Conceptual frameworks of synthetic lethality in clear cell carcinoma of the ovary (Review)

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Abstract. Targeting non-oncogenes may result in the selective death of cancer cells. Clear cell carcinoma of the ovary (CCC) may exhibit resistance against conventional chemotherapy and is associated with poor prognosis. The aim of the present report was to review synthetic lethality-based therapies for CCC. Previous English-language studies were reviewed to accumulate preclinical and clinical data on targeting synthetic lethal partners. Synthetic lethal interactions have a variety of types, involving components of a backup or parallel pathway with overlapping functions, components encoded by paralogous pairs, subunit components that form heteromeric complexes and components that are arranged in a single linear pathway. A set of candidate gene targets potentially resulting in synthetic lethality have been previously identified. HNF class homeobox, AT-rich interaction domain 1A, ATR serine/threonine kinase, ATM serine/threonine kinase, checkpoint kinase 1 and phosphatase and tensin homolog may be the key partner genes. A variety of loss of function genes in CCC are driver or passenger events and may function as synthetic lethal pairs under replication stress conditions. Further clinical studies will be required to investigate the safety and therapeutic effect of synthetic lethality pairs in CCC tumor types with replication stress.

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1. Introduction

Ovarian cancer is the seventh most common cancer among women globally (1). Clinicians are facing an increasing number of ovarian cancer cases diagnosed each year. This disease is associated with a poor prognosis as the majority of cases are diagnosed at an advanced stage (1). Clinical observations and molecular analyses have divided ovarian cancer into two major subtypes: Type 1 cancer types, which are composed of low grade serous cancer, endometrioid cancer, clear cell cancer and mucinous cancer; and type 2 cancer types, which include high grade serous cancers (HGSC), carcinosarcomas and undifferentiated carcinomas (2). Clear cell and endometrioid carcinomas arise in endometriosis [endometriosis-associated ovarian cancer (EAOC)] (2). HGSC was originally thought to develop from the ovarian surface epithelium and/or ovarian inclusion cysts (2). However, recent research has contradicted this and suggests that the majority of HGSC develops from fallopian tube fimbrial epithelium (3).

Recent promising advances in the field of cancer treatment have resulted in the development of successful strategies for molecular-targeted medicine (including small-molecule inhibitors and antibodies), clinical applications of immunotherapy and identification of synthetic lethal partners (4). Substantial progress has been made in the treatment of ovarian cancer through use of targeted therapies and immunotherapy (5). Anti-angiogenic therapy using bevacizumab, considered the most promising targeted therapy for ovarian cancer, may improve the overall survival time of patients with poor prognosis (6). One previous study also demonstrated the safety and antitumor activity of nivolumab, an anti-programmed cell death protein 1 (PD-1) antibody that blocks PD-1 signaling, in patients with platinum-resistant ovarian cancer (7). Since observations have questioned the prospect of using PD-ligand 1 (PD-L1) expression as a biomarker for discriminating responders from non-responders, it must be complemented by a superior predictive biomarker. Such a predictive biomarker must be able to select sensitive patients in order to reduce toxicity and costs and increase progression-free survival and overall survival time. In addition, resistance to therapy is a major problem due to molecular heterogeneity (4). The prioritized driver or passenger genes, including p53, BRCA1/2, DNA repair associated (BRCA1/2), AT-rich interaction domain 1A (ARID1A), phosphatase and tensin homolog (PTEN), phos-
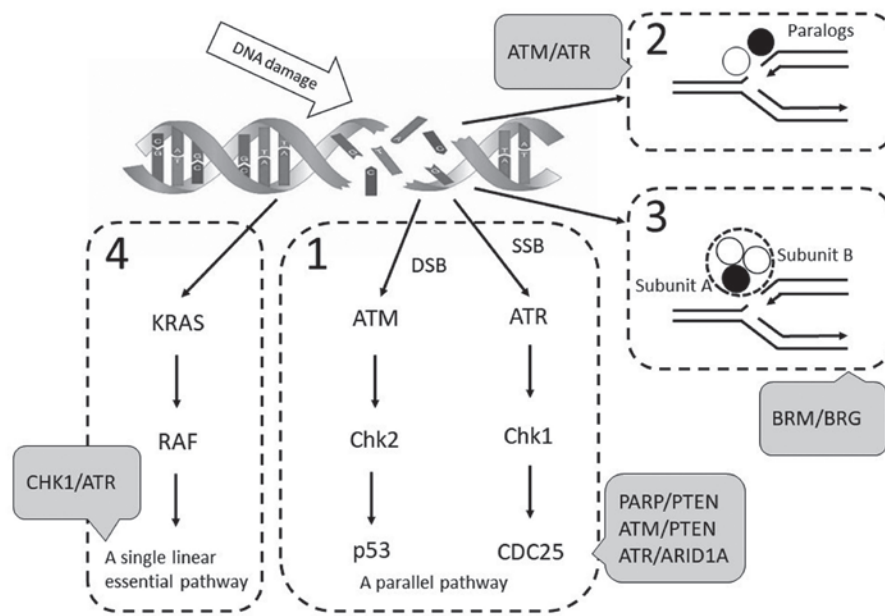
Figure 1. Landscape of synthetic lethal pairs. Synthetic lethal pairs were divided into four categories: (1) Components of a backup or a parallel pathway with overlapping functions; (2) components encoded by paralogous pairs; (3) Subunit components that form heteromeric complexes; and (4) components that are arranged in a single linear pathway. KRAS, KRAS proto-oncogene, GTPase; Chk, checkpoint kinase; ATR, ATR serine/threonine kinase; ATM, ATM serine/threonine kinase; p53, tumor protein p53; PARP, poly(ADP-ribose) polymerases; PTEN, phosphatase and tensin homolog; ARID1A, AT-rich interaction domain 1A; BRM, SWItch/Sucrose non-fermentable-related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2; BRG, SWItch/Sucrose non-fermentable-related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4.

phatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α (PIK3CA) and MYC proto-oncogene, bHLH transcription factor (c-MYC), exert loss- or gain-of-functions (4). Functional losses in tumor suppressor genes cannot be restored through small molecules or specific antibodies (8). Furthermore, the functions of intracellular oncogene products, including Ras and c-MYC, may be difficult to modulate directly due to the increasing cytotoxicity of normal cells (8).

The aim of the present report was to provide a review of synthetic lethality-based therapies for patients with ovarian cancer. Additionally, future perspectives on their plausible applications for novel therapeutic methods of clear cell carcinoma of the ovary (CCC) in the era of personalized medicine are provided.

2. Literature search

A computerized literature search was conducted to identify relevant studies reported in the English language. MEDLINE submissions (https://www.ncbi.nlm.nih.gov/pubmed) were searched for studies published between January 2000 and April 2018, combining the keywords 'ovarian cancer', 'ovarian clear cell carcinoma', 'carcinogenesis, 'synthetic lethality' and 'DNA damage repair'. A variety of combinations of these terms were used, depending on which database was searched. Each gene was also linked to the associated National Centre for Biotechnology Information Entrez Gene pages (http://www.ncbi.nlm.nih.gov/sites/entrez). Furthermore, the references of each article were searched to identify potentially relevant studies. Publications of original studies and review papers were included, while those documenting opinions, points of view or anecdotes were discarded.

3. Mutations and molecular heterogeneity of ovarian cancer

HGSC has been frequently associated with loss-of-function genes [including tumor protein p53 (p53), BRCA1/2, cyclin dependent kinase inhibitor 2A also known as p16[INK4a], RB transcriptional corepressor 1 and PTEN] (3). Previous genomic study has indicated that germline and somatic mutations in homologous recombination genes including BRCA1/2 and p53 may increase the risk of HGSC (9). Homologous recombination is essential for DNA damage repair, prevention of various mutations and maintenance of genomic integrity (10). HGSC tumor types also exhibit somatic loss of function of BRCA and its associated genes (3). Certain sporadic cancer types that share the molecular features of BRCA1/2-mutant tumor types may respond to similar therapeutic strategies (11). This trait is referred to as 'BRCAness'. Furthermore, the key oncogenic driver, c-MYC, and the G1/S phase regulatory gene, cyclin E (CCNE1), are frequently amplified in HGSC and are major factors in tumorigenesis (3). MYC-amplified cancer cells have been associated with elevated levels of DNA replication stress (12). Amplification of CCNE1 and mutation of BRCA1/2 genes are reportedly mutually exclusive in HGSC, suggesting that CCNE1 induces synthetic lethality in BRCA1/2-mutated cells (3).

