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•Review•

New insight into targeting the DNA damage response in the treatment of glioblastoma

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[ABSTRACT] Glioblastoma (GBM) is the most common invasive malignant tumor in human brain tumors, representing the most severe grade of gliomas. Despite existing therapeutic approaches, patient prognosis remains dismal, necessitating the exploration of novel strategies to enhance treatment efficacy and extend survival. Due to the restrictive nature of the blood-brain barrier (BBB), small-molecule inhibitors are prioritized in the treatment of central nervous system tumors. Among these, DNA damage response (DDR) inhibitors have garnered significant attention due to their potent therapeutic potential across various malignancies. This review provides a detailed analysis of DDR pathways as therapeutic targets in GBM, summarizes recent advancements, therapeutic strategies, and ongoing clinical trials, and offers perspectives on future directions in this rapidly evolving field. The goal is to present a comprehensive outlook on the potential of DDR inhibitors in improving GBM management and outcomes.

[KEY WORDS] Glioblastoma; DNA damage response; Small molecule inhibitors
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Introduction

Glioblastoma (GBM) is the most prevalent and aggressive form of primary brain cancer, classified by the World Health Organization (WHO) as a grade IV glioma, representing the highest level of malignancy [1, 2]. Characterized by a highly heterogeneous, genetically unstable, and extensively infiltrative tumor cell population, GBM exhibits significant resistance to standard therapies, with surgical resection alone proving insufficient for disease control [3]. In 2005, Professor Stupp introduced a multimodal treatment regimen, which remains the standard of care, integrating radiotherapy (RT) and temozolomide (TMZ) chemotherapy to improve patient outcomes. Fig. 1 shows the Stupp protocol and delineates clinical management strategies for newly diagnosed GBM patients across various age groups. Despite its widespread adoption, current statistics indicate that the median overall survival (OS) following this regimen ranges from 15 to 18 months, with a median progression-free survival (PFS) of approximately 7 months. The 5-year survival rate remains dismal, below 10%, positioning GBM among the most lethal cancers, alongside pancreatic and lung cancers [4-6].

The limited efficacy of this standard treatment is primarily attributed to the BBB and the intrinsic molecular and cellular heterogeneity of GBM, which contribute to poor therapeutic response and rapid disease recurrence. Once GBM recurs, therapeutic options are exceedingly limited, with a median OS of 24–44 weeks. These clinical challenges have driven the exploration of novel therapeutic strategies in recent years.

Among emerging approaches, the development of small-molecule inhibitors targeting the DNA damage response (DDR) pathway has gained significant attention. The DDR is a critical cellular network that orchestrates the detection, signaling, and repair of DNA damage, thus preserving genomic integrity and preventing oncogenesis. The Stupp regimen induces extensive DNA damage in GBM cells through RT and TMZ, consequently activating DDR pathways. Fig. 2 presents an overview of the primary types of DNA damage, with

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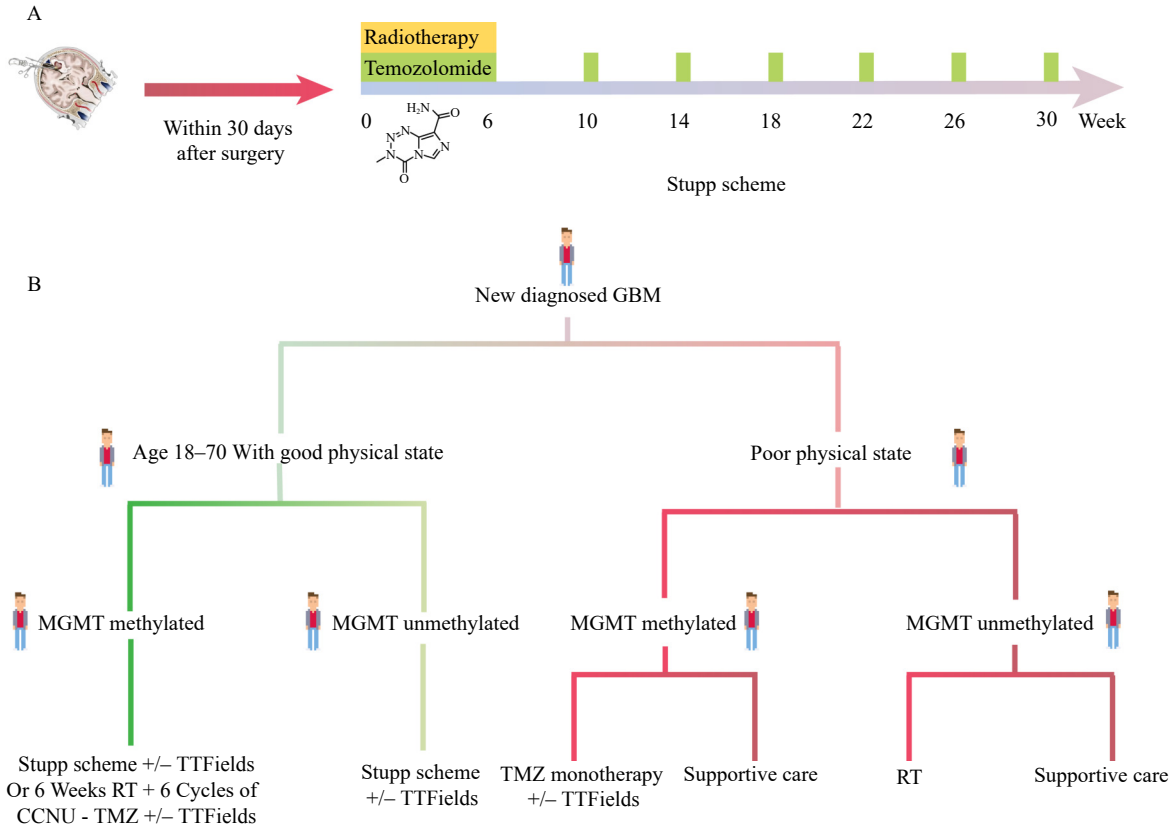


Fig. 1 Stupp scheme and standard of care for newly diagnosed patients with GBM. (A) Implement the Stupp scheme within 30 days after surgery. At the beginning of radiotherapy, TMZ was taken synchronously at a dose of 75 mg·m^{-2}·d^{-1} and was taken daily until the end of radiotherapy. End radiotherapy and stop taking medication. Six cycles of adjuvant chemotherapy will begin after 28 days. During adjuvant chemotherapy, each cycle lasts for 28 days (4 weeks), with TMZ taken on days 1–5 and rest on days 6–28 at a dose of 150–200 mg·m^{-2}·d^{-1}. (B) The treatment plans for different GBM populations are not completely the same. Since the MGMT methylation state can predict the effect of TMZ, it is considered not to choose TMZ for the treatment of patients with non-MGMT methylated tumors, especially when the risks brought by TMZ outweigh the benefits.

