type of DNA lesion activates a different pathway, there is a certain degree of overlap to maximize genome integrity. In that regard, BRCA2 plays an essential role in several DNA repair pathways, including DSB repair by homologous recombination (HR) and DNA crosslink repair by the FA pathway. The *BRCA2* gene was identified in 1995

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(Wooster *et al*. 1995) and has been the subject of intensive research over the past 20 years. In this review, we aim to summarize the most recent findings on the role of BRCA2 in the maintenance of genome stability and their implications for the development of new therapeutic approaches. The first part of this review is dedicated to the critical domains of the BRCA2 protein while the subsequent sections detail the role of BRCA2 in HR and replication fork protection. We also address the importance of BRCA2 in FA-dependent DNA repair as this pathway is essential to resolve DNA crosslink during replication.

BRCA2 structural and functional domains

The human *BRCA2* gene is located on the long arm of chromosome 13 (13q12.3) and is composed of 27 exons that encode for a protein of 3418 amino acids. BRCA2 has no apparent enzymatic activity despite initial conflicting evidence concerning a role in histone acetylation (Fuks *et al*. 1998, Siddique *et al*. 1998, Shin & Verma 2003, Choi *et al*. 2012). Due to its large size, the structural and functional characterization of BRCA2 has been particularly challenging; however, the recent reconstruction of full-length BRCA2, generated by electron microscopy, has revealed that it exists predominantly as a homodimer and has provided better mechanistic insights into the role of BRCA2 in DNA repair (Shahid *et al*. 2014). Several key structural elements have been identified in BRCA2 over the past two decades (Fig. 1): the BRC repeats, which consist of eight conserved motifs of about 35 amino acids (Bork *et al*. 1996, Bignell *et al*. 1997, Wong *et al*. 1997); the DNA-binding domain (DBD) composed of a long helical domain (HD) and three oligonucleotide/oligosaccharide-binding (OB) folds (Yang *et al*. 2002); and finally the C-terminal TR2 domain (Sharan *et al*. 1997). BRCA2 is a predominantly nuclear protein and its subcellular localization is controlled by two distinct nuclear localization signals (NLSs) (Yano *et al*. 2000) and a masked nuclear export signal (NES) (Jeyasekharan *et al*. 2013). Finally, BRCA2 acts as a hub and recruits several regulatory proteins including RAD51 (Mizuta *et al*. 1997, Sharan *et al*. 1997, Chen *et al*. 1998*b*), the partner and localizer of BRCA2 (PALB2)/FANCN (Sy *et al*. 2009, Zhang *et al*. 2009*a*,*b*) and FANCD2 (Hussain *et al*. 2004), supporting the notion that BRCA2 is a multifunctional protein involved in several biological pathways (Fig. 2). In the following sections, we will detail the relevance of these unique regions with regard to the functions of BRCA2 in maintaining genomic stability.

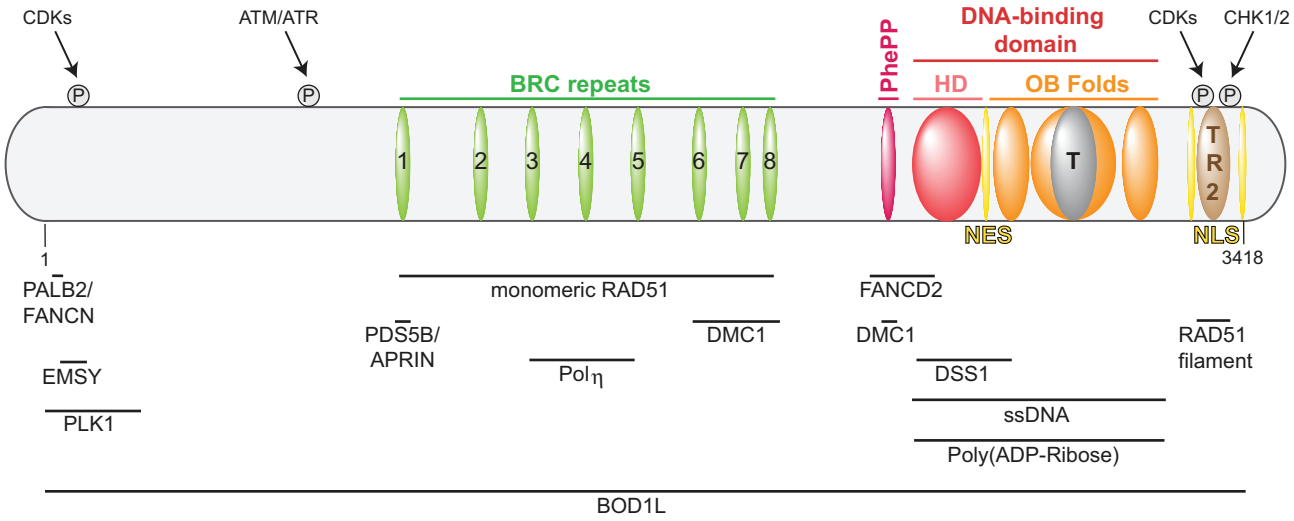

Figure 1
Structural domains and interaction partners of BRCA2. The N-terminal domain of BRCA2 is involved in several protein–protein interactions, including PALB2 and EMSY. BRCA2 contains eight BRC repeats located in the central portion of the protein; they are primarily involved in binding to monomeric RAD51, although they also are implicated in additional protein–protein interactions (PDS5B/APRIN and Polη). The BRCA2 DNA-binding domain (DBD) is composed of a helical domain (HD), three oligonucleotide/oligosaccharide-binding (OB) folds and a Tower domain (T). They promote BRCA2 binding to single-stranded DNA (ssDNA) and poly(ADP-Ribose). This domain also associates with DSS1. Adjacent to the DBD is a phenylalanine-proline-proline (PhePP) motif involved in the interaction with DMC1. This region is also implicated in the binding of FANCD2. The C-terminus of BRCA2 contains the TR2 domain, which interacts with RAD51 nucleofilaments. It also contains two distinct nuclear localization signals (NLSs) that are critical for BRCA2 nuclear localization. BRCA2 is posttranslationally modified by several cyclin-dependent (CDK, PLK1) and DNA damage-dependent (ATM/ATR, CHK1/2) kinases.