Oxidative stress induced by repeated hemorrhaging increases the susceptibility of endometriotic cells to DNA damage and subsequent malignant transformation, resulting in the development of type 1 cancer, named EAOC (13). Type 1 cancer has a high mutational burden: Somatic gene mutations identified include those in ARID1A mutations (40-50%), PIK3CA (40%), PTEN (20%), catenin beta 1 (CTNNB1; 16-54%), protein phosphatase 2 scaffold subunit α (20%),

KRAS proto-oncogene, GTPase (KRAS; 4-5%), microsatellite instability (13-50%) and overexpression of transcription factor hepatocyte nuclear factor-1β (HNF; >90% in CCC) (14). ARID1A is the most frequent driver mutation in EAOC (15). PIK3CA/protein kinase B/mechanistic target of rapamycin (mTOR) pathway is also commonly altered in CCC (16). Furthermore, the overexpression of HNF has been identified in a large proportion of CCC (17). Checkpoint kinase 1 (Chk1) has been revealed to be a downstream target of HNF and serve a role within the cell cycle checkpoint pathways (18). DNA damage increases the persistent phosphorylation of Chk1 and induction of G2/M phase cell cycle arrest in cells overexpressing HNF (19,20). HNF deletion, in turn, induces apoptosis, suggesting that enhanced levels of HNF may be essential for survival in CCC (17,20). Molecular changes, including those in HNF and Chk1, may be a manifestation of essential alterations in cell cycle regulation, detoxification and chemoresistance in CCC (13,18,21). Targeted therapy with specific inhibitors of Chk1 or the HNF-Chk1 axis may be explored as a potential treatment modality for patients with CCC (22). This knowledge may result in novel potential combination therapeutic methods, for instance chemotherapeutic agents and targeting of Chk1, which may overcome drug resistance and produce more successful disease treatment. In this regard, a number of important drivers have been identified in ovarian cancer, including BRCA1/2, p53, CCNE1, ARID1A, Chk1 and HNF. These alterations represent potential future therapeutic opportunities for CCC.

4. Synthetic lethality

The concept of tumor-selective synthetic lethality as a therapeutic strategy is as follows: Two genes are 'synthetically lethal' if concurrent loss of the two genes results in cellular lethality or cell death, whereas the deficiency of either alone is compatible with cellular viability (8). Specific inhibitors of the cancer driver genes or oncogenes may contribute to development of idiosyncratic toxicity (23). An example of synthetic lethality is PARP inhibition in BRCA1/2-deficient ovarian and/or breast cancer types (3,24,25). Since homologous recombination-associated genes, including BRCA1, BRCA2, RAD51 recombinase (RAD51), Fanconi anemia complementation group and p53 genes, are essential for DNA damage repair and survival, cancer cells may use an alternative approach (non-oncogenes) and become dependent upon the parallel route (26). Therefore, targeting non-oncogenes may result in the selective death of the cancer cells (27). If one gene, one paralog or one pathway is inactive (e.g., germline BRCA mutations), the loss or inhibition of a second functionally parallel gene or pathway (e.g., PARP inhibitions) may result in cell death specifically (26). Pharmacological inhibition of PARP alone may selectively kill homologous recombination deficient cancer cells but leave normal cells intact (26).

Synthetic lethality screening. The identification of synthetic lethal interactions is made possible by the SynLethDB database (http://histone.sce.ntu.edu.sg/SynLethDB/) (28). A comprehensive understanding of the synthetic lethality-related genes and their corresponding interactions is essential for developing novel therapeutics against cancer using network-based research

Table I. List of candidate synthetic lethality gene pairs those with germline and/or somatic mutation in four categories.

Components of a backup or a parallel pathway with overlapping functions.

PARP	BRCA
PARP	CDK12
PARP	PTEN
PARP	ATM
PARP	Cohesin
mTOR	TP53
VEGFR2	TP53
EGFR	TP53
CSNK1E	TP53
CTNNB1	TP53
CSNK1A1	TP53
CDK6	TP53
CSNK1A1	APC
TDO2	APC
CTNNB1	APC
BRAF	APC
IGF1R	APC
WNK1	APC
ATM	ATR
ATM	TP53
ATM	PTEN
ATM	PRKCA
ATR	XRCC1
ATR	TOP1
ATR	POLD1
ATR	ARID1A
CDK1	KRAS
MAPK14	KRAS
PRKDC	MYC
CSNK1E	MYC
CKS1B	PLK1
KRAS	PLK1
TRRAP	PIK3CA
HH	PIK3CA
HGS	CTNNB1
NLK	PTEN
POLB	MSH2
POLD1	ATR

Components encoded by paralogous pairs.

ATM	ATR
TRRAP	PIK3CA
CBP	EP300
BMR	BRG

Table I. Continued.

Subunit components that form heteromeric complexes.

