Role of BRCA Gene Dysfunction in Breast and Ovarian Cancer Predisposition

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Commentary

Role of BRCA gene dysfunction in breast and ovarian cancer predisposition
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Abstract

Tumor suppressor genes that perform apparently generic cellular functions nonetheless cause tissue-specific syndromes in the human population when they are mutated in the germline. The two major hereditary breast/ovarian cancer predisposition genes, BRCA1 and BRCA2, appear to participate in a common pathway that is involved in the control of homologous recombination and in the maintenance of genomic integrity. How might such functions translate into the specific suppression of cancers of the breast and ovarian epithelia? Recent advances in the study of BRCA1 and BRCA2, discussed herein, have provided new opportunities to address this question.

Keywords: breast cancer, DNA repair, homologous recombination, ovarian cancer, tumor suppressor genes

Introduction

Familial breast or ovarian cancer predisposition syndromes have long been recognized. Their genetic bases have become clear with the cloning of two major disease susceptibility genes, BRCA1 and BRCA2, termed herein ‘BRCA’ genes [1–4]. Each has characteristics of a tumor suppressor gene; inheritance within affected families follows an autosomal-dominant pattern of inheritance; and loss of heterozygosity (LOH) at the relevant gene locus is seen in familial tumors, with retention of the disease-disposing allele [6–8]. The spectrum of disease-associated mutations includes frequent truncating mutations and less frequent missense mutations. Although LOH is frequently detected at the BRCA1 or BRCA2 locus in sporadic breast cancer, the retained allele is almost always wild-type [9,10]. Thus, in contrast to the causal role of BRCA gene mutation in the hereditary syndrome, BRCA gene mutation in sporadic breast or ovarian cancer seldom conforms to Knudson’s model for tumor suppressor genes [11]. Cancer risk in BRCA gene mutation carriers may be increased modestly in other organs. However, highly penetrant, early-onset, site-specific cancer is restricted to the breast and ovary.

BRCA1 and BRCA2 homologs have been detected in several mammalian species, including the mouse. BRCA1 and BRCA2 are expressed ubiquitously [12–14]. Gene targeting experiments in the mouse [15–22] have revealed functional differences between true null and partial loss-of-function (hypomorphic) mutant alleles of BRCA genes. If these distinctions can be made in murine development, the same might be true in human disease. At its simplest,
a hypomorphic BRCA allele might exhibit lower penetrance for cancer than a true null allele. Because of the relative scarcity of individual BRCA1 mutated alleles and the existence of unidentified modifier genes, it has been difficult to estimate the penetrance of different disease-predisposing BRCA alleles. However, the position of a mutation in the BRCA1 or BRCA2 gene can affect the relative incidences of breast and ovarian cancer within a kindred [23,24]. These observations suggest that the breast and ovarian epithelia differ in their requirements for BRCA1 gene function. Whether this is a qualitative or quantitative difference is unknown.

BRCA1 germline mutations differ from those that affect BRCA2 with regard to the relative risk of developing other solid tumors. BRCA2 germline mutation carries an increased risk for cancers of the prostate, pancreas, gall-bladder/bile duct, and stomach, as well as for malignant melanoma [25]. BRCA2 mutation also appears to confer higher risks for male breast cancer [26]. BRCA1 mutation confers a higher incidence of ovarian cancer than does BRCA2 mutation [26]. There appear to be histologic differences between BRCA1-linked and BRCA2-linked breast tumors [27,28]. Taken together, these point to subtle differences between BRCA1 and BRCA2 germline mutations in their impact on tumorigenesis. At present, the mechanistic basis of these differences is unknown.

**Role of BRCA1 and BRCA2 in maintenance of genome integrity**

The BRCA1 and BRCA2 gene products (BRCA1 and BRCA2, respectively) function in the maintenance of genomic integrity, at least in part by cooperating with recombinational repair proteins. Both BRCA1 and BRCA2 form a complex with Rad51, a protein that has an established role in homologous recombination [17,29,30]. The BRCA1, BRCA2, and Rad51 proteins are coexpressed in the developing mouse embryo, and gene targeting of each revealed similar lethal phenotypes of nullizygous mouse embryos [14,16,17,31,32]. BRCA1, BRCA2, and Rad51 colocalized in S-phase nuclear foci in somatic cells, and upon the axial element of the developing synaptonemal complex of cells in meiotic prophase I [29,33]. The BRCA1 and BRCA2 proteins were also found to be complexed with one another in cell extracts [33], suggesting that these proteins collaborate on a common pathway of tumor suppression. A specific role for this complex in the S phase was implied by the rapid relocalization of BRCA1, BRCA2, and associated proteins to sites of DNA synthesis after exposure of cells to certain DNA-damaging agents in S phase [34,35]. The BRCA1 protein also interacts with the Rad50/MRE11/NBS1 complex, implicated in the response to double-stranded DNA breaks [36].

