EXPERIMENTAL CELL RESEARCH ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/yexcr

Review Article

Cycling with BRCA2 from DNA repair to mitosis

*Hyunsook Lee**

Department of Biological Sciences & Institute of Molecular Biology and Genetics, Seoul National University, 1 Gwanak-Ro, Gwanak-Gu, Seoul 151-742, Republic of Korea

ARTICLE INFORMATION

Article Chronology:
Received 13 June 2014
Received in revised form
3 October 2014
Accepted 6 October 2014

Keywords:
BRCA2
HDR (homology-directed recombination)
Replication fork
Spindle assembly checkpoint (SAC)
Cell cycle

ABSTRACT

Genetic integrity in proliferating cells is guaranteed by the harmony of DNA replication, appropriate DNA repair, and segregation of the duplicated genome. Breast cancer susceptibility gene *BRCA2* is a unique tumor suppressor that is involved in all three processes. Hence, it is critical in genome maintenance. The functions of BRCA2 in DNA repair and homology-directed recombination (HDR) have been reviewed numerous times. Here, I will briefly go through the functions of BRCA2 in HDR and focus on the emerging roles of BRCA2 in telomere homeostasis and mitosis, then discuss how BRCA2 exerts distinct functions in a cell-cycle specific manner in the maintenance of genomic integrity.

Contents

*Fax: +82 2 886 4335.
E-mail address: HL212@snu.ac.kr

http://dx.doi.org/10.1016/j.yexcr.2014.10.008

Please cite this article as: H. Lee, Cycling with BRCA2 from DNA repair to mitosis, Exp Cell Res (2014), http://dx.doi.org/10.1016/j.yexcr.2014.10.008

Control of genetic integrity by BRCA2

Individuals who inherit one defective copy of *BRCA2* are predisposed to early onset breast cancer [1]. *BRCA2* mutations are also associated with the cancers in the ovary and pancreas [2]. The first understanding of how *BRCA2* disruption leads to early onset cancer emerged from the analysis of mouse deficient in *Brca2* allele ($Brca2^{Tr/Tr}$) [3]. Cells from $Brca2^{Tr/Tr}$ mice exhibited hypersensitivity to irradiation and the inter-strand DNA crosslinking agent, mitomycin C. Metaphase chromosomes displayed chromosome breaks and radial chromosomes, the hallmarks of defective double-strand break (DSB) repair [3]. The finding that BRCA2 binds to Rad51 recombinase through its conserved BRC repeats [4,5] and also at the C-terminus [6] corroborated the involvement of BRCA2 in double strand break (DSB) repair, through the regulation of Rad51 nucleoprotein filament formation in HDR. The BRC repeats, a short stretch of repeated sequences found in the exon 11, bind to Rad51 monomers and the C-terminus binding stabilizes the oligomerization of Rad51 (Fig. 1) [7,8]. In HDR, DSBs are first resected and the resulting single stranded DNAs (ssDNA) coated by Rad51 nucleoprotein filaments, facilitating the ssDNA to invade into the homologous sister strand. The invading ssDNA serves as a primer for DNA synthesis, using the undamaged sister strand as the template, enabling the strand exchange. Therefore, HDR is error-free. BRCA2 is crucial in ensuring the intactness of HDR because it regulates both the strand invasion and the appropriate stabilization/disassembly of the oligomerized Rad51 [8]. Thus, the absence of BRCA2 results in the accumulation of DSBs and subsequent growth arrest [3].

Distinct from HDR, BRCA2 is also required for the fitness of DNA replication. In S phase, BRCA2 stabilizes Rad51 nucleoprotein filaments and prevents fork reversal, thereby protecting the nascent strands from resection by MRE11 nuclease [9]. The conserved C-terminus of BRCA2 (aa 3251–3318 in human) is critical in maintaining the fidelity of replication, as stabilization of Rad51 filament is required for fork protection. Loading Rad51 on damaged DNA was dispensable; therefore the protection of nascent replication tracks by BRCA2 is independent from its function in HDR. The absence of *Brca2* (mouse orthologue of human BRCA2) results in the disappearance of typical Y-shaped DNA junctions at replication forks in 2D-gels, consistent with the finding that BRCA2 inhibits the breakdown of stalled replication forks [10].