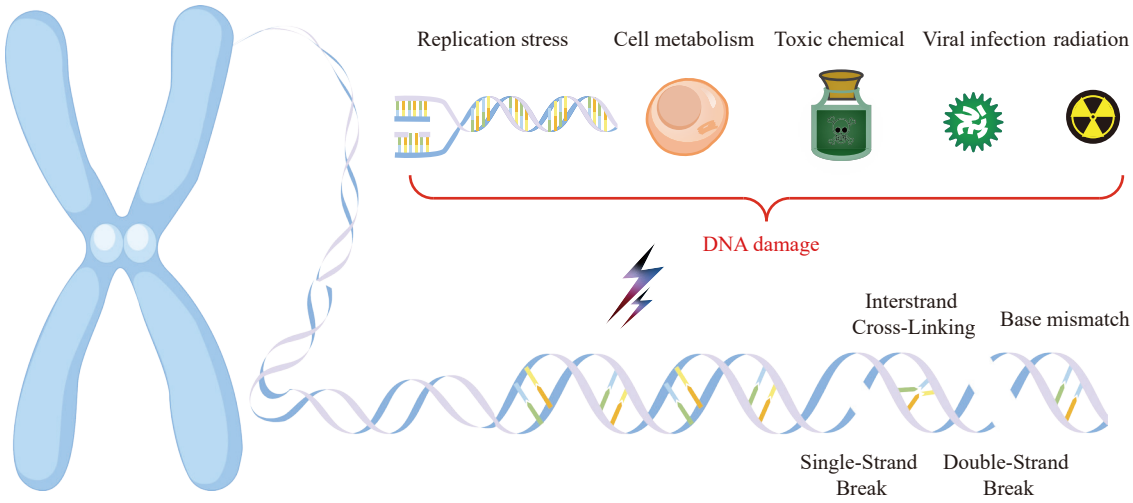


Fig. 2 The sources and types of DNA damage. Common sources of DNA damage include replication stress, cell metabolism, toxic chemicals, viral infections, and radiation. The main DNA damage includes base mismatches, crosslinks, and SSBs/DSBs.

double-strand breaks (DSBs) being the most cytotoxic, as they can result in complex genetic alterations such as insertions, deletions, and chromosomal translocations, ultimately leading to apoptosis [7]. Cells employ distinct repair mechanisms to resolve DSBs, primarily through homologous recombination (HR) and non-homologous end joining (NHEJ), each operating at specific cell cycle stages. Therapeutic strategies have focused on selectively inhibiting key DDR components,

thereby inducing synthetic lethality in tumor cells by disrupting essential repair processes (Fig. 3). Among DDR inhibitors, poly (ADP-ribose) polymerase inhibitors (PARPi) are the most extensively studied and have shown remarkable efficacy in ovarian cancer treatment, representing a significant milestone in precision oncology. In GBM, the combination of PARPi and temozolomide (TMZ, a chemotherapy drug in the Stupp scheme) is actively being explored for the treatment of

