Candidate synthetic lethality partners to PARP inhibitors in the treatment of ovarian clear cell cancer (Review)

NAOKI KAWAHARA, KENJI OGAWA, MIKA NAGAYASU, MAI KIMURA, YOSHIKAZU SASAKI and HIROSHI KOBAYASHI

Department of Obstetrics and Gynecology, Nara Medical University, Nara 634-8522, Japan

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Abstract. Inhibitors of poly(ADP-ribose) polymerase (PARP) are new types of personalized treatment of relapsed platinum-sensitive ovarian cancer harboring *BRCA1/2* mutations. Ovarian clear cell cancer (CCC), a subset of ovarian cancer, often appears as low-stage disease with a higher incidence among Japanese. Advanced CCC is highly aggressive with poor patient outcome. The aim of the present study was to determine the potential synthetic lethality gene pairs for PARP inhibitions in patients with CCC through virtual and biological screenings as well as clinical studies. We conducted a literature review for putative PARP sensitivity genes that are associated with the CCC pathophysiology. Previous studies identified a variety of putative target genes from several pathways associated with DNA damage repair, chromatin remodeling complex, PI3K-AKT-mTOR signaling, Notch signaling, cell cycle checkpoint signaling, *BRCA*-associated complex and Fanconi's anemia susceptibility genes that could be used as biomarkers or therapeutic targets for PARP inhibition. *BRCA1/2*, *ATM*, *ATR*, *BARD1*, *CCNE1*, *CHEK1*, *CKS1B*, *DNMT1*, *ERBB2*, *FGFR2*, *MRE11A*, *MYC*, *NOTCH1* and *PTEN* were considered as candidate genes for synthetic lethality gene partners for PARP interactions. When considering the biological background underlying PARP inhibition, we hypothesized that PARP inhibitors would be a novel synthetic lethal therapeutic approach for CCC tumors harboring homologous recombination deficiency and activating oncogene mutations. The results showed that the majority of CCC tumors appear to have indicators of DNA repair dysfunction similar to those in *BRCA*-mutation carriers, suggesting the possible utility of PARP inhibitors in a subset of CCC.

Correspondence to: Dr Hiroshi Kobayashi, Department of Obstetrics and Gynecology, Nara Medical University, 840 Shijo-cho, Nara 634-8522, Japan
E-mail: hirokoba@naramed-u.ac.jp

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1. Introduction

Epithelial ovarian cancer is an advanced and metastatic disease at presentation and responsible for over 50% of mortalities worldwide in female genital malignancies (1). The current standard treatment strategy for ovarian cancer is cytoreductive surgery followed by platinum- and taxane-based combination chemotherapy. Approximately 75% of patients with advanced ovarian cancer ultimately suffer from tumor recurrence with 20% of these patients having resistant disease (1). High rates of recurrence and low chemosensitivity are the two main factors that account for poor prognosis of this disease. Epithelial ovarian cancer is a highly heterogeneous disease characterized by at least two different subtypes, including distinct clinicopathologic characteristics, molecular pathogenesis, responses to treatment and patient prognosis (2). Each subtype also contains a distinct gene mutation profile and exhibits varied gene expression patterns. Type 1 ovarian cancer includes endometrioid cancer and clear cell cancer (CCC) (so-called endometriosis-associated ovarian cancer). Endometrioid cancer frequently possesses mutations in phosphatase and tensin homolog *(PTEN)*, catenin β1 *(CTNNB1)*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α *(PIK3CA)* and AT-rich interaction domain 1A *(ARID1A)* (3). *PIK3CA* and *ARID1A* are also commonly mutated in CCC and this tumor frequently shows hepatocyte nuclear factor-1β (HNF-1β) overexpression (3). Although Type 1 cancer often appears as low-stage disease, advanced CCC is a cancer that is highly aggressive with poor patient outcome. By contrast,

Type 2 ovarian cancer includes high-grade serous ovarian cancer (HGSC), which is the most common histotype of epithelial ovarian cancer and is characterized by advanced stage at onset. HGSC possesses nearly universal mutation in and dysfunction of (tumor protein p53) *TP53* as well as frequent germline and somatic *BRCA1/2* (BRCA1/2, DNA repair associated) mutations, occurring in at least 30% of tumors (3).

