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A DNA Repair Protein BRCA1 as a Potentially Molecular Target for the Anticancer Platinum Drug Cisplatin

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1. Introduction

Cancer is a leading cause of death in the world. The incidence of cancers is related to environmental factors, behavioral patterns, and genetic disorders. Cancer therapy usually aims to selectively destroy cancer cells while sparing normal tissue. Most chemotherapeutic agents function by damaging cancer cell DNA. The cellular responses to DNA damage are thus critical factors for determining the effectiveness of most cancer therapies (Ashworth, 2008). When normal cells are exposed to damage, DNA repair mechanism is induced. The DNA repair processes are the cellular responses associated with the restoration of the normal DNA nucleotide sequences. The DNA repair activity of the cell is an important determinant of a cells sensitivity to chemotherapeutic agents. It is known that resistance to DNA-damaging agents can be associated with increased cellular repair activities, while defects in DNA repair pathways result in hypersensitivity to damage (Kelley & Fishel, 2008; Quinn et al., 2003, 2009). Several studies have clearly demonstrated that the impairment or absence of genes or proteins responsible for DNA damage repair, frequently causes genomic instability, cell cycle arrest and apoptosis. The importance of these repair pathways is highlighted by the fact that more than 100 genes have been found in mammalian cells that are involved in some way in DNA damage repair pathways. The breast cancer susceptibility gene 1 (*BRCA1*) is a tumor suppressor gene involved in maintaining genomic integrity through multiple functions in DNA damage repair, transcriptional regulation, a cell cycle checkpoint and protein ubiquitination (Brzovic et al., 2001; Hashizume et al., 2001; Mark et al., 2005; Varma et al., 2005; Williams et al., 2004). In cancer cells, damage to *BRCA1* by the anticancer platinum drug cisplatin may lead to a loss of such functions and ultimately results in cancer cell death. In addition, preclinical and clinical studies have recently revealed that inactivation of the BRCA1 protein in cancer cells leads to chemosensitivity. Therefore, approaching the BRCA1 protein as a potential therapeutic target for cisplatin or other such platinum based drugs might be of interest for molecular-targeted cancer therapy. In this chapter, the biophysical characterization and functional consequences of the human *BRCA1* gene and the BRCA1 RING protein induced by cisplatin are described.

2. Breast cancer susceptibility gene 1 (*BRCA1*) and its encoded protein

In 1990, chromosome 17q21 was identified by linkage analysis as the location of a breast cancer susceptibility gene 1 or *BRCA1* (Hall et al., 1990). The entire gene covers approximately 100 kb

of genomic sequence, and was subsequently cloned four years later (Miki et al., 1994). BRCA1 is a tumor suppressor gene composed of 24 exons, with an mRNA that is 7.8 kb in length, and 22 coding exons that translate into a protein of 1863 amino acids (Fig. 1) with a molecular weight of 220 kDa (Brzovic et al., 1998). It has 3 major domains, including (1) the N-terminal RING finger domain (BRCA1 RING domain), (2) the large central segment with the nuclear localization signal (NLS), and (3) the BRCA1 C-terminal domain (BRCT). The BRCA1 protein plays an essential role in maintaining genomic stability associated with a number of cellular processes, including DNA repair, a cell cycle checkpoint, transcriptional regulation, and protein ubiquitination (Huen et al., 2010; O'Donovan & Livingston, 2010).

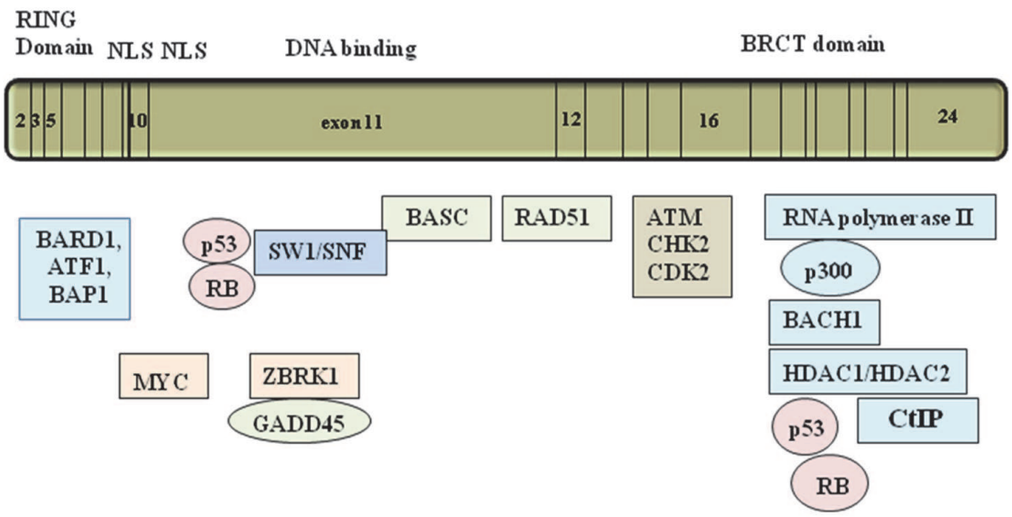


Fig. 1. Scheme of BRCA1 mRNA and sites of protein interaction

2.1 The BRCA1 RING domain

The N-terminal RING finger domain contains the conservative sequences of cysteine and histidine residues (C_3HC_4) necessary for specific coordination with two Zn^{2+} ions. The first 109 amino acids of BRCA1 protein constitute a protease-resistance domain. The solution structure of the BRCA1 RING domain revealed the existence of antiparallel α-helices at both ends, flanking the central RING motif (residues 24-64) and was characterized by a short antiparallel three-stranded β-sheet, and two large Zn^{2+}-binding loops, and a central α-helix (Brzovic et al., 2001)The two Zn^{2+}-binding sites are formed in an interleaved fashion in which the first and third pairs of cysteines (Cys24, Cys27, Cys44, and Cys47) form site I, and the second and fourth pairs of cysteines and a histidine (Cys39, His41, Cys61, and Cys64) form site II. It is an important domain since it might mediate a central role in macromolecular interactions to exert the tumor suppression functions. The solution structure together with yeast-two-hybrid studies revealed that the BRCA1 RING domain preferentially formed a heterodimeric complex with another RING domain BARD1 (BRCA1-associated RING domain 1) through an extensive four-helix-bundle interface (Brzovic et al., 2001; Wu et al., 1996). The binding interface is composed of residues 8-22 and 81-96 of BRCA1, and residues 36-48 and 101-116 of BARD1. The BRCA1-BARD1 complex requires each other for their mutual stabilities, and they are co-localized in nuclear dots during S phase but not the G phase of the cell cycle and in nuclear foci (Hashizume et al., 2001). The

progression to S phase by aggregation of nuclear BRCA1 and BARD1 implied the importance of both proteins for a DNA repair function (Jin et al., 1997). The BRCA1-BARD1 complex also exhibits enzymatic activity of an E3 ubiquitin ligase that specifically transfers ubiquitin to protein substrates that are essential for cellular viability (Hashizume et al., 2001; Xia et al., 2003). Cancer-predisposing mutations in the Zn^{2+}-binding sites were demonstrated not only to alter the affinity for Zn^{2+} and the native BRCA1 RING structure but also abolished the interaction with BARD1 and the E3 ligase activity (Morris et al., 2006). The results supported the importance of Zn^{2+} as a structural component, as it obviously played a critical role in the stabilization of the structure and function of the BRCA1 RING domain.