Functional data from the study of BRCA1- or BRCA2-mutated mice has confirmed a role for these genes in the maintenance of genomic integrity. Both BRCA2 and BRCA1 homozygous mutant cells exhibit ionizing radiation sensitivity, a frequent indicator of a DNA repair defect [17,20]. BRCA2 or BRCA1 homozygous mutant mouse embryonic fibroblasts (MEFs) from embryos reveal spontaneous chromosomal anomalies and chromosome breakage, which is consistent with a recombination defect [20,37]. A unique BRCA1 homozygous mutant embryonic stem cell clone revealed reduced efficiency of gene conversion in response to a site-specific double-stranded DNA break [38]. A defect in gene targeting (a process that is dependent on homologous recombination) in the same embryonic stem cell clone was improved by re-expression of wild-type BRCA1 [39]. BRCA1 or BRCA2 mutated cancer cell lines reveal abnormally delayed kinetics of double-strand break repair (DSBR) [18,40]. Definitive evidence linking BRCA1 function in DSBR with its tumor suppressor role came from the finding that wild-type, but not clinically defined mutant BRCA1 alleles, can restore efficient DSBR to a BRCA1-mutated breast cancer cell line [41]. The biochemical mechanisms of action of BRCA1 and BRCA2 in DSBR have yet to be determined. Where examined, BRCA1 mutant cells revealed defects in homologous recombination, but not in nonhomologous end-joining [22,27,38].

Although recombination would seem to be a unifying theme in these processes, other repair functions, such as the transcription-coupled repair of oxidative DNA damage, are defective in some BRCA1-mutated cells [22,42]. BRCA1 also plays a role in the G2/M checkpoint response to ionizing radiation, although this has not been observed in all BRCA1-mutated cells [21,41]. BRCA1 or BRCA2 homozygous mutation leads to severe aneuploidy, accompanied by centrosome amplification [21,43].

Genomic instability is characteristic of cancer cells, and it is not difficult to imagine that mutation in BRCA1 or BRCA2 might accelerate tumorigenesis, for example through promoting aneuploidy, chromosomal translocation or LOH events. If BRCA gene functional inactivation destabilizes the genome, tumor development might be compressed into a shorter time frame. In diseases such as breast or ovarian cancer, the incidence of which increases with advancing age, the ‘mere’ acceleration of disease progression could contribute to the early onset of disease that is characteristically seen in carriers of BRCA mutations. However, this does not provide an obvious explanation of the specifically increased risk of breast/ovarian cancer in BRCA gene mutation carriers. The following sections explore hypotheses that could account for this specificity.

**Collaboration between repair and checkpoint functions in tumorigenesis**

BRCA1 and BRCA2 nullizygous embryos die early in development, with a severe growth deficit accompanied
by elevated expression of the p53-responsive cell cycle inhibitor, p21 [16,44,45]. This suggests that not only failed DNA repair, but also the cell’s response to that failure might be relevant to BRCA gene biology. If BRCA1 and BRCA2 are DNA repair genes, then the p53/p21-mediated growth arrest seen in BRCA mutant tissue might represent a ‘checkpoint’ response to spontaneous DNA damage arising as a result of the failure of DNA repair processes. The above-noted chromosome breakage syndrome, described in BRCA2 or BRCA1 homozygous mutant MEFs, supports this idea [20,37].

These observations suggest a way to understand the role of BRCA gene mutation in tumorigenesis. Perhaps loss of BRCA gene function in an otherwise intact epithelial cell might lead to its death or arrest, because of activation of checkpoint functions. However, if BRCA gene mutation were to occur within a cell that had already suffered inactivation of critical DNA damage-responsive checkpoints, then the abnormalities in DNA structure resulting from BRCA gene loss might be tolerated, and might then manifest their potential as accelerators of tumor progression. This hypothesis would predict that checkpoint loss is a necessary precursor of BRCA gene inactivation in tumorigenesis.