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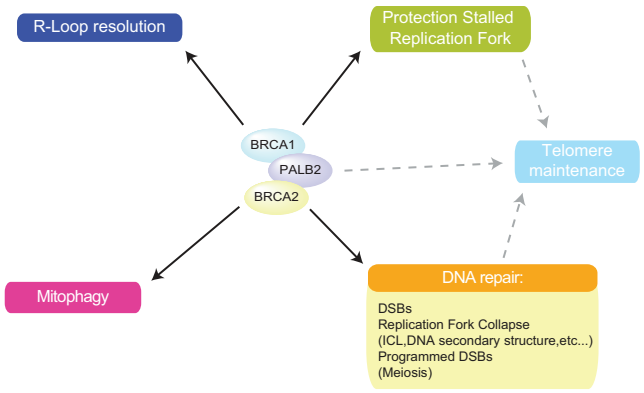

Figure 2
BRCA2 functions in the maintenance of genome stability. Bound to BRCA1 and PALB2, BRCA2 participates in multiple biological processes that are critical to maintain genome stability. First, BRCA2 is a key player in the repair of DNA lesions including DNA double-strand breaks (DSBs) and intrastrand crosslinks (ICLs). Moreover, BRCA2 has a DNA repair-independent function: it prevents nucleolytic degradation at stalled replication forks. Both of these functions are directly or indirectly involved in the maintenance of telomeres. BRCA2 is required for the processing of R-loops in collaboration with the TREX-2 complex. More recently, BRCA2 has been involved in mitophagy and the clearance of damaged mitochondria, thereby indirectly preserving genome stability.

BRCA2 is a central mediator of DSB repair by HR

DSBs are considered the most cytotoxic DNA lesions as one single unrepaired DSB can result in cell death (Bennett *et al*. 1993, Sandell & Zakian 1993). Furthermore, DSBs can lead to major genomic rearrangements including loss of chromosome segments and chromosomal translocations. Two main and mechanistically different pathways have evolved to repair these challenging DSBs: classical nonhomologous end joining (C-NHEJ) and HR (reviewed in Betermier *et al*. (2014), Guirouilh-Barbat *et al*. (2014)). Importantly, C-NHEJ is active throughout the cell cycle, unlike HR, which is restricted to the S/G2 phases. C-NHEJ requires little to no DNA end processing and functions by rapidly ligating both DNA ends. On the other hand, HR requires the formation of extended 3′ single-stranded DNA (ssDNA) tracks for homology search and strand invasion, a process called DNA end resection (Fig. 3). DNA repair pathway choice is controlled in mammalian cells by the tumor suppressors p53-binding protein 1 (53BP1) and BRCA1, which have an antagonistic relationship (Chapman *et al*. 2012, Escribano-Diaz *et al*. 2013, Tang *et al*. 2013). In G1 phase of the cell cycle, 53BP1 accumulates at DSBs by binding to dimethylated histone H4 (H4K20me2) (Huyen *et al*. 2004) and DSB-induced ubiquitylated Lys15 of histone H2A (H2AK15Ub) (Fradet-Turcotte *et al*. 2013). It results in an increased mobility of the chromatin surrounding the DSBs (Krawczyk *et al*. 2012, Lottersberger *et al*. 2015), although it remains unclear whether this is the case for all DNA breaks in the nucleus (Kruhlak *et al*. 2006, Soutoglou *et al*. 2007, Roukos *et al*. 2013). Additionally, 53BP1 promotes the recruitment of downstream effectors including the replication timing regulatory factor 1 (RIF1) (Chapman *et al*. 2013, Di Virgilio *et al*. 2013, Escribano-Diaz *et al*. 2013, Feng *et al*. 2013, Zimmermann *et al*. 2013), pax transactivation domain-interacting protein (PTIP) (Callen *et al*. 2013) and MAD2 mitotic arrest deficient-like 2 (MAD2L2) (Boersma *et al*. 2015, Xu *et al*. 2015), which are thought to limit the accessibility of BRCA1 to DSBs, thereby inhibiting DNA end resection. A recent report suggests that the association of PTIP with the nuclease Artemis (Wang *et al*. 2014) commits the cell into repairing DSBs by C-NHEJ. Altogether, these effector proteins promote C-NHEJ-mediated DSB repair preferentially in G1 phase of the cell cycle (reviewed in Zimmermann & de Lange (2014)).

In S/G2 phases, BRCA1 is recruited to DSBs, along with CtBP-interacting protein (CtIP) and the MRE11/RAD50/NBS1 (MRN) complex, to facilitate the optimal initiation of DNA end resection (reviewed in Lamarche *et al*. (2010); Fig. 3); however, the contribution of BRCA1 in promoting DNA end resection is not completely understood (Nakamura *et al*. 2010, Reczek *et al*. 2013, Cruz-Garcia *et al*. 2014, Polato *et al*. 2014). Extensive resection is subsequently carried out by the DNA replication ATP-dependent helicase-like homolog (DNA2), and the Exonuclease 1 (EXO1), with the help of the Bloom syndrome helicase (BLM) (Gravel *et al*. 2008, Huertas *et al*. 2008, Mimitou & Symington 2008, Nimonkar *et al*. 2008, 2011, Zhu *et al*. 2008, Cejka *et al*. 2010, Niu *et al*. 2010, Shim *et al*. 2010, Garcia *et al*. 2011). This two-step model of DNA end resection is primarily based on findings observed in yeast; therefore, it remains to be determined whether it is fully transposable to human cells. Exposed ssDNA stretches are rapidly coated by the Replication Protein A (RPA) complex, which protects them against nuclease cleavage and hairpin formation. In parallel to facilitating DNA end resection, BRCA1 promotes the recruitment of BRCA2 to DSBs (Chen *et al*. 1998*a*), a pivotal step in HR-mediated DSB repair. Indeed, BRCA2 stimulates the displacement of RPA and the loading of the RAD51 recombinase on ssDNA, thereby initiating homology search, strand invasion and strand exchange. Here, we discuss how BRCA2 promotes RAD51-mediated HR via its functional and structural domains. Furthermore, we review the different interactions involving BRCA2 and their relevance for HR-mediated DSB repair.