BRCA2 at the telomeres in S phase

Brca2-deficient MEFs exhibit progressive telomere shortening and end-to-end fusions. Telomere-FISH (Fluorescence in situ hybridization) analysis of *Brca2*-deficient cells displayed common fragile sites, reminiscent of defective replication at telomeres [11,12]. It was shown that BRCA2 loads Rad51 to facilitate telomere replication [11]; prevents the stalled replication fork collapse, particularly at the telomere lagging strand, in ATR-dependent manner [12]. These functions at telomeres are consistent with the role of

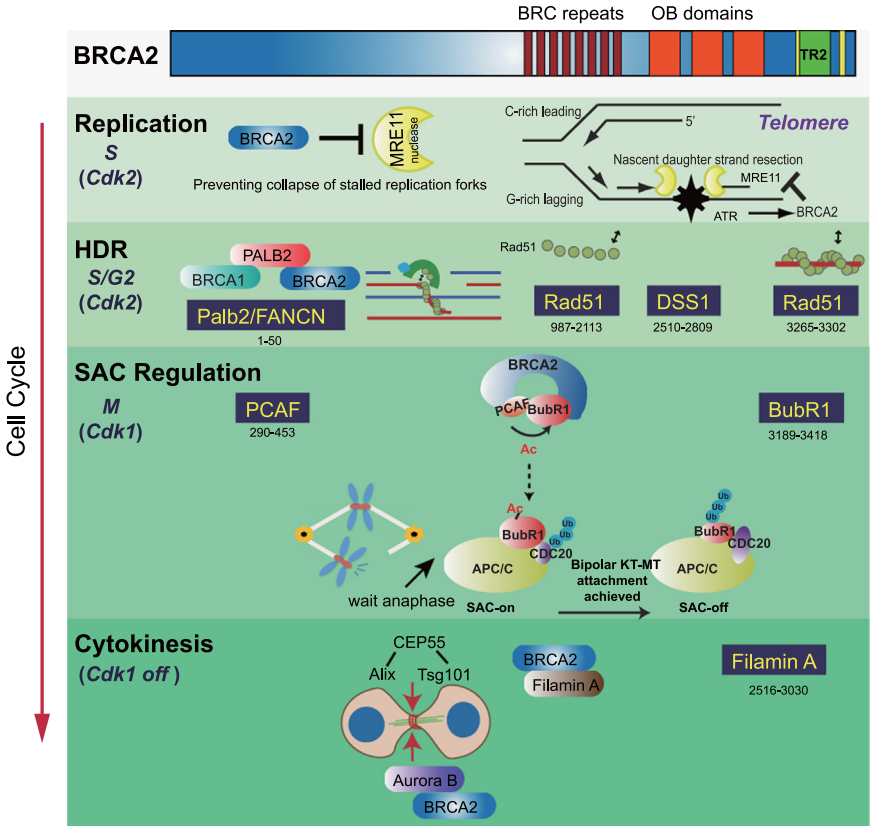

Fig. 1 – Multiple functions of BRCA2 in cell cycle progression are illustrated. Numbers below each protein denote the amino acid sequence of human BRCA2, responsible for binding. The illustration of BRCA2 at the telomere replication in S phase is the reproduction of Min et al. [12], and the role of BRCA2 in M phase is the reproduction of Choi et al. [18], with the permission from the Elsevier.

Please cite this article as: H. Lee, Cycling with BRCA2 from DNA repair to mitosis, Exp Cell Res (2014), http://dx.doi.org/10.1016/j.yexcr.2014.10.008

BRCA2 in global replication fork protection. However, as telomeres are composed of TTAGGG repeats, which is capable of forming secondary structures such as G-quadruplex, telomere lagging strands can be more susceptible to fork stallings [13]. *Brca2*-deficient MEFs exhibited telomere shortening and end-to-end joining, because the replication forks stalled frequently at the telomere lagging strand that were not protected.

Fanconi anemia and the breast cancer susceptibility

Fanconi anemia (FA) is a rare recessive genetic disease characterized by aplastic anemia in childhood, susceptibility to leukemia and cancer, with chromosome abnormalities. FA cells are hypersensitive to inter-strand DNA crosslinking agents such as cisplatin and mitotimycin C. There are 13 FA genes that participate in the recognition and repair of damaged DNAs [14]. BRCA2-deficiency shares common characteristics with FA: *Brca2*-deficient MEFs exhibit sensitivity to mitomycin C and exhibit radial structured chromosomes [3]. Indeed, it was found that *BRCA2* is also a FA gene, FANCD1 [15]. BRCA2/FACD1 interacts with other FA gene products including PALB2/FANCN [16]. As PABL2 links BRCA1 and BRCA2 binding in DNA damage response [17], the two breast cancer susceptibility genes that do not share any sequence homology reconcile in the FA pathway and participate in HDR (Fig. 1).

Emerging roles of BRCA2 in mitosis

BRCA2-deficient tumor cells also exhibit chromosome number instability (aneuploidy). Aneuploidy results from unequal segregation of chromosomes in mitosis. Because chromosomes are fully packed in mitosis (M phase), DNA damage and repair are limited at this stage. Therefore, there were implications that BRCA2 may participate in the regulation of chromosome segregation.