RAD52	BRCA
PARP1	RAD54B
PARP1	RAD51
BMR	BRG

Components that are arrangedin a single linear pathway.

Chk1	ATR
RAF1	KRAS

A synthetic lethal pair (left gene) of germline and/or somatic mutation gene (right gene).

platforms (29). The high mutational burden of cancer cells may contain genes that trigger susceptibility to synthetic lethality and are synthetic lethal interactors that indicate a therapeutic opportunity (30). Despite the high number of mutated genes and the consequential plethora of potential gene-gene interaction data in CCC, identifying synthetically lethal genes and their partners is challenging due to the difficulty of distinguishing true partners from errors (31). Genomic high-throughput experimental data may aid investigators to understand the synthetic lethal screening, including from high-throughput forward genetic screening approaches, genome-wide small interfering RNA (siRNA) or clustered regularly interspaced short palindromic repeat-based human cell line screening, and comprehensive *in silico* pipeline computational approaches, or a combination of these methods (32). Among these screenings, the dominant approach is high-throughput screening using RNA interference or compound libraries (32). At present, a kinome siRNA library of >40,000 siRNAs targeting >10,000 genes (four siRNAs per gene) is commercially available. In a previous study, a variety of human cancer cell lines with a particular tumor suppressor gene or oncogene were plated in arrayed siRNA library-coated wells using a library targeting protein networks (8). The hit list from the primary screen was then systematically narrowed. Candidate synthetic lethality genes were validated to confirm whether synthetic lethal pairs selectively kill cancer cells, but not normal cells (8). However, limitations for the screening-based approach are a high false positive rate of computational predictions and high cost.

Synthetic lethal gene pairs. In the present review, the synthetic lethal pairs were divided into four categories as described by Fang (8): i) Components of a backup or a parallel pathway with overlapping functions; ii) components encoded by paralogous pairs; iii) subunit components that form heteromeric complexes and iv) components that are arranged in a single linear pathway (Fig. 1).

Category 1: Components of a backup or a parallel pathway with overlapping functions. Mutational screening studies of synthetic lethality have been reported (8,33-36). The majority of the category 1 genes are associated with DNA damage

repair and cell survival. A high number of DNA double-strand breaks are repaired by BRCA-dependent homologous recombination (37). PARP1 may serve as an alternative or a backup pair (38). Preclinical studies revealed that proteins involved in DNA repair and response to damage, including BRCA1/2, X-ray repair cross complementing (XRCC)1, XRCC2, XRCC3, ATM serine/threonine kinase (ATM), ATR serine/threonine kinase (ATR), Chk1, Chk2, proliferating cell nuclear antigen, RAD51, MRE11 homolog, double strand break repair nuclease, ERCC excision repair 1, endonuclease non-catalytic subunit, p53, cyclin dependent kinase 12 (CDK12) and PTEN, in addition to the Fanconi anemia pathway, induce synthetic lethality with PARP inhibitors and are implicated as potential predictive markers for tumor cell response to PARP inhibitors (8,33). As presented in Table I, PARP inhibitors (Table I; A synthetic lethal pair) are currently under investigations as therapeutic agents for the treatment of cancer types with deficiencies in BRCA, CDK12, PTEN, ATM, ATR or Cohesin genes (Table I; Germline and/or somatic mutations) (34,35). Furthermore, comprehensive experiments have identified novel synthetic lethal gene pairs, including p53-ATM, p53-ATR, TP53-mTOR, p53-vascular endothelial growth factor receptor 2, p53-epidermal growth factor receptor, p53-transforming acidic coiled-coil containing protein 3, p53-MYC, p53-CTNNB1, p53-casein kinase 1 epsilon (CSNK1E), ATR-ARID1A, ATR-XRCC1, ATR-DNA topoisomerase I, ATR-DNA polymerase δ1, catalytic subunit, ATM-protein kinase C α, KRAS-CDK1, KRAS-polo like kinase 1 (PLK1), CDC28 protein kinase regulatory subunit 1-PLK1, APC-CTNNB1, APC-casein kinase 1 α1, APC-tryptophan 2,3-dioxygenase, CSNK1E-MYC, CTNNB1-hepatocyte growth factor-regulated tyrosine kinase substrate, PTEN-nemo like kinase and mutS homolog 2-DNA polymerase beta (32,34,36).