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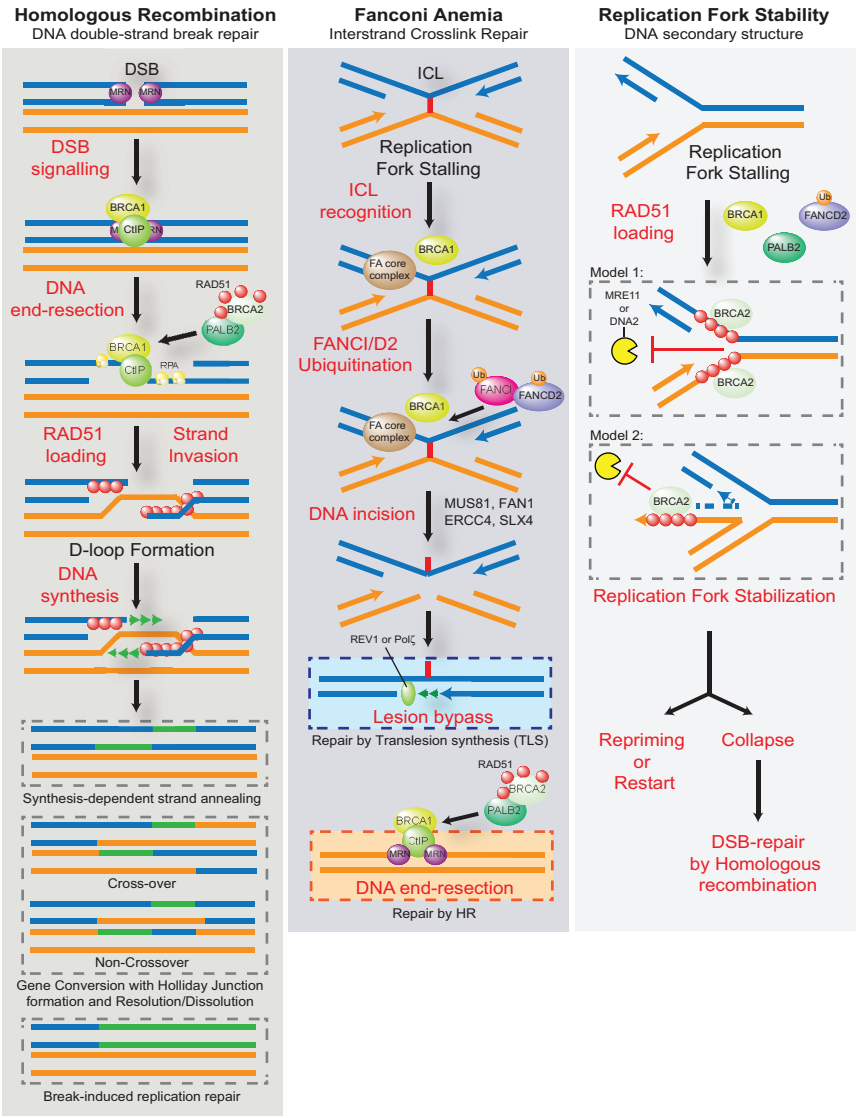

Figure 3

Role of BRCA2 during DSB repair, ICL repair and stabilization of stalled replication forks. (A) DSB is first detected by the MRE11–RAD50–NBS1 (MRN) complex, which triggers a cascade of phosphorylation and ubiquitylation events (not shown) that promote the recruitment of BRCA1 and CtIP to the break (reviewed in Dantuma & van Attikum 2016). In S/G2 phase of the cell cycle, CtIP, along with the exonucleases Exo1 and DNA2-BLM, promotes extensive DNA end-resection, a step that commits cells to repair DSBs by homologous recombination (HR). Next, loading of RAD51 on the 3′-resected end by the concerted action of BRCA1/PALB2 and BRCA2 initiates homology search and the formation of a D-loop, a structure that results from the invasion of the homologous template by the RAD51-coated DNA strand. DNA synthesis and processing of the D-loop by synthesis-dependent strand annealing, gene conversion or break-induced replication repair complete this error-free DNA repair process. (B) Recognition and repair of ICLs is initiated when two replication forks converge at the lesion. The subsequent recruitment of the proteins of the Fanconi anemia (FA) core complex (FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, FANCM) along with FANCT, FAAP100, MHF1, MHF2, FAAP20 FAAP24 and BRCA1 triggers monoubiquitylation of the heterodimer FANCI/FANCD2. Once activated, the heterodimer promotes nucleolytic incision at the converged replication forks and releases the ICL from one of the strands. The latter incision, also referred as the 'unhooking', is performed by a complex composed of the nuclease scaffold (SLX4) and the endonucleases ERCC4-ERCC1, MUS81-EME1 and FAN1. Depending on their structure, the parental DNA strands will be replicated by translesion synthesis (TLS) polymerases (REV1 or POLζ) or repaired by HR. (C) Following replication fork stalling, forks need to be protected from excessive resection. Although the exact molecular events that lead to their stabilization are still unclear, evidence support a role of BRCA1, BRCA2 and FANCD2 in promoting the loading of RAD51 at the fork, an event that is essential to protect the degradation of nascent strands by the nucleases MRE11 and DNA2. Whether RAD51 is loaded on ssDNA that arises on the parental strand or on the nascent strand is unknown (Models 1 and 2). The forks can be reprimed or restarted, a step that is orchestrated by the TLS polymerases. When submitted to sustained replication stress or when replication forks are unable to bypass roadblocks, forks collapse and the intervention of nucleases generates DSBs that are subsequently repaired by HR.

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How does BRCA2 facilitate RAD51 loading on ssDNA?

Upon its discovery, BRCA2 rapidly emerged as a critical component of the HR-mediated DSB repair pathway. *Brca2* deletion, similar to *Brca1* (Gowen *et al*. 1996, Hakem *et al*. 1996, Liu *et al*. 1996, Ludwig *et al*. 1997, Shen *et al*. 1998, Hohenstein *et al*. 2001) and *Rad51* null mutants (Lim & Hasty 1996, Tsuzuki *et al*. 1996), results in mouse embryonic lethality (Sharan *et al*. 1997, Suzuki *et al*. 1997). Interestingly, cells homozygous for a truncated *Brca2* allele are hypersensitive to genotoxic agents (Patel *et al*. 1998), providing the first direct evidence of BRCA2 involvement in DNA repair. This was further corroborated when a direct role for BRCA2 in HR was demonstrated in human and mouse cell lines using GFP-based reporter assays developed to measure HR (Moynahan *et al*. 2001).