Conditional deletion of *Brca2* allele in MEFs ($Brca2^{F11/F11}$; Fig. 2) displayed unequal chromosome segregations in time-lapse microscopy, suggesting a more direct role of BRCA2 in mitosis. Indeed, BRCA2 binds to BubR1, a critical component of spindle assembly checkpoint (SAC) that ensures equal segregation of duplicated genomes in mitosis [18]. At the kinetochore, BRCA2 functions as a scaffold by bringing P/CAF acetyltransferase to BubR1 and facilitates BubR1 acetylation and modulates APC/C activity [18,19]. Inhibition of BRCA2–BubR1 interaction in mice, by ectopic expression of the BubR1-binding domain of *Brca2*, (mB2-9; Fig. 2) led to spontaneous tumorigenesis, without perturbing HDR [18].

When the acetylation site of BubR1 is mutated to arginine in mice, the mice develop spontaneous cancers just like the mice deficient in BRCA2-BubR1 binding [20], corroborating that the acetylation of BubR1 is a tumor suppressive mechanism, innate in BRCA2 function in vertebrates.

Depletion of *BRCA2* is associated with multinucleation, indicative of defects in cytokinesis. BRCA2 was found with Myosin II at the midbody, suggesting that BRCA2 is involved in cytokinesis [21], although the localization of BRCA2 at the midbody was challenged due to the question of non-specificity of the antibody against BRCA2 [22]. Then it was shown that Filamin A, an actin-binding protein, binds to BRCA2 and recruits it to the midbody. BRCA2 binds to CEP55 at the midbody and affects the recruitment of ESCRT-associated proteins, Alix and Tsg101, thereby influencing the abscission of cell cleavage [23]. Notably, the role of BRCA2 in cytokinesis is regulated by Aurora B kinase [21] (Fig. 1). Taken together, BRCA2 controls proper cell division, as well as the fidelity of DNA replication and repair in interphase.

Domains, structure, mouse models of *Brca2*, and human mutations

BRCA2 is a large protein of ~400 kDa, composed of 27 exons. Exon 11 of BRCA2 is uniquely large and consists of 8 BRC repeats (Fig. 2). The crystal structure of BRC4 bound to Rad51 revealed how BRCA2 controls the monomeric Rad51 to form nucleoprotein filaments [24]. Downstream of BRC repeats, three oligonucleotide/oligosaccharide-binding (OB) folds and a helix-turn-helix (HTH)

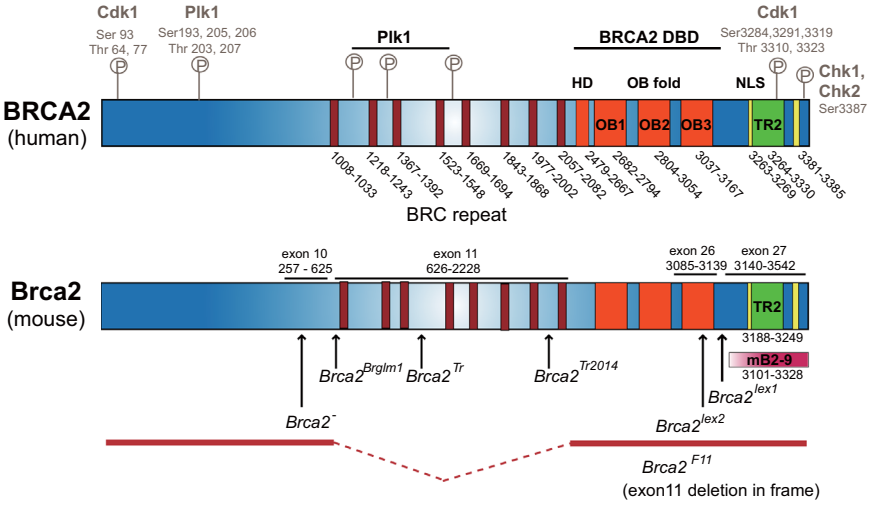

Fig. 2 – Top, BRCA2 functional domains and the sites phosphorylated by CDK, Plk1, Chk1, Chk2. Two NLS sites (3263–3269; 3381–3385) at the C-terminus are colored in yellow. Numbers denote the amino acid sequences of domains and motifs. Bottom, domains and motifs of mouse Brca2 and the targeting sites of mouse models indicated. mB2-9 is a transgenic mouse overexpressing the BubR1-binding domain of BRCA2 [18], and *Brca2*^{F11} is a conditional knockout allele deleting only exon 11 in frame [39].

Please cite this article as: H. Lee, Cycling with BRCA2 from DNA repair to mitosis, Exp Cell Res (2014), http://dx.doi.org/10.1016/j.yexcr.2014.10.008

Table 1 – Characteristics of *BRCA2* mutations in human cancer.