Recent advances for the development of efficient personalized therapy may lead to the development of successful strategies for molecular-targeted medicine (small-molecule inhibitors or antibodies), clinical applications of immunotherapy (PD-1 and -L1 antibodies) and identification of synthetic lethal partners (4). Advances in the treatment of HGSC through use of synthetic lethal approaches have also been made. Notably, inhibitors of [poly(ADP-ribose) polymerase] (PARP) are considered the most active and exciting new personalized target therapy for the treatment of ovarian cancer, especially relapsed platinum-sensitive HGSC (5). However, patients without BRCA1/2 mutations may also benefit from PARP inhibitors, suggesting a sensitive non-*BRCA1/2*-mutation subgroup (6).

The prevalence of CCC in Japan reaches up to 15-25% compared to those of North America and Europe with a reported prevalence of 1-12% (7,8). CCC showed a different genomic expression map from HGSC, which suggested a new target therapy (5). Despite many improvements in targeted therapy for ovarian cancer, exploration of novel synthetic lethal targets is required in CCC. Investigators have performed computational virtual screenings and further experimental validations to determine whether two-compound formulations are susceptible to synthetic lethality and may therefore indicate a therapeutic opportunity.

The aim of the present study was to determine the potential synthetic lethality gene partners for PARP inhibitions in CCC patients through virtual and biological screenings.

2. Systematic review of the literature using electronic search in the PubMed/Medline databases

The study aimed to determine the potential synthetic lethality gene partners for PARP inhibitions in patients with CCC through virtual and biological screenings as well as clinical studies. A PubMed (http://www.ncbi.nlm.nih.gov/pubmed) search of the relevant literature published between January 2000 and June 2017 was performed. The search strategy included the combination of key words: ovarian CCC, HGSC, synthetic lethality, PARP inhibitors, replication stress, DNA damage and repair, and genomic instability in the titles or abstracts of articles. English language publication search results from PubMed and references within the relevant articles were analyzed. To minimize selection bias, screening of the studies was independently performed by two of the co-authors (N.K. and K.O.) after agreeing on the selection criteria.

3. Future opportunities in the use of PARP inhibition in CCC

Cell DNA damage occurs continually through intrinsic and extrinsic mechanisms such as chemotherapy, ultraviolet radiation, smoking, reactive oxygene species and replication errors. Activation of the conserved DNA damage response (DDR) due to genomic instability requires various DNA repair genes (9). DDR deficiency results in replication stress, commonly induces replication fork slowing or stalling and also activates DNA repair checkpoint proteins [ataxia telangiectasia mutated *(ATM),* ATM- and Rad3-related *(ATR)*, checkpoint kinase 1 *(CHEK1)*], which prevent further DNA damage (10). DDR regulates cell cycle arrest, which enables DNA repair to occur. PARP1 plays a key role in numerous cell processes including DNA repair, replication and cell death/survival balance (11). PARP1 is mainly involved in the repair of DNA single-strand breaks. Accumulation of DNA double-strand breaks (DSBs) is generally repaired by the two DNA DSB repair pathways: Homologous recombination (HR) and non-homologous end joining (NHEJ). DNA repair defects are frequently encountered in human cancers, whereas DNA repair pathways mediated by PARP1 serve as backups (11). Approximately 50% of HGSC incur germline or somatic mutations in genes related to HR [BRCA1/2, BRCA paralogs, RAD51 (RAD51 recombinase), checkpoint activation genes and Fanconi's anemia genes] and the rest incur genetic alterations in mismatch repair (MMR) genes and other genes in the HR/DNA repair pathway at high frequencies (10). The global genome-wide mutational landscape revealed that the majority of HGSC patients harbor the actionable impact of germline and somatic mutations and DNA repair gene defects. HGSC cells harboring HR deficiencies are exceptionally sensitive to PARP inhibition. PARP inhibitors are an effective treatment strategy when they are used in *BRCA1/2*-mutated ovarian cancers, which has led to a shift in the treatment paradigm of this disease (12,13). The concept of synthetic lethality interactions can be exploited in tumors that harbor germline and somatic mutations causing defective DDR/DNA repair (14). Thus, not only *BRCA1/2* mutations, but also other HR deficiencies, have been established as a targeted therapy (14).

