Biochemical Pharmacology 80 (2010) 647–653

Contents lists available at ScienceDirect

Biochemical Pharmacology

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

Review

Fine tuning chemotherapy to match BRCA1 status

Melissa Price [a,b], Alvaro N.A. Monteiro [a,*]

[a] Risk Assessment, Detection, and Intervention Program, H. Lee Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA
[b] University of South Florida Cancer Biology PhD Program, Tampa, FL 33612, USA

ARTICLE INFO

Article history:
Received 4 March 2010
Accepted 14 May 2010

Keywords:
BRCA1
DNA damage
Synthetic lethality
Cancer
Tumor suppressor
Chemotherapy

ABSTRACT

Targeted cancer therapies have been primarily directed at inhibiting oncogenes that are overexpressed or constitutively active in tumors. It is thought that as the cell's circuitry gets re-wired by the constitutive activation of some pathways it becomes exquisitely dependent on this activity. Tumor cell death normally results from inhibiting constitutively active pathways. The dependence of tumor cells on the activity of these pathways has been called oncogene addiction. Approaches that aim to exploit loss of function, rather than gain of function changes have also become a powerful addition to our arsenal of cancer therapies. In particular, when tumors acquire mutations that disrupt pathways in the DNA damage response they rely on alternative pathways that can be targeted pharmacologically. Here we review the use of *BRCA1* as a marker of response to therapy with a particular focus on the use of Cisplatin and PARP inhibitors. We also explore the use of *BRCA1* as a marker of response to microtubule inhibitors and how all these approaches will bring us closer to the goal of personalized medicine in cancer treatment.

Contents

1. Introduction

Genomic instability is a hallmark of cancer and it is thought to underlie the cancer cell's ability to acquire a more aggressive character over time as well as to develop drug resistance. It provides copious genetic variation on which selection acts to provide the tumor with the ability to ignore tissue controls and evade chemotherapy. The acquisition of genomic instability depends on the disruption of the cell's fail-safe mechanisms to prevent the passing of potentially harmful mutations to daughter cells. These mechanisms are collectively called the cellular DNA damage response (DDR). The DDR is better visualized as a large network of redundant processes, rather than a series of specific pathways, that sense and locate damaged DNA, coordinate cell cycle progression by activating cell cycle checkpoints, and promote repair.

Cancer cells carrying activated oncogenes are prone to replication stress, including stalled replication forks that eventu-

Abbreviations: DDR, DNA damage response; DSB, double stranded break; HR, homologous recombination; NER, nucleotide excision repair; NHEJ, non-homologous end joining; NSCLC, non-small cell lung carcinoma; PARP, poly ADP ribose polymerase; siRNA, small interfering RNA; SSB, single stranded break.

* Corresponding author. Tel.: +1 813 7456321; fax: +1 813 7451720.
E-mail address: alvaro.monteiro@moffitt.org (Alvaro N.A. Monteiro).

0006-2952/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.bcp.2010.05.015

ally collapse and lead to the formation of double stranded DNA breaks. Premature termination of replication in these cells leads to a constitutive activation of the DDR and may result in activation of cell cycle checkpoints, induction of cell death or senescence [1–3]. Thus, it has been proposed that the DDR constitutes an earlier barrier to tumorigenesis, and full blown cancer can only develop by transposing this barrier [1,2]. Indeed, in early lesions markers of an activated DDR, such as phosphorylated forms of ATM, Chk2, p53, and H2AX reach maximal levels and precede allelic imbalance and mutations that disrupt cell cycle checkpoints [1–3]. Although in some cases disruption of these signaling pathways leads to lethality, in many cases there is compensation by other redundant pathways.

For cancer cells, the flip side of this Faustian arrangement is manifested as an increased sensitivity to DNA damaging agents such as chemotherapy drugs or radiotherapy. In addition, as cancer cells become inevitably over dependent on specific pathways, pharmacologic targeting of these already overburdened processes result in tumor cell death. Detailed understanding of signaling pathways and their status in cells will allow the efficient exploitation of the tumor's increased sensitivity and its overdependence on certain pathways. We have made significant progress in the last 20 years on both of these fronts. Intensive research has now provided a coherent, albeit incomplete, view of the DDR [4]. Conceptual and technological improvements now allow us to start building a framework for personalized medicine.

2. Cloning *BRCA1*

The notion of an inherited predisposition to breast cancer is an old one [5,6], but it had been difficult to tease apart the contributions of genetic factors from those of shared environment. The identification of one large kindred with 668 individuals from Utah was instrumental to exclude the role of shared environment in the predisposition [7]. This family, called kindred 107, presumably shared the same environment and diet but only one branch of the family displayed a disproportionate incidence of breast cancers [7]. Despite this significant advance it was not until the late 1980s that the nature of the genetic determinants began to be more clearly delineated. The evidence from a large number of cluster families strongly suggested that the predisposition to breast and ovarian cancer was best explained by a dominant single locus [8]. This was quickly followed by the mapping of *BRCA1* to the long arm of chromosome 17 [9,10]. The identification of probes mapping proximal to the *BRCA1* locus provided the ability to show that *BRCA1* was a tumor suppressor gene conforming to the two-hit hypothesis with loss of the wild type allele in the tumor [11]. The Breast Cancer Linkage Consortium further refined its location by combining families from across the globe [12].

BRCA1 was positionally cloned in 1994 ending one of the most competitive races in science [13,14]. Cloning of *BRCA2*, which increases the risk of male breast cancer as well, came right after *BRCA1* and was important to allow the development of comprehensive genetic testing to identify individuals at increased risk for breast cancer [15–17].

3. *BRCA1* as a marker for prognosis

With the development of genetic tests several groups started to look into how breast or ovarian cancer patients fared after the onset of disease depending on their *BRCA1* mutation status. Studies consistently showed that ovarian cancers with *BRCA* (*BRCA1* or *BRCA2*) mutations had a more favorable clinical outcome than sporadic cancers [18–26] although more subtle differences or even opposite results have also been recorded [27,28]. These studies have different designs, patient population, tumor stratification, and endpoint measures which complicate the interpretation of these results. Yet the studies suggest a trend in which ovarian tumors arising in *BRCA* carriers tend to have a better outcome. Because virtually all patients diagnosed with ovarian cancer are treated with platinum-based chemotherapy, the favorable outcomes may be directly related to an increased sensitivity of *BRCA*-linked tumors to platinum.

Because it was estimated that only approximately 10% of unselected epithelial ovarian cancers are attributable to germline mutations in *BRCA1* or *BRCA2*, and somatic mutations were thought to be rare in sporadic cancers [29–34] the implications of these results to ovarian cancer in general was thought to be limited. However, it is becoming increasingly clear that sporadic ovarian cancers inactivate *BRCA1* using different mechanisms. Reduced expression of *BRCA1* in ovarian cancers has been found in 13–90% of tumors suggesting that they might also respond well to Cisplatin-based therapy (reviewed in [35]).

