Roles of DNA damage repair and precise targeted therapy in renal cancer (Review)

YONGCHANG LAI*, ZHIBIAO LI*, ZECHAO LU*, HANXIONG ZHENG, CHIHENG CHEN, CAN LIU, YAFEI YANG, FUCAI TANG and ZHAOHUI HE

Department of Urology, The Eighth Affiliated Hospital of Sun Yat-sen University, Shenzhen, Guangdong 518033, P.R. China

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Abstract. The primary subtypes of renal cell carcinoma (RCC) include clear cell, papillary and chromophobe RCC. RCC occurs often due to loss of von Hippel-Lindau (VHL) and accumulation of lipids and glycogen, and RCC cells may exhibit sensitivity to the disruption of normal metabolism or homologous recombination gene defect. Although the application of molecular-targeted drugs (tyrosine kinase inhibitors) and immune checkpoint inhibitors has been recommended for the treatment of advanced RCC, more targets of DNA damage repair (DDR) signaling pathway involved in the synthetic lethal effect have been investigated. However, although achievements has been made in the exploration of the roles of DDR genes on RCC progression, their association has not been systematically summarized. Poly (ADP-ribose) polymerase (PARP) 1 inhibitors are used in tumors with BRCA1/2 DNA repair-associated mutations. PARP family enzymes perform post-translational modification functions and participate in DDR and cell death. Inhibitors of PARP, ataxia telangiectasia mutant gene and polymerase θ serve key roles in the treatment of specific RCC subtypes. PARP1 may serve as an important biological marker to predict the therapeutic effect of immune checkpoint inhibitors and evaluate the prognosis of patients with ccRCC with polybromo 1 mutation. Therefore, the roles of DDR pathway on RCC progression or treatment may hold promises for the treatment of certain specific types of RCC.

Correspondence to: Dr Fucai Tang or Professor Zhaohui He, Department of Urology, The Eighth Affiliated Hospital of Sun Yat-sen University, 3025 Shennan Zhong Road, Futian, Shenzhen, Guangdong 518033, P.R. China
E-mail: tangfc@mail.sysu.edu.cn
E-mail: hechh9@mail.sysu.edu.cn

*Contributed equally

Abbreviations: DDR, DNA damage repair; PARP, poly (ADP-ribose) polymerase; PARG, poly(ADP-ribose) glycohydrolase; NAD, nicotinamide adenine dinucleotide; nccRCC, non-clear cell renal cell carcinoma; pRCC, papillary renal cell carcinoma; chRCC, chromophobe renal cell carcinoma; OS, overall survival; HLRCC, hereditary leiomyomatosis and renal cell cancer; FH, fumarate hydratase; SDH PGL/PCC, succinate dehydrogenase-related hereditary paraganglioma and pheochromocytoma; CDRCC, collecting duct renal cell carcinoma; ICI, immune checkpoint inhibitor; PD-L1, programmed death ligand 1; VEGFR, vascular endothelial growth factor receptor; ATM, ataxia telangiectasia mutated; VHL, von Hippel-Lindau; HIF, hypoxia-inducible factor; TKI, tyrosine kinase inhibitor; ROS, reactive oxygen species; PBRM1, polybromo 1; SSB, single-strand break; XRCC1, X-ray repair cross complementary combination-1; NER, nucleotide excision repair; BER, base excision repair; HR, homologous recombination; NHEJ, non-homologous end joining; DSB, double-strand break; RIPK, receptor-interacting serine/threonine-protein kinase; TP53INP2, tumor protein p53-inducible nuclear protein 2

Key words: renal cell carcinoma, DNA damage repair, poly (ADP-ribose) polymerase, synthetic lethal, targeted therapy

Contents

1. Background

Physical external factors (ultraviolet, ionizing radiation), chemical drugs or poisons [benzo(a)pyrene, alkylating agents, platinum compounds, psoralens], as well as endogenous byproducts (metabolites, free radicals) result in numerous forms of DNA damage in cells (1). The primary pathways for DNA damage repair (DDR) include mismatch repair, nucleotide excision repair (NER) and base excision repair (BER) for single-strand break (SSB) and double-strand break (DSB) repair mechanisms (2).

Homologous recombination (HR), classical non-homologous end joining (NHEJ), alternative end joining and single strand annealing repair are key repair pathways of DSBs (3). The HR-based repair pathway, known as gene transformation pathway, is generally considered to be the sole error-free pathway that maintain DNA integrity and initial DNA

sequence. The poly (ADP-ribose) polymerase (PARP) family consists of 17 abundant nuclear enzymes that are present in the majority of eukaryotic cells and promote formation of ADP-ribose polymer (PAR) (4). DNA damage recruits and activates PARP-1 and PARP-2, leading to ADP-ribosylation at multiple sites. PARP-1 mediates several processes involved in DNA metabolism, such as single-strand damage repair, NER, DSB repair and regulation of chromatin structure (5). By identifying endogenous or exogenous DNA damage, PARP-1 aggregates and bind to the site of DNA strand breaks to participate in BER. In BER, PARP-1 is catalyzed and activated by synthesis of PAR polymers by PARylation. A series of repair proteins, such as X-ray repair cross complementary combination-1 (XRCC1) and DNA polymerase β, are assembled to repair the DNA damage sites (6).

PARP transfers the ribose group of nicotinamide adenine dinucleotide (NAD^+) to modify target biomolecules. This process is known as poly-ADP-ribosylation or PARylation, a reversible post-transcriptional modification that requires both PARP-1 and poly-ADP-ribose glycohydrolase (PARG) (7,8). PARylation by PARP-1 and its degradation by PARG participate in regulating DNA damage responses and biological functions (i.e., stress responses, metabolism) (9). The structure-specific recognition protein-1 is recruited to SSB in a PARP-dependent manner by interactions with the XRCC1, both of which are involved in SSB repair (10).