	BRCA2 allele		location	Characteristics	Reference
***BRCA2* mutation in cancer patients**	One wt allele	373G>T		MMC (mitomycin C)-sensitive	[40]
		Del ex 10-12	BRC repeat		
		1823_1825delA			
		3036_3039del4	BRC repeat		
		3374delA	BRC repeat		
		3683T>G	BRC repeat		
		6857delAA			
		7636delTT	Helical domain (HD)		
		8152_8154delT	OB fold (OB1)		
		8297_8300insTT	OB1		
		9254delATCAT	OB fold (OB3)		
		9514G>T			
Breast cancer families (data from Myriad genetic laboratory)	One wt allele	D2723H	OB fold (OB2)	HDR inactivated	[41]
		R3052W	OB3		
		R2659K	OB1		
		I2627F	OB1		
		G2748D	OB2		
		E2663V	OB1		
		D2723G	OB2		
		T2722R	OB2		
		R2336H			
		R2659T	OB1		
		L2653P	OB1	Inconclusive	
		D3095E	OB3		
		L2647P	OB1		
		D2723A	OB2		
		R2784W	OB2		
		L2865V	OB2		
		R2520Q	HD, Dss1-binding		
		A2643G	OB1		
FA patients	IVS19-1G>A	IVS19-1G>A	OB2	MMC-sensitive	[15]
	7691insAT	9900insA	HD; TR2		
	3033delAAAC	10204A>T	BRC repeat		
	IVS7+2T>G	IVS7+2T>G		MMC-sensitive; Acute Myeloid Leukemia (AML)	[42]
	8106G>C	204insA	OB1		
	IVS7+1G>A	5910C>G	BRC repeat		
	IVS7+2T>G	5146del4	BRC repeat		
	2816insA	1342C>A	BRC repeat	Brain Tumor, Wilms Tumor	
	886-887delGT	8447T>A	OB2		
	4876G>T	7757T>C	BRC repeat; HD		
	6174delT	9435T>A	BRC repeat; OB3		
	6174delT	886delGT	BRC repeat		
	5301insA	7690T>C	BRC repeat, HD		
	4150G>T	9424C>T	BRC repeat; OB3		

Please cite this article as: H. Lee, Cycling with BRCA2 from DNA repair to mitosis, Exp Cell Res (2014), http://dx.doi.org/10.1016/j.yexcr.2014.10.008

	IVS19-1G>A	IVS19-1G>A	OB2		
	7691insAT	9900insA	HD; TR2		
	7235G>A	5837TC>AG	BRC repeat	MMC-sensitive; AML	
	8415G>T	8732C>A	OB2		
Capan-1 (pancreatic cancer cell line)	One wt lost	6174delT	BRC repeat	IR-sensitive	[43]
				MMS (methylmethane sulfonate)-sensitive	[44]
				MMC-sensitive, HR defective, defective Rad51 foci formation	[45]
Ashkenazi mutation	One wt allele	6174delT	Only 2002aa exists		
Icelandic mutation	One wt allele	999del5	Only 256aa exists	This truncated BRCA2 is very unstable (*BRCA2* haploinsufficiency)	[46]

motif are found (Fig. 2, top). This BRCA2 COOH-terminal domain binds to DSS1 protein, deleted in split-hand/split-foot syndrome. Bound to DSS1, BRCA2 exerts binding to ssDNA. Hence, the ~800 amino acids containing three OB folds and HTH motif was named BRCA2DBD (DNA/DSS1-binding domain) (Fig. 1). The BRCA2DBD–DSS1 structure implies that OB folds recognize ssDNA and the HTH motif in dsDNA interaction, providing the explanation to some extent, for the stimulation of BRCA2 in Rad51-mediated HDR [25].

At the most C-terminus is the TR2 domain that stabilizes Rad51 nucleoprotein filament. Of note, Serine 3291 at this region is phosphorylated by cyclin-dependent kinases (CDK). Phosphorylation of S3291 reduced BRCA2–Rad51 binding and was low in S phase [26], indicative of cell cycle-dependent regulation of BRCA2 and Rad51 binding. However, another report argues that the C-terminus of BRCA2 is not crucial in HDR but is involved in the protection of replication forks [27]. TR2 domain, the C-terminus critical for protecting replication forks, and the BubR1-binding domain required for mitotic integrity all overlap in C-terminus (note the amino acid numberings in Fig. 2.). However, the functions are distinct particularly that BRCA2–BubR1 binding did not interfere with HDR [18]. It is speculative that the functions of BRCA2 is regulated differently in a cell cycle-dependent manner that the C-terminus is involved in replication fork protection in S phase, HDR in S/G2, and then binds to BubR1 in M phase. The code of multiple phosphorylations including S3291 and others by CDK1, Plk1, Chk1, Chk2 (Fig. 2), Aurora B kinases, etc. may be responsible (Fig. 1).