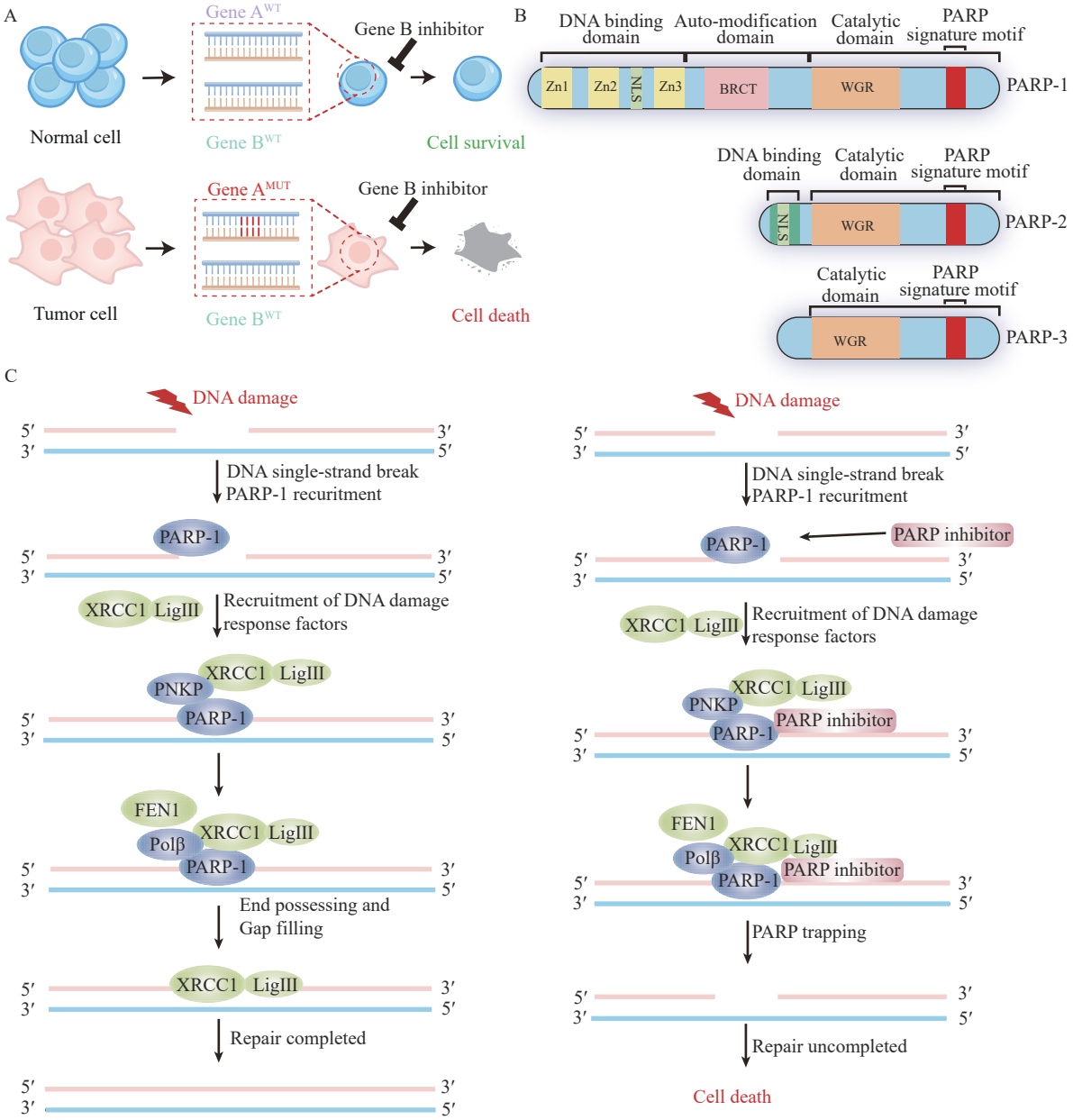


Fig. 3 The principle of synthetic lethality and the mechanism leading to cell death. (A) The mechanism of synthetic lethality. Synthetic lethality can be defined as the relationship that can occur between two genes where either one functioning maintains the viability of the cell; however, upon dysfunction of both genes, the cell becomes unviable. This will lead to the selective killing of cells that rely on these two gene-driven mechanisms, namely cancer cells, while allowing healthy cells to survive. (B) The domain of PARP1, PARP2 and PARP3. PARP1 is a DNA damage-specific sensor protein consisting of 3 distinct domains. The *N*-terminal DNA-binding domain includes three zinc finger motifs (ZnI., ZnII. recognize damaged DNA; ZnIII. involved in the connection between domains and activate proteins) and nuclear localization sequence (NLS). The auto-modification domain includes a carboxyl terminal of BRCA1 (BRCT) involved in DNA repair and cell signaling. The *C*-terminal catalytic (CAT) domain includes a tryptophan-glycine-arginine (WGR) domain, an alpha-helical domain (HD), and an ADP-ribosyl transferase (ART) domain. The CAT domain of PARP2 is 69% similar to PARP-1 but only accounts for 10%–15% of the total activity of PARP. PARP3 and PARP2 both have WGR domains and CAT domains but the PARP3 has proved that it is a MAR transferase. (C) The influence of PARP inhibitor in BER process.

GBM. In addition to PARP, several other DDR-associated proteins, whose expression or function is dysregulated in GBM, have been identified as potential therapeutic targets and will be examined in detail in the subsequent sections.

DDR targets

In contrast to the tightly regulated and limited proliferation of normal cells, cancer cells undergo uncontrolled division, which substantially increases the likelihood of endogenous DNA damage and places a significant strain on the DDR machinery. Research has identified at least 450 proteins involved in DDR, several of which have shown considerable therapeutic potential in various malignancies [8, 9]. In this chapter, we will focus on key DDR proteins that have gained prominence in GBM research, offering a concise overview of their current roles and therapeutic prospects. By discussing these critical targets, we aim to provide insights that could guide the development of innovative therapeutic strategies for GBM.

PARP family

PARP, a prominent target in the DDR pathway, has been implicated in various cellular processes, including DNA repair, carcinogenesis [10], metabolism, signaling [11], cell death, and gene transcription. The PARP family comprises 17 members, with PARP1, PARP2, and PARP3 being the primary enzymes involved in DDR activation following DNA damage [12]. This section mainly introduces PARP1 protein and its inhibitors.

PARP1, the most well-characterized member of the PARP family, accounts for approximately 90% of PARP activity in DDR. It facilitates the transfer of ADP-ribose units from nicotinamide adenine dinucleotide (NAD^+, donor substrate), its substrate, to acceptor proteins, thereby forming PAR chains. As a pivotal sensor within the DDR network, PARP1 is rapidly activated in response to DNA SSBs and coordinates their repair primarily through the base excision repair (BER) pathway. Upon detecting DNA lesions, the DNA-binding domain of PARP1 identifies and binds to damaged sites, leading to the cleavage of NAD^+ into nicotinamide and ADP-ribose. ADP ribose is used as the substrate to form a poly ADP-ribose complex including the acceptor protein and PARP1 itself. The ADP-ribose units are polymerized to form PAR chains, which recruit DNA repair proteins, including X-ray cross-complementing protein 1 (XRCC1), DNA ligase III, and DNA polymerase β, to the site of damage, facilitating efficient repair [13]. Beyond its role in BER, PARP1 has also been implicated in the NHEJ pathway *via* interactions with DNA-dependent protein kinase (DNA-PK) and Ku proteins and in HR in cooperation with MRE11 and ataxia-telangiectasia mutated kinase (ATM).

PARP2 was first identified in 1999 when it was demonstrated that PAR synthesis could still occur in mice lacking the *PARP1* gene, confirming PARP2's capacity to mediate PAR formation. Although the CAT domain of PARP2 shares 69% similarity with that of PARP1, PARP2 contributes only 10%−15% of total PAR synthesis [14, 15]. *PARP1* and *PARP2* have overlapping functions, and the simultaneous deletion of both genes is embryonically lethal in mice [16, 17]. However, mice with a single deletion of PARP1 remain viable and fertile [18, 19]. PARP3, while structurally related to PARP2 through its WGR and CAT domains, primarily functions as a mono-ADP-ribosyltransferase (MAR). Although it plays a role in SSB repair, PARP3 has been less extensively studiied [20].

PARPi represent the first class of DDR-targeted drugs to be developed and approved for clinical use, highlighting their critical role in exploiting synthetic lethality for cancer therapy. The concept of synthetic lethality, introduced by Stephen Friend in the late 20th century, provided the foundation for the development of PARPi [21]. In 2005, it was demonstrated that PARPi could selectively induce synthetic lethality in BRCA-mutant cells [21-22], a breakthrough that led to their subsequent approval for treating BRCA-mutant ovarian and breast cancers [21-23]. In recent years, PARPi have been explored for the treatment of central nervous system tumors, including GBM. Early preclinical studies combined PARPi with TMZ, revealing that inhibition of PARylation could reduce MGMT function, thereby sensitizing MGMT-unmethylated GBM cells to TMZ [24]. PARP inhibition restores TMZ sensitivity in GBM and glioma stem cells (GSCs) by compromising DNA repair protein function [24, 25]. Additionally, PARPi re-sensitize MSH6-deficient, mismatch repair (MMR)-deficient gliomas to TMZ by modulating BER pathway dynamics [26]. The combination of PARPi and TMZ is a promising strategy for overcoming chemotherapy resistance in GBM. However, early-phase clinical trials have reported significant toxicity, which limits the widespread application of this combination [27]. Furthermore, most currently available PARPi are excluded from the central nervous system (CNS) by the BBB, significantly limiting their efficacy in GBM treatment. In general, they could improve the efficacy of TMZ in the clinical treatment of CNS tumors, but brain penetration is a major limitation of the usage [28, 29]. New-generation PARPi with enhanced BBB permeability are under development to address this issue. Another critical limitation is that GBM patients derive limited benefit from PARPi due to the absence of BRCA mutations, emphasizing the need for combination therapies with other DDR inhibitors. For instance, phosphate inositol 3-kinase (PI3K) inhibitors reduce homologous recombination (HR) efficiency by downregulating RAD51 and BRCA1/2 expression, thereby enhancing the pro-apoptotic effects of PARPi in GBM cells [30, 31]. Similarly, PARP inhibitors can enhance the sensitivity of TMZ to radiotherapy and effectively prolong survival [32, 33]. Overall, PARPi are promising candidates for DDR-targeted therapies in GBM.