PARP inhibitors (PARPis) lead to cell death, notably in cells with defective DDR function, by trapping PARP-1 on damaged chromatin (11). Only three of the 17 members of the PARP enzyme family (PARP-1, PARP-2 and PARP-3) localize to the nucleus in response to early DNA damage and serve a crucial role in DDR (8). PARP1 has been implicated in the 10 hallmarks of cancer, while other PARPs modify certain cancer hallmarks, including PARP2 and PARP5a/5b, which modify cancer metabolism and replicative immortality, respectively (12).

Renal cell carcinoma (RCC) is one of the ten most common types of cancer in developed countries (13) and accounts for 2-3% of all adult tumors (14). RCC has a 2.2% incidence and 1.8% mortality rate worldwide (15). RCC is insensitive to traditional chemotherapy and radiotherapy and readily develops drug resistance; present treatment methods for localized RCC primarily include surgery, ablation and surveillance (16). Furthermore, targeted therapies for metastatic RCC are primarily focused on antiangiogenic therapy, such as inhibitors sunitinib and pazopanib, which are directed at the tyrosine kinase domain of vascular endothelial growth factor receptor (VEGFR) (17). In recent years, the combination of immunotherapy [programmed cell death 1/programmed cell death ligand (PD-L1) blockade] with tyrosine kinase inhibitors (TKIs) has increased the overall survival rate for patients with RCC (18,19). However, as a type of targeted therapy, the roles of PARPi direct to DDR in RCC treatment have not been fully explored.

Ongoing studies have been combined PARPi, antiangiogenic therapy and novel immunomodulators to improve the outcome of urinary tract tumors (20,21). In addition, studies have explored the association between DDR and prostate or bladder cancer progression and treatment (22-24). To the best of our knowledge, however, there is a lack of systematic reviews of DDR, PARP and RCC. Although PARPis have been investigated in prostate cancer treatment, their use in RCC requires additional investigation and molecular classification (25). Advanced stages of certain types of cancer develop resistance against PARPis (26). Therefore, optimization of the use of PARPis is a challenge. The present review article aimed to summarize the association between DDR pathway and RCC progression and treatment.

2. DDR, RCC progression and precision treatment

DDR and RCC. DDR genes can be useful for predicting progression and clinical benefits of immunotherapy for ccRCC (27). Multigene tests including DDR gene provide a more comprehensive risk assessment for patients with early-onset renal cancer in comparison with the control population in genome aggregation database (28,29). DDR gene may predict future prognosis of patients with ccRCC as well as immunotherapy response (30-32). Deleterious DDR gene alterations are associated with advanced ccRCC and may affect outcome of immunotherapy in ccRCC (29).

ccRCC is characterized by chromosomal instability, which is primarily caused by errors in DDR and affects DSB repair mechanisms (33). Among DSB repair mechanisms, NHEJ is an error-prone repair mechanism in which broken DNA ends are joined compared with HR repair in DNA integrity and initial DNA sequence (34). Genes encoding HR proteins include BRCA1, BRCA2, ataxia telangiectasia mutated (ATM) gene Rad3-associated kinase (ATR), BRCA1-associated RING domain 1, Bloom's syndrome (BLM) RecQ like helicase and RAD51 recombinase, and HR deficiency is defined by the inability to repair DNA damage by the normal HR repair pathway (35). Although a single gene mutation cannot result in cell death, mutations of both genes (i.e., BRCA1/2 and PARP1) lead to cell death and are considered to have a synthetic lethality effect (26).

Polymerase θ produces synthetic lethal effects with multiple DNA repair genes, such as BRCA1/2, making it key in HR-deficient cancer (36). Although PARP1 binds to DNA damage sites, PARPi may prevent PARylation, which in turn hinders recruitment of BER enzyme, impedes DNA repair and leads to DSBs and synthetic lethality in a HR-deficient mechanism (37). By contrast, the cytotoxicity of the captured PARP-DNA complexes is higher than that of the unrepaired SSBs induced by PARP inactivation, indicating that PARPi can be toxic by trapping the PARP enzyme on the DNA (38). PARP1/2 and other repair factors were activated and recruited by DNA breaks and clinical PARPis are considered to prolong the presence of PARP1/2 molecules at break sites and chromatin, called 'trapping' (39). Furthermore, PARP mediates DSB and NER damage repair, stability of replication forks and chromatin regulation of DNA (5).

PARPis, such as olaparib, niraparib, talazoparib and rucaparib, have been recently approved by the US Food and Drug Administration for treatment of ovarian and germline BRCA DNA repair associated mutant breast cancer (40). PARG inhibitors also promote sensitivity to radiation-induced DNA damage, inhibit the progression of replication fork and hinder the survival of cancer cells, further supporting the hypothesis that selective inhibition of PARG may prevent the survival of