Several recent developments in mouse models of BRCA-linked disease support this hypothesis. BRCA1 or BRCA2 mutant MEFs undergo growth arrest at early passage [20,37]. Both p53-dependent and p53-independent checkpoints appear to play a part in this growth arrest [20,22,46]. Recently, by use of the Cre-lox system, BRCA1 gene inactivation was achieved specifically in the breast of the adult mouse [47]. Such mice developed late-onset breast cancer, with frequent p53 mutation seen in tumors. When these mice were re-examined on a p53+/− genetic background, breast cancer was detected at higher frequency and with earlier onset [47]. This model indicates a permissive role for p53 mutation in BRCA-linked disease. Hemizygosity in p53 was also found to play a permissive role for breast tumor development in BRCA1+/− mice that had been exposed to ionizing radiation [48]. Mutation in p53 is common (occurring in approximately 30%) in spindled breast/ovarian cancer, but is considerably more common (occurring in approximately 60%) in BRCA-linked disease [49]. BRCA-linked disease has also been found to be associated with rare p53 mutant alleles, suggesting that novel p53 functions may be lost in BRCA-linked tumorigenesis [46,50]. The full spectrum of checkpoint(s) that are responsible for restraining cells mutated for BRCA1 or BRCA2 from continued proliferation remains to be defined. One recently identified candidate is the spindle checkpoint [46].

If BRCA-linked disease requires inactivation of checkpoint(s) followed by BRCA gene loss, then the tissue specificity of BRCA-linked disease might arise from a specific predisposition of the breast and ovarian epithelium to lose the function of such checkpoints. If so, the question shifts sideways – what determines the timing of inactivation of DNA damage checkpoints in breast/ovarian cancers?

Recombination and breast development

The breast epithelium undergoes distinct developmental programs during puberty and pregnancy. During puberty, in particular, rapid proliferation of breast tissue occurs, and the progeny of this proliferative burst are retained within the breast lobe. This is demonstrated by the finding that lobules of the breast are clonal [51–53]. In this way, breast epithelial cells have the potential to retain ‘memory’ of genetic alterations that occurred earlier in breast development. In contrast, some other epithelia that are characterized by rapid proliferation, such as the intestinal epithelium, shed cells continuously.

Radiation exposure in young women – in atomic bomb survivors or from iatrogenic causes – carries with it a specifically increased risk of subsequent breast cancer [54,55]. Women who were exposed to A bomb radiation at less than 20 years of age developed breast cancer with normal latency, suggesting that that risk was increased but that disease progression was unaffected. More recently, it became clear that A bomb exposure below the age of 10 years, before the onset of puberty, increased the risk of subsequent adult-onset breast cancer [56]. Perhaps this early impact of radiation exposure on breast cancer risk reflects the ‘memory’ of breast epithelial stem cells for genotoxic damage. Interestingly, a cohort of women who survived A bomb exposure developed early-onset breast cancer (<35 years of age), suggesting the existence of a susceptible genetic subgroup [57]. It has been suggested that this cohort may represent women with pre-existing BRCA gene germline mutations [58].

Do such observations tie in with BRCA gene biology? If a BRCA1+/− or BRCA2+/− mammary cell were to develop checkpoint defects and undergo LOH at the relevant BRCA locus early in breast development, then a number of daughter cells exhibiting this LOH event could be produced and retained within the affected lobe. Cancer risk could be multiplied in the breast epithelium by such an event, in proportion to the number of daughter cells retained after the LOH event (which might, at a maximum, constitute an entire lobe, comprising millions of at-risk epithelial cells). By contrast, other rapidly proliferating epithelia in which daughter cells are rapidly shed (such as the colonic epithelium) would not encounter this risk amplification mechanism. In this way, the clonality of the breast epithelium may, in part, account for the enhanced sensitivity of the breast to genotoxic damage as a mechanism of carcinogenesis.

Furthermore, if the BRCA1+/− genotype exhibits haploinsufficiency, then the risk of such early LOH events might be
increased. This model predicts that the years surrounding puberty are particularly important for BRCA1-linked disease, and that the breast epithelium may develop detectable genetic lesions in checkpoint and BRCA genes before the end of puberty. Although there is relatively little information that is directly pertinent to such mechanisms, one study [59] suggested that LOH events connected with BRCA1-linked disease might occur early in breast development.