The picture seems to be more complicated in the context of breast cancer. Retrospective studies on clinical outcomes of Ashkenazi Jewish women with breast cancer showed that *BRCA* mutation carriers had a poorer prognosis than non-*BRCA* mutation carriers [36,37]. Importantly, *BRCA1* mutation carriers had a worse overall survival if they did not receive adjuvant chemotherapy or adjuvant hormonal therapy [37]. Another study comparing *BRCA*-linked versus sporadic breast cancers found a trend towards a worse survival for *BRCA1*-associated ductal breast cancer [38]. A poorer prognosis for *BRCA1*-linked cancers was also found when comparing *BRCA1*-linked to other familial breast cancers [39]. However, in some cases no significant difference was noted [40,41]. Although there is some discordance in the results from these trials, which have the same caveats as the ones listed for ovarian cancer studies, there is evidence to suggest that *BRCA1* can be used as a prognostic marker.

4. A role for BRCA1 in the DNA damage response

In the last 15 years the role of *BRCA1* has come to a sharper focus. BRCA1 functions in at least two cellular processes: the regulation of transcription and in DNA repair (reviewed in [42–48]). Both functions seem to be central to its role in the DNA damage response (DDR). These discoveries provide a clear rationale to frame the use of BRCA1 not only as a prognostic marker but also as a predictor of clinical outcomes in response to therapy.

BRCA1 plays an important role in repair of double stranded breaks (DSBs) via homologous recombination (HR) [43,49]. DSB repair via HR occurs in late S or G2 phase when a newly synthesized sister chromatid can be used as a template [50,51]. Physically, BRCA1 can be visualized at DSB sites as foci by immunofluorescence, colocalizing with histone H2AX phosphorylated at Serine 139, also known as γ-H2AX [52]. H2AX is phosphorylated by ATM following DNA damage in large megabase regions that spread from the location of the break [53,54]. BRCA1 is involved in recruiting RAD51 to the DSB sites [55–57]. The RAD51 recombinase promotes strand invasion to use the sister chromatid DNA as a template to fix the DSB [58]. Underscoring the network structure of the DDR, BRCA1 has been shown to be required for multiple cell cycle checkpoints (reviewed in [59]). In addition, at least partially, BRCA1's tumor suppressor functions come from its other role as a transcription regulator for genes involved in DNA repair [60–69].

The participation of BRCA1 in DNA repair processes at multiple levels provides a solid rationale for using BRCA1 as a potential biomarker of response to genotoxic drugs. Data from in vitro and in vivo studies suggest that *BRCA1* status may be particularly suited to predict response to Cisplatin and to PARP inhibitors. Interest-

ingly, sensitivity to a different class of drugs, microtubule-interfering drugs such as taxanes and vinca alkaloids, depends on BRCA1 expression as well. Thus, BRCA1 has been proposed to be a differential modulator of response to chemotherapy [70]. Below, we discuss the relationship between BRCA1 status and response to these classes of drugs.

5. Taxanes

Microtubule-interfering agents, such as taxanes and vinca alkaloids, bind to microtubules and disrupt the dynamic polymerization and depolymerization of tubulin, needed for the appropriate segregation of chromosomes during mitosis [71].

When Taxol binds to microtubules it prevents their depolymerization which leads to arrest in mitosis [72–74]. Taxanes currently used for chemotherapy are Paclitaxel (Taxol) and Docetaxel (Taxotere). After treatment with Paclitaxel cells go through an abnormal mitotic exit with multi-nucleated cells, followed by apoptosis [74,75]. Paclitaxel preferentially kills transformed cells rather than non-transformed cells, which was the basis for the initial enthusiasm for the drug in cancer treatment. The difference in sensitivity did not originate from an intrinsic property of the transformed state but rather from the fact that transformed cell populations have a higher number of mitotic cells, which are more susceptible to the drug's action than non-mitotic cells [74]. Also, non-transformed cells resume normal proliferation after being released from the mitotic block by removal of Paclitaxel but transformed cells go into an abortive cell cycle with an abnormal chromosomal number and/or apoptosis [76]. By stabilizing microtubules, Paclitaxel disrupts mitotic spindle assembly and triggers the spindle checkpoint [77]. Defects in the spindle checkpoint have been associated with resistance to taxanes [78,79]. However, the picture is probably more complex as recent data have demonstrated that individual cells present a wide range of variation in their response to microtubule inhibitors and analysis of cell populations does not allow for the discrimination of these different responses [80,81].

Taxanes have been incorporated in the treatment of several cancers with promising results but neurotoxicity and bradycardia are both common side effects of Paclitaxel treatment [82]. Many patients suffer serious side effects caused by these drugs without experiencing a significant disease response. Thus, the emergence of BRCA1 as a possible predictor of response (reviewed in [83]) has sparked interest.

6. BRCA1 and taxanes

Recently, a large body of in vitro, pre-clinical, and clinical data has highlighted a possible requirement for BRCA1 in the response to taxanes and other microtubule-interfering drugs. In 2001, two independent papers implicated BRCA1 as a mediator of the cellular response to microtubule-interfering drugs [84,85]. A series of experiments using different methods and a panel of breast cancer cell lines have confirmed that low levels of BRCA1 correlate with resistance to taxanes and to Vinca alkaloids [70,84–88] (reviewed in [89]). Paclitaxel treatment leads to BRCA1-mediated activation of p38/MAPK and JNK/SAPK pathways [87,90]. BRCA1 promotes taxane-induced apoptosis but has the reverse effect on apoptosis induced by Cisplatin [70].

Evidence from mouse models (reviewed in [83]) and clinical studies also supports the role of BRCA1 in taxane sensitivity. Recently, several papers have explored the potential use of BRCA1 in lung cancer as a prognostic marker and as marker of clinical outcome after treatment. Results from these studies are variable but they clearly indicate that this is a promising line of research. Rosell et al. provided evidence that *BRCA1* levels could be used as a prognostic marker [91]. Overexpression of *BRCA1* mRNA was strongly associated with poor survival in chemonaive stages I, II, and IIIA NSCLC patients [91]. High *BRCA1* expression was also found to be a prognostic factor for both median and disease-free survival in stages IB and IIB surgically resected NSCLC patients [92].

Taron et al. performed the first study on whether *BRCA1* could be used as an indicator of chemoresistance in lung cancer. In a study of patients treated with Gemcitabine/Cisplatin in a neoadjuvant setting, tumors with low levels of *BRCA1* mRNA presented with a better outcome than those with high levels [93]. This is in line with the idea that low *BRCA1* levels correlate with increased sensitivity to DNA damaging agents. The authors suggested, based on their study and on pre-clinical data [70], that patients with low levels of *BRCA1* would benefit from single agent Cisplatin whereas patients with higher levels would benefit from single agent Docetaxel [93]. On the other hand, a study of patients with NSCLC treated with Gemcitabine/Cisplatin or Epirubicin/Gemcitabine failed to see any correlation between levels of *BRCA1* in tumors and response [94].

Interestingly, Wang et al. found a significant positive correlation between *BRCA1* expression and sensitivity to Docetaxel in malignant pleural effusions of NSCLC patients [95]. A negative correlation with Cisplatin sensitivity was also found in line with previous studies [93,95]. A study with 102 patients with advanced NSCLC treated with Gemcitabine plus Docetaxel showed that as levels of *BRCA1* mRNA increased the probability of response increased and risk of progression decreased [96]. A negative correlation between low levels of *BRCA1* and longer time to progression was found in a subset of 31 patients receiving Cisplatin-based second-line therapy [96].