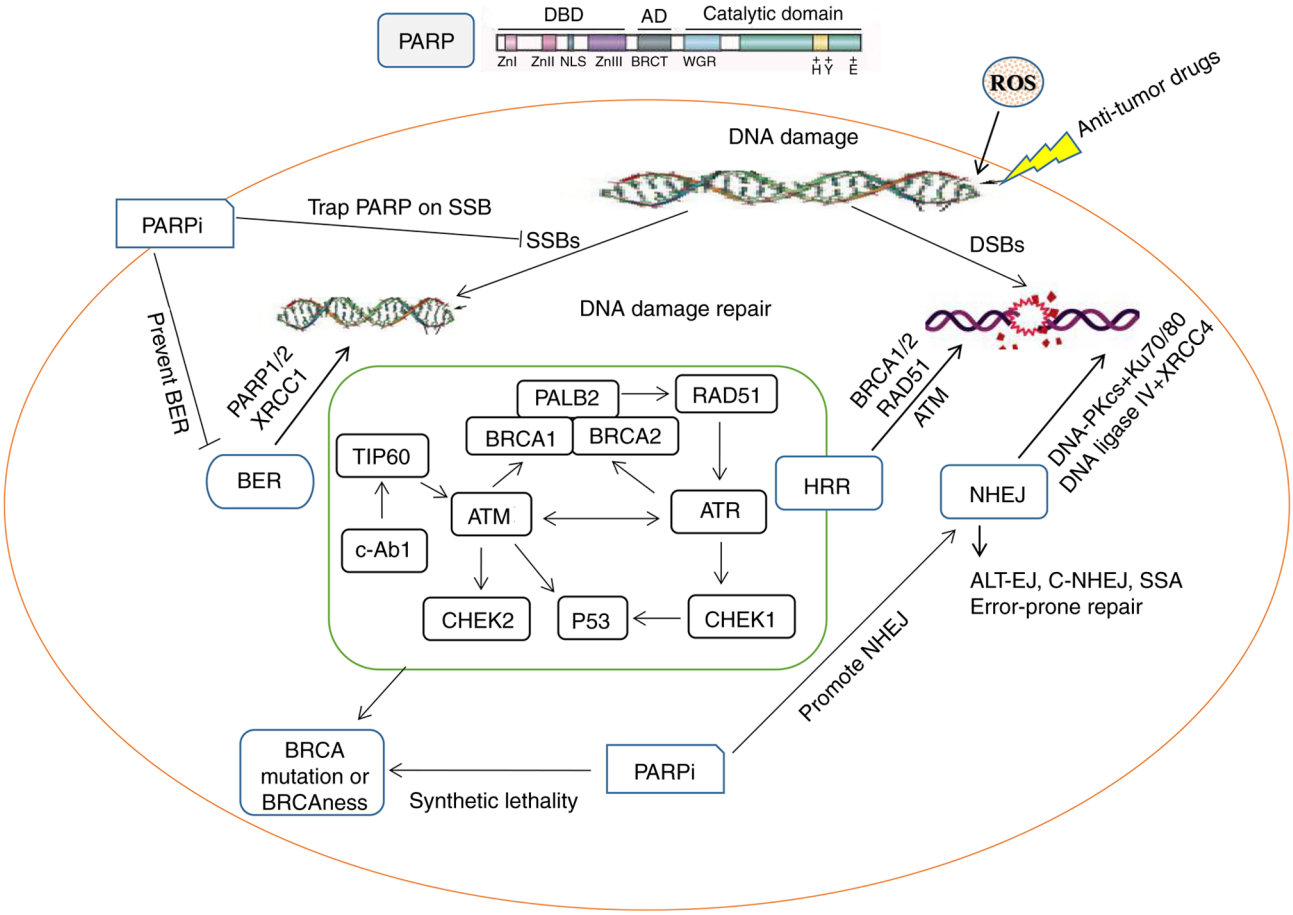

Figure 1. Roles of PARP-1 in DNA damage repair and synthetic lethality. DNA damage caused by SSBs and DSBs ccorrespond to different repair pathways. The simultaneous defects of the BER and HR repair pathways force transition to NHEJ repair, an error-prone repair mechanism that leads to cell death. BRCAness: defects in homologous recombination-mediated repair; BER, base excision repair; SSB, single-strand break; HRR, homologous recombination repair; DSB, double-strand break; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; ALT-EJ, alternative end joining; PARPi, poly-ADP-ribosomal polymerase inhibitor; DBD, DNA binding domain; AD, automodification domain; ROS, reactive oxygen species; XRCC1, X-ray repair cross complementary combination-1; PALB2, partner and localizer of BRCA2; RAD51, RAD51 recombinase; TIP60, lysine acetyltransferase 5; ATM, ataxia telangiectasia mutated; ATR, ATR serine/threonine kinase; CHEK, checkpoint kinase 1; C-NHEJ, non-homologous end joining; SSA, single strand annealing.

cancer cells (41). Therefore, although the action sites of PARG inhibitors and PARPi are different, PARPi destabilize replication forks and PARG inhibitors may complement PARPi in exacerbating the replication deficiencies of tumor cells by causing DNA damage, hindering DNA repair (42). The roles of PARP1 in DDR and synthetic lethality are shown in Fig. 1; Briefly, the DNA damage caused by SSBs and DSBs correspond to different repair pathways, while the simultaneous defects of the BER and HR repair pathways force transition to NHEJ repair, an error-prone repair mechanism that leads to cell death (Fig. 1). In addition, the DDR-associated target molecules are summarized and shown in Table I.

The histone PARylation factor 1 forms a joint active site with PARP1/2 and enables recognition of the DNA damage site by PARP1/2. The latter binds to the site of DNA damage and uses NAD^+ to convert receptor protein PAR into the ADP ribosomal polymer, thus facilitating the separation of PARP1/2 from the DNA break and subsequent repair (43). Following activation by DNA damage, PARP participates in genome integrity, tumor formation and stemness via the PARP1-Krüppel like factor 4 complex, thus regulating the expression of telomerase in tumor and embryonic stem cells (44). PARylation is a reversible post-transcriptional modification that requires PARP1 and PARG. By activating PARylation of target proteins, PARP regulates numerous physiological processes, including chromatin remodeling, DNA damage response, apoptosis and mitosis (45). Inhibition of PARG can also lead to synthetic lethality along with factors that inhibit DNA replication, such as checkpoint kinase 1 inhibitors. PARG inhibitors compensate for the decreased efficacy of PARPis with inhibition of DNA replication factors [i.e., Checkpoint kinase 1(CHK1) inhibitors] in ovarian cancer treatment (46). In addition to BRCA1/2 mutations, other HR repair-associated genes or predictive biomarkers are also currently explored in the early treatment of tumors by adjuvant and neoadjuvant therapy with PARPis (47).

The rs5751129 polymorphic genotype and mRNA expression levels of XRCC6 (Ku70) are associated with RCC etiology and may serve as a marker for increased susceptibility of the Taiwanese population to RCC (48). A non-invasive panel comprising circulating tumor cell and urine cellular polymorphisms of XPC (polymorphic site: rs2228001, A2815C) and XRCC1 (polymorphic site: rs25487, G1196A) showed high sensitivity for bladder and prostate cancer and

Table I. DNA damage repair-associated target and molecules.