2.2 The large central segment of BRCA1

The central segment of BRCA1 covers exon 11 (approximately 3500 bp) and constitutes approximately 60 percent of the coding region of the gene. Deletion of exon 11 results in removal of the nuclear localization signal of BRCA1. Biophysical characterization revealed that this domain was intrinsically disordered or natively unfolded under physiological conditions. This might potentially allow the BRCA1 central region to act as a long flexible scaffold, to mediate interactions with DNA, and perhaps a number of other proteins involved in the DNA damage response and repair (Mark et al., 2005). The reported binding partners to the central region were c-Myc, RB, p53, FANCA, RAD50, RAD51, JunB, and BRCA2 (Rosen et al., 2003). Recently, the BRCA1 central region has been shown to efficiently interact with p53, and stimulate p53-mediated DNA binding and transcriptional activities (Buck, 2008). This result indicated that the BRCA1 central segment facilitated the induction of cell cycle arrest and apoptosis in response to DNA damage. Furthermore, the association between the central region of BRCA1 and PALB2 (partner and localizer of BRCA2, also known as FANCN) was observed primarily through apolar bonding between their respective coiled-coil domains (Sy et al., 2009). PALB2 binds directly to BRCA1, and serves as the molecular scaffold for the formation of the BRCA1-PALB2-BRCA2 complex. BRCA1 mutations (L1407P and M1411T) identified in cancer patients were shown to disrupt the specific interaction between BRCA1 and PALB2, resulting in a defective homologous recombination (HR) repair and a compromised cell survival after DNA damage (Sy et al., 2009).

2.3 The BRCA1 C-terminal domain

The C-terminal region (residues 1646-1863) of BRCA1 contains two BRCT (BRCA1 C-terminal) domains in tandem (motif 1: amino acids 1653-1736; motif 2: amino acids 1760-1855). Each BRCT domain is characterized by a central, parallel four-stranded β-sheet with a pair of α-helices (α1 and α3) packed against one face, and a single α-helix (α2) packed against the opposite face of the sheet (Williams et al., 2001). The two BRCA1-BRCT repeats interact in a head-to-tail fashion. This domain serves as a multipurpose protein-protein interaction module that binds to other BRCT repeats or other protein domains with apparently unrelated structures (Watts & Brissett, 2010). Based on its physical interactions with other proteins, BRCA1 has been implicated in a wide array of cellular functions, including cell cycle regulation, DNA damage response, transcriptional regulation, replication and recombination, and higher chromatin hierarchical control (Starita & Parvin, 2003). The BRCA1-BRCT domain has been identified as a phosphopeptide recognition module, and is demonstrated to bind to the phosphorylated protein partners (BACH1 and

CtIP, containing the consensus sequence pSer-X-X-Phe) that is involved mainly in the control of the G2/M phase checkpoint and DNA damage repair (Varma et al., 2005; Williams et al., 2004). Several cancer-predisposing mutations in the BRCA1-BRCT domain resulted in destabilization of the structural integrity at the BRCT active sites, and abolished their affinities to synthetic BACH1 and CtIP phosphopeptides (Rowling et al., 2010). These findings provide a better understanding of the pathogenic BRCA1 mutations on functional mechanisms and tumorigenesis.

3. BRCA1 and DNA damage repair

A substantial amount of evidence that has implicated BRCA1 in the DNA damage repair pathways has been documented. BRCA1 co-localizes with RAD51 and BARD1 to nuclear foci (sites associated with repair of DNA caused by the damaging agents or γ-irradiation) (Hashizume et al., 2001; Scully et al., 1997). The nuclear foci is marked by the histone variant H2AX that was phosphorylated on Ser139 (known as γH2AX) (Rogakou et al., 1998). γH2AX is one of the initial recruiting factors for various checkpoints and DNA repair proteins, including Abraxas, RAP80, and BRCA1, at sites of DNA breaks (Foulkes, 2010). The H2AX signaling cascade begins to emerge with the finding that MDC1 (mediator of DNA damage checkpoint 1) is the main downstream factor in the pathway, and is required for the damage-induced focal accumulation of a number of DNA damage repair factors at the DNA breaks (Stucki et al., 2005).

BRCA1 plays a role in maintaining genome integrity through its role in DNA damage repair. Several observations have implicated BRCA1 in homologous recombination (HR), non-homologous end-joining (NHEJ and nucleotide excision repair (NER). A role for BRCA1 in HR-mediated repair is involved through its stable complex formation with BRCA2, which has a well-defined role in HR through its direct interaction with RAD51 (Bhattacharyya et al., 2000). RAD51 (the mammalian homolog of the Escherichia coli RecA protein) is a DNA recombinase that catalyzes strand exchange in an early step of HR (Baumann et al., 1996). PALB2 (the partner and localizer of BRCA2) has recently been identified as the bridging factor required for the BRCA1-BRCA2 association (Rahman et al., 2007). The BRCA1-PALB2 interaction was mediated by their respective coiled-coil domains, and was found to promote HR-mediated repair (Rahman et al., 2007). Importantly, missense mutations identified in the PALB2-binding region on BRCA1 disrupted the specific interaction of BRCA1 with PALB2, and compromised DNA repair in a gene conversion assay (Sy et al., 2009). Although these studies have revealed a molecular link between BRCA1 function and HR-mediated repair, the mechanism by which BRCA1 promotes HR through the PALB2-BRCA2-RAD51 axis remains unclear.

As an alternative to HR, there is a growing body of evidences, to indicate that a component of NHEJ is regulated by BRCA1. The exact role of BRCA1 in NHEJ, however, has not been well defined (Zhang & Powell, 2005). In the NHEJ pathway, the DNA-dependent protein kinase catalytic subunit (DNA-PKcs) and a Ku heterodimer of Ku80 and Ku70 are recruited to the sites of DNA DSBs for preparing the DNA ends before ligation by the XRCC4 ligase IV. The most possible explanation for BRCA1 being involved in NHEJ is its association with a NHEJ factor Ku80 (Chiba & Parvin, 2001; Wei et al., 2008). Many studies have provided strong evidences that the NHEJ pathway was impaired, both in vivo and in vitro, in BRCA1-deficient mouse embryonic fibroblasts and in the human breast cancer cell line HCC1937 which carries a homozygous mutation in the BRCA1 gene (Bau et al., 2004; Zhong et al., 2002).

4. BRCA1 and transcriptional regulation

As described earlier, BRCA1 contains a C-terminal transactivation domain as was first defined using the yeast two-hybrid system (Chapman & Verma, 1996; Monteiro et al., 1996). The transactivation domain was mapped to the region of the protein encoded by exons 21-24 using deletion constructs of BRCA1 fused to the GAL4 DNA binding domain. The BRCA1-BRCT domain has been implicated in the regulation of transcription of several genes responsible for DNA damage. The ability of BRCA1 to act as either a co-activator or a co-repressor of transcription may involve its ability to recruit the basal transcriptional machinery and other proteins that have been implicated in chromatin remodeling (Mullan et al., 2006). BRCA1 was capable of activating the p21 promoter (Somasundaram et al., 1997). One report claimed that BRCA1 participated in the stabilization of p53 in response to DNA damage, and served as a co-activator for p53 (Zhang et al., 1998). The interaction of BRCA1 and p53 potentially resulted in the redirection of p53-mediated transactivation from a pro-apoptotic target to genes involved in DNA repair and cell cycle arrest (Zhang et al., 1998). In addition, BRCA1 has been shown to interact with the RNA polymerase II holoenzyme (Scully et al., 1997). However, BRCA1 could repress the transcription of an estrogen receptor α (ERα) and its downstream estrogen responsive genes (Fan et al., 1999). The transcriptional repression activity of BRCA1 for ERα occurs by the association of the N-terminus of BRCA1 (residues 1-300) with the C-terminal activation function (AF-2) of ERα. Breast cancer-associated mutations of BRCA1 were found to abolish its ability to inhibit ERα activity (Fan et al., 2001). The repression activity exerted by BRCA1 involved the ability of BRCA1 to down-regulate levels of the transcriptional coactivator p300, which has also been shown to interact with the AF-2 domain of ERα (Fan et al., 2002). Further investigations revealed that overexpression of BRCA1 could inhibit the recruitment of the co-activators [steroid receptor co-activator 1 (SRC1), and amplified breast cancer 1 (AIB1)], and enhanced the recruitment of a co-repressor [histone deacetylase 1 (HDAC1)] to the progesterone response elements (PRE) of c-Myc.