**Mutagenesis models**

At first glance, generic cellular functions such as DNA repair/recombination would seem unlikely candidates for having tissue-specific functions. However, the precise genetic consequences of BRCA gene inactivation have yet to be fully defined. Defects in DNA repair are frequently accompanied by an increase in the mutation rate. An interesting example of potentially tissue-specific effects of mutagenesis came from a study of the impact of mismatch repair (MMR) defects on colon cancer. MMR dysfunction gives rise to characteristic frame-shift mutations across certain nucleotide repeat sequences. In MMR-defective colon cancers, frame-shift mutations were detected repeatedly within a purine-rich sequence in the type II transforming growth factor-β receptor gene sequence, resulting in its inactivation [60]. This suggested that MMR defects might promote colon cancer specifically by virtue of their characteristic mutagenic ‘signature’.

Could an analogous effect connect BRCA gene dysfunction to breast/ovarian cancer? There is as yet no indication that BRCA gene inactivation gives rise to a mutagenic event that is capable of delivering such specificity. However, ‘forward mutagenesis’ studies, which can provide unbiased information regarding mutagenesis, have not yet been reported for the BRCA genes. The full spectrum of mutagenesis attributable to BRCA gene inactivation is therefore unknown.

One similarity between the breast and the ovary is their regulation by estrogenic hormones. A positive correlation has been observed between estrogen exposure and breast cancer risk [61]. This effect may in large part reflect proliferative effects of estrogen upon its target tissues. In addition, however, some estrogen metabolites, which might be expected to accumulate in estrogen target tissues, have been shown to chemically modify DNA in vitro, and can promote carcinogenesis in some rodent models [62,63]. An estrogen target tissue might therefore suffer increased DNA damage directly from estrogen metabolites, giving rise to a ‘remote carcinogenesis’ mechanism (i.e. although potentially carcinogenic in other tissues, the pharmacokinetics of the carcinogen dictates a restricted site of action in vivo).

A defect in recombination could amplify the carcinogenic potential of this tissue-specific DNA damage. For example, work in prokaryotes has revealed a key role for homologous recombination in maintaining genomic integrity after DNA polymerase stalling/replication arrest (for review [64]). Bulky DNA adducts, such as those formed by estrogen metabolites, might be expected to induce DNA polymerase stalling when encountered by the replication machinery, placing particular stress on efficient recombination to prevent genomic instability. Error-prone recombination can give rise to chromosome translocation, LOH events, and other large-scale genome rearrangements that are characteristic of tumor cells (for review [65]). One can imagine how tissue-specific DNA damage, BRCA gene dysfunction, and the clonal expansion of breast epithelial cells within the lobule (as discussed above) might collaborate to promote breast cancer above other cancers in BRCA-linked disease.

Clearly, the interplay between genotoxic damage and carcinogenesis is not limited to the breast. The gastrointestinal tract, for example, must handle heavy loads of genotoxic agents. However, this epithelium may be protected by the rapid shedding of epithelial cells, which would ensure that only stem cells could potentially form tumors. Such a difference in the physiology of these epithelia may make the gastrointestinal tract less prone to a recombination defect than the breast. At the same time, experimental evidence for this concept is lacking.

The accumulation of a carcinogen at the target site would seem to be a prerequisite for local carcinogen action. This process might therefore also involve other genotoxic agents that accumulate in the breast epithelium or surrounding fat. Hints of this are seen in the property of human mammary lipid extracts to promote single-stranded DNA breaks in cultured primary human mammary epithelial cells [66].