Several mouse models of *Brca2* revealed the functions of BRCA2 [28]. Targeting sites of some of the representative mouse models relevant to this review are illustrated in Fig. 2 (bottom). $Brca2^{Tr/Tr}$ mice [29] and the $Brca2^{Tr2014}$ mice [30] were the first viable knockout mice that developed thymic lymphomas in 12 weeks after birth. These mice were targeted in exon 11 and the resultant transcript harbored first three BRC repeats [29] or 7 BRC repeats (Fig. 2, bottom). It is interesting that the more BRC repeats left, the viability increased (10% versus 20% in $Brca2^{Tr/Tr}$ and $Brca2^{Tr2014}$ mice). $Brca2^{-/-}$ or the $Brca2^{Brglm1/Brglm1}$ mice that were targeted at exon 10 exhibited early embryonic lethality.

Targeting exon 27 resulted in hypersensitivity to irradiation [31] or DNA crosslinking agents with reduced life span [32]. Embryonic stem cells from these mice ($Brca2^{lex1/lex2}$) fail to protect stalled replication forks, consistent with the notion that the stabilization of Rad51 nucleoprotein filament is required for replication fork protection.

Analyses on the *BRCA2* mutation in somatic cancers are rare, and the studies in *BRCA2* mutations are mostly from familial cancers. As summarized in Table 1, *BRCA2* mutations in Icelandic and Ashkenazi populations are large deletional mutations resulting in the loss of most of the C-terminus, including BRC repeats and thereafter. Similarly, Capan-1 pancreatic cancer cell line also shows deletion of more than half of the C-terminus in one allele, and complete loss of the other allele. In other breast cancer families and FA patients, the types of mutations in the mutated *BRCA2* allele are small deletions, insertional, and missense mutations, most of them affecting BRC repeats, OB folds, and/or helical domains. Consequently, the cells exhibit sensitivity to MMC and HDR defects (Table 1). As the functional studies of these mutations are far from complete, the mutations associated with the defects in mitosis or cytokinesis is not well defined. However, Choi et al. [18] had reported that the mutations of *BRCA2* in human breast cancer patients that exhibited problems in mitotic BubR1 acetylation were not restricted to the

Please cite this article as: H. Lee, Cycling with BRCA2 from DNA repair to mitosis, Exp Cell Res (2014), http://dx.doi.org/10.1016/j.yexcr.2014.10.008

BubR1-binding C-terminus, suggesting that not only the direct binding site but modifications in other regions also play critical roles in regulating mitosis. Similarly, conditional deletion of exon 11 in mice displayed problems in mitosis, although this region is not directly related to BubR1 binding [18]. Therefore, the mutations listed in Table 1 might also affect other functions of BRCA2.

Coordinating multiple functions of BRCA2 in cell cycle

BRCA2 plays multiple functions throughout the cell cycle (Fig. 1). In response to DNA damage, Chk1 and Chk2 kinase phosphorylate BRCA2 at the C-terminus and regulates the association with Rad51 [33]. Phosphorylation of S3291, which dissociates Rad51 filaments, takes place in G2 and promotes the entry into mitosis. In addition to S3291, there are multiple phosphorylation sites at the C-terminus that links the Rad51 disassembly to mitotic entry [34]. At the N-terminus, there are more serine and threonine residues phosphorylated by CDK [26] (Fig. 2, top). DSB repair must be suppressed before entry into mitosis, because active DSB repair in mitosis will result in undesirable chromosome alterations [35]. CDK1 activation has shown to interfere with HDR [36]. Therefore, phosphorylation of BRCA2 by CDK1 may participate in uncoupling BRCA2's function from replication and HDR before entry into mitosis.

Plk1 also phosphorylates BRCA2 at multiple sites, at the N-terminus [37] and in exon 11 between BRC repeats [38] (Fig. 2). DNA damage inhibits the phosphorylation by Plk1 and is enhanced in cells progressing through G2/M. Therefore, the phosphorylation of BRCA2 by Plk1 may alter the spectrum of BRCA2 binding proteins, enabling BRCA2 to function in mitosis. Consistent with this, *Brca2*$^{F11/F11}$ MEFs (Fig. 2, bottom) exhibit problems in chromosome segregation, although the P/CAF-interacting N-terminus and the BubR1-interacting C-terminus of BRCA2 are intact [18], suggesting that Plk1-dependent phosphorylation at this central domain may play a role for BRCA2 to execute function in mitosis. In mitotic exit, Aurora B associates with, and probably phosphorylates, BRCA2 at the midbody, which is likely to control cytokinesis [21]. Aurora A kinase has also been implicated in BRCA2-associated cancers, and therefore is likely to participate in the regulation of BRCA2 in cell cycle.

Concluding remarks

Over the last two decades, efforts in BRCA2 research confirmed that it is a multifaceted protein, changing its partners and roles as cells progress through the cell cycle. It is undoubtedly the most important tumor suppressor in keeping the genome and chromosome intact. How BRCA2 is regulated in different cell cycle stages and changes its localization to crucial sites are largely unknown and awaits future investigation. The fact that one large tumor suppressor BRCA2 exerts all these functions in different stages of cell cycle may imply that BRCA2 coordinates all these discussed functions to maintain genome integrity in vertebrates. Unveiling the link will be most interesting, and may have clinical implications as well.