A, SSB

DNA damage repair	Target	Inhibitor
BER	PARP	Rucaparib, PJ34, NU1025, Benzamide, Picolinamide
	OGG1	TH5487

B, DSB

DNA damage repair	Target	Inhibitor
HR	ATM	Wortmannin, KU-55933, KU-60019, AZD1390, AZ32, AZD0156
	ATR	Berzosertib, Elimusertib, Ceralasertib
	CHK1	MK8776, Prexasertib
	CHK2	Silmitasertib, TTP22
	RAD51	Amuvatinib, RI-1 (RAD51 inhibitor 1)
ALT-EJ	Polymerase θ	Novobiocin
NHEJ	DNA-PK	NU7441, Wortmannin, PIK-75, NU7026, 6-Nitroveratraldehyde, KU-0060648, Nedisertib, AZD7648, Samotolisib
	DNA ligase IV	SCR7
	MRE11 endonuclease	PFM01

C, Other

DNA damage repair	Target	Inhibitor
Not specific or clear	MTH1	(S)-crizotinib
Not specific (HR, NHEJ or others)	Topoisomerase	Doxorubicin

SSB, single-strand break; DSB, double-strand break; BER, base excision repair; PARP, poly-ADP-ribosomal polymerase; HR, homologous recombination; OGG1, 8-oxoguanine DNA glycosylase; ATM, ataxia telangiectasia mutated; ATR, ATR serine/threonine kinase; CHK, checkpoint kinase; RAD51, RAD51 recombinase; PK, protein kinase; MRE11, MRE11 homolog, double strand break repair nuclease; MTH1, nudix hydrolase 1; ALT-EJ, alternative end joining; NHEJ, non-homologous end joining.

RCC screening (49). The XRCC1 Arg194 allele and urinary 8-hydroxy-2 deoxyguanosine levels and total arsenic concentration are predictive factors for RCC prognosis (50). In addition, dual PARP and RAD51 inhibitor conjugates disrupt resistance mechanisms to olaparib treatment in breast cancer cells regardless of the mutation status of BRCA (51). BRCA1-associated protein 1 (BAP1) encodes a widely expressed deubiquitinase of histone H2A, resulting in increased sensitivity of bromodomain and extra-terminal inhibitors to BAP1-deficient cancer (such as cutaneous and uveal melanoma and ccRCC) (52).

Role of PARP in synthetic lethal effects and cell death. PARP is associated with necroptosis, autophagy and other types of cell death (53). PARP is cleaved by activated caspases both *in vitro* and *in vivo*, resulting into two fragments of 24 and 89 kDa, which is deemed to be a hallmark of the apoptosis (54). By contrast with caspase-3 and mutated exosites, caspase-7 uses RNA to promote proteolysis of PARP1 and other RNA-binding proteins (55). The 24 kDa DNA-binding domain may block the DNA-repair enzyme function at the divided chromatin site, while the 89 kDa fragment-containing catalytic domain cannot be activated by DNA breaks. Eventually, enzyme activity of PARP is lost, which promotes the induction of cell apoptosis (56,57). Following oxidative stress and DNA damage, PARP1 plays a dual function in regulating necrosis and autophagy. PARP1 overactivation results in ATP depletion and necrotic cell death, while its normal activation enhances autophagy via the serine threonine kinase 11/protein kinase AMP-activated catalytic subunit α2/mammalian target of rapamycin pathway, thereby increasing cell survival (58).

Loss or inactivation of PARP1 delays starvation-induced autophagy, which plays an important role in contributing to survival during nutrient starvation conditions to optimize the usage of limited energy supplies, while autophagy and PARP1 activation exert a pro-survival effect following

nutrient deprivation (59). In addition to autophagy and apoptosis, necroptosis caused by tumor necrosis factor (TNF)-related apoptosis-inducing ligand, which mediates the receptor-interacting serine/threonine-protein kinase (RIPK) 1/RIPK3-dependent activation of PARP1 pathway, is associated with liver injury (60). Unlike the induction of apoptosis, necrosis and other forms of cell death, parthanatos is a PARP1-dependent and caspase-independent cell-death pathway (61). During PARP1-mediated cell death, mitochondrial protein apoptosis-inducing factor is released and transferred to the nucleus (62). In BRCA wild-type) ovarian cancer, PARP inhibition promotes ferroptosis by suppressing solute carrier family 7 member 11 and synergizing with ferroptosis inducers (63). Antioxidants and the PARP1 inhibitor olaparib rescue the death of RCC cells triggered by zafirlukast, a cysteinyl leukotriene receptor 1 antagonist, dependent on that of hypoxia-inducible factor (HIF)-2α (64). Therefore, the understanding of the association between PARP and forms of cell death as well as its role in gene stability is key for design of novel chemotherapeutic drugs for various types of cancer.

Certain PARP family enzymes exhibit poly-catalyzed enzymatic activity, whereas others are characterized by mono-catalyzed enzymatic activity (Table II) (65). PARPis competitively bind to the NAD^+ binding sites of the PARP1/2 enzymes and inhibit PARylation, improving the clinical benefits in BRCA mutant tumors (Table I). The use of the oral inhibitor of PARP1/2 olaparib has been approved by FDA. This compound is primarily used for treatment of patients with ovarian cancer containing the BRCA1/2 mutation (66). Patients with breast and ovarian cancer who possess BRCA1/2 mutations or deletions may benefit from PARP1 and PARP2 inhibitors (67). Ovarian cancer cells with higher expression of $NADP^+$ are more sensitive to PARPi (68). Synthetic lethality enables PARPis to achieve their desired efficacy in clinical trials (26,69,70). Presently, the PARPi is used in tumors with BRCA1/2 mutations, such as those derived from breast and ovarian cancer, and ongoing research is exploited beyond germline BRCA mutations to identify suitable biomarkers to predict treatment response (71).