Category 2: Components encoded by paralogous pairs (paralogs). DNA damage response pathway factors, including ATM and ATR, result in a parallel signaling cascade that is activated by replication stress and uses a complex and coordinated set of proteins to maintain genomic stability (39). ATR is considered among the top candidates of the category 2 genes, as ATR inhibitors are entering clinical trials and have therapeutic utility (34). cAMP-response element binding protein (CREBBP) serves a role in growth by coupling chromatin remodeling to transcription factor recognition (40). The CREBBP paralog, p300/EP300, is a synthetic-lethal gene in CREBBP-deficient cancer types (41). SWItch/Sucrose non-fermentable (SWI/SNF)-related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2 (BRM) and SWI/SNF-related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 (BRG) are DNA-dependent ATPases of the SWI/SNF chromatin remodeling complex (42). Synthetic lethality may be explained by BRM or BRG paralog insufficiency (42). Two pair genes are organized in the networks of paralogs (42).

Category 3: Subunit components that form heteromeric complexes. The SWI/SNF complex facilitates the homologous recombination-dependent processes, including the recruitment of BRM, BRG, ARID and RAD molecules to DNA double-strand breaks (43). In a similar manner to PARP1

inhibitors, the suppression of RAD52 reduces homologous recombination and results in synthetic lethality in cells deficient in BRCA1/2 or associated proteins (including partner and localizer of BRCA2, RAD51B/C/D and XRCC2/3), whilst sparing normal cells (44). RAD51/RAD54B and PARP1 have been reported to function as synthetic lethal interactors, where it was thus revealed that PARP1 may be a novel candidate drug target in RAD51/RAD54B-deficient cells (45). Chromatin remodeling proteins are often contained within multiprotein complexes (43).

Category 4: Components that are arranged in a single linear pathway. The ATR and Chk1 kinases, critical mediators of the DNA damage response pathway, maintain cell survival and protect cells from replication stress (46). These two kinases are currently the focus of ongoing clinical trials (47). Inhibition of Raf-1 proto-oncogene serine threonine kinase (RAF1) is a synthetic lethal target in KRAS mutant tumor types (48). The ATR-Chk1 and KRAS-RAF1 pathways function as a cancer-specific synthetic lethality between two proteins in the same pathway (47,48).

The present review discussed recent developments in the synthetic lethality gene pairs in four categories, which includes licensed inhibitors in preclinical and clinical trials: i) PARP inhibitors for homologous recombination deficient cancer types; ii) disruption of the ATM paralog ATR; iii) deficiency of BRM or BRG in an essential multiprotein complex and iv) two proteins in the same pathway, ATR and Chk1. Recent clinical studies reported the evidence for the use of PARP inhibitors in high-grade serous ovarian cancer with germline or somatic BRCA1/2 mutations (49).

5. Synthetic lethal partners in CCC

Preclinical and clinical data of targeting synthetic lethal partners for the treatment of CCC cell lines and patients with CCC, respectively, are discussed as follows. Firstly, previous literature suggests a lack of prognostic and early detection markers available for CCC (21). However, Arakawa *et al* (50) reported that tissue factor pathway inhibitor 2 may be a useful serum marker for the detection of CCC. In addition, the overexpression of transcription factor HNF (>90%) (17) and somatic mutations of ARID1A (15) and PIK3CA (~50%) (51) are common genetic changes reported in CCC (52). In previous study, suppression of HNF expression resulted in apoptotic cell death in CCC cell lines, indicating that HNF may be associated with tumor survival (18). Thus, HNF may be suggested as a desirable candidate for targeted cancer therapy. However, the pharmacological inhibition of HNF may be particularly toxic for normal cells as this transcription factor is expressed in the liver, digestive tract, pancreas and kidneys (18). Chk1 has been identified as a downstream target of HNF, demonstrating that the overexpression or persistent phosphorylation of Chk1 is a characteristic feature of the HNF-overexpressing CCC (18). The HNF-Chk1 axis serves a critical role in the cell cycle arrest at G2/M phase and DNA repair (20). CCC is sensitive to Chk1 inhibitors as they induce a high degree of HNF-induced replication stress (22). The HNF-Chk1 axis is a main pathway for cell survival in CCC (20). These data suggest that the inhibition of Chk1 may be lethal in HNF-overexpressing CCC cells.