Acknowledgments

I apologize that many wonderful works could not be cited due to space limitations. I thank I. Park, H. Kim, and K. Hwang in Lee laboratory for their help in preparation of this manuscript. The lab is funded by the Korean NRF (2012M3A9A 8052645 and 2013 R1A2A1A 01009184) and Samsung Science and Technology Foundation (BA130103069).

REFERENCES

[1] R. Wooster, G. Bignell, J. Lancaster, S. Swift, S. Seal, J. Mangion, N. Collins, S. Gregory, C. Gumbs, G. Micklem, Identification of the breast cancer susceptibility gene BRCA2, Nature 378 (1995) 789–792.
[2] T.B.C.L. Consortium, Cancer risks in BRCA2 mutation carriers, J. Natl. Cancer Inst. 91 (1999) 1310–1316.
[3] K.J. Patel, V.P. Yu, H. Lee, A. Corcoran, F.C. Thistlethwaite, M.J. Evans, W.H. Colledge, L.S. Friedman, B.A. Ponder, A.R. Venkitaraman, Involvement of Brca2 in DNA repair, Mol. Cell 1 (1998) 347–357.
[4] A.K. Wong, R. Pero, P.A. Ormonde, S.V. Tavtigian, P.L. Bartel, RAD51 interacts with the evolutionarily conserved BRC motifs in the human breast cancer susceptibility gene brca2, J. Biol. Chem. 272 (1997) 31941–31944.
[5] S.C. West, Molecular views of recombination proteins and their control, Nat. Rev. Mol. Cell Biol. 4 (2003) 435–445.
[6] S.K. Sharan, M. Morimatsu, U. Albrecht, D.S. Lim, E. Regel, C. Dinh, A. Sands, G. Eichele, P. Hasty, A. Bradley, Embryonic lethality and radiation hypersensitivity mediated by Rad51 in mice lacking Brca2, Nature 386 (1997) 804–810.
[7] F. Esashi, V.E. Galkin, X. Yu, E.H. Egelman, S.C. West, Stabilization of RAD51 nucleoprotein filaments by the C-terminal region of BRCA2, Nat. Struct. Mol. Biol. 14 (2007) 468–474.
[8] O.R. Davies, L. Pellegrini, Interaction with the BRCA2 C terminus protects RAD51–DNA filaments from disassembly by BRC repeats, Nat. Struct. Mol. Biol. 14 (2007) 475–483.
[9] K. Schlacher, N. Christ, N. Siaud, A. Egashira, H. Wu, M. Jasin, Double-strand break repair-independent role for BRCA2 in blocking stalled replication fork degradation by MRE11, Cell 145 (2011) 529–542.
[10] M. Lomonosov, S. Anand, M. Sangrithi, R. Davies, A.R. Venkitaraman, Stabilization of stalled DNA replication forks by the BRCA2 breast cancer susceptibility protein, Genes Dev. 17 (2003) 3017–3022.
[11] S. Badie, J.M. Escandell, P. Bouwman, A.R. Carlos, M. Thanasoula, M.M. Gallardo, A. Suram, I. Jaco, J. Benitez, U. Herbig, M.A. Blasco, J. Jonkers, M. Tarsounas, BRCA2 acts as a RAD51 loader to facilitate telomere replication and capping, Nat. Struct. Mol. Biol. 17 (2010) 1461–1469.
[12] J. Min, E.S. Choi, K. Hwang, J. Kim, S. Sampath, A.R. Venkitaraman, H. Lee, The breast cancer susceptibility gene BRCA2 is required for the maintenance of telomere homeostasis, J. Biol. Chem. 287 (2012) 5091–5101.
[13] H.J. Lipps, D. Rhodes, G-quadruplex structures: in vivo evidence and function, Trends Cell Biol. 19 (2009) 414–422.
[14] A.D. D'Andrea, Susceptibility pathways in Fanconi's anemia and breast cancer, N. Engl. J. Med. 362 (2010) 1909–1919.
[15] N.G. Howlett, T. Taniguchi, S. Olson, B. Cox, Q. Waisfisz, C. De Die-Smulders, N. Persky, M. Grompe, H. Joenje, G. Pals, H. Ikeda, E.A. Fox, A.D. D'Andrea, Biallelic inactivation of BRCA2 in Fanconi anemia, Science 297 (2002) 606–609.
[16] N. Rahman, S. Seal, D. Thompson, P. Kelly, A. Renwick, A. Elliott, S. Reid, K. Spanova, R. Barfoot, T. Chagtai, H. Jayatilake, L. McGuffog, S. Hanks, D.G. Evans, D. Eccles, Breast Cancer Susceptibility