5. BRCA1 and protein ubiquitination

The BRCA1 protein displays an E3 ubiquitin ligase activity through its RING domain, and this activity is enhanced when it exists as a heterodimer with the BARD1 RING domain (Xia et al., 2003). In vitro and in vivo studies have indicated that the BRCA1-BARD1 complex was capable of autoubiquitination that paradoxically stabilized the protein complex, and that also activated its in vitro E3 ligase activity with other proteins (Chen et al., 2002; Wu-Baer et al., 2010). However, the substrate specificity of the BRCA1 E3 ligase activity and its biological relevance to tumor suppression function are still unknown. Putative substrates for ubiquitination by the BRCA1-BARD1 RING complexes have recently emerged from in vitro and in vivo studies such as the nucleosomal histones H2A and its variant H2AX, RNA polymerase II, γ-tubulin, nucleophosmin/B23, and estrogen receptor α (ERα) (Eakin et al., 2007; Horwitz et al., 2007; Parvin, 2009; Sato et al., 2004; Starita et al., 2005; Thakar et al., 2010). BRCA1 can form a RING heterodimer E3 ligase activity with BARD1, and this is required for the recruitment of BRCA2 and RAD51 to damaged sites for HR repair (Ransburgh et al., 2010). Many cancer-predisposing mutations in the BRCA1 RING domain, that inhibited the E3 ligase activity and its ability to accumulate at damaged sites, were defective in homologous recombination that is critical for tumor suppression (Morris et al.,

2006, 2009; Ransburgh et al., 2010). Moreover, BRCA1 accumulation at the sites of DSBs occurred rapidly (within 20 s), and the RING structure was required (residue 1-200 of BRCA1) for the rapid recruitment with Ku80 at damaged sites in response to non-homologous end joining (Wei et al., 2008). Missense mutations in the BRCA1 RING domain significantly reduced their accumulations at DSBs, and abolished the association with Ku80. Therefore, the loss of the BRCA1 E3 ligase activity rendered cancerous cells hypersensitive to DNA-damaging agents,and clearly demonstrated a significant role for ubiquitnation in the DNA damage response and DNA repair activity (Ransburgh et al., 2010; Ruffner et al., 2001). Thus ubiquitination is involved in key steps that properly conduct the DNA repair process after DSBs.

Several reports have shown that the BRCA1 E3 ligase was capable of in vitro monoubiquitination of histones H2A and its variant H2AX (Thakar et al., 2010). This implied a BRCA1 function in regulating chromatin structure in the context of transcriptional regulation and DNA repair. Hyperphosphorylated RNA polymerase II (RNAPII) at its carboxyl terminal domain (CTD), consists of multiple repeats of the heptapeptide (YSPTSPS), involved in a generalized response to UV irradiation. It also served as a substrate for the BRCA1-dependent ubiquitination that was proposed to facilitate BRCA1 function in DNA repair by inhibiting DNA transcription, and then recruiting other DNA repair proteins at a lesion (Starita et al., 2005). Recently, It was found that the BRCA1-mediated ubiquitination of RNAPII prevented a stable association of some transcription factors (TFIIE and TFIIH) in the transcriptional preinitiation complex, and thus blocked the initiation of mRNA synthesis (Horwitz et al., 2007). Ubiquitination of the preinitiation complex was not targeting proteins for degradation by proteasome but rather the ubiquitin moiety itself interfered with the assembly of basal transcription factors at the promoter (Horwitz et al., 2007). Nucleoplasmin B23 and γ-tubulin were found to be the candidate substrates of the BRCA1 E3 ligase activity in vivo (Parvin, 2009; Sato et al., 2004). Both proteins were present in centrosomes, and apparently were not targeted for degradation by BRCA1-mediated modifications. The results indicated that ubiquitination of nucleoplasmin B23 and γ-tubulin played a vital role in regulating the centrosome number and maintenance of genomic stability by unknown mechanisms. Recently, the BRCA1 protein has been shown to inhibit ERα transcriptional activity, and to induce repression of estrogen response genes and cell proliferation (Xu et al., 2005). A potential explanation for the regulation of estrogen signaling by BRCA1 was the ERα ubiquitination and degradation mediated by the BRCA1 E3 ligase activity (Dizin & Irminger-Finger, 2010; Eakin et al., 2007). Conversely, the BRCA1-associated protein 1 (BAP1) is a deubiquitinating enzyme that can interact with the BRCA1 RING domain (Jensen et al., 1998). It was shown that BAP1 inhibited the BRCA1 autoubiquitination, and the nucleophosmin/B23 ubiquitination mediated by the BRCA1 E3 ligase activity (Nishikawa et al., 2009). Down-regulation of BAP1 in cells also resulted in the retardation of the S phase and ionizing irradiation hypersensitivity, a phenotype similar to BRCA1 deficiency. This again indicated that the BRCA1-BARD1 complex and the BAP1 protein coordinately regulated ubiquitination during a DNA damage response and the cell cycle.

6. Cisplatin

Cisplatin [*cis*-diamminedichloroplatinum(II)] is the platinum-based anticancer drug and is most effective in the treatment of metastatic testiscular cancers, ovarian, head, neck, bladder,

cervical and lung cancers (Kelland, 2007). Although widely used as a well established anticancer drug in cancer chemotherapy, cisplatin displays major toxic side effects, such as nephrotoxicity, nausea and vomiting and neurotoxicity. In addition to its toxic side effects, a major limitation of cisplatin chemotherapy is the development of genetic mechanisms of resistance. The effectiveness of cisplatin depends on the drug uptake, and the actual amount that reacts with cellular targets.

6.1 Cisplatin-DNA adducts

It is generally accepted that DNA is the most important intracellular target of cisplatin. When cisplatin is dissolved in aqueous solution, chloride ions are displaced to allow the formation of aquated species, which are the reactive forms of the compound (Pinto and Lippard, 1985). The concentration of chloride ions influences the reactivity of cisplatin. After intravenous administration it is relatively less reactive in the extracellular space where the physiological chloride concentration is about 100 mM, but on crossing the plasma membrane, it is activated in the intracellular space where the chloride concentration drops to 2-3 mM. Chlorine groups of cisplatin are easily replaced by water molecules to allow the formation of aqauted species in a stepwise manner. Activated cisplatin is a potent electrophile that will react with any nucleophile, including the sulfhydryl groups on proteins and nucleophilic groups on nucleic acids. DNA is attacked by activated cisplatin at guanine residues in position N7, in double stranded DNA from the side of the major groove. The attack is apparently preceeded by an electrostatic attraction between the positively charged platinum (II) complex and the negatively charged phosphodeoxyribose DNA backbone and facilitated by bidirectional diffusion along the backbone. The initial attack of DNA by activated cisplatin is followed by the replacement of the remaining chloro ligand before the adduct forms an intramolecular attack on a second purine residue (either guanine or adenine). The hydration rate constant of the monoaqua form was faster than that of diaqua form ($2.38x10^{-5}$ s^{-1} compared to $1.4x10^{-5}$ s^{-1}) (Cubo et al., 2009).

The anticancer activity of cisplatin potentially results from the modification of DNA through a covalent cross-link or platinum (Pt)-DNA adduct (Fig. 2). The DNA adducts interfere with DNA replication and transcription, and ultimately lead to cell death by cancer (Ahmad, 2010; Wang & Lippard, 2005). The predominant adducts formed by cisplatin in vitro are 1,2-intrastrand crosslinks. Quantitative studies show that the 1,2-intrastrand d(GpG), and d(ApG) crosslinks account for 65% and 25%, respectively (Fichtinger-Schepman et al., 1985; Eastman, 1986). They alter the DNA structure, block replication and transcription and activate a programmed cell death (apoptosis). X-ray diffraction of the crosslinked dinucleotide *cis*-$Pt(NH_3)_2$[d(pGpG)] reveals that the intrastrand cisplatin crosslink produces a severe local distortion in the DNA double helix, leading to unwinding and kinking. These crosslinks bend and unwind the duplex. The altered structure is recognized by high-mobility-group (HMG) proteins and other proteins. The binding of HMG proteins to cisplatin-modified DNA has been postulated to potentiate the anticancer activity of the drug.