PIKK family

PI3K and phosphoinositol 3-kinase associated protein kinase (PIKK) are two structurally related kinase families that

play pivotal roles in regulating cellular growth, survival, and DDR. Dysfunction of PIKK members and abnormal activation of the PI3K/AKT/mTOR signaling pathway are associated with various diseases, including GBM. Within the PIKK family, six atypical serine/threonine protein kinases have been identified, of which ATM, ATM and Rad3-related kinase (ATR), and DNA-dependent protein kinase (DNA-PK) are particularly integral to the DDR and have significant impacts on cancer progression and therapeutic response. This section focuses on these critical DDR targets [34].

DNA-PK is a key serine/threonine protein kinase belonging to the PIKK family. As a key protein kinase in genomic DNA repair, it controls the DNA and is used to maintain genomic integrity. The DNA-PK complex consists of a DNA-dependent protein kinase catalytic subunit (DNA-PKcs) and the Ku70/80 heterodimer. The Ku70/Ku80 heterodimer first recognizes and binds to DSBs, subsequently recruiting DNA-PKcs to form the active DNA-PK complex [35, 36].

DNA-PK plays a central role in the DDR, primarily facilitating DSB repair through three distinct pathways: NHEJ, alternative NHEJ (alt-NHEJ), and HR. NHEJ, the primary repair mechanism in eukaryotic cells, is characterized by its rapid yet error-prone nature, as it directly ligates broken DNA ends without requiring sequence homology. Despite its lower fidelity compared to HR, NHEJ is the predominant pathway throughout the cell cycle, especially during interphase [37, 38], and can be completed within 30 min, whereas HR requires several hours [39].

Preclinical and clinical studies have shown that DNA-PKcs is frequently dysregulated in numerous cancers, including GBM and melanoma. DNA-PKcs drives key oncogenic processes such as angiogenesis, metastasis, and primary tumor development, highlighting the direct interplay between DDR mechanisms and cancer progression. These findings underscore the significance of DNA-PKcs as a promising target for anti-metastatic therapies [40]. Moreover, DNA-PKcs inhibition has been explored as a synthetic lethality strategy in tumors harboring deficiencies in HR-related factors such as BRCA1, BRCA2, CHK2, Rad50, PTIP, and PAXIP [41]. Notably, inhibition of miR-1193, which leads to the accumulation of DSBs and increases genomic instability, sensitizes GBM cells with DNA-PKcs deficiencies, providing a preclinical basis for targeting DNA-PKcs-deficient tumors through synthetic lethal approaches [42]. Recent studies have further delineated the role of DNA-PK in GBM pathogenesis, reinforcing its potential as a therapeutic target in this highly aggressive malignancy.

ATM and ATR protein are key serine/threonine protein kinases [43]. Although structurally similar, ATM and ATR are activated by distinct types of DNA damage and govern different DDR processes [44-46]. ATM is primarily activated in response to DSBs, with the MRE11-RAD50-NBS1 (MRN) complex serving as a critical mediator. Upon DSB recognition, the MRN complex binds to double-stranded DNA (dsDNA) and then recruits ATM homodimers to the damage site, initiating ATM activation through monomerization and autophosphorylation at key residues, including Ser1981, Ser367, Ser1893, and Ser2996. In addition, acetylation of lysine (Lys) at site 3016 by the KAT5/Tip60 histone acetyltransferase further promotes ATM activation [47, 48]. Once activated, ATM phosphorylates a wide array of downstream effectors, including p53, checkpoint kinase 1 (CHK1), CHK2, H2AX, Rad17, DCLK1, ROCK2, and Artemis, triggering a complex signaling cascade. This cascade leads to cell cycle checkpoint activation at the G_1/S and G_2/M transitions [49, 50], inducing cell cycle arrest and allowing time for DDR through HR or NHMJ before the cell progresses into mitosis (Fig. 4D) [51, 52].

Pharmacological inhibition of ATM kinase represents a promising approach for enhancing radiosensitivity in tumors [53]. AZD1390, a brain-penetrant ATM inhibitor, has demonstrated significant radiosensitizing effects in a subset of orthotopic GBM models [54-56]. ATM inhibitors have also shown efficacy in radiosensitizing GBM CSCs, suggesting that, when combined with conventional therapies, these inhibitors could improve the prognosis of GBM patients [57]. Additionally, ATRX, a chromatin remodeler, is frequently mutated in H3F3A-mutant pediatric GBM and in isocitrate dehydrogenase (IDH)-mutant grade 2/3 adult gliomas. QIN *et al*. reported that GBM cells harboring ATRX mutations exhibit heightened sensitivity to ATM inhibition [58].

ATM, ATR, and DNA-PK are three important regulators in the DDR pathway [59, 60]. While ATM and ATR are activated by different types of DNA damage, they exhibit functional compensation within the DDR. Deficiency in one pathway may be partially offset by activation of the other [61]. Although ATM primarily responds to DSBs and ATR to SSBs and replication stress, they converge on shared downstream targets, collectively mediating checkpoint activation and DDR. ATM and DNA-PKcs also exhibit complementary functions in DDR, and simultaneous deletion causes lethality in mice at the embryonic stage, revealing a synthetic lethality between ATM and DNA-PK mutations. Co-inhibition of these pathways exacerbates DSB accumulation, which leads to extensive resection by the CTBP-interacting protein (CtIP)-mediated excision, generating large single-stranded DNA (ssDNA) regions that trigger apoptosis *via* the activation of the ATR/CHK1/p53/Puma axis [62].

ATR is mainly involved in the response of DNA SSB repair, which monitors DNA damage by detecting ssDNA in cells. Its ability to block cell cycle checkpoints reveals a role when faced with replication stress: the high replication stress faced by the bulk replication of cancer cells requires the assistance of ATR. This finding suggests that we can induce cell death by combining ATR inhibition with genetic or chemically induced DNA replication stress.