In summary, there is a growing body of exciting clinical evidence showing that low levels of *BRCA1* confers sensitivity to platinum [70,85,97,98] and resistance to microtubule drugs such as Paclitaxel, Docetaxel, and Vinorelbine [70,85,97]. BRCA1 seems to be involved in the inverse relationship between genotoxic agents and microtubule-interfering drugs [99]. Thus, caution will need to be exercised when interpreting data from combination (*e.g.* Cisplatin and Docetaxel) therapy. In any event, exploration of *BRCA1* as a biomarker in lung cancer will potentially lead to better prediction of single agent chemotherapy in the context of neoadjuvant or second-line treatment.

7. Cisplatin: teaching new tricks to an old dog

Cisplatin targets cellular DNA creating inter- and intra-strand cross links which distort the DNA and inhibit DNA replication, recombination and transcription [100]. Several pathways are involved in repairing these cross link lesions but primarily they are repaired by the Nucleotide Excision Repair (NER) pathway (reviewed in [101]). During NER a single stranded DNA break (SSB) intermediate is formed. If this SSB is not repaired before replication it leads to replication fork collapse and the generation of a double stranded break (DSB)[102]. DSBs can then be repaired by HR or by non-homologous end joining (NHEJ). While HR repair is limited to late S-phase and G2, NHEJ repair of DSBs occur in all phases of the cell cycle [50]. NHEJ is the most utilized mechanism in mammalian cells but is an error-prone process that may lead to reduced survival [103,104]. Cell lines derived from patients with *Xeroderma pigmentosum* and *Fanconi anemia* are NER-deficient and HR-deficient, respectively, and are extremely sensitive to Cisplatin treatment [105].

Cisplatin does not specifically target cancer cells and can be extremely toxic to normal tissue causing irreversible damage. The dose limiting toxicity of Cisplatin is mainly nephrotoxicity, neurotoxicity, and myelosuppression [106,107]. Despite its toxicity, Cisplatin is widely used in cancer treatment (reviewed in [107]). The identification of tumors which are more likely to respond (for

example, those with disruption of *BRCA1*) is likely to result in a broader therapeutic range for Cisplatin.

It is possible that lessons learned with BRCA1 and response to Cisplatin may also be extrapolated to other genotoxic agents. Many pre-clinical and clinical studies have found that *BRCA1*$^{-/-}$ cells are sensitive to a wide spectrum of DNA damaging drugs [108]. Cells deficient for *BRCA1* are more sensitive to doxorubicin, an anthracycline that targets topoisomerase II and is used in breast cancer treatment [109,110]. Drugs that interfere with topoisomerases I or II produce double stranded breaks when the replication machinery encounters the DNA lesions. Breast cancer clinical studies with anthracyclines in the neoadjuvant setting showed the same trend in which *BRCA1/2* carriers had a better clinical response rate than did non-carriers [111]. Along similar lines, *BRCA1*$^{-/-}$ cells are also more sensitive to topotecan, an alkaloid that inhibits topoisomerase I and is used for treatment of ovarian cancer [109]. Further clinical studies will be needed to clarify the role of *BRCA1* in the response to these drugs in the clinical setting.

8. Restoration of BRCA proficiency by back mutation: a novel mechanism for resistance

Early experiments showed that mouse *Brca1*-defective cells were sensitive to Cisplatin [55]. Conversely, reconstitution of *BRCA1*-deficient cells with full length BRCA1 leads to increased resistance to Cisplatin [88]. Upon treatment with Cisplatin tumors arising in *Brca1*$^{-/-}$; *Tp53*$^{-/-}$ mice displayed an increase in cell death, a decrease in the number of mitotic cells, and no RAD51 foci formation when compared to *Tp53*$^{-/-}$ tumors [112]. Human breast cancer xenografts deficient in *BRCA1* responded better to in vivo Cisplatin treatment than xenografts of tumors formed with *BRCA1*-reconstituted cells [113].

There is mounting clinical evidence suggesting that Cisplatin-based treatment may be effective in treating *BRCA1*-associated cancers [114–116]. Similarly encouraging results were obtained with triple-negative breast tumors in the neoadjuvant setting [117]. Triple-negative tumors, which do not express estrogen or progesterone receptors, and do not contain amplification of *HER2/Neu* shared phenotypic features with *BRCA1*-linked tumors, although the two groups may not overlap completely. Interestingly, among the factors associated with platinum response was a low *BRCA1* mRNA expression or *BRCA1* promoter methylation, suggesting that *BRCA1* status could be used to predict response in sporadic breast cancers as well [117].

Over the years several different mechanisms of platinum resistance have been indentified, mostly using in vitro models (reviewed in [118]). However, there has been considerable debate about whether the mechanisms identified in cell lines operate in human tumors [118]. Recently, a novel mechanism of resistance to platinum drugs and PARP inhibitors was identified in *BRCA*-deficient tumors and cell lines, respectively [119–122]. In these cases, emergence of resistance was linked to restoration of HR through reversion mutation (reviewed in [123]). While most of the available data pertains to restoration of HR by reversion of *BRCA2* mutations [119–121], reversion of *BRCA1* mutations have also been observed [122]. Although the mechanisms have not been fully elucidated these mutations restore the reading frame of the protein and consequently its HR function [118]. A detailed knowledge of these mechanisms will be instrumental to improve chemotherapy results.

9. PARP inhibitors: adapting synthetic lethality to fight cancer

The concept of synthetic lethality originated with studies in *Drosophila* and in yeast [124–128]. Two genes can be defined as synthetic lethal when deletion (or markedly decrease in expression) of either in isolation does not affect viability but the combination leads to lethality. The current use of PARP (poly ADP ribose polymerase) inhibitors in patients with *BRCA*-related tumors is based on the concept of synthetic lethality.

The idea to use PARP inhibitors in *BRCA*-deficient cells stemmed from observations made in cells derived from *Parp1*$^{-/-}$ mice [129–133]. PARP1 is an enzyme that recognizes SSBs, is involved in base excision repair, and interacts with other base excision repair proteins such as XRCC1, DNA ligase III, and DNA polymerase beta to repair lesions in single stranded DNA [134]. Mice deficient in PARP are viable, fertile, and do not develop early onset tumors [131,135]. In the absence of PARP1, SSBs remain present for longer periods of time before being repaired [136]. In S-phase, the retention of unrepaired SSBs increases the likelihood of replication fork collapse and generation of a DSB. Although DSB can be repaired by HR or NHEJ [137–140], HR is the preferred mode during S-phase. The importance of HR-mediated repair in *Parp1*$^{-/-}$ was revealed by a significant increase in RAD51 foci and in sister chromatid exchange when compared to *Parp1*$^{+/+}$ cells [133]. These experiments led to the notion that PARP-deficient cells might be over dependent on HR.

As *BRCA1* and *BRCA2* have been shown to be important for HR [49,141,142] it was predicted that cells deficient in these genes might have increased sensitivity to PARP inhibitors [129,143]. As predicted, inhibition of PARP by pharmacologic compounds or by siRNA led to a decrease in clonogenic survival of *Brca1*- and *Brca2*-deficient mouse ES cells when compared to *Brca1*- and *Brca2*-proficient ES cells, with an increase in the formation of γ-H2AX foci, a marker for DSBs [129]. Along similar lines, *BRCA2*-deficient cells and their xenografts were also shown to be hypersensitive to PARP inhibitors [143].