Based on a literature search, we initially identified differentially expressed genes and genomic mutations throughout the ovarian cancer between CCC and HGSC, which were recapitulated in CCC cell lines *in vitro*, in xenografts *in vivo* and in a comprehensive analysis of clinical data (15-21). We then explored virtual and biological screenings against synthetic lethal gene partners of PARP inhibition in ovarian cancer. The majority of samples were derived from patients with HGSC. Of the candidate genes that were likely to be synthetic lethal with PARP inhibitors, we selected genes that were frequently mutated, amplified, or upregulated in CCC.

This review focused on the future opportunities of the use of PARP inhibition in anticancer therapeutics for CCC. Identifying genetic biomarkers of the effects of synthetic lethal drug sensitivity also provides an approach to the development of targeted therapies for CCC.

4. Candidate mutated genes for enhancing the therapeutic ratio achieved by PARP inhibitors in CCC (Table IA)

PARP inhibitors are mandatory to improve the success of ovarian cancer therapy in the clinical setting (15). Loss-of-function mutations or reduced levels of genes involved in homologous repair sensitize cancer cells to treatment with PARP inhibitors. PARP1 silencing and inhibition were found to be synthetic lethal in ovarian cancers deficient in specific genes involved in the DDR such as *BRCA1/2* and *P53* with

impaired HR. Approximately 50% of epithelial ovarian cancers had germline (20-50%) and/or somatic (10%) loss-of-function mutations in HR genes (16,17). Mutated HR genes belong to DDR, *BRCA1*-associated, Fanconi's anemia-related and *RAD51*-related genes. Notably, HR mutation frequency was almost similar in serous and non-serous ovarian cancers (16). It is currently unclear, however, whether PARP1 inhibitors are capable of killing CCC cells using a synthetic lethal treatment strategy. Since CCC tumors have a variety of DDR gene mutations and activation of oncogenes, there is considerable interest in finding synthetic lethal partners of PARP inhibitor sensitivity. Previous studies of gene-expression profiling and proteomics, next-generation sequencing, genomic mutations, methylation status, chromosomal amplification and loss of heterozygosity (LOH) are discussed in the context of CCC biology (18-21). Furthermore, investigators have developed a new method to predict the synthetic lethality interactions: Synthetic lethality gene pairs may be predicted in functional genomic screening approaches such as CRISPR and siRNA in cancer cells treated with or without PARP inhibitors (22,23).

Firstly, we identified potential targetable genomic mutations in CCC using an extensive literature search (24,25). Patients with CCC (64%) had ≥1 somatic mutation (24). These included *ARID1A*; *PIK3CA*; *PTEN*; *KRAS* proto-oncogene, GTPase (KRAS); NRAS proto-oncogene, GTPase; B-Raf proto-oncogene, serine/threonine kinase *(BRAF)*; zinc-finger protein 217; AKT serine/threonine kinase *(AKT)*; TP53; Wnt/β-catenin *(CTNNB1)*; microsatellite instability; mutL homolog 1; SRC proto-oncogene, non-receptor tyrosine kinase; ETS proto-oncogene 1, transcription factor; protein kinase DNA-activated, catalytic polypeptide; APC membrane recruitment protein 1; AT-rich interaction domain 2; B cell CLL/lymphoma 11A; CREB binding protein; erb-b2 receptor tyrosine kinase 2 *(ERBB2)*; exostosin glycosyltransferase 1; Fanconi anemia complementation group D2; mutS homolog 6 *(MSH6)*, neurofibromin 1 *(NF1)*; notch 1 *(NOTCH1)*, nuclear mitotic apparatus protein 1; phosphodiesterase 4D interacting protein; protein phosphatase 2 scaffold subunit Aalpha *(PPP2R1A)*; ring finger protein 213; spectrin repeat containing nuclear envelope protein 1; CUB and Sushi multiple domains 3; latrophilin 3; LDL receptor related protein 1B; speckle type BTB/POZ protein *(SPOP)*; speckle type BTB/POZ protein *(KMT2D)* and *TP53* (21,24-27). The genetic mutations related to chromatin remodeling, DNA repair signaling, PI3K-AKT-mTOR, Notch signaling and *CTNNB1* pathway may be involved in CCC biology (27). The frequently mutated genes were *PIK3CA* (60%), *ARID1A* (50%) and *PTEN* (10%) in CCC (27-31). Somatic mutations of these genes are common genetic changes. PIK3CA-Akt-mTOR pathway is commonly altered in CCC. Genes involved in chromatin remodeling, *ARID1A*, *PPP2R1A*, *SPOP* and *KMT2D*, were mutated across CCC tumors (26). In *ARID1A* mutant tumour cells, inhibition of ATR triggers genomic instability and cell death (32). Furthermore, tumor suppressor PTEN is mutated in a large number of cancers (33). Somatic *PTEN* mutations, PTEN c.678delC, PTEN c.968insA and PTEN p.R233X, were detected in CCC (16). *PTEN* loss associated with HR deficiency increased chemosensitivity and therapeutic ratio (34). siRNA screening strategies also identified a synthetic lethal genetic interaction between *PTEN* (35,36) and *ATM* as well as *PTEN* and nemo-like kinase *(NLK)* (33). Thus, *PTEN* may play a role in cisplatin and PARP inhibitor sensitivity in CCC.