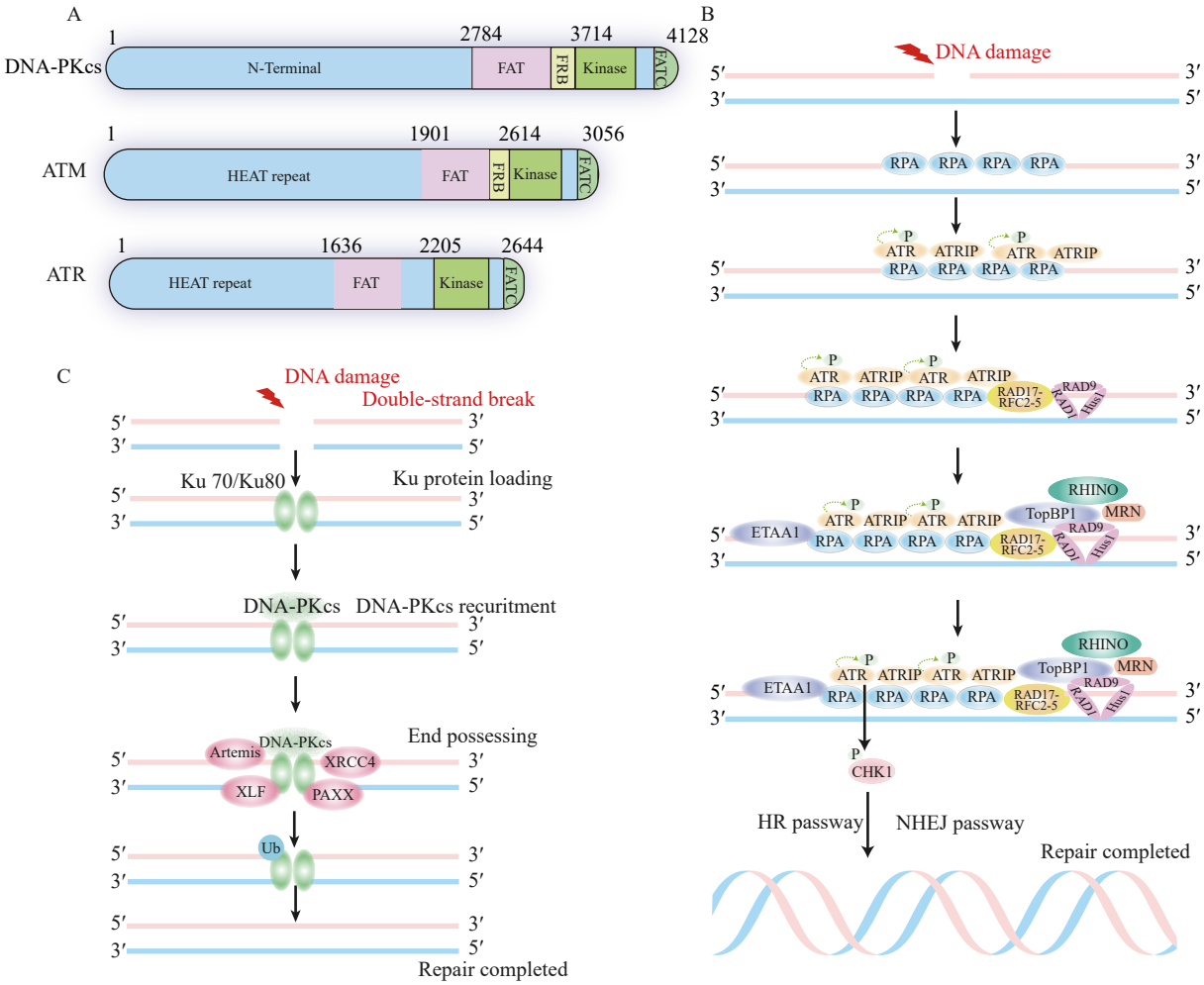
ATR is active during the S phase, sensing stressed replication forks and coordinating a multifaceted response to DNA replication stress. It helps to ensure the completion of DNA replication and to preserve the integrity of the genome. ATR protects cells against replication stress by preventing replication fork collapse and by inducing G_2/M arrest through activation of the checkpoint kinase CHK1, which is important for cancer cells undergoing replication stress during rapid proliferation [63]. Consequently, co-inhibition of ATR and CHK1 can induce replication catastrophe, leading to selective cancer cell death [64, 65].

ATR inhibition is particularly lethal in ATM-deficient cells due to ATM's critical role in DSB repair and checkpoint activation [66, 67]. This synthetic lethal interaction between ATM and ATR is especially pronounced in chronic lymphocytic leukemia and gastric cancer, where combined inhibition leads to pronounced DNA damage accumulation and apoptosis [68, 69]. Given the limited efficacy of PARP inhibitors in BRCA-wildtype GBM, the combination of ATR and PARP inhibitors has emerged as a promising strategy. Preclinical studies have shown that co-targeting ATR and PARP extends survival in mouse models of glioma stem cell-derived orthotopic tumors, regardless of their inherent sensitivity to PARP inhibition [70].

Wee1

Wee1 kinase is a crucial serine/threonine kinase that regulates cell cycle progression, particularly at the G_2/M checkpoint [71]. Primarily localized in the nucleus, Wee1 plays a central role in coordinating DNA replication and preventing premature mitotic entry by phosphorylating cyclin-dependent kinases (CDK1 and CDK2), thereby delaying cell cycle progression when DNA damage is detected [72]. Dysregulation of Wee1 can have dual consequences: excessive G_2 arrest leading to apoptosis or unchecked transition through the G_2/M checkpoint, allowing the propagation of cells with damaged DNA. The latter can result in progeny cells carrying genomic instability [73]. Studies in mice with Wee1 knockout have shown that mammalian Wee1 plays a key role in maintaining genome integrity, and Wee1 deficiency results in embryonic lethality (Fig. 5).

Targeting Wee1 in cancer cells, particularly in combination with DNA-damaging agents, can induce mitotic catastrophe, thereby promoting a DNA damage-dependent apoptotic response [74, 75]. Recent studies have further elucidated Wee1's broader involvement in DDR mechanisms. Elevated expression of Wee1 has been observed across multiple can-