In the context of HR, the main function of BRCA2 is to promote the formation of RAD51 filaments on ssDNA. This in turn allows homology search and DNA strand invasion (Yuan *et al*. 1999), which is central to initiating DNA synthesis using the invading strand as a primer, and ultimately, HR-mediated DSB repair (Fig. 3). BRCA2 binds to monomeric RAD51 via its BRC repeats (Wong *et al*. 1997, Chen *et al*. 1998*b*) and the crystal structure of the BRC4 repeat in complex with RAD51 revealed that two distinct clusters of residues in the BRC repeats control RAD51 binding (Pellegrini *et al*. 2002, Galkin *et al*. 2005, Rajendra & Venkitaraman 2010). Although the BRC repeats are highly conserved between mammalian species (Bignell *et al*. 1997), the individual repeats differ greatly from one another within a species, suggesting a specific role for each BRC in RAD51 binding. In fact, the BRC repeats have been subdivided into two groups (BRC1-4 and BRC5-8) that, via distinct mechanisms, facilitate the loading of RAD51 onto ssDNA (Carreira & Kowalczykowski 2011). Consistent with the role of the BRC repeats in contacting RAD51, several mutations, which affect the structure of the BRC repeats and thereby weaken RAD51 binding, have been associated with cancer predisposition (Chen *et al*. 1999, Li *et al*. 1999).

Apart from the BRC repeats, BRCA2 interacts with RAD51 through its C-terminal TR2 domain. Instead of binding to monomeric RAD51, the TR2 domain stabilizes RAD51 nucleofilaments (Davies & Pellegrini 2007, Esashi *et al*. 2007). Several findings suggest that the C-terminal region of BRCA2 is critical for HR-mediated DSB repair. For instance, overexpression of the TR2 domain in wild-type human cells results in a 50% reduction in an HR-mediated DSB repair assay (Esashi *et al*. 2005). Furthermore, cells lacking the C-terminal region of *Brca2* are hypersensitive to irradiation (Morimatsu *et al*. 1998, Donoho *et al*. 2003) and display reduced HR activity in GFP-based reporter assays (Moynahan *et al*. 2001, Tutt *et al*. 2001), providing direct evidence of the importance of the TR2 domain in DSB repair. This has been further corroborated in mice, where *Brca2* C-terminal deletion results in increased overall tumor incidence and decreased survival (McAllister *et al*. 2002, Donoho *et al*. 2003), as well as in human, where the deletion of the C-terminal region of BRCA2 is associated with an early onset of breast and ovarian cancers (Hakansson *et al*. 1997). Interestingly, minimal constructs of BRCA2 encompassing the DBD and the BRC repeats require the C-terminus of BRCA2 in order to efficiently promote HR in *Brca2* mutant hamster cells (Siaud *et al*. 2011). Finally, CDK phosphorylation of the TR2 domain has been shown to reduce BRCA2–RAD51 binding and promotes the disassembly of RAD51 complexes at the entry of mitosis (Esashi *et al*. 2005, Davies & Pellegrini 2007, Esashi *et al*. 2007, Ayoub *et al*. 2009), which could provide a way to turn off HR-mediated DSB repair in mitosis. This step may be critical to maintain genomic stability given that active DSB repair jeopardizes proper chromosome segregation in mitosis (Lee *et al*. 2014, Orthwein *et al*. 2014, Benada *et al*. 2015). Phosphorylation of BRCA2 C-terminus by the checkpoint kinases CHK1/CHK2 may also be relevant for BRCA2 function in HR (Fig. 2) (Bahassi *et al*. 2008). Altogether, these findings suggest that the regulation of the function associated with BRCA2 TR2 domain plays a central role in HR-mediated DSB repair.

Importance of BRCA2 DBD during DNA repair

A large portion of BRCA2 is dedicated to binding ssDNA: this function is mediated by a HD and three OB folds within the BRCA2 DBD (Yang *et al*. 2002). Several proteins involved in genome stability are characterized by the presence of one or more OB folds, including RPA (reviewed in Flynn & Zou (2010)). Interestingly, a fusion protein of BRCA2 BRC repeats and the large RPA subunit is able to partially restore HR in *Brca2* mutant cells, suggesting that the major function of the BRCA2 OB folds is to target BRCA2 to ssDNA and thereby promote RAD51 loading (Saeki *et al*. 2006). Among the BRCA2 OB folds, OB2 contains an insert of 130 amino acids named the tower domain, which improves binding to ssDNA and has been inferred to bind dsDNA (Yang *et al*. 2002).

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Several cancer-associated BRCA2 mutations in the DBD have been linked to defects in HR-mediated DSB repair (reviewed in Guidugli *et al*. (2014)), further testifying to the importance of the DBD for BRCA2 function in HR.

The BRCA2 DBD does not exclusively bind ssDNA. Indeed, the BRCA2 DBD associates with the deleted in split hand/split foot 1 (DSS1) protein (Marston *et al*. 1999), an interaction that is critical not only for HR-mediated DSB repair but also for BRCA2 ability to limit the accumulation of R-loops, a nucleic acid structure composed of an RNA:DNA hybrid and a displaced ssDNA (Sollier & Cimprich 2015). Initial studies showed that DSS1 depletion results in the persistence of RAD51 foci at DSBs (Gudmundsdottir *et al*. 2004) and reduces BRCA2 protein levels (Li *et al*. 2006), but failed to define a clear role for DSS1 in HR. Subsequently, DSS1 has been found to be involved in masking a NES in BRCA2 and thereby controlling both BRCA2 and RAD51 nuclear localization (Jeyasekharan *et al*. 2013). New insight suggests also that DSS1 physically interacts with RPA to promote its unloading and its replacement by RAD51 on ssDNA (Zhao *et al*. 2015).

Besides ssDNA, the BRCA2 DBD binds to poly(ADP-ribose) (PAR) (Zhang *et al*. 2015). Interestingly, PARylation mediates the rapid recruitment of BRCA2 to DNA lesions upon laser microirradiation, which in turn promotes EXO1 mobilization and DNA end resection (Zhang *et al*. 2015), suggesting a BRCA1- and RAD51-independent function of BRCA2 in HR.

BRCA2 acts as a scaffold for additional DSB-related factors

A significant portion of BRCA2 is dedicated to binding RAD51. Nevertheless, BRCA2 is involved in additional protein–protein interactions. In particular, the N-terminal region of BRCA2 associates with the PALB2/FANCN (Xia *et al*. 2006), which physically links BRCA1 to BRCA2 in a cell cycle-dependent manner (Sy *et al*. 2009, Zhang *et al*. 2009*a*,*b*, Orthwein *et al*. 2015). This interaction is critical for the recruitment of BRCA2 to DSBs and for its role in HR (Xia *et al*. 2006, Oliver *et al*. 2009, Sy *et al*. 2009, Zhang *et al*. 2009*a*,*b*). Mutations in either *BRCA2* or *PALB2* that disrupt this interaction result in a drastic reduction in HR-mediated DSB repair. Importantly, these mutations are associated with breast cancer predisposition and FA syndrome (reviewed in Pauty *et al*. (2014) and Guidugli *et al*. (2014)).