As PARP trapping activity may exceed the inhibitory potential of PARylation reactions, the clinical exploration processes for the antitumor activity of PARPis are different (72). Moreover, the supply domain of PARP1 binds to the nicotinamide-riboni site of NAD^+; PARPis simulate the nicotinamide structural domain and competitively bind the Ni binding site of PARP, which leads to partial binding to the receptor binding site of PARP (73). As NAD^+ competitors are prone to off-target effects, a novel inhibitor of PARP1 that specifically targets the histone-dependent PARP1 activation pathway has been developed to overcome the limits of NAD-like PARP1 inhibitors, which exhibit high specificity to PARP1 and a potentially potent therapeutic effect on urological tumors (74). In addition, classical NAD-like PARP1 inhibitors may inhibit the survival of normal kidney epithelial cells at high concentrations, whereas novel non-NAD-like PARP1 inhibitors are only active against malignant cells (75). As PARP activity is associated with various types of cell death, development of PARP activators that contribute to tumor cell death is being investigated (Table II).

Renal cancer and precision therapy. RCCs are classified into three primary histopathological classifications as follows: ccRCC, pRCC and chRCC, with a proportion of incidence 70-75%, 10-16% and 5%, respectively (76). Non-ccRCC (nccRCC) include the pRCC, chRCC, unclassified, collecting duct, and translocation carcinoma (77). As most prevalent subtype of RCC, Approximately 70% of the ccRCC cases are are linked to the mutation or inactivation of a tumor suppressor gene, namely von Hippel-Lindau (VHL), resulting in activation of the HIF/VEGF pathway (78). TKIs targeting VEGFR are key RCC treatment drugs (18). VEGFR-based TKIs, such as sunitinib and pazopanib, have been the mainstay of treatment for patients with advanced RCC. However, RCC cells are prone to develop drug resistance to VEGFR-TKIs, which limits the efficacy of targeted therapy (79). Recently, several therapeutic options have been approved (immunotherapy and immunotherapy/TKIs) for first-line treatment of metastatic ccRCC, such as axtinib + pembrolizumab or avelumab, nivolumab + cabozantinib or ipilimumab and pembrolizumab + lenvatinib (Fig. 2) (19).

To date, various abnormal gene indicators of RCC have been detected and evaluated. The mutations of polybromo 1 (PBRM1), BRCA1-associated protein 1 and lysine demethylase 5C genes affect the outcome of targeted therapy with sunitinib in patients with metastatic ccRCC (80). Global tumor cell expression profile may be altered by loss of PBRM1 in ccRCC, thereby influencing the responsiveness to immune checkpoint therapy (81). The increase in expression levels of p53 and alteration of targets of the rapamycin pathway, such as neurofibromin 1 and phosphatidylinositol-4,5-biphosphate 3-kinase catalytic subunit α, may be associated with resistance of patients following first-line VEGF-directed therapy (82). Cyclin-dependent kinase inhibitor 2A and MET proto-oncogene receptor tyrosine kinase are the most frequently altered somatic genes in nccRCC tumors and are treated by cabozantinib (83).

In a patient with chRCC, biallelic TSC complex subunit 2 mutations have been associated with a notable response to temsirolimus (84). Atezolizumab and bevacizumab have been shown to be safe and produce an objective response in patients with RCC and variant histology or >20% sarcomatoid differentiation, particularly in patients with PD-L1-positive tumors (85). Belzutifan, a HIF-2 inhibitor, has been approved by the FDA for treatment of patients with VHL syndrome-associated RCC that do not require immediate surgery (86). However, in clinical trials, only some ccRCC patients appear to be benefit from the HIF-2 inhibitors, and using intact p53 pathway status may be premature to predict sensitivity ccRCC patients to HIF-2 inhibitors (87). Compared with normal kidney cells, benzo[4]helicenium shows specific killing efficiency against RCC, selectively damaging mitochondria and DNA in RCC cancer cells, providing a potential targeted drug for RCC precision therapy (88).

DDR genes and precision treatment of renal cancer. Resistance to targeted therapies remains a key obstacle in clinical treatment of cancer. Sunitinib induces genomic instability of RCC cells by affecting the interaction of microtubule-associated protein 1A/1B-light chain 3-II and PARP1 (89). As a PARPi, olaparib reverses drug resistance

Table II. PARP-associated catalyzed enzymatic activity and inhibitors.

PARP family member	Catalyzed enzymatic activity	Inhibitor
PARP1	Poly	Talazoparib, Olaparib, Rucaparib, Veliparib, Iniparib, Fluzoparib, Pamiparib, Stenoparib, Venadaparib, Niraparib, AG-14361, NMS-P118, Picrasidine M, BYK204165, ME0328, E7449, 4-Hydroxyquinazoline, Mefuparib
PARP2	Poly	Venadaparib, Pamiparib, Stenoparib, A-966492, E7449, Niraparib, Olaparib, Veliparib, BYK204165, UPF 1069, Mefuparib
PARP3	Mono	ME0328, Niraparib
Tankyrase-1	Poly/Oligo	XAV-939, MN64, RK-287107, G007-LK, E7449, Mefuparib
Tankyrase-2	Poly/Oligo	XAV-939, MN64, RK-287107, NVP-TNKS656, WIKI4, G007-LK, E7449, Mefuparib
PARP7	Mono	RBN012759, GeA-69
PARP10	Mono	OUL35
PARP14	Mono	Atamparib, PARP14 inhibitor H10
PARP Activiator	Not applicable	Licochalcone D, 4',5,7-Trimethoxyflavone, Ferruginol, Hellebrigenin, Polyporenic acid C

PARP, poly (ADP)-ribosomal polymerase.