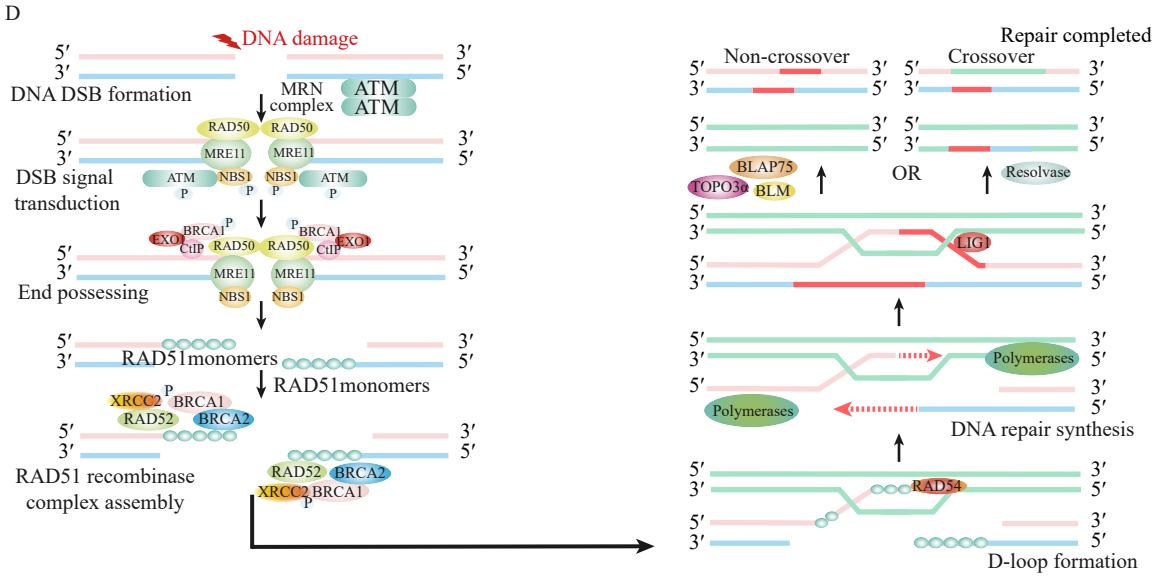


Fig. 4 Three PIKK family kinase domains and their involvement in DDR processes. (A) The domain of DNA-PKcs, ATM, and ATR. DNA-PKcs consist of 4128 amino acids. The amino terminal of the DNA-PKcs is a domain with helical and HEAT domains and different phosphorylation clusters, with the FAT domain in the middle. The PRD and the FATC motif are located at the carboxyl terminal. The FAT and FATC domains surround the catalytic domain, serving to stabilize the conformational change of the catalytic core and regulate kinase activity. ATM consists of 3056 amino acids, and ATR consists of 2644 amino acids. The protein structures of ATM/ATR are similar, and both contain a large N-terminus α-solenoid (containing N-terminal and intermediate HEAT repeat regions, known as N-HEAT and M-HEAT, respectively), FAT domain, kinase domain and FATC domain. The N-terminal supercoiled HEAT repeat region of ATR is the binding region of ATRIP and an important region for ATR kinase activation. (B) ATR participates in the process of DNA repair. After SSB appears, RPA coats ssDNA. Then ATR and other required regulatory factors are recruited and activated: ATRIP, 9-1-1 complex, TopBP1, etc. ATRIP binds to RPA and then to ATR to form a complex. The ATRIP-ATR complex subsequently phosphorylates 9-1-1. Phosphorylated 9-1-1 then binds to TOPBP1, which triggers the ATR signaling cascade. (C) DNA-PK participates in the process of DNA damage repair. The specific process is that after DSBs occur, the DSB two ends are recognized and bound by Ku70/80, after which DNA -PKcs is recruited and associated to form the DNA-PK complex. The two DNA-PKs bind the broken DNA ends while recruiting the subsequent NHEJ repair factors XRCC4, XRCC4-like factor (XLF) as well as DNA Ligase IV to repair the broken DNA. (D) ATM participates in the process of DNA repair.

cer types, including GBM, breast cancer, leukemia, liver cancer, colorectal cancer, and melanoma [76]. High expression of Wee1 is believed to be associated with poor prognosis in GBM, highlighting its role in regulating the G_2 checkpoint as a viable therapeutic target, especially in treatment-resistant GBM. CRISPR-Cas9 screening of patient-derived GSCs revealed that the synthetic lethality observed in GBM is driven by the simultaneous loss of Wee1 and PKMYT1, suggesting that dual inhibition could be an effective therapeutic approach [77]. Wee1 inhibition has also demonstrated the potential to enhance the efficacy of radiotherapy. However, preclinical studies combining Wee1 inhibitors, such as adavosertib, with TMZ in GBM models have shown limited success, primarily due to the poor BBB permeability of the Wee1 inhibitor [78, 79]. Tumors harboring p53 mutations are particularly dependent on the G_2 checkpoint and Wee1 activity, making them highly susceptible to Wee1 inhibition. In such cases, targeting Wee1 can improve the effectiveness of chemotherapy with minimal additional toxicity. For example, Wee1 inhibition in p53-negative tumors can improve the efficiency of chemotherapy drugs without serious side effects [80]. Current research strategies focus on combining Wee1 inhibitors with other DNA-damaging therapies, such as PARP inhibitors, chemotherapy, and radiotherapy, to exploit synthetic lethality and enhance antitumor efficacy.

PRMT5

Arginine methylation, a prevalent post-translational modification in mammals, plays a crucial role in regulating histone function. The protein arginine methyltransferase (PRMT) family is responsible for catalyzing the methylation of arginine residues, utilizing S-adenosylmethionine (SAM) as a methyl donor [81]. Extensive research has elucidated the involvement of PRMTs in diverse cellular processes, including DDR, transcriptional regulation, cell cycle control, epigenetics, and RNA metabolism [82-85]. PRMT protein family has 9 main members. Available research evidence suggests that PRMT5 overexpression may play a critical role in a variety of cancers, including B and T cell lymphoma, melanoma [86], lung cancer, GBM [87], breast cancer [88, 89], and so on. Recent studies have focused on leveraging PRMT5 as a therapeutic target to harness its antitumor potential. This section specifically examines the role of PRMT5 in the DDR.

PRMT5 is an epigenetic regulator localized in both the nucleus and cytoplasm, catalyzing mono- and symmetric di-

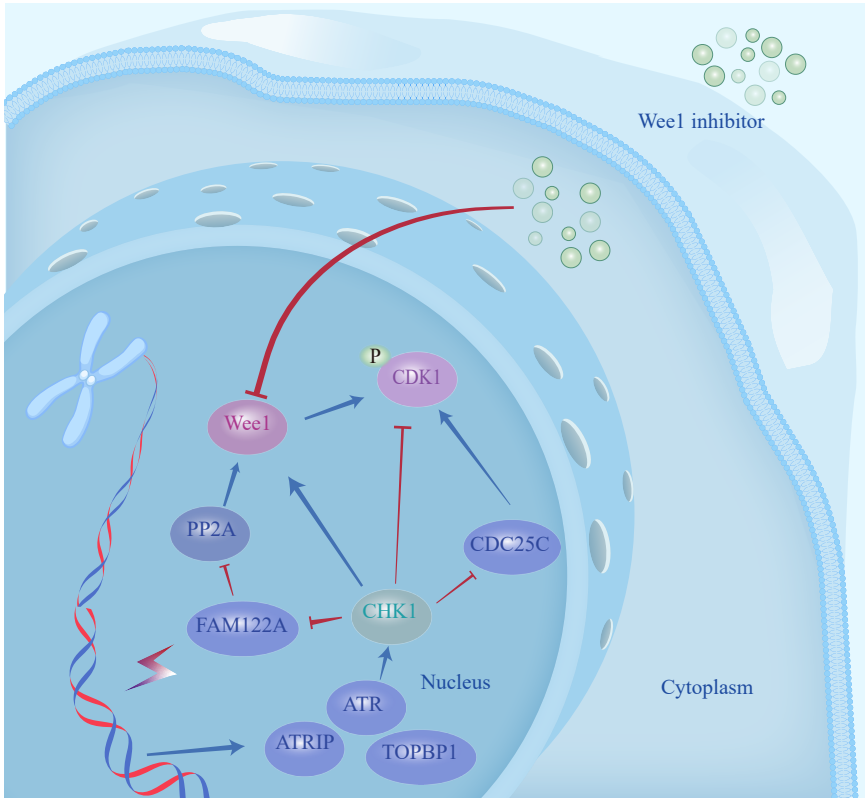


Fig. 5 Wee1 protein structure and function. DNA undergoes SSBs, the ATR signaling pathway is activated, and Chk1 is phosphorylated and activated. The activated Chk1 simultaneously phosphorylates Cdc25C and Wee1, inhibiting Cdc25C and activating Wee1. Inhibiting Wee1 effectively circumvents cell cycle arrest, prematurely inducing tumor cells to enter mitosis, thereby triggering replication stress and mitotic catastrophes, ultimately leading to cell death.