Several additional interactions involving BRCA2 have been identified and studied in HR-mediated DSB repair. In particular, BRCA2 interacts with the nuclear protein EMSY through its N-terminus. This interaction may play a role in chromatin remodeling at DSBs (Hughes-Davies *et al*. 2003, Cousineau & Belmaaza 2011), but its exact relevance to DSB repair requires further investigation. The cohesin-associated protein PDS5B/APRIN is another BRCA2-interacting protein that is important for HR. Unlike PALB2 and EMSY, PDS5B interacts with BRCA2 through its first BRC repeat in a cell cycle-dependent manner; abrogation of this interaction or depletion of endogenous PDS5B by RNA interference results in a significant reduction in HR (Brough *et al*. 2012). The importance of the PDS5B–BRCA2 interaction in DSB repair was further confirmed in *Drosophila*, where it has recently been shown to be involved in HR-dependent meiotic recombination at the nuclear envelope (Kusch 2015). The role of BRCA2 in meiosis is not restricted to its interaction with PDS5B. Indeed, loss of *Brca2* in plants (Siaud *et al*. 2004, Seeliger *et al*. 2012) and mice (Sharan *et al*. 2004) led to impaired meiosis, likely due to Brca2 binding with the meiosis-specific recombinase DNA meiotic recombinase 1 (DMC1) via a phenylalanine-proline-proline (PhePP) motif in BRCA2 (Dray *et al*. 2006, Thorslund *et al*. 2007, Seeliger *et al*. 2012). Nevertheless, disruption of the PhePP motif in mice had no impact on meiosis (Biswas *et al*. 2012), suggesting that additional domains in BRCA2 mediate its function during meiosis. Indeed, a recent report showed that the BRC repeats of BRCA2 directly bind to DMC1 and stimulate DMC1-mediated DNA strand exchange (Martinez *et al*. 2016). Altogether, BRCA2 coordinates both RAD51- and DMC1-mediated recombination events, thereby promoting DSB repair in both somatic and germinal cells.

BRCA2 is a guardian of genomic stability upon replication stress

DNA replication fork stalling represents a constant threat for the maintenance of genomic integrity (Zeman & Cimprich 2014). To circumvent replication stress, cells have evolved complex responses that prevent replication forks from collapsing and that deal with roadblocks which restrain their progression (Berti & Vindigni 2016). Here, we discuss the role of BRCA2 in the protection and restart of stalled forks as well as in the processing of transcription-induced DNA:RNA hybrids (R-loops). Finally, we review the novel therapeutic approaches that have emerged from these findings.

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BRCA2 protects stalled replication forks from nucleolytic degradation

During DNA replication, progression of the replication forks can be hampered by many elements including DNA lesions (base damages, SSBs, ICLs), secondary structures (G-quadruplex and R-loops), repetitive elements and nucleotide pool depletion (Zeman & Cimprich 2014). This process triggers an ataxia telangiectasia mutated (ATM)- and Rad3-related (ATR)-dependent signaling pathway that activates a cell cycle checkpoint and facilitates replication fork processing (reviewed in Flynn & Zou (2011)) (Fig. 3). Depending on the nature and the persistence of the stress, stabilized forks can either restart or collapse (Berti & Vindigni 2016). To promote restarting of forks, nascent strands need to undergo limited resection. While the exact mechanism by which resection contributes to the processing of stalled replication forks is currently unknown, both its inhibition and its overactivation are detrimental for replication fork restart (Buis *et al*. 2008, Hashimoto *et al*. 2010, Schlacher *et al*. 2011). Two key nucleases, the meiotic recombination 11 (MRE11) and DNA2, are thought to drive this step (Costanzo *et al*. 2001, Trenz *et al*. 2006, Hashimoto *et al*. 2010, Buisson *et al*. 2014, Thangavel *et al*. 2015); however, the mechanism(s) by which these nucleases recognize and process stalled forks remain unclear. Recent studies suggest that poly (ADP-ribose) polymerase 1 (PARP1) and the histone methyltransferase complex PTIP/mixed-lineage leukemia protein 3 et 4 (MLL3/4) promote the recruitment of MRE11 to stalled forks (Bryant *et al*. 2009, Ying *et al*. 2012, Chaudhuri *et al*. 2016). On the other hand, DNA2 acts together with the Werner syndrome ATP-dependent helicase (WRN) at reversed replication forks (Thangavel *et al*. 2015). The current model proposes that DNA2 and MRE11 accumulate on different types of stalled forks depending on their structures and the moment at which they appear (Karanja *et al*. 2014, Higgs *et al*. 2015, Thangavel *et al*. 2015). Nevertheless, the recent finding that the Fanconi-associated nuclease 1 (FAN1) is also implicated in replication fork recovery (Lachaud *et al*. 2016, Chaudhury *et al*. 2014) suggests that this model is much more complex than initially anticipated.

Limited resection that occurs at stalled forks needs to be tightly regulated as uncontrolled nucleolytic degradation leads to genomic instability in Fanconi anemia (FA)- and *BRCA1/2*-deficient cancer cells (Schlacher *et al*. 2011, Schlacher *et al*. 2012, Ying *et al*. 2012, Berti & Vindigni 2016). BRCA2 is a key player in the processing of replication forks. For instance, stalled replication forks, characterized by the formation of Y-shaped DNA intermediates on two-dimensional gel electrophoresis, disappear quickly after replication stress is induced in *BRCA2*-deficient cells (Lomonosov *et al*. 2003). Although BRCA2 has never been detected at stalled replication forks, its colocalization with PALB2, RAD51, proliferating cell nuclear antigen and RPA at replication stress-induced foci (Buisson *et al*. 2014) and its ability to protect the nascent DNA strand from degradation by MRE11 in DNA fiber assays (Schlacher *et al*. 2011, Ying *et al*. 2012, Buisson *et al*. 2014) suggest that it plays a direct role in stalled replication fork processing. The current model places RAD51 nucleofilament stabilization by BRCA2 as a key step for the protection of nascent replication tracks: nascent DNA strand protection requires that BRCA2 interacts with monomeric RAD51 through its BRC repeats and stabilizes RAD51 filaments via its TR2 domain (Schlacher *et al*. 2011). Consequently, cells under replication stress block the CDK-mediated phosphorylation of the TR2 domain (S3291) (Fig. 1), which is known to abolish the binding of BRCA2 to nucleofilaments (Esashi *et al*. 2005). This inhibition is driven by ATR signaling and the components of the core Hippo pathway, large tumor suppressor kinase 1 (LATS1) and Ras association domain family 1 isoform A (RASSF1A) (Pefani *et al*. 2015). Interestingly, the inability of a BRCA2 S3291A mutant to rescue the stalled fork stability in *BRCA2*-deficient cells suggests that a dynamic phosphorylation of this residue is required to complete replication fork recovery (Schlacher *et al*. 2011). BRCA2 also promotes the association of RAD51 with stressed replication forks by facilitating its phosphorylation by polo-like kinase 1 (PLK1) (Yata *et al*. 2014). This function relies on a direct interaction between the CDK2-phosphorylated N-terminal domain of BRCA2 (T77 site) and the phospho-binding polo box domain of PLK1 (Fig. 1). Finally, stalled fork protection does not depend on the ability of BRCA2 to interact with DNA, suggesting that the main role of BRCA2 at stalled replication forks is to load and stabilize polymerized RAD51 (Schlacher *et al*. 2011).