6.2 Cisplatin-protein adducts

The interaction of cisplatin with proteins is of particular significance, and is believed to play an important role in distribution of the drug and the inactivation responsible for determining its efficacy and toxicity (Casini et al., 2008; Sun et al., 2009; Timerbaev et al., 2006). It is intriguing, that protein adducts affect some crucial aspects of protein structure

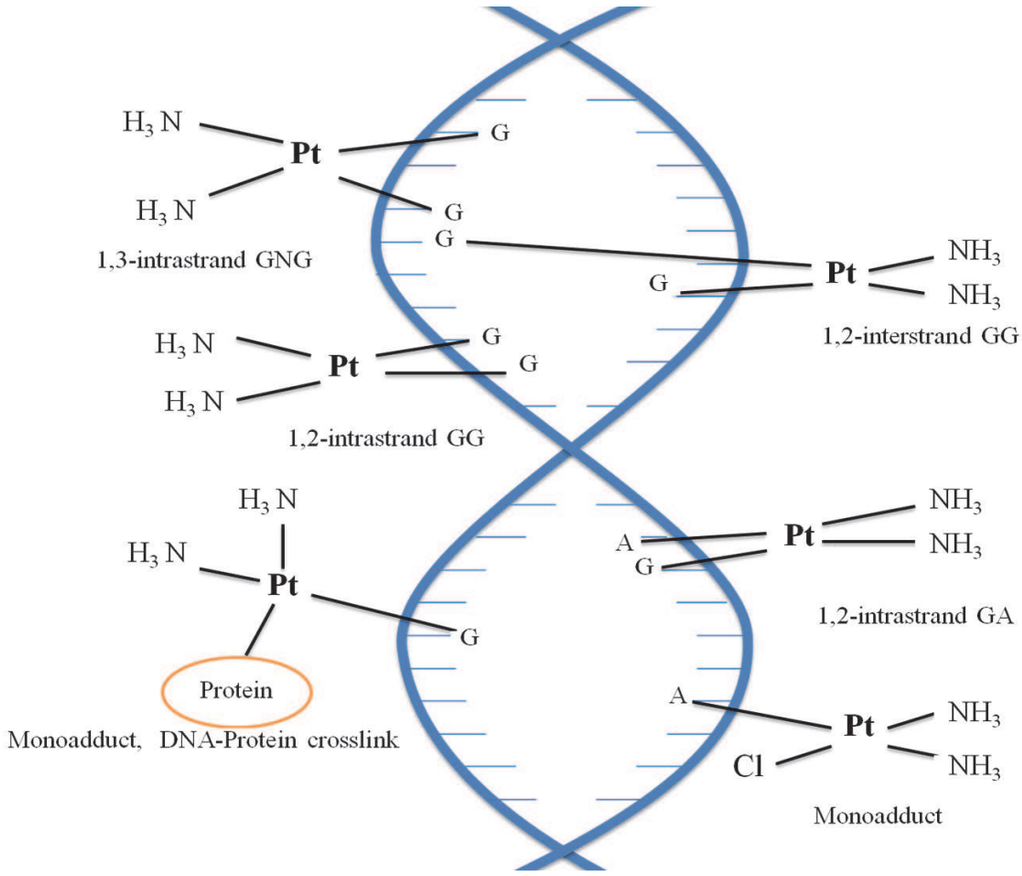


Fig. 2. Common cisplatin-DNA adducts

and functions. For instance, the platination of human serum albumin caused partial unfolding of the protein structure at a high drug concentration, and induced intermolecular crosslinks possibly at Cys34 and/or Met298 via bifunctional adducts or via NH_3 release (Ivanov et al., 1998; Neault & Tajmir-Riahi, 1998). Myoglobin, a small protein, containing a heme group required for the transport of oxygen in skeletal muscles and myocardial cells, formed intramolecular mono- and bi-functional adducts with cisplatin. Its putative platinum-binding sites were His116 and His119 (Zhao & King, 2010). A number of intramolecular crosslinks also occurred with ubiquitin adducts (Casini et al., 2009). The loss of activity of the C-terminal heat shock protein 90 after protein aggregation was reported to be a consequence of cisplatin binding but it did not exhibit any conformational change (Ishidaa et al., 2008). It is intriguing, that cisplatin can cause a structural perturbation of a synthetic peptide containing a Zn^{2+} finger domain. The platinum coordinates to Zn^{2+}-binding sites to induce Zn^{2+} ejection and subsequently the loss of the protein tertiary structure. This implies that cisplatin can inhibit critical biological functions regulated by Zn^{2+} finger proteins. Such a mechanism has been discussed in the apoptosis process mediated by the interaction of cisplatin and platinum-based compounds with Zn^{2+} finger transcriptional factors (Bose et al., 2005). Likewise, the nucleocapsid Zn^{2+} finger NCp7 protein, a protein required for the recognition and packaging of viral RNA, became attached to some platinum compounds, when its ability to bind nucleic acid was changed and prevented viral infectivity (de Paula et al., 2009; Musah, 2004).

7. *BRCA1* and its encoded product as potentially molecular targets for cisplatin for cancer therapy

In recent years, there has been significant progress made in evaluating what happens when BRCA1 is inactivated so it cannot respond to DNA damage in cancer cells, in other words, taking advantage of the inherent weakness of the BRCA1 dysfunction in cancer cells. These cells have increased sensitivity to DNA-damaging agents that eventually result in major genomic instability and cell death (Amir et al., 2010; Ashworth, 2008; Helleday et al., 2008; Lieberman, 2008; Powell & Bindra, 2009; Quinn et al., 2009; Tassone et al., 2009; Zhu et al., 2009). Cancerous cells with inactivated BRCA1 had defects in DNA repair of double strand breaks (DSBs) (Farmer et al., 2005; Kennedy et al., 2004; Litman et al., 2008). Moreover, extensive investigations have revealed the relevance of the BRCA1-mediated ubiquitination to DNA repair functions. Mutations in the BRCA1 RING domain resulted in the loss of the E3 ubiquitin ligase activity, and conferred hypersensitivity of the cancerous cells to DNA-damaged chemotherapy and γ-irradiation (Ransburgh et al., 2010; Ruffer et al., 2001; Wei et al., 2008).

It was initially reported that overexpression of BRCA1 in the human breast cancer MCF7 cell line resulted in an increased resistance to cisplatin (Husain et al., 1998). Furthermore, antisense or siRNA-based inhibition of endogenous BRCA1 expression promoted the increased sensitivity to cisplatin that was associated with the decreased DNA repair by NER and an increased apoptosis (Lafarge et al., 2001; Quinn et al., 2003). This indicates that the reduced BRCA1 expression observed in sporadic cancers may also be exploited for DNA damage-based chemotherapy (James et al., 2007; Quinn et al., 2009). In a similar situation, BRCA1-deficient mouse embryonic stem cells displayed defective DNA repair and a 100-fold increased sensitivity to the alkylating agent mitomycin C and cisplatin than those containing wild-type BRCA1 (Bhattacharyya et al., 2000; Moynahan et al., 2001). This sensitivity was reversed upon correction of the BRCA1 mutation in mouse embryonic fibroblast cells with a disrupted BRCA1 (Fedier et al., 2003). Reconstitution of BRCA1 in the cells via transfection meant that BRCA1 functions were regained, and resulted in a reduced level of cancer cell death, following treatment with cisplatin or other DNA damaging agents (Quinn et al., 2003). Moreover, more recent evidence has revealed the implication of BRCA1 in cisplatin-resistant breast and ovarian cancer cell lines. These cells that acquired resistance to DNA-damaging agents was mediated by a secondary mutation in BRCA1. This mutation restored the BRCA1 protein expression and function for DNA repair, causing the cancer cells to become more tolerant to cisplatin (Swisher et al., 2008; Tassone et al., 2003; Wang & Figg, 2008). Recently, a number of clinical studies have examined the utilization of this BRCA1 dysfunction in response to the DNA-damaging drug cisplatin. A pathological complete response (pCR) with excellent compliance was observed in cancer patients with BRCA1 mutations (Byrski et al., 2009; Font et al., 2010; Quinn et al., 2007; Silver et al., 2010; Taron et al., 2004). This indicates that patients with BRCA1 dysfunction gain more benefit from treatments that exert their effects by causing DNA damage.