methylation of arginine residues on histones (e.g., H2A and H4 at Arg3, H3 at Arg2 and Arg8) and non-histone proteins (e.g., EGFR, AR, p53, RAD9). These methylation reactions are facilitated by its cofactor, methylosome protein 50 (MEP50) [90-93]. As a key modulator of genomic stability, PRMT5 regulates DDR by methylating critical proteins such as 53BP1, FEN1 [94], RAD9 [93], RUVBL1 [95], and TDP1 [96], thereby influencing HR and NHEJ pathways, which are essential for repairing DSBs and resolving replication stress-induced lesions. Preclinical studies indicate that PRMT5 inhibition can synergize with other DDR inhibitors. For instance, combining PRMT5 inhibitors with olaparib in PARP inhibitor-resistant human acute myeloid leukemia cell lines significantly reduced cell viability [97]. Additionally, PRMT5 inhibitors have been explored in combination with chemotherapy, showing that PRMT5 inhibition sensitizes cells to cytotoxic agents like cisplatin [98]. In 2016, two Science publications reported the "synthetic lethal" effect of PRMT5 inhibition in tumors with methylthioadenosine phosphorylase (MTAP) deletions [99, 100], marking a significant advancement in targeting PRMT5 for cancer therapy. Another study highlighted PRMT5 as a critical vulnerability in MTAP-deficient cells, suggesting that targeting the CDKN2A/MTAP axis could be a promising therapeutic approach [101]. These findings suggest that PRMT5 inhibitors hold significant potential, both as monotherapies and in combination with other treatments.

In GBM, elevated PRMT5 expression is strongly associated with poor patient prognosis [87]. Both genetic knockdown and pharmacological inhibition of PRMT5 have demonstrated significant antitumor effects in GBM models [102, 103], leading to impaired tumor growth and reduced clonogenic capacity in patient-derived GSC lines [104]. Among the emerging PRMT5 inhibitors, LLY-283 has shown particular promise due to its ability to cross the BBB, making it the first brain-penetrant PRMT5 inhibitor currently under clinical investigation. Although no PRMT5 inhibitors have been approved for clinical use yet, the development of brain-penetrant PRMT5-targeting drugs could offer a novel therapeutic strategy for GBM.

CHK1

CHK1 is a serine/threonine kinase that serves as a central regulator of DDR by controlling cell cycle checkpoints. As a key effector downstream of ATR, CHK1 is activated in response to replication stress and DNA damage, coordinating the cellular response by phosphorylating and recruiting regulatory proteins. Once activated, CHK1 promotes the degradation of CDC25A, leading to reduced CDK1/2 activity and arresting cell cycle progression to allow for DDR [105]. CHK1 can also phosphorylate CDC25C and WEE1 to regulate mitotic entry and G_2/M checkpoint [106]. Additionally, CHK1 contributes to homologous recombination repair by regulating RAD51 and BRCA2 [107, 108] and can induce apoptosis

when DNA damage is beyond repair [109, 110]. High CHK1 expression is correlated with poor prognosis, treatment resistance, and disease recurrence, highlighting its therapeutic potential as a drug target [111]. Inhibition of CHK1 has been shown to enhance the cytotoxicity of chemotherapeutic agents in p53-deficient cancers, both *in vitro* and in animal models [112]. Similar to the function of ATR inhibitors, CHK1 inhibitors exacerbate the damage caused by PARP inhibition. GSCs are the main cause of difficulties in the treatment of various types of GBM. Through two methods of reverse phase protein microarray and kinase inhibitor library screening, it has been demonstrated that the combined inhibition of PDK1 and CHK1 represents a potential effective therapeutic approach that can reduce the growth of human GBM [113]. Moreover, the combination of CHK1 inhibition with ribonucleotide reductase subunit 2 (RRM2) inhibition has demonstrated synthetic lethality in GBM cells, with combinations like Triapine and the CHK1 inhibitor Rabusertib showing potent antitumor effects [114]. There is growing evidence supporting the combined use of CHK1 inhibitors with PARP inhibitors to enhance therapeutic efficacy in PARP-resistant tumor models [115]. Altogether, CHK1 represents a valuable therapeutic target with significant potential for drug development, particularly in combination with other DDR inhibitors.

RAD 51

HR is distinguished by its use of a homologous DNA sequence as a repair template, requiring the damaged DNA strand to locate and invade a homologous DNA molecule. A key player in this process is RADiation sensitive 51 (RAD51), a protein critical for HR-mediated repair. The *RAD51* gene is indispensable, as its knockout results in embryonic lethality in mice [116]. Human RAD51 is a 37 kDa protein whose *N*-terminal domain can interact with ssDNA, dsDNA, and BRCA2 proteins, while its *C*-terminal domain binds DNA through Loop1 and Loop2 [117, 118]. RAD51 is responsible for identifying and invading homologous DNA sequences, enabling accurate and efficient repair of DSBs [119]. The HR process begins with nucleolytic resection of the DSB ends, generating 3' single ssDNA tails. These ssDNA tails are initially coated with replication protein A (RPA), which is subsequently displaced by RAD51, forming a RAD51-ssDNA nucleoprotein filament. This filament is crucial for the homology search and strand invasion, leading to the formation of a displacement loop (D-loop) on the undamaged homologous chromatid. The undamaged strand is then used as a template for high-fidelity DNA synthesis, facilitated by additional HR proteins [120]. Precise control of RAD51 expression is critical in normal cells, as aberrant recombination can lead to genomic instability and oncogenesis [120, 121]. Overexpression of RAD51 has been observed in several cancer types and is closely associated with poor prognosis [122], including in pancreatic cancer [123], NSCLC [124], breast cancer, and GBM [125]. RAD51 overexpression, which leads to excessive recombination, not only promotes cancer progression but also enables cancer cells to resist DNA-damaging agents [126, 127]. The oncogenic transcription factor FoxM1, which is overexpressed in multiple cancers, including GBM, directly upregulates RAD51 expression. In recurrent GBM, FoxM1 expression is significantly elevated, and its knockdown has been shown to suppress RAD51 levels, thereby sensitizing GBM cells to TMZ and highlighting the role of the FoxM1-RAD51 axis in mediating chemotherapy resistance [128]. As a result, RAD51 is considered a clinically relevant biomarker.