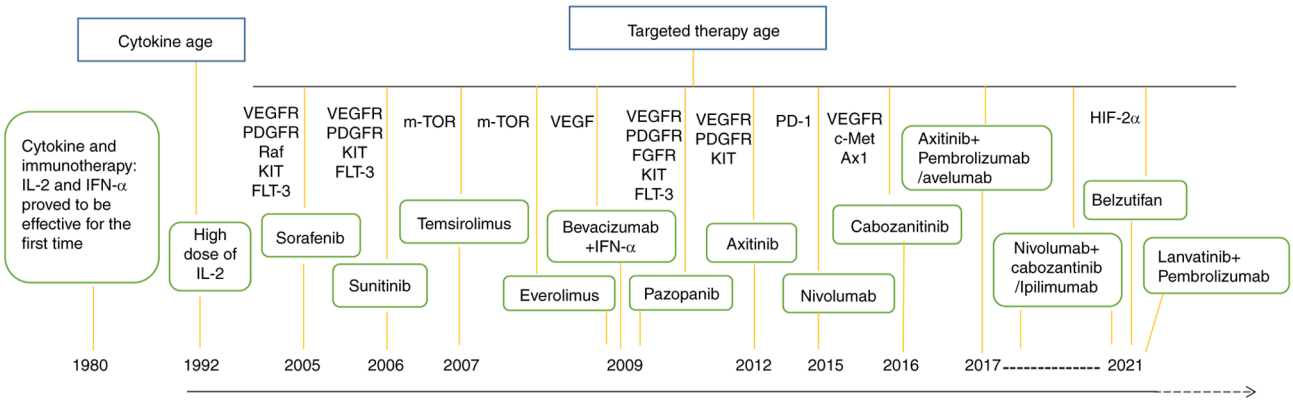

Figure 2. Timeline for exploration of metastatic renal cell cancer treatment drugs approved by Food and Drug Administration and the corresponding targets.

to sorafenib in liver cancer (90). A total of 27-32% of RCC tissue samples have mutations in HR genes, while PARPi agents (such as niraparib, talazoparib and rucaparib) that target DDR mutations may be effective treatment options for RCC (91). Due to increased PARP1 expression and decreased PARG levels, ccRCC is accompanied by increased levels of poly(ADPribose) (pADPr). The development of ccRCC is associated with accumulation of pADPr (75). VHL-deficient RCC is associated with downregulation of DNA repair induced by hypoxia, conferring increased sensitivity to PARPis (92). Impaired DNA repair ability, which is associated with the BRCA1A complex, sensitizes folliculin-deficient RCC cells to olaparib treatment (93). Therefore, it is desirable to explore the combination effect between VEGFR-TKIs and PARPi in RCC (Fig. 3). The PARP and PARPi function in modulation of RCC tumor cell death was shown in Fig. 3.

In addition to DNA damage, PARPs serve metabolic regulatory roles and are involved in obesity, which modulates carbohydrate and lipid metabolism and guides pathologically metabolic abnormalities (94). PARPs act as cofactors of nuclear receptors or transcription factors that are activated in a lipid-responsive manner. PARPs modulate lipid metabolism and homeostasis, while activation PARP disrupts lipid metabolism signal (95). As aforementioned, ccRCC is often associated with VHL mutations or deletions, which affect its metabolic properties and enhances sensitivity to glutathione peroxidase 4 inhibitors that induce ferroptosis (96). Glutaminase inhibitors inhibit pyrimidine synthesis and increase levels of reactive oxygen species in VHL-deficient RCC cells, leading to DNA replication stress and suppression of $VHL^{-/-}$ RCC cell proliferation, while olaparib, a PARPi, inhibits proliferation of these cells by acting in a synergistic mechanism with glutaminase inhibitors (97). This combined