Secondly, ATR and Chk1 are a synthetic lethal pair of two proteins in the same pathway and maintain cancer cell survival under replication stress (47). Inhibitors of ATR and Chk1 are currently undergoing clinical trials and may represent a promising strategy for cancer therapy (47). Furthermore, a randomized phase II trial study has been conducted to assess whether adding ATR kinase inhibitor M6620 to standard treatment with gemcitabine hydrochloride is more effective than gemcitabine hydrochloride alone in treating patients with ovarian, primary peritoneal or fallopian tube cancer (trial number, NCT02595892) (53). A phase II single arm pilot study has been conducted to determine the objective response rate of single agent Chk1/2 inhibitor (LY2606368) in patients with germline BRCA mutation-associated breast or ovarian cancer, high-grade serous cancer and triple-negative breast cancer (trial number, NCT02203513) (54). The latter study provided positive proof of concept of the efficacy and tolerability of the Chk1/2 inhibitor in patients with ovarian cancer (54). From such studies it may be assumed that ovarian cancer cells, including CCC cells, exhibit an increased reliance on the ATR-Chk1 axis for cell survival.

Thirdly, CCC cells commonly lack compensatory DNA damage response machinery, as mutations in ARID1A represent one of the most common molecular alterations in CCC (15). ARID1A deficiency reportedly triggers genomic instability and apoptosis in ATR-deficient cells (32). These data suggest that ARID1A may be a synthetic lethal partner of ATR.

Finally, the PTEN mutations are also commonly observed in CCC (31). siRNA screening strategies identified PTEN and ATM as synthetically lethal partners (55). One preclinical study demonstrated that ATM inhibition resulted in DNA damage, cell cycle arrest and apoptosis specifically in PTEN-deficient cells (55). PARP inhibition also sensitized cancer cells to genotoxic stress in PTEN-deficient cells (56). Although a variety of loss of function genes, including in HNF, ARID1A, PIK3CA and PTEN, in CCC are driver or passenger events, these genes may function as synthetic lethal pairs under replication stress conditions (16).

6. Conclusions

The present article summarized recent advances in molecular understanding of synthetic lethal partners. CCC, the most common type 1 ovarian cancer in Japan, demonstrated chemoresistance resulting in poor prognosis (57). Novel potential targets in CCC therapy were additionally discussed. The development of novel cancer drugs is a time-consuming and expensive process with a high rate of failure in late-stage clinical trials (58). The synthetic lethality strategy to identify novel partners for potential genetic mutations has emerged to overcome this challenge (5,8). Homologous recombination deficiency including BRCA1/2 or p53 mutations combined with an increase in replication stress may result in a tumor being more susceptible to PARP inhibition (38,45,49,56). Since these particular genes are rarely observed to be mutated in CCC, there is considerable interest in identifying alternative therapeutic options of PARP inhibitor sensitivity (2). Synthetic lethal interactions have a variety of types, involving genes that function as a critical backup, paralog genes derived from the

same ancestral gene, subunit genes of a multiprotein complex or genes that belong to a single linear signaling pathway (8). The present review highlighted promising candidate genes, including p53 and BRCA1-regulated stress-inducible genes and genes involved in the regulation of replication initiation, relevant DNA repair factors and cell cycle distribution, which may be associated with the observed deficiency in homologous recombination capacity. Among these synthetic lethal pairs, the genetic ablation of the DNA repair response genes located in parallel signaling pathways may be one of the important patterns resulting in synthetic lethality. Investigators have unraveled a set of candidate gene targets hypothetically resulting in synthetic lethality. HNF, ARID1A, ATR, ATM, Chk1 and PTEN may be the key genes in CCC (18,32,47,52,55). Notably, the HNF-Chk1 axis was specifically upregulated in CCC (18). ARID1A mutation-driven cancer cells may rely on HNF overexpression for survival, predicting the potential association between ARID1A and HNF determining synthetic lethality. The pharmacological inhibition of Chk1 is also likely to be synthetically lethal to ARID1A. These predicted genes are promising candidates for in-depth investigation and experimental validation to accumulate significant data for the application of clinical trials. Further clinical studies are required to investigate the safety and therapeutic effects of synthetic lethality pairs in CCC tumor types with replication stress.

In conclusion, the development of synthetic lethal approaches may expedite the formation of novel concepts regarding targeted cancer therapeutics in the future, and this strategy represents a potentially paradigm-shifting initiative. An understanding of high-confidence synthetic lethal interaction pairs may aid in the development of cancer therapies.

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Authors' contributions

SM collected data regarding the signaling pathways and underlying mechanism of synthetic lethality using the SynLethDB database. KI, EN and SM performed the literature search and supervised the study. YY, KO and NK made substantial contribution to conception of the study. HK contributed to the study design and interpretation of included research studies. The final version of the manuscript has been read and approved by all authors.

Ethics approval and consent to participate

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Consent for publication

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Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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