**Transcriptional functions of BRCA1 and BRCA2**

BRCA1 and BRCA2 have each been proposed to function as transcriptional regulators [67–70]. Indeed, BRCA1 and BRCA2 can form complexes with various transcription factors and chromatin remodeling proteins [71–75]. If the BRCA genes regulate the expression of a specific set of target genes, then the identification of these targets might reveal tissue-specific functions of BRCA1 or BRCA2 that are relevant to breast and ovarian cancer. Several candidate target genes of BRCA1 have been identified. Notably, some of these are DNA damage/stress responsive genes and, in some cases, are p53 dependent [76–78]. Both BRCA1 and BRCA2 can interact with p53 [79–81]. Overexpressed BRCA1 is toxic to cells and can stabilize p53 [82,83]. In view of the repair functions of the BRCA genes and the genetic interactions between p53 mutation and BRCA gene mutation, discussed above, the relationship between BRCA genes and products and p53 may be complex. Evaluation of BRCA–p53 interactions may reveal novel functions of p53 [46,50].
Transient overexpression of BRCA1 can modify estrogen receptor-dependent promoter functions [84]. However, estrogen receptor mutation is a frequent event in BRCA-linked breast cancer, suggesting that tumorigenesis caused by BRCA gene mutation affects pathways other than those controlled by the estrogen receptor. A broader analysis of the physiologic effects of BRCA gene products on transcription functions may clarify which genes are directly transcriptionally regulated by BRCA gene products, and which of these are relevant to tumor suppression.

Conclusion

It is not yet clear which properties of the BRCA genes account for their tissue-specific actions. Genome stability and transcription functions may each be relevant to BRCA gene-mediated tumor suppression. How such functions are applied to the breast and ovary may become clear from a more detailed understanding of the biology of the BRCA genes and of these epilitha.

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References

1. Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, King MC: Linkage of early-onset familial breast cancer to chromosome 17q21. Science 1996, 250:1864–1869.
2. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W, et al: A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994, 266:66–71.
3. Wooster R, Neuhausen SL, Mangion J, Quirk Y, Ford D, Collins N, Nguyen K, Seal S, Tran T, Averill D, et al: Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. Science 1994, 265:2088–2090.
4. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, Collins N, Gregory S, Gumbs C, Micklem G: Identification of the breast cancer susceptibility gene BRCA2. Nature 1995, 378:799–802.
5. Smith SA, Easton DF, Evans DG, Ponder BA: Allele losses in the region 17q12-21 in familial breast and ovarian cancer involve the wild-type chromosome. Nature Genet 1992, 2:128–131.
6. Neuhausen SL, Marshall CJ: Loss of heterozygosity in familial tumors from three BRCA1-linked kindreds. Cancer Res 1994, 54: 6069–6072.
7. Collins N, McManus R, Wooster R, Mangion J, Seal S, Lakhani SR, Orrison W, Daly PA, Ford D, Easton DF, et al: Consistent loss of the wild type allele in breast cancers from a family linked to the BRCA2 gene on chromosome 13q12-13. Oncogene 1995, 10:1673–1675.
8. Gudmundsson J, Johannesdottir G, Berghoffson JT, Arason A, Ingvarsson S, Egilsson V, Barkardottir RB: Different tumor types from BRCA2 carriers show wild-type chromosome deletions on 13q12-13. Cancer Res 1995, 55:4830–4832.