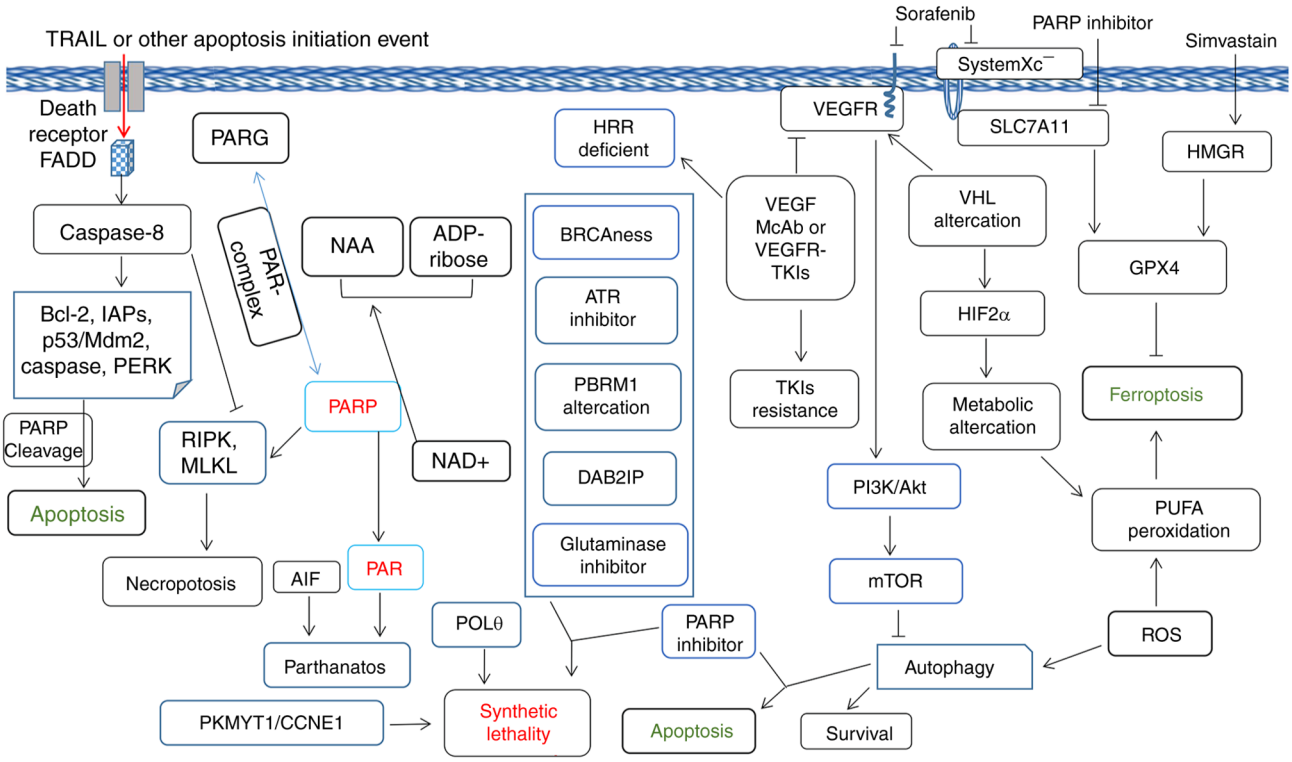

Figure 3. Role of PARP and the mechanism of PARPi in modulation of RCC tumor cell death. Interactions between PARPi, VHL, apoptosis, ferroptosis, autophagy, necroptosis, VEGFR and other synthetic lethality factors associated with RCC therapy provide potential novel therapeutic targets beyond targeted therapy. NAA, nicotinamide; ATR, ataxia telangiectasia mutated gene Rad3-associated kinase; VHL, von Hippel-Lindau; HIF, hypoxia-inducible factor; VEGFR, vascular endothelial growth factor receptor; TKI, tyrosine kinase inhibitor; mTOR, mammalian target of rapamycin; ROS, reactive oxygen species; TRAIL, TNF-related apoptosis-inducing ligand; IAP, inhibitors of apoptosis protein; HMGR, 3-hydroxy-3-methyl glutaryl coenzyme A reductase; FADD, Fas-associating protein with a novel death domain; PBRM1, polybromo 1; HRR, homologous recombination repair; MLKL, mixed lineage kinase domain-like protein; RIPK, receptor-interacting serine/threonine-protein kinase; PUFA, polyunsaturated fatty acid; POLθ, polymerase θ.

treatment supports the development of novel treatment strategies that target VHL-deficient RCC and chemoresistant ovarian cancers (97,98). By utilizing hypoxia-inducible lipid droplet associated protein, the VHL/HIF-2α pathway may induce ferroptosis by upregulating lipid peroxidation levels (99).

The Warburg effect, demonstrated by increased glycolytic intermediate labeling, decreased pyruvate dehydrogenase flow and decreased tricarboxylic acid cycle labeling, has been observed in various primary ccRCC cases (100). By regulating PARP1 expression, lipid metabolism-associated drugs simvastatin and tanshinone I inhibit proliferation of melanoma and renal tumour cells (101). Therefore, PARP inhibition may exert a synergistic inhibitory effect on tumor growth of ccRCC with other metabolic inhibitory molecules (97). The gene mutations of RCC are heterozygous both at the primary site and metastatic lesions, but the distant metastatic lesions may exihibit more significant growth and invasion phenotype, which may be associated with the function of the DDR response. Therefore, the primary site, and, particularly the metastatic lesions, should be considered for the evaluation of metastatic RCC.

RCC is non-sensitive to chemoradiotherapy; however, its mechanism remains unknown. The increase of PARP1 in RCC cells leads to radioresistance and certain PARP1 inhibitors enhance sensitivity of radiotherapy in human RCC xenograft and head and neck squamous cell carcinoma cell models (102,103). DAB adaptor protein 2 interactive protein (DAB2IP) can degrade PARP1 by forming a complex with PARP1 and E3 ligases, causing DAB2IP deficient RCC cells acquire resistance to ionizing radiation (102). Inhibition of DNA repair by radiation therapy combined with veliparib accelerates induction of tumor cell senescence and induces expression of immune stimulators to activate cytotoxic T lymphocytes and mediate antitumor response (104). Patients with ccRCC with high exosome component 1 show poor prognosis; exosome component 1 cleaves single-stranded DNA and sensitizes human ccRCC cells to PARPis (105).

Increased progression-free survival has been noted in patients with advanced RCC treated with first-line nivolumab combined with cabozantinib compared with those treated with sunitinib (106). PARP1 low expression protein levels are associated with higher patient overall survival following treatment with immune checkpoint inhibitors (ICIs) (107). The overall survival and progression-free survival of patients with PBR-mutated 1 (PBRM1) ccRCC treated with nivolumab were significantly increased in the PARP1-low group compared with that noted in the PARP1-high expression (107). Inactivation of PBRM1 occurs in 40% of ccRCC cases and contributes to a synthetic lethal effect for PARP and ATR inhibitors, which provides a basis for evaluating the efficacy of these inhibitors in treatment of patients with PBRM1-deficient cancer (108). DEAD/H-box helicase 11 may be a novel biomarker for patients with RCC resistance to TKIs and immunotherapy and may predict PARPi sensitivity in RCC (109).

In collecting duct RCC (CDRCC), expression levels of baculoviral IAP repeat containing 5, pituitary tumor-transforming gene 1 regulator of sister chromatid separation, centromere protein F and cyclin-dependent kinase inhibitor 3 [specific marker genes of cancer stem cells (CSCs)] are associated with poor, while inhibitors of PARP, histone deacetylase 2 and fibroblast growth factor receptor are effective against CSCs and may serve as potential therapeutic options for CDRCC (110). ATM is a key tumor suppressor gene found in almost 3% of RCC and is involved in HR repair (Fig. 1). ATM mutation may affect RCC tumor response to veliparib (a PARPi), which produces months of disease control, decreased levels of lactate dehydrogenase and improved performance status, as demonstrated in a case report of pRCC (111). A case for niraparib to sorafenib-axitinib-everolimus-resistance metastatic ccRCC with BAP1-Frame shift mutation has achieved a partial response and lasted for 5 months (112). Although has not been formally clinically tested, to the best of our knowledge, the above cases provide examples for the use of PARPi in the treatment of certain type of RCC. By producing fumarate, fumarate hydratase (FH) was defined as DNA repair required in NHEJ in cells (113). Inactivation or germline mutations of FH lead to hereditary leiomyomatosis and RCC (HLRCC), while loss of FH and accumulation of fumarate lead to decreased G2 checkpoint, which increases the possibility of endogenous DNA damage (114). Succinate dehydrogenase (SDH)-related hereditary paraganglioma and pheochromocytoma is another hereditary cancer syndrome associated with mutations in SDH. These mutations suppress the HR DNA repair pathway, thus rendering tumor cells susceptible to synthetic lethality by PARPi (115). Metabolites associated with germline mutations of FH and SDH genes (SDHA, SDHB, SDHC and SDHD) suppress HR repair pathway, conferring sensitivity to PARPis *in vivo* experiment or in clinical trials (116,117).