Secondly, we focused on somatic mutations in genes in which drugs are applied and which are known to be involved in the repair of DNA and are functionally activated in CCC. These included *BRCA1/2*, *ATR*, *ATM*, BRCA1-associated RING domain 1 *(BARD1)*, MRE11 homolog, double-strand break repair nuclease *(MRE11)*, MMR genes, partner and localizer of *BRCA2*, *RAD51*, MAP kinse-ERK kinase mitogen-activated protein kinase kinase 1, *KRAS*, *TP53*, cyclin dependent kinase inhibitor 2A *(CDKN2A)*, *ERBB2* and *NF1*. The literature search provides examples of mutated genes: *BRCA1* (BRCA1 1135insA), *BRCA2* (BRCA2 p.S368X), *ATM* (ATM c.5441delT), *CHEK2* (CHEK2 p.S428F and CHEK2 del exon 1-7) and *MRE11* (MRE11A c.1196insTT) (16).

We also summarized key characteristics of these genes. Loss-of-function mutations of the *BRCA1/2* genes occurred more frequently in HGSC compared to CCC (73 vs. 54%, 89 vs. 80%) (5), while somatic *BRCA* mutations were detected in CCC (16). *ATR* and *ATM* are cell cycle checkpoint kinases. Cell cycle checkpoint signaling pathways are required for DDR and then genomic stability. Inhibitors of the DDR pathways such as *ATR*, *ATM*, *CHEK1* and *CHEK2* are currently undergoing preclinical and early-phase clinical trials as single agents and in combinatorial regimens, including PARP inhibitors (10,37,38). *ATR* inhibitors are currently assessed in clinical trials and show promising results (37). *ATM* is a synthetic lethal partner of PARP, TP53, or topoisomerase DNA I (39). *BARD1* is overexpressed in CCC (40). The *BRCA1/BARD1* complex is an HR DNA repair component. Partner and localizer of *BRCA2 (PALB2)* play a role in DNA repair as a partner of *BRCA1/2*. *RAD51* family members functions in the early stage of HR DNA repair. Abnormal MMR expression was identified in 6% of CCC (33). Defective DNA MMR generates MRE11 mutations and sensitizes cancer cells to PARP1 inhibition, showing the synthetic lethality between *MRE11* and PARP1 (41). *MSH6* is a synthetic lethality partner of: dihydrofolate reductase; DNA polymerase β, catalytic subunit; DNA polymerase γ, catalytic subunit; or PTEN-induced putative kinase 1. mTOR pathway genes are often mutated in CCC (42). Thus, mTOR inhibitor may be one of the most promising approaches in CCC. Activating mutations in *KRAS* are identified in CCC. KRAS is a synthetic lethality partner of *XIAP* or *RAD51* (43). *TP53* is a synthetic lethality partner of *ATM*, *ATR*, *CHEK1*, *ID1*, or mTOR (44). LOH is detected at the CDKN2A/2B loci in CCC (45). *CDKN2A* is a synthetic lethality partner of *RB1*. *ERBB2* expression was upregulated in CCC (26). A synthetic lethality can be achieved with combined *EGFR* and PARP inhibition (46). *NF1* and PARP are also synthetic lethality pairs (44). Taken together, a subset of CCC cells may be sensitive to PARP inhibition, which can be predicted by defects in HR DNA repair of DSBs (14).