The efficacy of a PARP inhibitor (AZD-2281) has also been verified in *Brca1*$^{-/-}$;*Tp53*$^{-/-}$ mice with mammary adenocarcinomas [144]. Importantly, there is also evidence that PARP inhibitors in combination with Cisplatin have even greater effect than the any of the two drugs alone [144]. In NSCLC and breast carcinoma xenografts treated with the PARP inhibitor and Cisplatin displayed significantly reduced tumor volume compared to Cisplatin monotherapy [145,146].

Results from a Phase I clinical trial using Olaparib (AZD-2281) in a cohort enriched in carriers of *BRCA1* or *BRCA2* mutations with refractory disease was recently reported [147]. Although not designed to assess efficacy, this trial reported durable objective responses in confirmed carriers of *BRCA1* or *BRCA2* mutations [147]. Of the nineteen *BRCA* mutation carriers treated solely with the PARP inhibitor 63% had a clinical benefit [147]. An important characteristic about the PARP inhibitors is that wild type cells are relatively unaffected by the drug and therefore toxicity should be low. This trial also confirmed these predictions as there was little to no toxicity reported even in mutation carriers [147].

PARP inhibitors currently under investigation are competitive inhibitors of NAD+, the substrate of PARP. Some of the first PARP inhibitors were nicotinamides and benzamides but the specificity to the PARP enzyme rather than other enzymes that uses NAD+ as a substrate was relatively low [148,149]. Chemical modifications based around these original structures led to more potent, specific, and soluble drugs that are going through clinical trials today [150].

Recently, it was also found that PTEN deficiency leads to a defect in HR. Similar to the case involving *BRCA* mutations, the HR defect caused by PTEN deficiency sensitizes cells to PARP inhibitors [151]. In addition, the use of siRNA screens to systematically look for synthetic lethal interactions with specific drugs is also likely to provide a wealth of potential targets [152]. The proof of principle for the use of synthetic lethality approaches provided by the encouraging results with PARP inhibitors will certainly add impetus to the search for synthetic lethal interactions that can be used in the clinic [101,153,154].

10. Conclusion: is it the dawn of personalized medicine?

The accumulation of evidence that *BRCA*-deficient tumors respond well to Cisplatin and/or PARP inhibitors opens the possibility of fine tuning therapy to achieve maximal results with minimal side effects. Translating this knowledge into common practice clinical treatment is likely to be a smooth process as there are already genetic tests to reliably identify carriers of germline mutations. More importantly, the information from lung cancer trials using *BRCA1* levels as a predictor to drug response in tumors arising in individuals that are not mutation carriers suggests that the concept of tailoring therapy to the status of *BRCA1* could be extended to a larger group of patients [91–96]. In addition, the successful application of the synthetic lethality concept indicates that the identification of effective chemotherapy drugs for individual tumors is a clear possibility.

Certainly, several hurdles still have to be transposed. For example, we know very little about how tumor heterogeneity influences drug responses. Solid tumors are often an agglomerate of tumor and stromal cells of different origins such as fibroblasts, inflammatory and endothelial cells with a complex network of paracrine interactions. Knowledge of how these interactions can be harnessed to improve response will be one of the main challenges ahead. Likewise, tumor cells are also genetically and epigenetically heterogeneous. It is conceivable that certain subpopulations in the tumor respond different to certain drugs allowing for the mergence of resistance. Understanding how different tumors vary in their composition will help us to identify combination therapies and to tailor scheduling to obtain maximum efficacy.

Although these are issues that we are just now beginning to understand it is clear that just as the discovery of the *BRCA1* gene led the way for finding predisposition genes for hereditary cancer and a detailed understanding of DNA repair, the discovery of therapies tailored to specific genetic mutations can lead to a wide array of novel approaches in personalized medicine.

Acknowledgements

The work in the laboratory is supported by the National Institutes of Health (RO1 CA116167; U56 CA 118809), the National Functional Genomics Center (U.S. Department of Defense), the James & Esther King Florida Biomedical Research Program, and the Florida Breast Cancer Foundation. The authors are indebted to members of the Monteiro Lab for helpful discussions.