Since PARP is associated with various forms of cell death, such as apoptosis, autophagy and necroptosis, numerous PARP activators have been developed that exhibit inhibitory effects on RCC cells. For example, tumor protein p53-inducible nuclear protein 2 (TP53INP2) activates expression of PARP in patients with ccRCC and the overexpression of TP53INP2 inhibits ccRCC cell proliferation, migration and invasion (118). The induction of apoptosis in RCC cells is accompanied by elevation of reactive oxygen species (ROS) levels and induction of cleaved-PARP expression (119). PARP activation also plays a key role in necroptosis induced by glutamate, which is blocked by necrostatin-1 (120). Oridonin, a key ingredient of traditional Chinese medicine Rabdosia rubescens, enhances cytotoxicity of 5-fluorouracil in RCC cells by enhancing activity of PARP1 and inducing necroptosis (121). By increasing ROS levels, decreasing pro-PARP and increasing cleaved PARP expression levels, shikonin, a component of traditional Chinese medicine Comfrey, triggers programmed death of different types of RCC cell (122).

DDR and renal protection. Inhibition of angiogenesis may be associated with cardiovascular and kidney toxicity (123,124), as well as liver injury (125). Genetic deletion or suppression of PARP1 appears to be protective against toxic insult in various organs (i.e., hemodynamic dysfunction, multiple organ failure in patients with sepsis) (126,127). Pharmacological suppression or genetic deletion of PARP1 markedly decreases cisplatin-induced kidney injury, suggesting that pharmacological inhibition of PARP may be a promising method for inhibiting nephropathy caused by cisplatin (128). By attenuating the intrarenal inflammatory cascade, amelparib, a PARPi, exerts favorable effects in an mice model of ischemic acute kidney injury and promotes hypoxic HK-2 cell proliferation (129). Olaparib, a clinically approved PARPi for the treatment of HR-deficient tumors, improves organ function, suppresses inflammatory responses and expedites wound healing in severe burn injury (130). Therefore, genetic deletion or suppression of PARP1 may have a protective effect in various organs, suggesting the detoxification and synergism effect of PARPis on RCC treatment. Although there is no evidence to suggest that accumulation of renal toxicity is associated with occurrence of RCC, inhibition of PARP has a key protective effect on the kidney and its role in the prevention or treatment of RCC is worth investigation.

3. Future directions

Currently, the primary indications for the use of PARPis include tumors with BRCA1/2 mutation (131). However, identification of additional predictive biomarkers is key to determine the treatment options according to the RCC molecular characteristics (132). Drugs that promote HR repair defects in tumor cells (i.e., PI3K inhibitors, cyclin-dependent kinase inhibitors) may increase sensitivity to PARPis (133-136). As a specific polymerase θ inhibitor, novobiocin is combined with PARPi in treatment of HR-deficient tumors, as well in tumors that have acquired PARPi resistance (137). In addition, with the wider clinical use of PARPi, whether long-term inhibition of PARP activity may lead to mutations or protection in normal cells, or other unknown negative or positive effects, will more thoroughly be verified.

In ovarian cancer specimens, PARP1 and PD-L1 are negatively correlated (138). PARPi upregulates expression of PD-L1 by inactivating GSK3β in breast tumors and the antitumor effect of PARPi combined with PD-L1 is significantly increased *in vivo* compared with that of PD-L1 treatment alone (139). In immunotherapy, however, cytotoxic T lymphocyte-associated protein 4 antibody but not PD-1/PD-L1 blocker synergistically causes immune-mediated tumor clearance and survival benefit with PARPi in hereditary ovarian cancer (140). Therefore, combination of PARPi and ICIs in treatment of RCC should be investigated in future.

In addition to immunotherapy, development of synthetic lethal associated targets [such as protein kinase, membrane associated tyrosine/threonine 1)/cyclin E1 and e-cadherin/ROS1 inhibitor] may offer novel directions for tumor therapy (141,142). In addition, dual PARP and RAD51 or other DNA repair target inhibitor conjugates have the potential to overcome resistance mechanisms to PARPi. The positive results of inhibition of PARP in other DDR-associated genes, such as PALB2 (partner and localized of BRCA2) in prostate cancer, may benefit further explorations of PARP inhibition in RCC treatment. Therefore, DDR genes are key tumor targets involved in various forms of cell death. The application of

DDR inhibitors (such as PARPi) and other targeted, immunotherapy and tumor metabolism-associated drugs in RCC should be explored in future.

4. Conclusion

RCC incidence and mortality rate are high worldwide and lack useful immunotherapy options. The enzymatic activity or expression level of DDR genes, particularly PARP1, may serve as potential tumor therapeutic targets. Moreover, PARP1 may serve as a key biological marker to predict the therapeutic effect of ICIs and evaluate prognosis of patients with ccRCC. The role of DDR pathways in RCC progression may provide potential therapeutic targets for treatment of certain types of RCC.

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Authors' contributions

YCL, FCT, ZCL, HXZ, CHC, CL, YFY and ZHH contributed to manuscript writing. CHC, CL, YFY and ZHH conceptualized the study. YCL constructed tables and figures. FCT, ZBL, HZH and YCL critically revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Availability of data and materials

Not applicable.

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Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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