5. Upregulated genes enhancing synthetic lethality of PARP inhibitors in CCC (Table IB)

Differentially expressed genes in human CCC tissues were identified using high-throughput tissue microarray technology

Table I. Candidate genes enhancing synthetic lethality of PARP inhibitors in CCC.

A, Candidate mutated genes for enhancing the therapeutic ratio achieved by PARP inhibitors in CCC

Official symbol	Official full name	Function	Candidate synthetic lethality gene partners	Somatic mutations in CCC	Refs.
ARID1A	AT-rich interaction domain 1A	Chromatin remodeling	ATR		26,30, 31,32
ATM[a]	Ataxia telangiectasia mutated serine/threonine kinase	DNA repair checkpoint	PARP, TOP1, ATR	Somatic HR mutation in CCC, ATM c.5441delT	16,37, 39
ATR[a]	TM and Rad3-related	DNA repair checkpoint	PARP		10,29, 37,38
BARD1[a]	BRCA1-associated RING domain 1	HR	PARP	Expression of spliced isoforms of BARD1 was typical for clear cell carcinoma (51)	39,40
BRCA1/2[a]	BRCA1, DNA repair associated	HR	PARP	Somatic HR mutation in CCC, BRCA1 1135insA, BRCA2 p.S368X	5,16
CDKN2A	Cyclin dependent kinase inhibitor 2A	Cell cycle regulator	RB1		45
CHEK1[a]	Checkpoint kinase 1	DNA repair checkpoint	ATR, MYC, TP53, Wee1, p21	CHK1 is a homologous recombination gene	10,29
CHEK2	Checkpoint kinase 2	DNA repair checkpoint		CHEK2 p.S428F and CHEK2 del exon 1-7	9,16
CREBBP	CREB binding protein		p300		58
ERBB2	erb-b2 receptor tyrosine kinase 2, HER2	Oncogene	PARP		26,46
FANCD2	Fanconi anemia complementation group D2	DNA repair	PARP, POLQ		67
KRAS	KRAS proto-oncogene, GTPase	Oncogene	XIAP, RAD51		43
LZTS1	Leucine zipper tumor suppressor 1	Tumor suppressor	CDKN2A/2B		45
MLH1	mutL homolog 1	DNA mismatch repair	ATR		27,33, 39
MRE11A[a]	MRE11 homolog, double strand break repair nuclease	DNA repair	PARP	Somatic HR mutation in CCC, MRE11A c.1196insTT	41
MSH6	mutS homolog 6	DNA mismatch repair	DHFR, POLB, POLG, PINK1		
MTOR	Mechanistic target of rapamycin kinase	Cell cycle regulator	TP53		42,44
NF1	Neurofibromin 1	Oncogene	PARP		44
NOTCH1	Notch 1	Cell processes	ERBB2, EGFR		68
PIK3CA	Phosphatidylinositol-4,5 bisphosphate3-kinase catalytic subunit alpha	Oncogene	TRRAP, Hh		27,29
PPP2R1A	Protein phosphatase 2 scaffold subunit Aalpha	Cell growth	PLK	7% of CCC had mutations in PPP2R1A.	30
PRKDC	Protein kinase, DNA-activated, catalytic polypeptide	DNA repair	MYC, MSH3		24

Table I. Continued.

A, Candidate mutated genes for enhancing the therapeutic ratio achieved by PARP inhibitors in CCC

Official symbol	Official full name	Function	Candidate synthetic lethality gene partners	Somatic mutations in CCC	Refs.
PTEN	Polypeptide phosphatase and tensin homolog	Tumor suppressor	PARP, ATM, NLK	10% of CCC had mutations in PTEN. Somatic HR mutation in CCC, PTEN c.678delC, PTEN c.968insA, PTEN p.R233X	16,28, 33
RAD51C	RAD51 paralog C	DNA repair	PARP		14,43
PALB2	Partner and localizer of BRCA2	BRCA2 complex	PARP		69
TP53	Tumor protein p53	Cell cycle regulator	ID1, CHK1, ATM, ATR, mTOR		3,39,44
XRCC5	X-ray repair cross complementing 5	DNA repair	Ku		50