Please cite this article as: H. Lee, Cycling with BRCA2 from DNA repair to mitosis, Exp Cell Res (2014), http://dx.doi.org/10.1016/j.yexcr.2014.10.008

Collaboration, D.F. Easton, M.R. Stratton, PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene, Nat. Genet. 39 (2007) 165–167.
[17] F. Zhang, J. Ma, J. Wu, L. Ye, H. Cai, B. Xia, X. Yu, PALB2 links BRCA1 and BRCA2 in the DNA-damage response, Curr. Biol. 19 (2009) 524–529.
[18] E. Choi, P.G. Park, H.O. Lee, Y.K. Lee, G.H. Kang, J.W. Lee, W. Han, H.C. Lee, D.Y. Noh, S. Lekomtsev, H. Lee, BRCA2 fine-tunes the spindle assembly checkpoint through reinforcement of BubR1 acetylation, Dev. Cell 22 (2012) 295–308.
[19] E. Choi, H. Choe, J. Min, J.Y. Choi, J. Kim, H. Lee, BubR1 acetylation at prometaphase is required for modulating APC/C activity and timing of mitosis, EMBO J. 28 (2009) 2077–2089.
[20] I. Park, H.O. Lee, E. Choi, Y.K. Lee, M.S. Kwon, J. Min, P.G. Park, S. Lee, Y.Y. Kong, G. Gong, H. Lee, Loss of BubR1 acetylation causes defects in spindle assembly checkpoint signaling and promotes tumor formation, J. Cell Biol. 202 (2013) 295–309.
[21] M.J. Daniels, Y. Wang, M. Lee, A.R. Venkitaraman, Abnormal cytokinesis in cells deficient in the breast cancer susceptibility protein BRCA2, Science 306 (2004) 876–879.
[22] S. Lekomtsev, J. Guizetti, A. Pozniakovsky, D.W. Gerlich, M. Petronczki, Evidence that the tumor-suppressor protein BRCA2 does not regulate cytokinesis in human cells, J. Cell Sci. 123 (2010) 1395–1400.
[23] G. Mondal, M. Rowley, L. Guidugli, J. Wu, V.S. Pankratz, F.J. Couch, BRCA2 localization to the midbody by filamin A regulates cep55 signaling and completion of cytokinesis, Dev. Cell 23 (2012) 137–152.
[24] L. Pellegrini, D.S. Yu, T. Lo, S. Anand, M. Lee, T.L. Blundell, A.R. Venkitaraman, Insights into DNA recombination from the structure of a RAD51–BRCA2 complex, Nature 420 (2002) 287–293.
[25] H. Yang, P.D. Jeffrey, J. Miller, E. Kinnucan, Y. Sun, N.H. Thoma, N. Zheng, P.L. Chen, W.H. Lee, N.P. Pavletich, BRCA2 function in DNA binding and recombination from a BRCA2–DSS1–ssDNA structure, Science 297 (2002) 1837–1848.
[26] F. Esashi, N. Christ, J. Gannon, Y. Liu, T. Hunt, M. Jasin, S.C. West, CDK-dependent phosphorylation of BRCA2 as a regulatory mechanism for recombinational repair, Nature 434 (2005) 598–604.
[27] K. Schlacher, H. Wu, M. Jasin, A distinct replication fork protection pathway connects Fanconi anemia tumor suppressors to RAD51–BRCA1/2, Cancer Cell 22 (2012) 106–116.
[28] B. Evers, J. Jonkers, Mouse models of BRCA1 and BRCA2 deficiency: past lessons, current understanding and future prospects, Oncogene 25 (2006) 5885–5897.
[29] L.S. Friedman, F.C. Thistlethwaite, K.J. Patel, V.P. Yu, H. Lee, A.R. Venkitaraman, K.J. Abel, M.B. Carlton, S.M. Hunter, W.H. Colledge, M.J. Evans, B.A. Ponder, Thymic lymphomas in mice with a truncating mutation in Brca2, Cancer Res. 58 (1998) 1338–1343.
[30] F. Connor, D. Bertwistle, P.J. Mee, G.M. Ross, S. Swift, E. Grigorieva, V.L. Tybulewicz, A. Ashworth, Tumorigenesis and a DNA repair defect in mice with a truncating Brca2 mutation, Nat. Genet. 17 (1997) 423–430.
[31] M. Morimatsu, G. Donoho, P. Hasty, Cells deleted for Brca2 COOH terminus exhibit hypersensitivity to gamma-radiation and premature senescence, Cancer Res. 58 (1998) 3441–3447.
[32] G. Donoho, M.A. Brenneman, T.X. Cui, D. Donoviel, H. Vogel, E.H. Goodwin, D.J. Chen, P. Hasty, Deletion of Brca2 exon 27 causes hypersensitivity to DNA crosslinks, chromosomal instability, and reduced life span in mice, Genes Chromosomes Cancer 36 (2003) 317–331.