Therefore, it is important to continue elucidating *BRCA1*/BRCA1-dependent pathways to design molecular–targeted therapy for the platinum treatment of cancer cells by taking advantage of their impairment of the *BRCA1*/BRCA1 repair capacity and BRCA1-dependent ubiquitination inactivated by cisplatin.

7.1 Cellular repair of cisplatin-damaged *BRCA1*

Preliminary results from our laboratory have indicated that the cisplatin-modified *BRCA1* gene sequence was resistant to restriction endonuclease cleavage, and indicated that cisplatin preferentially formed 1,2-intrastrand d(GpG) cross-links (Ratanaphan et al., 2009). The drug inhibited *BRCA1* amplification in a dose-dependent manner. It has been found that cisplatin-treated, *BRCA1* exon 11, of adenocarcinoma MCF-7 cells exhibited a time dependent recovery after drug exposure to the cells at 37°C for 6 h, with an initial low level of lesion removal during the first 4 h (Fig. 3). A more complete lesion removal was observed with over 90% of 50 μM cisplatin after 18 h of repair time. However, only 30% of the lesion repair was observed at a higher cisplatin concentration of 200 μM (Ratanaphan et al., 2009).

From a host cell reactivation assay, the result indicated that a reduction in cellular reactivation of the drug-damaged reporter gene encoding plasmid was a consequence of an increase in platination levels within the transcribed reporter gene. This indicated that the cellular response to cisplatin reflected its intrinsically low capacity for removal of cisplatin-*BRCA1* adducts. Following cisplatin-induced *BRCA1* adducts, a number of cellular repair proteins, excluding BRCA1, are responsible for recognizing and processing the removal of DNA damage. NER is a major process for removing platinum-damaged DNA. This process requires an ATP-dependent multiple protein complex that recognizes the bending induced on DNA by cisplatin. The NER complex has a dual role that can unwind the DNA strands (helicase), and excise the damage strand (endonuclease) of about 24-32 nucleotides in length, containing a platinum lesion. DNA resynthesis factors are recruited at the site of the incised DNA, and employ the opposite strand as template to fill in the gap in concert with DNA ligases. Two distinct sub-pathways of NER that may be involved, are transcription-coupled repair (TCR) and/or global genomic repair (GGR). TCR preferentially repairs transcribed strands of the RNA polymerase II-transcribed active gene, while GGR repairs throughout the genome (Shuck et al., 2008). Recently, the suppression of ERCC1 expression in a HeLa S3 cell line by small interfering RNA (siRNA) led to a decrease in the repair activity of cisplatin-induced DNA damage along with a decrease in cell viability against platinum-

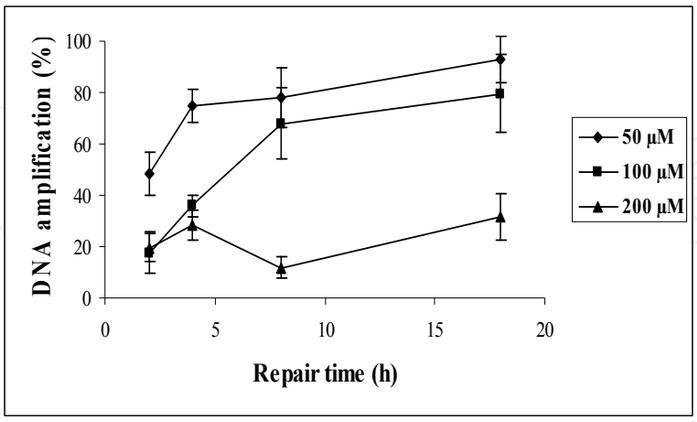


Fig. 3. Cellular repair of cisplatin-damaged 3,426-bp *BRCA1* exon 11. MCF-7 cells were incubated with medium plus cisplatin at various concentrations (50–200 μM) for 6 h. The cells were washed twice with PBS and fresh medium was added. The genomic DNA was then extracted at 2, 4, 8 and 18 h and used as the template for the QPCR assay (Ratanaphan et al., 2005, 2009).

based drugs (Chang et al., 2005). Recombination pathways can also be involved as repair systems responsible for DNA damage induced by the anticancer drug cisplatin. Recombination-deficient *E. coli* mutants were sensitive to cisplatin and exhibited a decreased survival by four orders of magnitude in comparison with the parental strain at a cisplatin concentration of 75-80 μM (Zdraveski et al., 2000). Many recombination-deficient strains showed a sensitivity to the drug equal to that of the NER-deficient strains. Double mutations in recombination and NER proteins were approximately 4-fold more sensitive to cisplatin than the corresponding single mutants. This indicates that recombination and NER pathways play roles that are independent of each other in protecting cells from cisplatin-induced damage. Impaired recombination DNA repair in yeast and prostate cancer cell lines also showed an increased sensitivity to cisplatin (Wang et al., 2005).

7.2 Inhibition of *BRCA1* transcriptional transactivation

The one hybrid GAL4 transcription assay is used to study the effect of cisplatin on transcriptional transactivation. The level of transcriptional transactivation is inversely proportional to the amount of platinum-*BRCA1* adducts. The results are most likely due to inhibition of transcription of the reporter plasmid that resulted from interstrand crosslinks (Ratanaphan et al., 2009). The transcriptional transactivation activity of *BRCA1* has previously been reported by fusing the C-terminal domain of *BRCA1* to a heterogenous DNA-binding domain (Chapman and Verma, 1996). The BRCT domain (amino acids 1380-1863) of human *BRCA1* scores positively in transcriptional activation trap experiments using various forms of so-called "one hybrid assay".The *BRCA1*-fused DNA-binding domain activates transcription in a cell-free system to a similar extent as a dose of the powerful activator, VP16 (Scully et al., 1997). A *GAL4:BRCA1* has also been introduced in yeast- and mammalian-based transcription assays to characterize the deleterious mutations in the 3/ -terminal region of the *BRCA1* (Vallon-Christersson et al., 2001). The transcriptional activity reflects a tumor-suppressing function of the BRCA1 protein.

In order to investigate whether the drug-damaged *BRCA1* is able to transactivate the expression of a firefly luciferase gene, DNA repair-proficient MCF-7 cells were transiently transfected with the cisplatin-damaged pBIND-BRCT along with the reporter plasmid pG5Luc. The firefly luciferase activity was significantly decreased at a cisplatin concentration of 12.5 μM (Fig. 4).

It has been hypothesized that the BRCT domain could transactivate the expression of another reporter gene. The reporter gene pSV-β-galactosidase was used for this purpose. It was of interest, that the level of transactivation was significantly higher when co-transfected with the pBIND-BRCT than with the parental pBIND (Fig. 5). This indicated that the GAL4-BRCT domain may stimulate the pSV-β-galactosidase. However, the expression of β-galactosidase was decreased to the level of β-galactosidase alone when co-transfected with the platinated pBIND-BRCT. It was again of interest that, β-galactosidase expression was dramatically diminished when both the pSV-β-galactosidase and the pBIND-BRCT were platinated (Fig. 6). Expression of β-galactosidase from the pSV-β-galactosidase can be transactivated both by the GAL4 domain of the pBIND and pBIND-BRCT. Acting upon the GAL4 DNA sequence similarity, the GAL4 protein alone can stimulate the expression of β-galactosidase. However, the degree of transactivation was slightly higher by the pBIND-BRCT. This indicates that the BRCT domain on the fusion protein is able to transactivate the β-galactosidase gene-bearing pSV-β-galactosidase. When platinated pSV-β-galactosidase is co-transfected with the pBIND

or the pBIND-BRCT, a relatively lower expression of β-galactosidase was observed. The transcription level of β-galactosidase expression was reduced from 2-2.5 fold to 1.3 fold in both plasmids. Considering the data from the proficiency in repairing cisplatin-*BRCA1* adducts, it demonstrated that over 80% of the DNA lesion was repaired 8 h after cisplatin removal. Thus, it is possible that, during the repair time, RNA polymerase II or other transcriptional machineries may be blocked at any lesion on DNA (Jung & Lippard, 2003, 2006; Tornaletti et al., 2003).