B, Upregulated genes enhancing synthetic lethality of PARP inhibitors in CCC

Official symbol	Official full name	Function	Candidate synthetic lethality gene partners	Refs.
AURKA	Aurora kinase A	Cell cycle regulator	MYC	5,51
CCNE1[a]	Cyclin E1	Cell cycle regulator	PARP	47,54
CKS1B[a]	CDC28 protein kinase regulatory subunit 1B	Cell cycle regulator	PLK1	48
ERBB2	erb-b2 receptor tyrosine kinase 2 (HER2)	Oncogene	NOTCH1 PARP	26,46
HNF1B	Hepatocyte nuclear factor-1β	Transcription factor	CHEK1	49
PTEN[a]	Phosphatase and tensin homolog	Tumor suppressor	PARP, ATM, NLK, (nemo like kinase)	33,35, 36
XRCC5	X-ray repair cross complementing 5	DNA repair	Ku	50

C, Synthetic lethal gene partners based on chemoresistance-related genes in CCC

Official symbol	Official full name	Function	Candidate synthetic lethality gene partners	Refs.
CHEK1[a]	Checkpoint kinase 1	DNA repair checkpoint	ARR, MYC, TP53, Wee1, p21	29,60,61, 62,63
DNMT1[a]	DNA methyltransferase 1	Methyltransferase	PARP	56,64
FGFR2[a]	Fibroblast growth factor receptor 2	Oncogene	PTEN	57
ERBB2[a]	erb-b2 receptor tyrosine kinase 2	Oncogene	PARP	26
MYC[a]	MYC proto-oncogene, bHLH transcription factor	Oncogene	PTEN	52,58
NOTCH1[a]	Notch 1	Cell processes	EGFR	27,59,66

[a]*BRCA1/2*, but also *ATM*, *ATR*, *BARD1*, *CCNE1*, *CHEK1*, *CKS1B*, *DNMT1*, *ERBB2*, *FGFR2*, *MRE11A*, *MYC*, *NOTCH1* and *PTEN* were considered as candidate genes for synthetic lethality gene partners for PARP inhibitors.

and proteomic screening (18). Previous studies summarized the characteristics of potential genomic alterations that activate the CCC-specific gene ontology, canonical pathways and functional networks (18,19). Among the genes overexpressed in CCC, we selected the genes showing growth inhibition by knockdown experiments. These analyses revealed a significant

representation in the cell cycle regulation and DNA repair pathways (18-20). Overexpression of *HNF-1β* (>90%), *CHEK1*, X-ray repair cross complementing *(XRCC)* 5, cyclin *(CCN)* E1 and CDC28 protein kinase regulatory subunit 1B *(CKS1B)* is a common genetic change in CCC (28,29,47-49). A novel role for transcription factor *HNF-1β* in DDR was identified (49). CCC cells are dependent on the HNF-1β-CHEK1 axis for cell survival (15). CCC cells exhibit the upregulation of HNF-1β expression and accumulate G1/S cell cycle arrest, which results in the constitutive expression of the activated CHEK1 in response to DNA damage (49). DNA repair protein XRCC5 functions as the repair of DNA DSBs by NHEJ (50). XRCC5 is the subunit of the Ku heterodimer protein, which is also known as ATP-dependent DNA helicase II. The cell-cycle regulators were frequently overexpressed (cyclin A and E) or downregulated cyclin-dependent kinase inhibitor 1B *(CDKN1B)*, also known as $p27^{Kip1}$ in CCC. Various oncogenes enhance the replication stress and increase the genomic instability of cancer cells (51-53). Overexpression of the oncogene *CCNE1* has been observed in tumors, which also results in chromosomal instability characterized by accumulation of chromosome copy number aberrations. *CCNE1* copy-number gain and overexpression have an impact following unfavorable outcome in CCC (47). Amplification of *CCNE1* and mutation of *BRCA1/2* genes appear to be mutually exclusive, despite the high individual frequencies of such mutations in cancer (54). This suggests that *CCNE1* induces synthetic lethality in *BRCA1/2*-mutated cells (54). CKS1B is a modulator of the cyclin-dependent kinase; cyclin-dependent serine/threonine-protein kinase *CDC28*. A high throughput screening revealed that *CKS1B* is a synthetic lethality partner of *PLK1* (48). Although a variety of genes in CCC are passenger events, these genes may function as synthetic lethal pairs under the replication stress condition.