9. Futreal PA, Liu Q, Shattuck-Eidens D, Cochran C, Gumbs C, Seal S, Barfoot R, Collins N, Bignell G, Patel S, Hamoudi R, Larsson C, Wiseman RW, Berchuck A, Iglehart JD, Marks JR, Ashworth A, Stratton MR, Futreal PA: BRCA2 mutations in primary breast and ovarian cancers. Science 1994, 266:120–122.
10. Lancaster JM, Wooster R, Mangion J, Phelan CM, Cochran C, Gumbs C, Seal S, Barfoot R, Collins N, Bignell G, Patel S, Hamoudi R, Larsson C, Wiseman RW, Berchuck A, Iglehart JD, Marks JR, Ashworth A, Stratton MR, Futreal PA: BRCA2 mutations in primary breast and ovarian cancers. Nature Genet 1996, 13:238–240.
11. Knudson AG Jr: Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 1971, 68:820–823.
12. Marquis ST, Rajan JV, Wynshaw-Boris A, Xu J, Yin GY, Abel KJ, Weber BL, Chodosh LA: The developmental pattern of Brca1 expression implies a role in differentiation of the breast and other tissues. Nature Genet 1995, 11:17–26.
13. Lane TF, Deng C, Elson A, Lyu MS, Kozak CA, Leder P: Expression of Brca1 is associated with terminal differentiation of ectodermally and mesodermally derived tissues in mice. Genes Dev 1995, 9:2712–2722.
14. Rajan JV, Marquis ST, Gardner HP, Chodosh LA: Developmental expression of Brca2 colocalizes with Brca1 and is associated with proliferation and differentiation in multiple tissues. Dev Biol 1997, 184:385–401.
15. Gownen LC, Johnson BL, Latour AM, Sulkik KK, Koller BH: BRCA1 deficiency results in early embryonic lethality characterized by neuroepithelial abnormalities. Nature Genet 1996, 12:191–194.
16. Hakem R, de la Pompa JL, Sirard C, Mo R, Woo M, Hakem A, Wakeham A, Potter J, Reitmair A, Billia F, Erope H, Hui CC, Roberts J, Robertson J, Mak TW: The tumor suppressor gene Brca1 is required for embryonic cellular proliferation in the mouse. Cell 1996, 85: 1009–1023.
17. Sharan SK, Morimoto M, Albrecht U, Lim DS, Regol E, Dinh C, Sands A, Echeige H, Hasty P, Bradley A: Embryonic lethality and radiation hypersensitivity mediated by Rad51 in mice lacking Brca2. Nature 1997, 386:804–810.
18. Connor F, Bertwistle D, Mee PJ, Ross GM, Swift S, Grigorieva E, Tybulewicz VL, Ashworth A: Tumorigenesis and a DNA repair defect in mice with a truncating Brca2 mutation. Nature Genet 1997, 17: 423–430.
19. Friedman LS, Thistlethwaite FC, Patel KJ, Yu VP, Lee H, Venkitaraman AR, Abel KJ, Carlton MB, Hunter SM, Colledge WH, Evans MJ, Ponder BA: Thymic lymphomas in mice with a truncating mutation in Brca2. Cancer Res 1998, 58:1338–1343.
20. Shen SX, Weaver Z, Xu X, Li C, Weinstein M, Chen L, Guan XY, RAB22 and RAB163/mouse
21. Xu X, Weaver Z, Linke SP, Li C, Gotay J, Wang WX, Harris CC, RAB22 and RAB163/mouse
22. Smith SA, Easton DF, Evans DG, Ponder BA: Allele losses in the region 17q12-21 in familial breast and ovarian cancer involve the wild-type chromosome. Nature Genet 1992, 2:128–131.
23. Gudmundsson J, Johannesdottir G, Berghoffson JT, Arason A, Ingvarsson S, Egilsson V, Barkardottir RB: Different tumor types from BRCA2 carriers show wild-type chromosome deletions on 13q12-13. Cancer Res 1995, 55:4830–4832.
24. Knudson AG Jr: Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 1971, 68:820–823.
25. Marquis ST, Rajan JV, Wynshaw-Boris A, Xu J, Yin GY, Abel KJ, Weber BL, Chodosh LA: The developmental pattern of Brca1 expression implies a role in differentiation of the breast and other tissues. Nature Genet 1995, 11:17–26.
50. Smith PD, Hasty P: A mutation in mouse rad51 results in an early embryonic lethal that is suppressed by a mutation in p53. Mol Cell Biol 1996, 16:7133–7143.