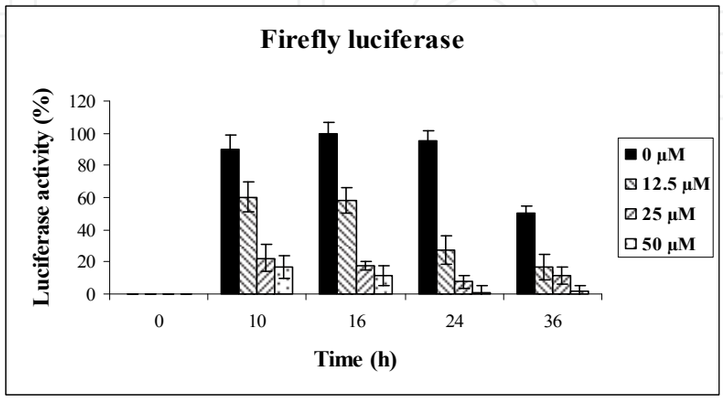


Fig. 4. Time course of firefly luciferase expression. The pBIND-BRCT was incubated with cisplatin at concentrations of 0, 12.5, 25 and 50 µM and then co-transfected with the pG5Luc plasmid into MCF-7 cells. A cell lysate was prepared at 10, 16, 24 and 36 h after transfection. Firefly luciferase expression is detected by the Dual-Luciferase® Reporter Assay System. The data were derived from four independent experiments ± standard deviations (SD) (Ratanaphan et al., 2009).

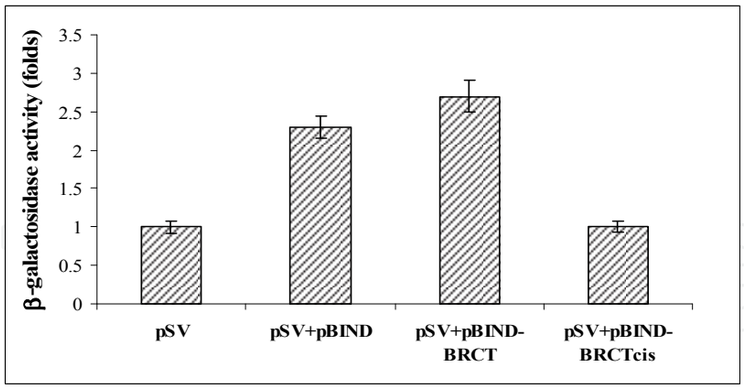


Fig. 5. Transcriptional transactivation. The pBIND or pBIND-BRCT was co-transfected with pSV-β-galactosidase. Cell lysates were prepared at 16 h after transfection. β-galactosidase activity was detected using the β-galactosidase assay. The data were derived from four independent experiments ± standard deviations (SD) (Ratanaphan et al., 2009).

Several investigations have revealed transcriptional inhibition on DNA templates, containing the site-specific Pt-DNA adducts. The mammalian RNA polymerase II and *E. coli* RNA polymerase did not catalyze the transcriptional reactions when the DNA template strands carried the 1,2-intrastrand d(GpG) and d(ApG) adducts, whereas those polymerases

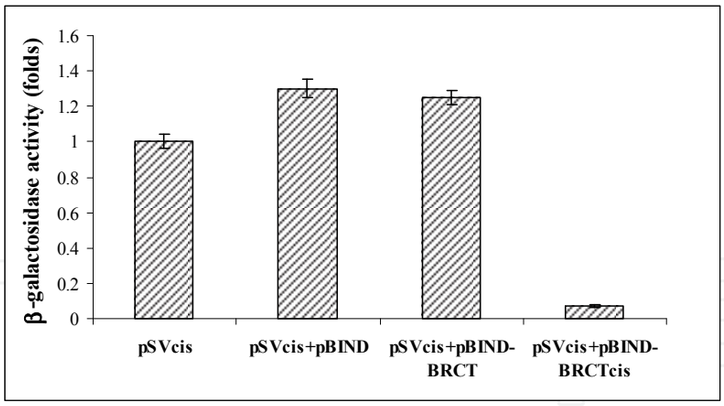


Fig. 6. Transcriptional transactivation of platinated pBIND-BRCT on platinated pSV-β-galactosidase. The platinated pSV-β-galactosidase (with cisplatin at a concentration of 12.5 μM) was co-transfected with non-platinated pBIND and pBIND-BRCT or platinated pBIND-BRCT. Cell lysates were prepared at 16 h after transfection. β-galactosidase expression was detected using the β-galactosidase assay. The data were derived from four independent experiments ± standard deviations (SD) (Ratanaphan et al., 2009).

could transcribe the complementary templates which had no DNA lesions on the template strands (Corda et al., 1991). Transcription of globally platinated DNA templates by SP6 and T7 RNA polymerases were also blocked primarily at 1,2-d(GpG) and d(ApG) Pt adducts, and to a lesser extent at the interstrand crosslink (Tornaletti, 2005). Bifunctional Pt-DNA adducts were much more effective at impeding transcription progression than monofunctional DNA adducts (Tornaletti, 2005). Moreover, cisplatin caused a dose-dependent inhibition of mRNA synthesis. Treatment of human fibroblast cells with 50 μM cisplatin for 24 h resulted in a 55% decrease in mRNA level and a reduced expression of $p21^{WAF1}$ protein. This indicated that cisplatin inhibited the transcription of the *$p21^{WAF1}$* gene (Ljungman et al., 1999). Recently, the processing of site-specific Pt-DNA crosslinks in mammalian cells was investigated (Ang et al., 2010). Site-specific platinated oligonucleotides, containing 1,2-d(GpG) and 1,3-d(GpTpG) adducts, were inserted into an expression vector between its promoter and a luciferase reporter gene. Transcription inhibitions that occurred by blocking passage of the RNA polymerase complex through the 1,2-d(GpG) and 1,3-d(GpTpG) adducts were 50% and 37.7% of the unplatinated controls for vectors, repectively. An X-ray crystal structure of RNA polymerase II showed stalling at the 1,2-intrastrand d(GpG) crosslink to explain the physical block of transcription by the cisplatin-DNA adduct (Damsma et al., 2007). Disruption of chromatin remodeling was another mechanism by which a cisplatin adduct could interfere with transcription. Nucleosomal DNA, containing the 1,2-d(GpG) or 1,3-d(GpTpG) intrastrand crosslinks, enforced a characteristic rotational positioning of the DNA around the histone octamer such that the Pt adduct faced inward towards the histone core (Ober and Lippard, 2008). Increased solvent accessibility of the platinated DNA strand was observed, and this indicated it might be caused by a structural perturbation in proximity of the DNA lesion. In addition, the nucleosomes treated with cisplatin exhibited a significant decrease in heat-induced mobility (Wu et al., 2008). These effects also indicated that a cisplatin assault could inhibit transcription by altering the native nucleosomal organization, and limiting the nucleosomal sliding that protected access of the RNA polymerase to the DNA template.

It has been suggested that inhibition of transcription by cisplatin was a critical determinant of cell-cycle arrest in the G2 phase because cells could not synthesize the mRNA necessary to pass into mitosis, and this eventually led to apoptosis. Possible mechanisms to explain this inhibitory process can be divided into three categories; (1) hijack of transcription factors (2) physical block of RNA polymerase, and (3) inhibition of chromatin remodeling (Todd & Lippard, 2009). A number of proteins have been identified that specifically recognize the distorted Pt-DNA adducts, including transcription factors. The upstream binding factor (UBF), a member of the HMG-domain proteins, is a ribosomal RNA transcription factor. hUBF can bind the 1,2-intrastrand adducts with a high K_d of 60 pM (Jordan & Carmo-Fonseca, 1998). Treatment of DNA with cisplatin inhibited ribosomal RNA synthesis by competing with hUBF for its natural binding site in an in vitro transcription assay (Zhai et al., 1998). The TATA-binding protein (TBP) is a critical transcription factor for all three mammalian RNA polymerases (pol I, II, and III). TBP binding to the DNA duplex, containing the 1,2-intrastrand d(GpG) crosslinks of cisplatin, was similar to that of the TATA-promoter binding in terms of structural and affinity aspects with a K_d of 0.3 nM (Jung et al., 2001). It was shown that TBP interacted directly with cisplatin-damaged DNA, and the introduction of exogenous cisplatin-modified DNA into the HeLa whole cell extract could sequester TBP and inhibit transcription 3-to 4-fold more than undamaged DNA (Vichi et al., 1997). Collectively, the failure of RNA synthesis resulted from the hijack of transcription factors by Pt-DNA adducts, that prevented the assembly of transcriptional elongation complexes at their normal promoter sequence and inhibited the transcriptional process. Significant reduction in transcriptional transactivation of cisplatin-modified *BRCA1* in the presence of a second expression vector containing multiple cisplatin-damaged sites could address the lack of or the unavailability of cellular transcription factors at cisplatin-*BRCA1* lesions. Damage of *BRCA1*, if not properly repaired, may lead to its functional impairment in cancerous cells which ultimately induce programed cell death.