BRCA2 partners contribute to replication fork protection

As mentioned previously, BRCA1 and PALB2 promote the recruitment of BRCA2 at DSBs, but recent findings suggest that they may play a similar role at stalled replication forks. Indeed, PALB2 colocalizes with BRCA2 at stalled and

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collapsed replication forks in HeLa cancer cells (Buisson *et al*. 2014) and replication forks are destabilized in *Brca1*-deficient mouse ES cells upon replication stress (Schlacher *et al*. 2012).

Several factors, including FANCD2 and the newly identified protein biorientation of chromosomes in cell division 1 like (BOD1L), coimmunoprecipitate with BRCA2 and promote stalled fork protection through the stabilization of RAD51 filaments (Schlacher *et al*. 2012, Higgs *et al*. 2015). BOD1L actively inhibits the processing of nascent strands by DNA2, BLM and FBH1 proteins (Higgs *et al*. 2015), but it remains unclear how the interplay of BRCA2 and BOD1L is functionally relevant in this context. Similarly, the BRCA2–FANCD2 interaction has been observed in both two hybrids of yeast and coimmunoprecipitation experiments (Hussain *et al*. 2004, Wang *et al*. 2004, Higgs *et al*. 2015); however, its relevance for stalled replication fork protection has yet to be elucidated. FANCD2 affects several important biological pathways including DNA synthesis, replication fork restart and alternative end-joining repair, all of which could influence the recovery of stalled forks (Lossaint *et al*. 2013, Kais *et al*. 2016, Lachaud *et al*. 2016, Michl *et al*. 2016). As detailed in the following section, FANCD2 needs to be monoubiquitylated to promote ICL repair; however, at stalled replication forks, the role of this posttranslational modification is largely debated (Schlacher *et al*. 2012, Raghunandan *et al*. 2015). Furthermore, the involvement of FANCD2 in resolving replication stress has mainly been described in *BRCA1/2*-deficient tumors; thus, the cooperation of FANCD2 with BRCA2 in the protection of stalled replication fork is still debated in normal cells.

Recent findings involve additional factors in the maintenance of genomic stability upon replication stress. In particular, the nucleosome-remodeling factor chromodomain helicase DNA-binding protein 4 (CHD4) was recently shown to promote resistance to replicative stress in *BRCA1/2*-deficient cells (Guillemette *et al*. 2015, Chaudhuri *et al*. 2016). Thus, the latter discovery provided insight into the mechanism by which factors accumulate at stalled replication forks impact its processing. Moreover, it highlights the interesting possibility that new players in the stabilization of replication remain to be identified.

Role of BRCA2 in replication forks processing

Cells must complete the replication of their genetic material before division. To achieve this goal while maintaining genomic stability, they have evolved multiple alternative ways to deal with stalled replication forks. First, cells can counteract the presence of DNA lesions by restarting stalled forks through fork repriming or fork reversal (Berti & Vindigni 2016). While fork repriming relies mainly on the activity of translesion synthesis (TLS) polymerases (Berti & Vindigni 2016), recent findings support a role of RAD51 and BRCA2 in fork reversal and restart (Petermann *et al*. 2010, Yata *et al*. 2014, Raghunandan *et al*. 2015, Zellweger *et al*. 2015). This observation remains debatable as replication restart is not impacted in *RAD51*- and *BRCA2*-deficient cells using a DNA fiber assay (Schlacher *et al*. 2011).

When replication forks experience prolonged replication stress or when stalled forks failed to restart, they collapse and their processing by nucleases such as MUS81 lead to the generation of one-ended DSBs (Berti & Vindigni 2016) (Fig. 3). Repair of these breaks by HR restores a proper template for DNA replication and limits genomic instability. DSBs can also arise when replication forks encounter roadblocks that are particularly hard to bypass such as the covalent linkage between the Watson and Crick strands of DNA that are formed in ICLs. These DNA lesions are induced by compounds such as platinum-based cisplatin or mitomycin C (MMC), and are particularly toxic in patients that suffer from FA.

FA is a rare autosomal recessive disease caused by the inactivation of one of the 19 FA genes and is characterized by a spectrum of clinical disorders, including congenital abnormalities, progressive bone marrow failure and predisposition to cancer development (Ceccaldi *et al*. 2016). *BRCA2* has been classified as an FA-like gene following the discovery of a subgroup of patients suffering from FA due to a mutation in *BRCA2* (Howlett *et al*. 2002). At the molecular level, the processing and repair of ICLs is initiated by the coordinated action of the FA core complex (composed of FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, FANCM), as well as FANCT, FAAP100, MHF1, MHF2, FAAP20, FAAP24 and BRCA1, upon the convergence of two replication forks to the lesion (reviewed in Ceccaldi *et al*. (2016); Fig. 3). Following the accumulation of the FA core complex to an ICL, monoubiquitylation of the FANCD2–FANCI heterodimer by the E3 ubiquitin ligase FANCL promotes its loading on chromatin. This ubiquitination event is central to the recruitment of multiple downstream effectors: the nuclease complexes that promote ICL unhooking via DNA incision, the polymerases that promote TLS and the HR proteins that promote DSB repair (Zhang & Walter 2014). TLS polymerases enable replication by bypassing a lesion on one DNA strand while HR drives repair on the second parental strand

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where a one-ended DSB has been generated by the DNA incision (Fig. 3). Interestingly, recombination-associated DNA synthesis may also contribute to DNA repair at stalled forks. In this condition, the interaction of BRCA2 and PALB2 with polymerase η (Polη) has been suggested to promote the extension of D-loop substrates following RAD51-mediated strand invasion (Buisson *et al*. 2014).