References

[1] Bartkova J, Horejsi Z, Koed K, Kramer A, Tort F, Zieger K, et al. DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis. Nature 2005;434:864–70.
[2] Gorgoulis VG, Vassiliou LV, Karakaidos P, Zacharatos P, Kotsinas A, Liloglou T, et al. Activation of the DNA damage checkpoint and genomic instability in human precancerous lesions. Nature 2005;434:907–13.
[3] Bartkova J, Rezaei N, Liontos M, Karakaidos P, Kletsas D, Issaeva N, et al. Oncogene-induced senescence is part of the tumorigenesis barrier imposed by DNA damage checkpoints. Nature 2006;444:633–7.
[4] Harper JW, Elledge SJ. The DNA damage response: ten years after. Mol Cell 2007;28:739–45.
[5] Broca PP. Traité des tumeurs. Paris: Asselin; 1866.
[6] Lynch HT, Krush AJ, Lemon HM, Kaplan AR, Condit PT, Bottomley RH. Tumor variation in families with breast cancer. JAMA 1972;222:1631–5.
[7] Gardner EJ, Stephens FE. Breast cancer in one family group. Am J Hum Genet 1950;2:30–40.
[8] Newman B, Austin MA, Lee M, King MC. Inheritance of human breast cancer: evidence for autosomal dominant transmission in high-risk families. Proc Natl Acad Sci USA 1988;85:3044–8.
[9] Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, et al. Linkage of early-onset familial breast cancer to chromosome 17q21. Science 1990;250:1684–9.
[10] Narod SA, Feunteun J, Lynch HT, Watson P, Conway T, Lynch J, et al. Familial breast-ovarian cancer locus on chromosome 17q12–q23. Lancet 1991;338:82–3.
[11] 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. Nat Genet 1992;2:128–31.
[12] Easton DF, Bishop DT, Ford D, Crockford GP. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. The Breast Cancer Linkage Consortium. Am J Hum Genet 1993;52:678–701.
[13] Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994;266:66–71.
[14] Davies K, White M. Breakthrough: The Race to Find the Breast Cancer Gene. New York: John Wiley & Sons; 1996.
[15] Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, et al. Identification of the breast cancer susceptibility gene BRCA2. Nature 1995;378:789–92.
[16] Tavtigian SV, Simard J, Rommens J, Couch F, Shattuck-Eidens D, Neuhausen S, et al. The complete BRCA2 gene and mutations in chromosome 13q-linked kindreds. Nat Genet 1996;12:333–7.
[17] Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. J Clin Oncol 2002;20:1480–90.
[18] Rubin SC, Benjamin I, Behbakht K, Takahashi H, Morgan MA, LiVolsi VA, et al. Clinical and pathological features of ovarian cancer in women with germ-line mutations of BRCA1. N Engl J Med 1996;335:1413–6.
[19] Cass I, Baldwin RL, Varkey T, Moslehi R, Narod SA, Karlan BY. Improved survival in women with BRCA-associated ovarian carcinoma. Cancer 2003;97:2187–95.
[20] Ben David Y, Chetrit A, Hirsh-Yechezkel G, Friedman E, Beck BD, Beller U, et al. Effect of BRCA mutations on the length of survival in epithelial ovarian tumors. J Clin Oncol 2002;20:463–6.
[21] Ramus SJ, Fishman A, Pharoah PD, Yarkoni S, Altaras M, Ponder BA. Ovarian cancer survival in Ashkenazi Jewish patients with BRCA1 and BRCA2 mutations. Eur J Surg Oncol 2001;27:278–81.
[22] Tan DSP, Rothermundt C, Thomas K, Bancroft E, Eeles R, Shanley S, et al. "BRCAness" syndrome in ovarian cancer: a case-control study describing the clinical features and outcome of patients with epithelial ovarian cancer associated with BRCA1 and BRCA2 mutations. J Clin Oncol 2008;26:5530–6.
[23] Aida H, Takakuwa K, Nagata H, Tsuneki I, Takano M, Tsuji S, et al. Clinical features of ovarian cancer in Japanese women with germ-line mutations of BRCA1. Clin Cancer Res 1998;4:235–40.
[24] Boyd J, Sonoda Y, Federici MG, Bogomolniy F, Rhei E, Maresco DL, et al. Clinicopathologic features of BRCA-linked and sporadic ovarian cancer. JAMA 2000;283:2260–5.
[25] Majdak EJ, Debniak J, Milczek T, Cornelisse CJ, Devilee P, Emerich J, et al. Prognostic impact of BRCA1 pathogenic and BRCA1/BRCA2 unclassified variant mutations in patients with ovarian carcinoma. Cancer 2005;104:1004–12.
[26] Chetrit A, Hirsh-Yechezkel G, Ben-David Y, Lubin F, Friedman E, Sadetzki S. Effect of BRCA1/2 mutations on long-term survival of patients with invasive ovarian cancer: the national Israeli study of ovarian cancer. J Clin Oncol 2008;26:20–5.
[27] Johannsson OT, Ranstam J, Borg A, Olsson H. Survival of BRCA1 breast and ovarian cancer patients: a population-based study from southern Sweden. J Clin Oncol 1998;16:397–404.
[28] Pharoah PD, Easton DF, Stockton DL, Gayther S, Ponder BA. Survival in familial, BRCA1-associated, and BRCA2-associated epithelial ovarian cancer. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) Familial Ovarian Cancer Study Group. Cancer Res 1999;59:868–71.
[29] Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet 1998;62:676–89.
[30] Berchuck A, Heron KA, Carney ME, Lancaster JM, Fraser EG, Vinson VL, et al. Frequency of germline and somatic BRCA1 mutations in ovarian cancer. Clin Cancer Res 1998;4:2433–7.
[31] Merajver SD, Pham TM, Caduff RF, Chen M, Poy EL, Cooney KA, et al. Somatic mutations in the BRCA1 gene in sporadic ovarian tumours. Nat Genet 1995;9:439–43.
[32] Takahashi H, Behbakht K, McGovern PE, Chiu HC, Couch FJ, Weber BL, et al. Mutation analysis of the BRCA1 gene in ovarian cancers. Cancer Res 1995;55:2998–3002.
[33] Matsushima M, Kobayashi K, Emi M, Saito H, Saito J, Suzumori K, et al. Mutation analysis of the BRCA1 gene in 76 Japanese ovarian cancer patients: four germline mutations, but no evidence of somatic mutation. Hum Mol Genet 1995;4:1953–6.
[34] Futreal PA, Liu Q, Shattuck-Eidens D, Cochran C, Harshman K, Tavtigian S, et al. BRCA1 mutations in primary breast and ovarian carcinomas. Science 1994;266:120–2.
[35] Weberpals JI, Clark-Knowles KV, Vanderhyden BC. Sporadic epithelial ovarian cancer: clinical relevance of BRCA1 inhibition in the DNA damage and repair pathway. J Clin Oncol 2008;26:3259–67.
[36] Robson ME, Chappuis PO, Satagopan J, Wong N, Boyd J, Goffin JR, et al. A combined analysis of outcome following breast cancer: differences in survival based on BRCA1/BRCA2 mutation status and administration of adjuvant treatment. Breast Cancer Res 2004;6:R8–17.
[37] Goffin JR, Chappuis PO, Begin LR, Wong N, Brunet JS, Hamel N, et al. Impact of germline BRCA1 mutations and overexpression of p53 on prognosis and response to treatment following breast carcinoma: 10-year follow up data. Cancer 2003;97:527–36.