7.3 Cisplatin binding to the BRCA1 RING domain

The types of adduct formed with cisplatin are distinctive and dependent on the accessibility of the platinum center and protein side-chains (Ivanov et al., 1998; Peleg-Shulman et al., 2002). The BRCA1 RING domain has been found to form favourable intramolecular and intermolecular cross-links caused by cisplatin (Atipairin et al., 2010). Although cisplatin has been demonstrated to induce protein dimerization and has caused perturbations in some protein structures, the secondary structure of the BRCA1 RING domain in the apo-form was maintained and underwent more folded structural rearrangement after increasing cisplatin concentrations as judged by an increase in the negative CD spectra at 208 and 220 nm. It was possible that cisplatin might bind to the unoccupied Zn^{2+}-binding sites and caused the structural changes. The binding constant of the in vitro platination was $3.00 \pm 0.11 \times 10^6$ M^{-1}, and the free energy of binding (ΔG) was -8.68 kcal Mol^{-1}. In addition, the CD spectra of BRCA1 pre-incubated with Zn^{2+} gave identical profiles to indicate that cisplatin could interact with other residues rather than the Zn^{2+}-binding sites and barely affected the overall conformation of the Zn^{2+}-bound BRCA1. In order to locate the binding site of cisplatin on the BRCA1 (1-139) protein, in-gel tryptic digestion of the free BRCA1 and the cisplatin-BRCA1 adducts (molar ratio 1:1) were subjected to analysis by LC-MS. A unique fragment ion of 656.29^{2+} was obtained from the cisplatin-BRCA1 adduct digests. Tandem mass spectrometric analyses of this fragment ion indicated that the ion arose from

$[Pt(NH_3)_2(OH)]^+$ that was attached to a BRCA1 peptide ^{111}ENNSPEHLK^{119} (Fig. 7) (Berners-Price et al., 1992).

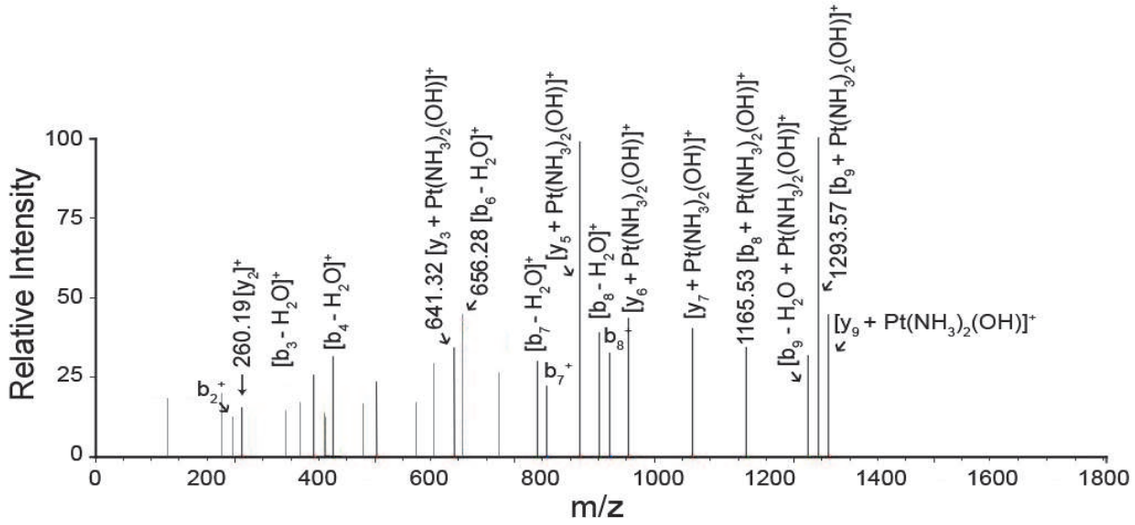


Fig. 7. The product-ion spectrum of the MS/MS analysis for the 656.29^{2+} ion. It indicated that $[Pt(NH_3)_2(OH)]^+$ is attached to a peptide ^{111}ENNSPEHLK^{119} of BRCA1 (Atipairin et al., 2010).

7.4 Thermal stability of the cisplatin-BRCA1 adducts

Thermal denaturation was monitored by circular dichroism (CD) to follow heat-induced unfolding which determined the effect of cisplatin binding on the stability of the BRCA1 RING domain. The BRCA1(1-139) protein pre-incubated with or without Zn^{2+} was incubated with cisplatin, and the CD spectra showed identical changes with an increase in ellipticity when the temperature was raised from 15°C to 95°C (Fig. 8). It indicated that the folded proteins gradually lost their ordered structures. When cooling to 20°C after being heated at 95°C, the CD spectrum partially recovered. This indicated that the reversibility of the unfolding/refolding process was incomplete. The melting temperatures of the BRCA1(1-139) proteins were about 74°C and 83°C in the absence and presence of Zn^{2+}, respectively (Fig. 9). This indicated that the BRCA1 RING domain was more thermostable by about 9°C upon Zn^{2+}-binding. Thus, it supported the important role of Zn^{2+} in the determination and stabilization of the local secondary structure in the RING domain. It was notable that cisplatin at a concentration of 10 μM had similar melting temperatures to those observed for Zn^{2+} binding to the BRCA1 RING domain. However, higher melting temperatures were observed at a 10-fold concentration of cisplatin (100 μM). These data indicated that cisplatin binding to the BRCA1 RING domain conferred an enhanced thermostability by 13°C. Resistance to thermal denaturation of the cisplatin-modifed BRCA1 RING domain might result from the favourably intramolecular and intermolecular crosslinks driven by the free energy (Atipairin et al., 2010).

7.5 Inactivation of BRCA1 E3 ligase activity by cisplatin

To gain further insights into the functional consequences of cisplatin-induced BRCA1, the BRCA1 RING protein was platinated in vitro by cisplatin at various concentrations. The results showed that the relative E3 ligase activity was inversely proportional to the

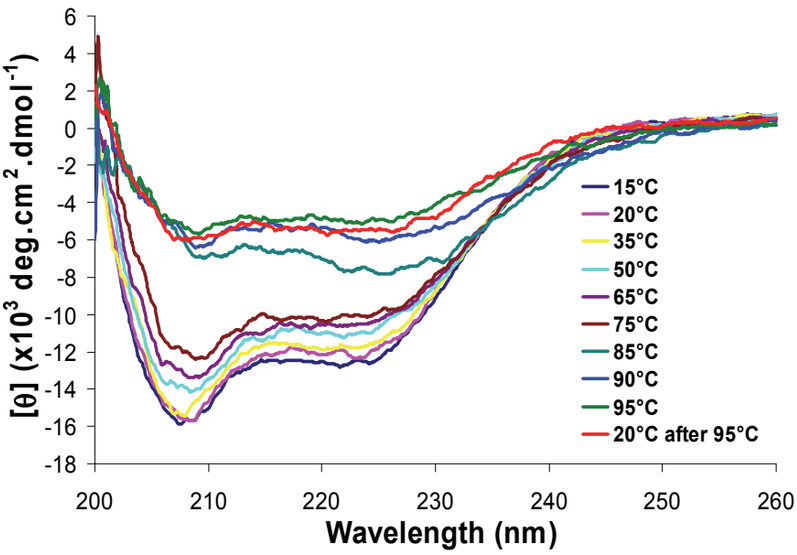


Fig. 8. Thermal transition of the cisplatin-BRCA1 adducts in the presence of Zn^{2+}. The BRCA1(1-139) proteins (10 μM) after pre-incubation with a 3 molar equivalent ratio of Zn^{2+} to protein were mixed with cisplatin concentrations of 10 μM. Samples were incubated in the dark at ambient temperature for 24 h. The measurements were performed from 15°C to 95°C with a heating rate of 1°C/min. After heating to 95°C, the measurement at 20°C was also performed. The CD spectra were plotted between the mean residue ellipticity and wavelength (Atipairin et al., 2010).