During these processes, BRCA2 has long been thought to promote repair by its function in HR (discussed previously). However, the importance of BRCA2 and RAD51 in the protection of stalled forks raises the possibility of their involvement in the stabilization/processing of forks that encounter ICLs. Indeed, RAD51 localizes in the proximity of ICLs independently of FANCD2 and before the detection of DSBs (Long *et al*. 2011, Wang *et al*. 2015). Further investigation will be required to determine whether BRCA2 participates in the loading of RAD51 at ICLs before the formation of DSBs.

BRCA2 safeguards the integrity of DNA against specific secondary structures

Across the genomic landscape, the formation of secondary structures challenges DNA replication (Zeman & Cimprich 2014). In BRCA2-depleted cells, the accumulation of R-loops as well as the inability of cells to maintain telomere integrity (telomeres are G-rich regions that can form G-quadruplexes) suggests that BRCA2 facilitates DNA replication across challenging DNA structures. Interestingly, the ability of BRCA2 to process R-loops and maintain telomeres integrity may be independent of its functions at stalled fork protection and in DNA repair (discussed below).

BRCA2 limits R-loops accumulation R-loops are highly stable structures that are formed when a nascent RNA transcript interacts with a complementary DNA sequence, a phenomenon that results in the formation of an RNA:DNA hybrid and a displaced ssDNA. In normal cells, R-loops often formed at gene promoters and terminators, and their life time is regulated by RNAse H1, which degrades RNA:DNA hybrids, and by putative helicases (Aquarius Intron-Binding Spliceosomal Factor (AQR) and senataxin (SETX)), which specifically unwind R-loops (Sollier & Cimprich 2015). Although these loops have an important role in the regulation of gene expression and immunoglobulin class switching (reviewed in Sollier & Cimprich (2015)), their uncontrolled accumulation impedes the progression of replication forks and creates genomic instability. R-loop-linked genomic instability is particularly exacerbated in BRCA1/2 tumors cells as well as in cells isolated from FA patients (Kee & D'Andrea 2012, Hatchi *et al*. 2015). Consistent with this observation, depletion of BRCA2, BRCA1 or the FAgenes (FANCD2, FANCA, FANCM, FANCL) lead to the accumulation of R-loop and to a concomitant increase in the number of chromosomal aberrations in these cells (Bhatia *et al*. 2014, Garcia-Rubio *et al*. 2015, Hatchi *et al*. 2015, Schwab *et al*. 2015). Nevertheless, it remains largely unclear how R-loops promote genomic instability in this context. Interestingly, R-loops do not accumulate in RAD51-depleted cells, supporting a model where BRCA2 impacts R-loop formation independently of its ability to recruit and stabilize RAD51 on ssDNA (Bhatia *et al*. 2014). BRCA2 was proposed to limit the accumulation of R-loops by cooperating with the TREX-2 complex, which is involved in mRNP biogenesis and export (Bhatia *et al*. 2014). The interaction of BRCA2 with TREX-2 complex may occur via DSS1 (Fig. 1); however, further investigation will be required to validate this hypothesis. The role of BRCA2 in preventing the formation of RNA:DNA hybrids differs greatly from the role of BRCA1 in this process. Indeed, the mutational signatures of specific transcription termination sites are different in *BRCA1*- and *BRCA2*-null tumors (Hatchi *et al*. 2015), supporting the hypothesis that both BRCA proteins target R-loops in different regions of the genome (Hatchi *et al*. 2015). Moreover, BRCA1 counteracts the accumulation of R-loops by recruiting SETX to a subset of transcription termination regions from highly transcribed genes (Hatchi *et al*. 2015). It is still unclear how BRCA2 is involved in limiting R-loops, but as mentioned above, other components of the FA pathway contribute to their regulation. Thus, it is possible that BRCA2 collaborates with FA genes to limit the appearance of the RNA:DNA hybrids and its associated genomic instability. In these conditions, resolution of R-loops is dependent on the translocase activity of FANCM (Schwab *et al*. 2015).

BRCA2 protects telomere integrity Telomeres are another tedious DNA structure to replicate due to the presence of a highly repetitive G-rich sequence (TTAGGG). As the maintenance of telomeres is essential to prevent genomic instability, two mechanisms safeguard their integrity: (1) the maintenance of telomere length and (2) the formation of a protective telomeric structure, the T-loop or cap, which prevents their recognition by DNA repair signaling (Doksani & de Lange 2014). Telomere length is maintained by the concomitant actions of the replication machinery and of a specialized reverse

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transcriptase (telomerase) (Blackburn & Collins 2011). Alternatively, elongation is achieved by an HR-mediated process, called the alternative lengthening of telomeres (ALTs). Interestingly, HR factors such as RAD51 facilitate the formation of T-loop structures (reviewed in Doksani & de Lange (2014)).

The idea that BRCA2 is involved in telomere maintenance originates from the observation that the conditional knock-out (cKO) of *Brca2* leads to telomere shortening in mice (Badie *et al*. 2010, Min *et al*. 2012). Although BRCA2 is required to load RAD51 on telomeres (Badie *et al*. 2010), the exact mechanism by which it safeguards telomere integrity is still not clearly defined. The detection of telomere fusions in BRCA2 cKO cells suggests that it facilitates telomere capping potentially by modulating the formation of T-loops. Furthermore, the presence of telomere abnormalities in these cells suggests that BRCA2 is required to limit replication stress at telomeres (Badie *et al*. 2010, Min *et al*. 2012). Consistent with a role of BRCA2 in assisting the replication of G-rich sequences at telomeres, a stabilizer of G-quadruplex structures (pyrodostatin (PDS)) was shown to induce lethality in *BRCA2*-deficient cells (Zimmer *et al*. 2016). Thus, the current model proposes that BRCA2 safeguards telomeric integrity by facilitating their replication (Badie *et al*. 2010, Min *et al*. 2012, Zimmer *et al*. 2016). Interestingly, BRCA1 participates in the protection of stalled forks in G-quadruplex structures (Zimmer *et al*. 2016) but is dispensable for the maintenance of telomere length (Badie *et al*. 2010). Altogether, these findings suggest that the role of BRCA2 in the maintenance of telomeres is independent of BRCA1.