6. Synthetic lethal gene partners based on chemoresistance-related genes in CCC (Table IC)

The persistent existence of cancer stem cells plays a role in therapeutic drug resistance and cancer recurrence, which are the common cause for serious morbidity in cancer patients. Research studies have identified putative target genes associated with stem cell chemoresistance (55). Multiple oncogenes may function as attractive candidates that are involved in malignant behavior and acquisition of a chemoresistant phenotype. A number of user-friendly databases and tools in scientific workflows have been integrated to facilitate data analysis. The comprehensive information in the QIAGEN database (http://www.sabiosciences.com/rt_pcr_product/HTML/PAHS-176Z.html) has been compiled from research publications. Genetic data on stem cell markers (n, 89) are publically available from this database. We selected 14 genes as the CCC-specific genes from this database using the PubMed literature search. Six genes were identified: *ERBB2*; fibroblast growth factor receptor 2 (*FGFR2*); MYC proto-oncogene, bHLH transcription factor (*MYC*); *NOTCH1*; *CHEK1*; and DNA methyltransferase 1 (*DNMT1*). These were predicted as synthetic lethality gene partners for PARP inhibitors (26,27,56-58). Overexpression of oncogenes *ERBB2*, *FGFR2* and *MYC* in CCC cells accelerates the DNA replication stress, accumulates DNA DSBs and associates with synthetic lethality to PARP1 inhibitors (46-52). A contextual synthetic lethality exists between the combined inhibition of *ERBB2* and *PARP* (46). Simultaneous inhibition of *ERBB2* and *NOTCH1* also uncovers a synthetic lethal relationship (59). DNA damage or the presence of unreplicated DNA induces cell cycle arrest in G2/M phase in a manner regulated by *CHEK1* in CCC cells overexpressing HNF-1β (60). *CHEK1* is reportedly a synthetic lethality partner of *ATR*, *MYC*, *TP53*, *WEE1* G2 checkpoint kinase (WEE1), or cyclin-dependent kinase inhibitor 1A *(CDKN1A)*, also known as $p21^{CIP1}$ (29,61-63). DNMT1 maintains methylation patterns following DNA replication. Combining DNMT1 inhibition and PARP inhibitors cause synthetic lethality (64). PARP inhibition prevents XRCC1 interaction with several DNA repair proteins, including DNMT1 and thereby insufficient organization of base excision repair (64). We can provide chemoresistance or stem cell-related genes for synthetic lethality pairs of PARP inhibitors in CCC. This study has the potential to strengthen the fact that activating oncogene mutations or amplifications (for example, *ERBB2*, *FGFR2*, *MYC*, *KRAS* and *PIK3CA*) suggest a synthetic lethal-based therapeutic strategy (57).

7. Discussion

This article reviewed the conceptual biology leading to the prediction of novel synthetic lethality pairs and discussed the rationale for antitumor strategies in CCC (37). We conducted a literature review for putative PARP sensitivity genes associated with CCC pathophysiology. A variety of target genes were identified from DNA repair pathways, chromatin remodeling complex, PI3K-AKT-mTOR pathways, Notch signaling pathways, cell cycle checkpoint signaling pathways, BRCA-associated pathways and Fanconi's anemia susceptibility genes. *ATM*, *ATR*, *BARD1*, *BRCA1/2*, *CCNE1*, *CHEK1*, *CKS1B*, *DNMT1*, *ERBB2*, *FGFR2*, *MRE11A*, *MYC*, *NOTCH1* and *PTEN* were considered as candidate genes for synthetic lethality gene partners for PARP inhibitors.