[38] Brekelmans CTM, Seynaeve C, Menke-Pluymers M, Bruggenwirth HT, Tilanus-Linthorst MMA, Bartels CCM, et al. Survival and prognostic factors in BRCA1-associated breast cancer. Ann Oncol 2006;17:391–400.
[39] Stoppa-Lyonnet D, Ansquer Y, Dreyfus H, Gautier C, Gauthier-Villars M, Bourstyn E, et al. Familial invasive breast cancers: worse outcome related to BRCA1 mutations. J Clin Oncol 2000;18:4053–9.
[40] Lee JS, Wacholder S, Struewing JP, McAdams M, Pee D, Brody LC, et al. Survival after breast cancer in Ashkenazi Jewish BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 1999;91:259–63 [see comments].
[41] Verhoog LC, Brekelmans CT, Seynaeve C, van den Bosch LM, Dahmen G, van Geel AN, et al. Survival and tumour characteristics of breast-cancer patients with germline mutations of BRCA1. Lancet 1998;351:316–21.
[42] Narod SA, Foulkes WD. BRCA1 and BRCA2: 1994 and beyond. Nat Rev Cancer 2004;4:665–76.
[43] Scully R, Livingston D. In search of the tumour-suppressor functions of BRCA1 and BRCA2. Nature 2000;408:429–32.
[44] Bertwistle D, Ashworth A. Functions of the BRCA1 and BRCA2 genes. Curr Opin Genet Dev 1998;8:14–20.
[45] Venkitaraman AR. Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell 2002;108:171–82.
[46] Welcsh PL, King MC. BRCA1 and BRCA2 and the genetics of breast and ovarian cancer. Hum Mol Genet 2001;10:705–13.
[47] Deng CX, Brodie SG. Roles of BRCA1 and its interacting proteins. Bioessays 2000;22:728–37.
[48] Dapic V, Monteiro AN. Functional implications of BRCA1 for early detection, prevention, and treatment of breast cancer. Crit Rev Eukaryot Gene Expr 2006;16:233–52.
[49] Moynahan ME, Chiu JW, Koller BH, Jasin M. Brca1 controls homology-directed DNA repair. Mol Cell 1999;4:511–8.
[50] Jackson SP, Bartek J. The DNA-damage response in human biology and disease. Nature 2009;461:1071–8.
[51] Arnaudeau C, Lundin C, Helleday T. DNA double-strand breaks associated with replication forks are predominantly repaired by homologous recombination involving an exchange mechanism in mammalian cells. J Mol Biol 2001;307:1235–45.
[52] Paull TT, Rogakou EP, Yamazaki V, Kirchgessner CU, Gellert M, Bonner WM. A critical role for histone H2AX in recruitment of repair factors to nuclear foci after DNA damage. Curr Biol 2000;10:886–95.
[53] Rogakou EP, Pilch DR, Orr AH, Ivanova VS, Bonner WM. DNA double-stranded breaks induce histone H2AX phosphorylation on serine 139. J Biol Chem 1998;273:5858–68.
[54] Rogakou EP, Boon C, Redon C, Bonner WM. Megabase chromatin domains involved in DNA double-strand breaks in vivo. J Cell Biol 1999;146:905–16.
[55] Bhattacharyya A, Ear US, Koller BH, Weichselbaum RR, Bishop DK. The breast cancer susceptibility gene BRCA1 is required for subnuclear assembly of Rad51 and survival following treatment with the DNA cross-linking agent cisplatin. J Biol Chem 2000;275:23899–903.
[56] Lundin C, Schultz N, Arnaudeau C, Mohindra A, Hansen LT, Helleday T. RAD51 is involved in repair of damage associated with DNA replication in mammalian cells. J Mol Biol 2003;328:521–35.
[57] Scully R, Chen J, Plug A, Xiao Y, Weaver D, Feunteun J, et al. Association of BRCA1 with Rad51 in mitotic and meiotic cells. Cell 1997;88:265–75.
[58] Baumann P, Benson FE, West SC. Human Rad51 protein promotes ATP-dependent homologous pairing and strand transfer reactions in vitro. Cell 1996;87:757–66.
[59] Deng CX. BRCA1: cell cycle checkpoint, genetic instability, DNA damage response and cancer evolution. Nucleic Acids Res 2006;34:1416–26.
[60] Monteiro AN. BRCA1: exploring the links to transcription. Trends Biochem Sci 2000;25:469–74.
[61] Monteiro AN. Participation of BRCA1 in the DNA repair response... via transcription. Cancer Biol Ther 2002;1:187–8.
[62] Ouchi T, Monteiro AN, August A, Aaronson SA, Hanafusa H. BRCA1 regulates p53-dependent gene expression. Proc Natl Acad Sci USA 1998;95:2302–6.
[63] MacLachlan TK, Somasundaram K, Sgagias M, Shifman Y, Muschel RJ, Cowan KH, et al. BRCA1 effects on the cell cycle and the DNA damage response are linked to altered gene expression. J Biol Chem 2000;275:2777–85 [in Process Citation].
[64] MacLachlan TK, Takimoto R, El-Deiry WS. BRCA1 directs a selective p53-dependent transcriptional response towards growth arrest and DNA repair targets. Mol Cell Biol 2002;22:4280–92.
[65] Somasundaram K, Zhang H, Zeng YX, Houvras Y, Peng Y, Zhang H, et al. Arrest of the cell cycle by the tumour-suppressor BRCA1 requires the CDK-inhibitor p21WAF1/CiP1. Nature 1997;389:187–90.
[66] Takimoto R, MacLachlan TK, Dicker DT, Niitsu Y, Mori T, El Deiry WS. BRCA1 transcriptionally regulates damaged DNA binding protein (DDB2) in the DNA repair response following UV-irradiation. Cancer Biol Ther 2002;1:177–86.
[67] Zhang H, Somasundaram K, Peng Y, Tian H, Zhang H, Bi D, et al. BRCA1 physically associates with p53 and stimulates its transcriptional activity. Oncogene 1998;16:1713–21.
[68] Welcsh PL, Owens KN, King MC. Insights into the functions of BRCA1 and BRCA2. Trends Genet 2000;16:69–74.
[69] Welcsh PL, Lee MK, Gonzalez-Hernandez RM, Black DJ, Mahadevappa M, Swisher EM, et al. BRCA1 transcriptionally regulates genes involved in breast tumorigenesis. Proc Natl Acad Sci USA 2002;99:7560–5.
[70] Quinn JE, Kennedy RD, Mullan PB, Gilmore PM, Carty M, Johnston PG, et al. BRCA1 functions as a differential modulator of chemotherapy-induced apoptosis. Cancer Res 2003;63:6221–8.