Novel therapeutic approaches

Multiple chemotherapeutic agents induce replication stress either by producing DNA damages that block replication fork progression (such as alkylating agents (temozolomide, MMC, etc.) and platinum compounds (cisplatin, carboplatin, etc.)) or by slowing down their progression via the depletion of nucleotide pools (such as nucleoside and base analogs (gemcitabine, 5-fluorouracil, etc.)) (Dobbelstein & Sorensen 2015). Tumors that are deficient in *BRCA*1/2 genes are particularly susceptible to these replication poisons as they are neither efficient at protecting cells from replication stress nor capable of repairing DSBs by HR (detailed within this special issue by Dhillon *et al*. (2016)). Consequently, these tumor cells ultimately die from high levels of genomic instability.

Aside from these traditional chemotherapeutics, compounds targeting the signaling cascade that are triggered upon ssDNA damage can also induce replication stress (Dobbelstein & Sorensen 2015). Among those, small molecules that inhibit the function of PARP1 (PARP inhibitors (PARPi)) are particularly potent at inducing cell death in *BRCA1/2*-deficient tumors (Bryant *et al*. 2005, Farmer *et al*. 2005). Unfortunately, tumors acquire resistance to PARPi through the restoration of HR-mediated DSB repair. For instance, relapse is observed when cells acquire mutations in genes that block DNA end resection (*53BP1*, *MALD2L2*) in *BRCA1*-deficient cells while secondary mutations in *BRCA2* can rescue its functions in HR (Lord & Ashworth 2013). Resistance of the tumors to PARPi thus raise new challenges for cancer treatment.

Interestingly, recent findings in *BRCA1/2*-deficient cells revealed that resistance to PARPi can occur in an HR-independent manner by acquiring mutations that rescue replication fork stability (Chaudhuri *et al*. 2016, Kais *et al*. 2016, Michl *et al*. 2016). Deletion of *PARP1*, *PTIP* and *CHD4* as well as FANCD2 overexpression provide increased resistance to replication stress in *BRCA1/2*-deficient cells (Schlacher *et al*. 2012, Guillemette *et al*. 2015, Chaudhuri *et al*. 2016, Kais *et al*. 2016, Michl *et al*. 2016). Although the exact mechanisms by which these proteins participate in the stabilization of stalled replication forks remain elusive, these observations provide a rational to target these factors in the case of relapse/resistance to current therapies. The lethality induced by FANCD2 abrogation in *BRCA2*-deficient cells (Michl *et al*. 2016) can be exploited therapeutically to treat *BRCA2*-deficient tumors. Similarly, the mediator of RAP80 interactions and targeting subunit of 40 kDa (MERIT40), a subunit of the receptor-associated protein 80 (RAP80) ubiquitin recognition complex involved in the targeting of BRCA1 to DNA damage sites, has recently been implicated in the processing of ICLs and could be an interesting target for anticancer therapy (Jiang *et al*. 2015). Indeed, the increased chromosomal aberrations observed in *Merit40*- and *Brca2*-deficient mouse embryonic fibroblasts highlights the relevance of targeting MERIT40 in *BRCA2*-deficient tumor cells.

Although cell death is not an obligate immediate consequence of replication stalling (Schlacher *et al*. 2011, 2012), cells that are unable to deal with replication stress accumulate high levels of chromosomal aberrations. The mechanisms by which replication poisons promote cell death in tumors undergoing high levels of replication stress are elusive. Nevertheless, excessive replication

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stress and concomitant synthetic lethality occurs in *BRCA2*-deficient mice as well as in human cells treated with pyridostatin (PSD), a small molecule that stabilizes G4 structures that assemble on G-rich DNA strands (Zimmer *et al*. 2016). Consistent with the ability of this molecule to stabilize replication roadblocks, PSD leads to replication stress in cells depleted in BRCA1 or RAD51 (Zimmer *et al*. 2016). Thus, PSD could provide a therapeutic alternative for treating *BRCA1/2*-deficient tumors. Importantly, it may provide another ways to counteract the growth of *BRCA1*-deficient tumors that have acquired resistance to the PARP inhibitor Olaparib through the loss of *53BP1* or *MAD2L2,* as PSD efficacy is conserved in these conditions (Zimmer *et al*. 2016).

Conclusion and future directions

BRCA2 is a key player in the maintenance of genomic stability. In the past few years, we have witnessed major contributions delineating the role of BRCA2 in HR-mediated DSB repair. Moreover, we have come to the understanding that BRCA2 is a central factor in the protection of stalled replication forks. Aside from these functions, this multifaceted protein is involved in numerous other biological processes that impact genome stability, including chromosome segregation during mitosis and cell cycle progression (addressed in Lee 2014). Indeed, aneuploidy is a common feature of *BRCA2*-deficient cells and this phenomenon is linked to BRCA2 functions in the regulation of centrosome duplication (Schlacher *et al*. 2012, Guillemette *et al*. 2015, Chaudhuri *et al*. 2016, Kais *et al*. 2016, Michl *et al*. 2016), cytokinesis (Daniels *et al*. 2004, Mondal *et al*. 2012) and spindle assembly checkpoint during M phase (Choi *et al*. 2012). Future investigation will be vital to understand how the integration of all BRCA2 functions preserves genome integrity. In particular, *in vivo* phosphorylation of BRCA2 by the ATM and ATR has been detected in response to DNA damage (Matsuoka *et al*. 2007); however, its biological relevance has yet to be determined. Furthermore, novel functions of BRCA2 have been reported and could influence our model of its role in genome stability. Although BRCA2 functions have so far taken place in the nucleus, a recent study raises the intriguing possibility that BRCA2, along with BRCA1 and multiple proteins of the FA pathway (FANCA, FANCF, FANCL, FANCD2), facilitates mitophagy, a cytoplasmic process that targets damaged mitochondria to selective autophagy (Sumpter *et al*. 2016). Mitophagy is critical to maintain low level of mitochondrial reactive oxygen species (mtROS), and recent evidence suggests that the accumulation of mtROS impacts transformation and tumors progression (Chourasia *et al*. 2015). Therefore, understanding BRCA2 functions in the cytoplasm may shed new light on its role as a tumor suppressor. Collectively, efforts in elucidating the different roles of BRCA2 have already offered exciting opportunities to treat patients affected by BRCA2-related pathologies. We believe that continued efforts in BRCA2 research will open new therapeutic options for the prevention and the treatment of breast, ovarian and pancreatic cancer.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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