51. Tsuziki T, Fuji Y, Sakurai K, Tominaga Y, Nakao K, Sekiguchi M, Matsusako A, Yoshimura Y, Morita T: Targeted disruption of the Rad51 gene leads to lethality in embryonic mice. Proc Natl Acad Sci USA 1996, 93:6236–6240.

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

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

54. Chen JI, Silver D, Cantor S, Livingston DM, Scully R: BRCA1, BRCA2, and Rad51 operate in a common DNA damage response pathway. Cancer Res 1999, 59 (suppl):1752s–1756s.

55. Zhong Q, Chen CF, Li S, Chen Y, Wang CC, Xiao J, Chen PL, Sharp ZD, Lee HF: Association of BRCA1 with the hRad50-hMre11-p95 complex and the DNA damage response. Science 1999, 285:429–437.

56. Patel KJ, Yu VP, Lee H, Corcoran A, Thistlethwaite FC, Evans MJ, Colledge WH, Friedman LS, Ponder BA, Venkitaraman AR: Involvement of Brca2 in DNA repair. Mol Cell 1998, 1:347–357.

57. Moyer NA, Chi JW, Koller BH, Jasin M: Brca1 controls homology-directed DNA repair. Mol Cell 1999, 4:511–518.

58. Stavens-Larson J, Goen LW, Latour AM, Mo R, Nishimori I, Xiong G, Feunteun J: Gamma-rays-induced death of human cells carrying mutations of BRCA1 or BRCA2. Oncogene 1999, 18:7900–7907.

59. Foray N, Randazzo M, Marot D, Pernicaudet M, Lenior G, Feunteun J: Brca2-negative embryonic stem cells display a decreased homologous recombination frequency and an increased frequency of non-homologous recombination that is corrected by expression of a brca1 transgene. Oncogene 1999, 18:7900–7907.

60. Hui CC, Mak TW: Brca2 is a component of the RNA polymerase II holoenzyme. Mol Cell 1999, 4:1093–1099.

61. Goen LW, Avrutskaya AV, Latour AM, Koller BH, Leadon SA: BRCA1 required for transcription-coupled repair of oxidative DNA damage. Science 1998, 281:1006–1012.

62. Tutt A, Gabriel A, Bertwistle D, Connor F, Paterson H, Peacock J, Ross G, Ashworth A: Absence of Brca2 causes genome instability by chromosome breakage and loss associated with centrosome amplification. Curr Biol 1999, 9:1107–1110.

63. Suzuki A, da Pompio JL, Hakem R, Elia A, Yoshida R, Mo R, Nishimori I, Chauang F, Nakahama A, Ito A, Fukimoto M, Hui CC, Mak TW: Brca2 is required for embryonic cellular proliferation in the mouse. Genes Dev 1999, 13:1242–1252.

64. Hakem R, da Pompio JL, Elia A, Potter J, Mak TW: Partial rescue of Brca1 (−/−) early embryonic lethality by p53 or p21 null mutation. Mol Endocrinol 1999, 13:298–302.

65. Lee H, Trainer AH, Friedman LS, Thistlethwaite FC, Evans MJ, Ponder BA, Venkitaraman AR: Mitotic checkpoint inactivation fosters translocation in cells lacking the breast cancer susceptibility gene, Brca2. Mol Cell 1999, 4:1–10.

66. Xue W, Wagner KU, Larson D, Weaver Z, Li C, Ried T, Hennighausen L, Wynshaw-Boris A, Deng CX: Conditional mutation of Brca1 in mammary epithelial cells results in blunted ductal morphogenesis and tumour formation. Nature Genet 1999, 22:37–43.

67. Minna JD, Backlund DC, Hicks MW, Goen LC, Godfrey V, Koller BH: Mammary tumor formation in p53- and Brca1-deficient mice. Cell Growth Diff 1999, 10:1–10.

68. Crook T, Brooks LA, Crossland S, Osn P, Barker KT, Waller J, Philip E, Smith PD, Tylug I, Pett J, Parker G, Allardy M, Crompton MR, Gunter-Smith S: p53 mutations in colorectal cancers but not a mutator phenotype in BRCA1- and BRCA2-associated breast tumours. Oncogene 1998, 17:1681–1689.

69. Smith PD, Crossland S, Parker G, Osn P, Brooks L, Waller J, Philip E, Crompton MR, Gunter-Smith BA, Allardy M, Crook T: Novel p53 mutations selected in BRCA-associated tumours which dissociate transformation suppression from other wild-type p53 functions. Oncogene 1999, 18:2451–2459.

70. Kardon EC, Smith GH: An entire functional mammary gland may arise from a single cell. Development 1998, 125:1921–1930.
77. Harkin DP, Bean JM, Miklos D, Song YH, Truong VB, Englert C, Christians FC, Ellisien LW, Maeheswaran S, Oliner JD, Haber DA: Induction of GADD45 and JNK/SAPK-dependent apoptosis following inducible expression of BRCA1. Cell 1999, 97:575–586.

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

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

80. Marmorstein LY, Ouchi T, Aaronson SA: The BRCA2 gene product functionally interacts with p53 and RAD51. Proc Natl Acad Sci USA 1998, 95:13869–13874.

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

82. Wilson CA, Payton MN, Elliott GS, Buaas FW, Cajuila EE, Grosshans D, Ramos L, Reese DM, Slamond DJ, Calzone FJ: Differential subcellular localization, expression and biological toxicity of BRCA1 and the splice variant BRCA1-delta11b. Oncogene 1999, 14:1–16.

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

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

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