[33] E.M. Bahassi, J.L. Ovesen, A.L. Riesenberg, W.Z. Bernstein, P.E. Hasty, P.J. Stambrook, The checkpoint kinases Chk1 and Chk2 regulate the functional associations between hBRCA2 and Rad51 in response to DNA damage, Oncogene 27 (2008) 3977–3985.
[34] N. Ayoub, E. Rajendra, X. Su, A.D. Jeyasekharan, R. Mahen, A.R. Venkitaraman, The carboxyl terminus of Brca2 links the disassembly of Rad51 complexes to mitotic entry, Curr. Biol. 19 (2009) 1075–1085.
[35] A. Orthwein, A. Fradet-Turcotte, S.M. Noordermeer, M.D. Canny, C.M. Brun, J. Strecker, C. Escribano-Diaz, D. Durocher, Mitosis inhibits DNA double-strand break repair to guard against telomere fusions, Science 344 (2014) 189–193.
[36] M. Krajewska, A.M. Heijink, Y.J. Bisselink, R.I. Seinstra, H.H. Sillje, E.G. de Vries, M.A. van Vugt, Forced activation of Cdk1 via wee1 inhibition impairs homologous recombination, Oncogene 32 (2013) 3001–3008.
[37] H.R. Lin, N.S. Ting, J. Qin, W.H. Lee, M phase-specific phosphorylation of BRCA2 by Polo-like kinase 1 correlates with the dissociation of the BRCA2–P/CAF complex, J. Biol. Chem. 278 (2003) 35979–35987.
[38] M. Lee, M.J. Daniels, A.R. Venkitaraman, Phosphorylation of BRCA2 by the Polo-like kinase Plk1 is regulated by DNA damage and mitotic progression, Oncogene 23 (2004) 865–872.
[39] J. Jonkers, R. Meuwissen, H. van der Gulden, H. Peterse, M. van der Valk, A. Berns, Synergistic tumor suppressor activity of BRCA2 and p53 in a conditional mouse model for breast cancer, Nat. Genet. 29 (2001) 418–425.
[40] S. Gutierrez-Enriquez, Y.C.T. Ramon, C. Alonso, A. Corral, P. Carrasco, M. Cornet, J. Sanz, M. Ribas, M. Baiget, O. Diez, Ionizing radiation or mitomycin-induced micronuclei in lymphocytes of BRCA1 or BRCA2 mutation carriers, Breast Cancer Res. Treat. 127 (2011) 611–622.
[41] D.J. Farrugia, M.K. Agarwal, V.S. Pankratz, A.M. Deffenbaugh, D. Pruss, C. Frye, L. Wadum, K. Johnson, J. Mentlick, S.V. Tavtigian, D.E. Goldgar, F.J. Couch, Functional assays for classification of BRCA2 variants of uncertain significance, Cancer Res. 68 (2008) 3523–3531.
[42] S. Meyer, W.D. Fergusson, A.B. Oostra, A.L. Medhurst, Q. Waisfisz, J.P. de Winter, F. Chen, T.F. Carr, J. Clayton-Smith, T. Clancy, M. Green, L. Barber, O.B. Eden, A.M. Will, H. Joenje, G.M. Taylor, A cross-linker-sensitive myeloid leukemia cell line from a 2-year-old boy with severe Fanconi anemia and biallelic FANCD1/BRCA2 mutations, Genes Chromosomes Cancer 42 (2005) 404–415.
[43] F. Xia, D.G. Taghian, J.S. DeFrank, Z.C. Zeng, H. Willers, G. Iliakis, S.N. Powell, Deficiency of human BRCA2 leads to impaired homologous recombination but maintains normal nonhomologous end joining, Proc. Natl. Acad. Sci. USA 98 (2001) 8644–8649.
[44] M. Bogliolo, R.M. Taylor, K.W. Caldecott, G. Frosina, Reduced ligation during DNA base excision repair supported by BRCA2 mutant cells, Oncogene 19 (2000) 5781–5787.
[45] S.L. Edwards, R. Brough, C.J. Lord, R. Natrajan, R. Vatcheva, D.A. Levine, J. Boyd, J.S. Reis-Filho, A. Ashworth, Resistance to therapy caused by intragenic deletion in BRCA2, Nature 451 (2008) 1111–1115.
[46] E.K. Mikaelsdottir, S. Valgeirsdottir, J.E. Eyfjord, T. Rafnar, The Icelandic founder mutation BRCA2 999del5: analysis of expression, Breast Cancer Res. 6 (2004) R284–R290.

Please cite this article as: H. Lee, Cycling with BRCA2 from DNA repair to mitosis, Exp Cell Res (2014), http://dx.doi.org/10.1016/j.yexcr.2014.10.008