Firstly, the assembly of HR proteins at sites of DNA damage led to the activation of signal transducers, including ATM, ATR, and DNA-dependent protein kinase *(DNA-PK)*, which activate downstream effectors, CHEK1/2, and in turn DNA repair pathways. During DDR, the checkpoint signal transducers/effectors such as ATM/CHEK2 and ATR/CHEK1 regulate G1/S and G2/M checkpoints, respectively, and induce cell cycle arrest (9). ATM mutations in parallel to the ATR-CHEK1 axis induce high replication stress (16). The HR deficiency caused by ATM mutations sensitizes tumor cells to potent inhibitors of PARP-mediated signaling (39). Inhibitors of ATM may be a promising strategy for cancer therapy (38). *ATR* and *CHEK1* are synthetic lethal pairs between two proteins in the same pathway and maintain cancer cell survival under replication stress (10,29). CCC have been assumed to demonstrate an increased reliance on the HNF-1β-CHEK1 axis for cell survival (49). Significant genes involved in synthetic lethality with *CHEK1* are reported to be *ATR*, *MYC*, *TP53*, *WEE1* and *CDKN1A* (29,61-63). ATR inhibition is currently assessed in early-phase clinical trials as single agents and in combination strategies, including PARP inhibitors (37). Inhibitors of the major components of the DDR such as *ATM*, *ATR*, *DNA-PK*, *CHEK1* and *CHEK2* would be used to confer

chemosensitivity upon CCC. Therefore, PARP inhibitors may induce synthetic lethality in CCC tumors with mutated genes that regulate HR repair and associated events such as cell cycle checkpoints. Although a variety of loss-of-function and gain-of-function genes in CCC are passenger events, the DNA repair genes, such as *ATM*, *ATR*, and *CHEK1*, may function as synthetic lethal pairs under the replication stress condition.

Secondly, activating oncogene mutations or amplifications are putative synthetic lethality gene partners for PARP inhibitors in CCC. Overexpression of oncogenes, *ERBB2*, *MYC* and *CCNE1*, in CCC activates MAPK and PI3K signaling pathways (26). It has been shown that *ERBB2* and *MYC* represses cellular DSB repair potentials due to an increase in replication stress (46). A contextual synthetic lethality can be achieved with combined oncogenes and PARP inhibition. Therefore, PARP inhibitors demonstrate synthetic lethality in CCC tumors with activating oncogene mutations and oncogene amplifications (46). Furthermore, synthetic lethality partners for *ERBB2* mutant and overexpression using functional and profiling screenings are considered to be SWI/SNF subunits, NF-κB pathway, STAT3 pathways, MAP kinases, Wnt signaling, Src family kinases, cyclin-dependent kinases and Notch signaling (65). *CCNE1* amplification and *BRCA1/2* inactivation are mutually exclusive and known to promote genomic instability and tumor progression (54). Thus, PARP inhibitors may sensitize CCC cells with oncogene mutant and overexpression to cisplatin in a synthetic lethal manner.

Thirdly, Notch signaling, chromatin remodeling, PI3K-AKT-mTOR and CTNNB1 pathways may promote malignant transformation of CCC (27). Notch signaling controls cell processes, including cancer cell and cancer stem cell fate determination. NOTCH2 expression is specifically downregulated in CCC (66). Notch signaling and ERBB2 appear to be mutually exclusive, demonstrating that Notch signaling is also a potential synthetic lethal partner of ERBB2 (67).

Finally, tumor suppressors *ARID1A* and *PTEN* are mutated in a large number of cancers. The mutations are also commonly observed in CCC (33). *PTEN* is a synthetic lethality partner for *PARP*, *ATM*, or *NLK*, while *ARID1A* and *ATR* are synthetic lethal pairs (33,35,36). Applications of PARP inhibition are now being expanded to tumor suppressor genes *ARID1A* and *PTEN*.

In conclusion, our study aimed to examine the possible synthetic lethality gene partners for PARP inhibitors among genes aberrantly expressed in CCC. Increasing efforts have been focused on the identification of synthetic lethality gene partners for PARP inhibitors in a variety of cancers (68). Most PARP inhibitors have been investigated in HGSC, but not CCC, showing promising efficacy in patients with BRCA mutations and HR deficiency. In this review, virtual screening genes were selected and some genes were further tested via *in vitro* and *in vivo* assays. Considering the biological background underlying PARP inhibition, we hypothesized that PARP inhibitors would also be a novel synthetic lethal therapeutic approach for CCC tumors harboring activating mutations and overexpressed genes. The majority of CCC tumors appear to have indicators of DNA repair dysfunction similar to those in BRCA-mutation carriers in HGSC, suggesting the possible utility of PARP inhibitors in a subset of CCC. An improved understanding of the synthetic lethality on treatment strategies may facilitate a transition from chemotherapy alone to combination with synthetic lethality treatment strategies in CCC. In the future the use of PARP inhibitors may be extended beyond tumors with BRCA1/2 mutations.

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