[71] Yamada HY, Gorbsky GJ. Spindle checkpoint function and cellular sensitivity to antimitotic drugs. Mol Cancer Ther 2006;5:2963–9.
[72] Schiff PB, Horwitz SB. Taxol stabilizes microtubules in mouse fibroblast cells. Proc Natl Acad Sci USA 1980;77:1561–5.
[73] Jordan MA, Toso RJ, Thrower D, Wilson L. Mechanism of mitotic block and inhibition of cell proliferation by taxol at low concentrations. Proc Natl Acad Sci USA 1993;90:9552–6.
[74] Long BH, Fairchild CR. Paclitaxel inhibits progression of mitotic cells to G1 phase by interference with spindle formation without affecting other microtubule functions during anaphase and telephase. Cancer Res 1994;54:4355–61.
[75] Jordan MA, Wendell K, Gardiner S, Derry WB, Copp H, Wilson L. Mitotic block induced in HeLa cells by low concentrations of paclitaxel (Taxol) results in abnormal mitotic exit and apoptotic cell death. Cancer Res 1996;56:816–25.
[76] Trielli MO, Andreassen PR, Lacroix FB, Margolis RL. Differential Taxol-dependent arrest of transformed and nontransformed cells in the G1 phase of the cell cycle, and specific-related mortality of transformed cells. J Cell Biol 1996;135:689–700.
[77] Wassmann K, Benezra R. Mitotic checkpoints: from yeast to cancer. Curr Opin Genet Dev 2001;11:83–90.
[78] Sudo T, Nitta M, Saya H, Ueno NT. Dependence of paclitaxel sensitivity on a functional spindle assembly checkpoint. Cancer Res 2004;64:2502–8.
[79] Anand S, Penrhyn-Lowe S, Venkitaraman AR. AURORA-A amplification overrides the mitotic spindle assembly checkpoint, inducing resistance to Taxol. Cancer Cell 2003;3:51–62.
[80] Gascoigne KE, Taylor SS. Cancer cells display profound intra- and interline variation following prolonged exposure to antimitotic drugs. Cancer Cell 2008;14:111–22.
[81] Shi J, Orth JD, Mitchison T. Cell type variation in responses to antimitotic drugs that target microtubules and kinesin-5. Cancer Res 2008;68:3269–76.
[82] McGuire WP, Rowinsky EK, Rosenshein NB, Grumbine FC, Ettinger DS, Armstrong DK, et al. Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. Ann Intern Med 1989;111:273–9.
[83] De Ligio JT, Velkova A, Zorio DA, Monteiro AN. Can the status of the breast and ovarian cancer susceptibility gene 1 product (BRCA1) predict response to taxane-based cancer therapy? Anticancer Agents Med Chem 2009;9:543–9.
[84] Mullan PB, Quinn JE, Gilmore PM, McWilliams S, Andrews H, Gervin C, et al. BRCA1 and GADD45 mediated G2/M cell cycle arrest in response to antimicrotubule agents. Oncogene 2001;20:6123–31.
[85] Lafarge S, Sylvain V, Ferrara M, Bignon YJ. Inhibition of BRCA1 leads to increased chemoresistance to microtubule-interfering agents, an effect that involves the JNK pathway. Oncogene 2001;20:6597–606.
[86] Chabalier C, Lamare C, Racca C, Privat M, Valette A, Larminat F. BRCA1 downregulation leads to premature inactivation of spindle checkpoint and confers paclitaxel resistance. Cell Cycle 2006;5:1001–7.
[87] Gilmore PM, McCabe N, Quinn JE, Kennedy RD, Gorski JJ, Andrews HN, et al. BRCA1 interacts with and is required for paclitaxel-induced activation of mitogen-activated protein kinase kinase kinase 3. Cancer Res 2004;64:4148–54.
[88] Tassone P, Tagliaferri P, Perricelli A, Blotta S, Quaresima B, Martelli ML, et al. BRCA1 expression modulates chemosensitivity of BRCA1-defective HCC1937 human breast cancer cells. Br J Cancer 2003;88:1285–91.
[89] Gilmore PM, Quinn JE, Mullan PB, Andrews HN, McCabe N, Carty M, et al. Role played by BRCA1 in regulating the cellular response to stress. Biochem Soc Trans 2003;31:257–62.
[90] Harkin DP, Bean JM, Miklos D, Song YH, Truong VB, Englert C, et al. Induction of GADD45 and JNK/SAPK-dependent apoptosis following inducible expression of BRCA1. Cell 1999;97:575–86.
[91] Rosell R, Skrzypski M, Jassem E, Taron M, Bartolucci R, Sanchez JJ, et al. BRCA1: a novel prognostic factor in resected non-small-cell lung cancer. PLoS One 2007;2:e1129.
[92] Bartolucci R, Wei J, Sanchez JJ, Perez-Roca L, Chaib I, Puma F, et al. XPG mRNA expression levels modulate prognosis in resected non-small-cell lung cancer in conjunction with BRCA1 and ERCC1 expression. Clin Lung Cancer 2009;10:47–52.
[93] Taron M, Rosell R, Felip E, Mendez P, Souglakos J, Ronco MS, et al. BRCA1 mRNA expression levels as an indicator of chemoresistance in lung cancer. Hum Mol Genet 2004;13:2443–9.
[94] Wachters FM, Wong LSM, Timens W, Kampinga HH, Groen HJM. ERCC1, hRad51, and BRCA1 protein expression in relation to tumour response and survival of stage III/IV NSCLC patients treated with chemotherapy. Lung Cancer 2005;50:211–9.
[95] Wang L, Wei J, Qian X, Yin H, Zhao Y, Yu L, et al. ERCC1 and BRCA1 mRNA expression levels in metastatic malignant effusions is associated with chemosensitivity to cisplatin and/or docetaxel. BMC Cancer 2008;8:97.
[96] Boukovinas I, Papadaki C, Mendez P, Taron M, Mavroudis D, Koutsopoulos A, et al. Tumor BRCA1, RRM1 and RRM2 mRNA expression levels and clinical response to first-line gemcitabine plus docetaxel in non-small-cell lung cancer patients. PLoS One 2008;3:e3695.
[97] Quinn JE, James CR, Stewart GE, Mulligan JM, White P, Chang GKF, et al. BRCA1 mRNA expression levels predict for overall survival in ovarian cancer after chemotherapy. Clin Cancer Res 2007;13:7413–20.