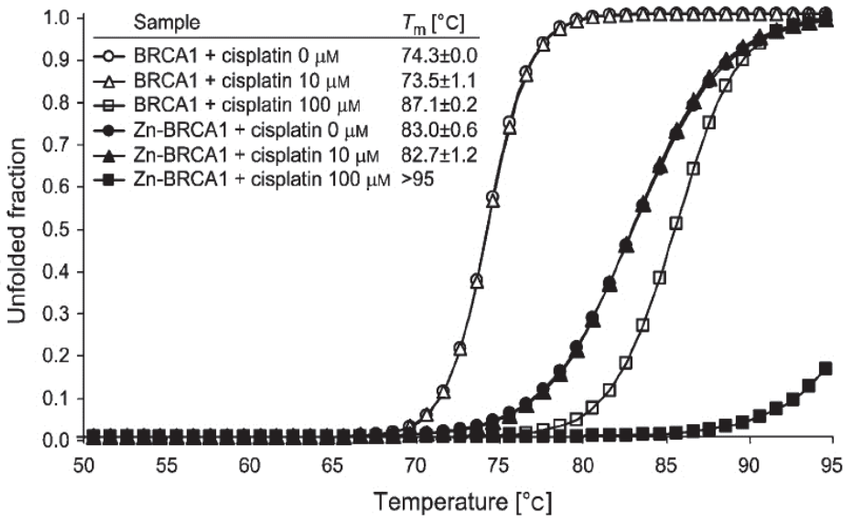


Fig. 9. Thermal denaturation curves of the cisplatin-BRCA1 adducts. The BRCA1(1-139) protein (10 μM) without Zn^{2+} and after pre-incubation with a 3 molar equivalent ratio of Zn^{2+} to protein were mixed with various concentrations of cisplatin (0, 10, and 100 μM). Samples were incubated in the dark at ambient temperature for 24 h before CD measurements. The CD signals at 208 nm were measured, and the unfolded fraction as a function of temperature was plotted (Atipairin et al., 2010).

concentration of the drug (Fig. 10). An increase in platinum concentration was accompanied by a high amount of BRCA1 adducts and a low amount of native BRCA1 protein. To address whether the inhibition of the E3 ligase activity resulted from the formation of BRCA1 adducts or a reduced amount of the BRCA1 subunit, a ten-fold excess amount of the platinated BRCA1 was assayed for the E3 ligase activity. The result demonstrated that platination of BRCA1 was indeed involved in the inhibition of the E3 ligase activity (Atipairin et al., 2011a).

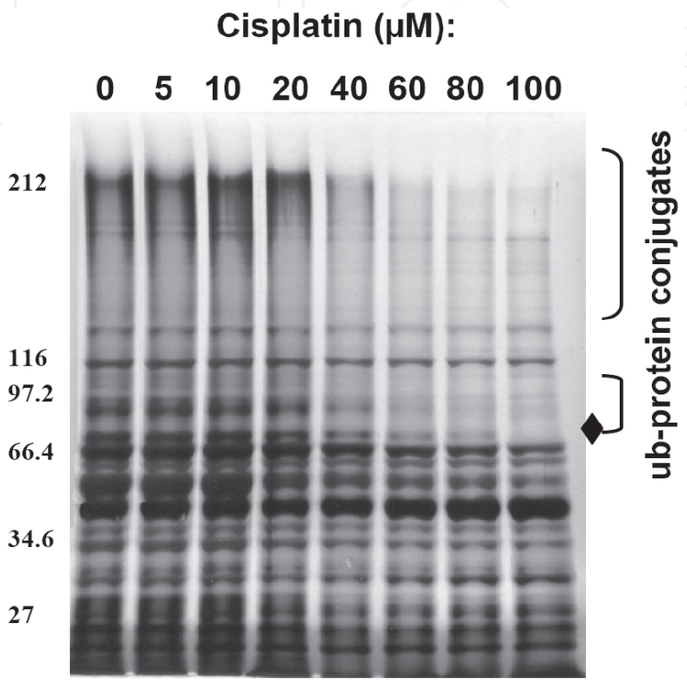


Fig. 10. *In vitro* ubiquitin ligase activity of cisplatin-BRCA1 complexes. Two μg of the drug-BRCA1 adducts with a number of defined concentrations of cisplatin was assayed for the ubiquitin ligase activitiy. An apparent ubiquitinated product (as indicated by the filled diamond) was markedly reduced as the concentration of platinum increased (Atipairin et al., 2011a).

8. Conclusion

We have demonstrated an in vitro inactivation of *BRCA1*/BRCA1 by the anticancer platinum drug cisplatin. The transcriptional activation of cisplatin-modified *BRCA1*, when tested in a "one-hybrid GAL4 transcriptional assay", was inversely proportional to cisplatin doses and was dramatically diminished in the presence of a second expression vector containing multiple cisplatin-damaged sites. This indicates a repair-mediated transcriptional transactivation of cisplatin-damaged *BRCA1* as well as the lack or unavailability of cellular transcription factors at cisplatin-*BRCA1* lesions. The BRCA1 protein contained a preformed structure in the apo-form with structural changes and more resistance to limited proteolysis after Zn^{2+} binding. Cisplatin-bound protein exhibited an enhanced thermostability, resulting from the favourable intermolecular crosslinks driven by the free energy. Only the apo-form, not the holo-form, of BRCA1 underwent a more folded structural rearrangement with the retention of protein structure

upon cisplatin binding with the preferential His117 site of the BRCA1 peptide ^{111}Glu-Asn-Asn-Ser-Pro-Glu-His-Leu-Lys^{119}. BRCA1 E3 ubiquitin ligase activity was also inactivated by the drug. These data could raise the possibility of selectively targeting the BRCA1 DNA repair for cisplatin in cancer chemotherapy.

As mentioned earlier, the BRCA1-BARD1 RING complex has an E3 ubiquitin ligase function that plays essential roles in response to DNA damage and DNA repair. Evidence from several preclinical and clinical studies have provided data showing that many cancer-predisposing mutations within the BRCA1 RING domain demonstrated a loss of ubiquitin ligase and repair of DNA double-strand break activities (Atipairin, et al., 2011a, 2011b; Morris et al., 2006, 2009; Ransburgh et al., 2010). Furthermore, the BRCA1-associated cancers conferred a hypersensitivity to ionizing radiations and chemotherapeutic agents. Therefore, it would be of great interest to identify a relationship between BRCA1-mediated ubiquitination and chemosensitivity by approaching the BRCA1 RING domain as a potentially molecular target or predictor with cisplatin.

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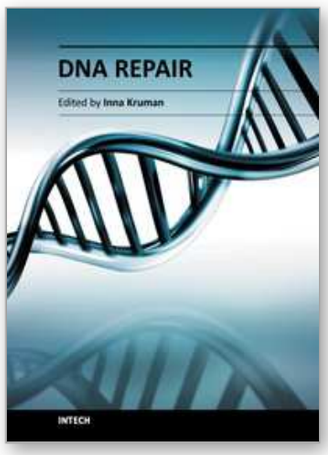
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The book consists of 31 chapters, divided into six parts. Each chapter is written by one or several experts in the corresponding area. The scope of the book varies from the DNA damage response and DNA repair mechanisms to evolutionary aspects of DNA repair, providing a snapshot of current understanding of the DNA repair processes. A collection of articles presented by active and laboratory-based investigators provides a clear understanding of the recent advances in the field of DNA repair.

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