[98] Husain A, He G, Venkatraman ES, Spriggs DR. BRCA1 up-regulation is associated with repair-mediated resistance to cis-diamminedichloroplatinum(II). Cancer Res 1998;58:1120–3.
[99] Stordal B, Davey R. A systematic review of genes involved in the inverse resistance relationship between cisplatin and paclitaxel chemotherapy: role of BRCA1. Curr Cancer Drug Targets 2009;9:354–65.
[100] Chu G. Cellular responses to cisplatin. The roles of DNA-binding proteins and DNA repair. J Biol Chem 1994;269:787–90.
[101] Helleday T, Petermann E, Lundin C, Hodgson B, Sharma RA. DNA repair pathways as targets for cancer therapy. Nat Rev Cancer 2008;8:193–204.
[102] McHugh PJ, Sones WR, Hartley JA. Repair of intermediate structures produced at DNA interstrand cross-links in *Saccharomyces cerevisiae*. Mol Cell Biol 2000;20:3425–33.
[103] Sargent RG, Brenneman MA, Wilson JH. Repair of site-specific double-strand breaks in a mammalian chromosome by homologous and illegitimate recombination. Mol Cell Biol 1997;17:267–77.
[104] Phillips JW, Morgan WF. Illegitimate recombination induced by DNA double-strand breaks in a mammalian chromosome. Mol Cell Biol 1994;14:5794–803.
[105] Plooy AC, van DM, Berends F, Lohman PH. Formation and repair of DNA interstrand cross-links in relation to cytotoxicity and unscheduled DNA synthesis induced in control and mutant human cells treated with cis-diamminedichloroplatinum(II). Cancer Res 1985;45:4178–84.
[106] Rosenberg B. Fundamental studies with cisplatin. Cancer 1985;55:2303–6.
[107] Kelland L. The resurgence of platinum-based cancer chemotherapy. Nat Rev Cancer 2007;7:573–84.
[108] Kennedy RD, Quinn JE, Mullan PB, Johnston PG, Harkin DP. The role of BRCA1 in the cellular response to chemotherapy. J Natl Cancer Inst 2004;96:1659–68.
[109] Fedier A, Steiner RA, Schwarz VA, Lenherr L, Haller U, Fink D. The effect of loss of Brca1 on the sensitivity to anticancer agents in p53-deficient cells. Int J Oncol 2003;22:1169–73.
[110] Sylvain V, Lafarge S, Bignon YJ. Dominant-negative activity of a Brca1 truncation mutant: effects on proliferation, tumorigenicity in vivo, and chemosensitivity in a mouse ovarian cancer cell line. Int J Oncol 2002;20:845–53.
[111] Chappuis PO, Goffin J, Wong N, Perret C, Ghadirian P, Tonin PN, et al. A significant response to neoadjuvant chemotherapy in BRCA1/2 related breast cancer. J Med Genet 2002;39:608–10.
[112] Shafee N, Smith CR, Wei S, Kim Y, Mills GB, Hortobagyi GN, et al. Cancer stem cells contribute to cisplatin resistance in Brca1/p53-mediated mouse mammary tumors. Cancer Res 2008;68:3243–50.
[113] Tassone P, Di Martino MT, Ventura M, Pietragalla A, Cucinotto I, Calimeri T, et al. Loss of BRCA1 function increases the antitumor activity of cisplatin against human breast cancer xenografts in vivo. Cancer Biol Ther 2009;8:648–53.
[114] Moiseyenko VM, Protsenko SA, Brezhnev NV, Maximov SY, Gershveld ED, Hudyakova MA, et al. High sensitivity of BRCA1-associated tumors to cisplatin monotherapy: report of two cases. Cancer Genet Cytogenet 2010;197:91–4.
[115] Byrski T, Gronwald J, Huzarski T, Grzybowska E, Budryk M, Stawicka M, et al. Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy. J Clin Oncol 2010;28:375–9.
[116] Byrski T, Huzarski T, Dent R, Gronwald J, Zuziak D, Cybulski C, et al. Response to neoadjuvant therapy with cisplatin in BRCA1-positive breast cancer patients. Breast Cancer Res Treat 2009;115:359–63.
[117] Silver DP, Richardson AL, Eklund AC, Wang ZC, Szallasi Z, Li Q, et al. Efficacy of neoadjuvant cisplatin in triple-negative breast cancer. J Clin Oncol 2010;28:1145–53.
[118] Borst P, Rottenberg S, Jonkers J. How do real tumors become resistant to cisplatin? Cell Cycle 2008;7:1353–9.
[119] Edwards SL, Brough R, Lord CJ, Natrajan R, Vatcheva R, Levine DA, et al. Resistance to therapy caused by intragenic deletion in BRCA2. Nature 2008;451:1111–5.
[120] Sakai W, Swisher EM, Jacquemont C, Chandramohan KV, Couch FJ, Langdon SP, et al. Functional restoration of BRCA2 protein by secondary BRCA2 mutations in BRCA2-mutated ovarian carcinoma. Cancer Res 2009;69:6381–6.
[121] Sakai W, Swisher EM, Karlan BY, Agarwal MK, Higgins J, Friedman C, et al. Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. Nature 2008;451:1116–20.
[122] Swisher EM, Sakai W, Karlan BY, Wurz K, Urban N, Taniguchi T. Secondary BRCA1 mutations in BRCA1-mutated ovarian carcinomas with platinum resistance. Cancer Res 2008;68:2581–6.
[123] Ashworth A. Drug resistance caused by reversion mutation. Cancer Res 2008;68:10021–3.
[124] Dobzhansky T. Genetics of natural populations. XIII. Recombination and variability in populations of *Drosophila pseudoobscura*. Genetics 1946;31:269–90.
[125] Lucchesi JC. Synthetic lethality and semi-lethality among functionally related mutants of *Drosophila melanogaster*. Genetics 1968;59:37–44.
[126] Pan X, Ye P, Yuan DS, Wang X, Bader JS, Boeke JD. A DNA integrity network in the yeast *Saccharomyces cerevisiae*. Cell 2006;124:1069–81.
[127] Boone C, Bussey H, Andrews BJ. Exploring genetic interactions and networks with yeast. Nat Rev Genet 2007;8:437–49.
[128] Hartman JL, Garvik B, Hartwell L. Principles for the buffering of genetic variation. Science 2001;291:1001–4.
[129] Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434:917–21.
[130] de Murcia JMn, Niedergang C, Trucco C, Ricoul Ml, Dutrillaux B, Mark M, et al. Requirement of poly(ADP-ribose) polymerase in recovery from DNA damage in mice and in cells. Proc Natl Acad Sci USA 1997;94:7303–7.
[131] Wang ZQ, Stingl L, Morrison C, Jantsch M, Los M, Schulze-Osthoff K, et al. PARP is important for genomic stability but dispensable in apoptosis. Genes Dev 1997;11:2347–58.
[132] Conde C, Mark M, Oliver FJ, Huber A, de Murcia G, Menissier-de Murcia J. Loss of poly(ADP-ribose) polymerase-1 causes increased tumour latency in p53-deficient mice. EMBO J 2001;20:3535–43.
[133] Schultz N, Lopez E, Saleh-Gohari N, Helleday T. Poly(ADP-ribose) polymerase (PARP-1) has a controlling role in homologous recombination. Nucleic Acids Res 2003;31:4959–64.
[134] Dantzer F, Schreiber V, Niedergang C, Trucco C, Flatter E, De La Rubia G, et al. Involvement of poly(ADP-ribose) polymerase in base excision repair. Biochimie 1999;81:69–75.
[135] Wang ZQ, Auer B, Stingl L, Berghammer H, Haidacher D, Schweiger M, et al. Mice lacking ADPRT and poly(ADP-ribosyl)ation develop normally but are susceptible to skin disease. Genes Dev 1995;9:509–20.
[136] Ding R, Pommier Y, Kang VH, Smulson M. Depletion of poly(ADP-ribose) polymerase by antisense RNA expression results in a delay in DNA strand break rejoining. J Biol Chem 1992;267:12804–12.
[137] Petrini JH. The mammalian Mre11-Rad50-nbs1 protein complex: integration of functions in the cellular DNA-damage response. Am J Hum Genet 1999;64:1264–9.
[138] Ferguson DO, Alt FW. DNA double strand break repair and chromosomal translocation: lessons from animal models. Oncogene 2001;20:5572–9.
[139] Khanna KK, Jackson SP. DNA double-strand breaks: signaling, repair and the cancer connection. Nat Genet 2001;27:247–54.
[140] D'Amours D, Jackson SP. The Mre11 complex: at the crossroads of dna repair and checkpoint signalling. Nat Rev Mol Cell Biol 2002;3:317–27.
[141] Moynahan ME, Pierce AJ, Jasin M. BRCA2 is required for homology-directed repair of chromosomal breaks. Mol Cell 2001;7:263–72.
[142] Tutt A, Bertwistle D, Valentine J, Gabriel A, Swift S, Ross G, et al. Mutation in Brca2 stimulates error-prone homology-directed repair of DNA double-strand breaks occurring between repeated sequences. EMBO J 2001;20:4704–16.
[143] Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 2005;434:913–7.
[144] Rottenberg S, Jaspers JE, Kersbergen A, van der Burg E, Nygren AO, Zander SA, et al. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. Proc Natl Acad Sci USA 2008;105:17079–84.
[145] Miknyoczki SJ, Jones-Bolin S, Pritchard S, Hunter K, Zhao H, Wan W, et al. Chemopotentiation of temozolomide, irinotecan, and cisplatin activity by CEP-6800, a poly(ADP-ribose) polymerase inhibitor. Mol Cancer Ther 2003;2:371–82.
[146] Donawho CK, Luo Y, Luo Y, Penning TD, Bauch JL, Bouska JJ, et al. ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models. Clin Cancer Res 2007;13:2728–37.
[147] Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 2009;361:123–34.
[148] Southan GJ, Szabo C. Poly(ADP-ribose) polymerase inhibitors. Curr Med Chem 2003;10:321–40.
[149] Rankin PW, Jacobson EL, Benjamin RC, Moss J, Jacobson MK. Quantitative studies of inhibitors of ADP-ribosylation in vitro and in vivo. J Biol Chem 1989;264:4312–7.
[150] Ratnam K, Low JA. Current development of clinical inhibitors of poly(ADP-ribose) polymerase in oncology. Clin Cancer Res 2007;13:1383–8.
[151] Mendes-Pereira AM, Martin SA, Brough R, McCarthy A, Taylor JR, Kim JS, et al. Synthetic lethal targeting of PTEN mutant cells with PARP inhibitors. EMBO Mol Med 2009;1:315–22.
[152] Bartz SR, Zhang Z, Burchard J, Imakura M, Martin M, Palmieri A, et al. Small interfering RNA screens reveal enhanced cisplatin cytotoxicity in tumor cells having both BRCA network and TP53 disruptions. Mol Cell Biol 2006;26:9377–86.
[153] Kaelin Jr WG. The concept of synthetic lethality in the context of anticancer therapy. Nat Rev Cancer 2005;5:689–98.
[154] Kennedy RD, D'Andrea AD. DNA repair pathways in clinical practice: lessons from pediatric cancer susceptibility syndromes. J Clin Oncol 2006;24:3799–808.