Novel Advances and Strategies for GBM

Noval small molecules from natural products

Since its introduction, TMZ has been the standard first-line chemotherapeutic agent for GBM, significantly extending patient survival. However, GBM's intrinsic tumor heterogeneity frequently leads to the rapid development of resistance, limiting the long-term efficacy of TMZ [129]. As a result, identifying potent small-molecule drugs to either replace or complement TMZ remains a key focus in GBM therapy. Natural products have long been a valuable source for discovering bioactive compounds with potential as novel therapeutic agents. One such compound is Stellettin B (STELB), a triterpenoid isolated from the South China Sea sponge *Jaspis stelifera*. Recent studies have demonstrated, for the first time, that STELB can cross the BBB and sensitize GBM cells to radiotherapy and TMZ by inhibiting HR repair. This inhibition is partly achieved by reducing PI3K protein levels, consistent with reports that PI3K is regulated through polyubiquitination. Subsequent investigations revealed that STELB enhances the therapeutic efficacy of PARP inhibitors in GBM by downregulating BRCA1/2 and RAD51, key proteins involved in HR-mediated DNA DSB repair [130, 131]. Another promising natural compound is cedrol, derived from *Cedrus atlantica*. In preclinical studies, cedrol exhibited synergistic effects with TMZ in both *in vitro* and *in vivo* models. In TMZ-resistant GBM cell lines, cedrol reduced the expression of resistance-associated proteins, including MGMT and MDR1, while inducing DNA damage and promoting apoptosis. However, further characterization of cedrol's ability to penetrate the BBB is needed [132]. Salinomycin, initially isolated from *Streptomyces albus*, also exhibits potent anticancer properties. Salinomycin induces DNA damage and impairs HR repair by downregulating RAD51 through autophagy-mediated mechanisms. Currently, salinomycin derivatives are being developed to enhance its therapeutic potential [133]. Cholesterol efflux and lipid raft redistribution have been shown to play a role in overcoming TMZ resistance in GBM. Ginsenosides, specifically Rg1 and CK, have been found to modulate cholesterol metabolism and lipid raft organization, thereby restoring TMZ sensitivity in glioblastoma cells. Zou *et al*. these ginsenosides could effectively enhance the therapeutic efficacy of TMZ by regulating cholesterol homeostasis, positioning them as potential synergistic agents for TMZ-based therapy [134]. Given the widespread use of alkylating agents like TMZ in treating brain tumors, understanding the

mechanisms of resistance is crucial. Activation of AMP-activated protein kinase (AMPK) by TMZ has been linked to increased apoptosis in GBM cells, likely through the promotion of p53 activation and inhibition of mTORC1 signaling. AMPK has emerged as a key mediator in this process [135]. Additionally, ROCK2 has been identified as a critical factor for maintaining TMZ resistance in gliomas. Fasudil, a ROCK2 phosphorylation inhibitor, has shown significant efficacy in reducing the proliferation of TMZ-resistant gliomas both *in vitro* and *in vivo* by enhancing TMZ chemosensitivity. These findings provide compelling evidence for considering fasudil as a therapeutic option in the clinical management of TMZ-resistant gliomas [136]. Oroxylin A, a natural flavonoid derived from *Scutellaria radix*, has shown potential in reversing TMZ resistance in glioma cells. ZHAO *et al.* reported that oroxylin A sensitizes TMZ-resistant glioma cells by inhibiting the IP3R1/AKT/*β*-catenin pathway, highlighting its potential as a reversal agent for TMZ resistance [137]. Further studies revealed that oroxylin A enhances TMZ sensitivity by suppressing the HIF-1α/hedgehog signaling pathway and directly inhibiting Gli1 activation [138, 139]. Collectively, these findings suggest that oroxylin A holds considerable promise as a multifaceted agent in GBM therapy.

The potential for discovering novel scaffold molecules targeting the DDR from natural products for the treatment of GBM is often underestimated. Many existing DDR-targeting drugs struggle with limited applicability in central nervous system (CNS) tumors due to poor blood-brain barrier (BBB) permeability—an issue that is particularly critical in GBM treatment. Therefore, screening natural products for bioactive compounds with better BBB penetration and enhanced therapeutic potential offers a promising strategy.

The pathogenesis of GBM

The pathogenesis of GBM is highly complex. Unraveling its regulatory mechanisms and identifying therapeutic targets could open new avenues for GBM treatment. Hypoxia is known to drive the expansion of GSCs, although the precise mechanisms remain unclear. Studies have shown that hypoxia-inducible factor-1α (HIF-1α) activates the Notch pathway, which is crucial for the hypoxia-mediated maintenance of GSCs. This activation enhances GSC sensitivity to hypoxic conditions, positioning HIF-1α as a compelling therapeutic target in GBM [139, 140]. Additionally, extracellular vesicles derived from hypoxic GBM play a role in the bloodstream, contributing to increased BBB permeability [141]. GBM's invasive behavior is another hallmark of its malignancy, driven by the expression of specific proteins. Mixed lineage kinase 3 (MLK3) is highly expressed in high-grade gliomas and is particularly prominent in primary and recurrent GBM. MLK3 promotes GBM cell migration and invasion by remodeling the actin cytoskeleton through MLK3-EPS8 signaling [142]. TRAF4, a scaffold protein with E3 ubiquitin ligase activity, has also been implicated in the invasion and metastasis of various cancers. In GBM, TRAF4 stabilizes Caveolin-1, enhancing GSC stemness and resistance to TMZ, providing a potential therapeutic strategy to improve patient outcomes [143]. MicroRNAs (miRNAs), a class of endogenous small non-coding RNAs, are often dysregulated in GBM. MiR-1258 has been shown to inhibit malignant proliferation, therapeutic resistance, migration, and invasion of GBM cells *in vitro*, as well as suppress tumor growth in xenograft models [144]. Advances in bioinformatics and analytical techniques are continually deepening our understanding of GBM. Single-nucleus RNA sequencing (snRNA-seq) and spatial transcriptomics (ST) have identified expression patterns of immune checkpoints and revealed intratumoral heterogeneity in GBM, suggesting that TIM-3, VISTA, PSGL-1, and VSIG-3 may be promising therapeutic targets [145]. Furthermore, MAP4K1 has been identified as a potential target for cancer immunotherapy, showing high expression in glioma cells from human GBM specimens. MAP4K1 not only drives oncogenic processes, such as cell proliferation and tumor growth but also remodels the tumor immune microenvironment by inhibiting the infiltration of $CD8^+$ tumor-infiltrating lymphocytes into the tumor site [146].

Novel DDS targeting GBM

The BBB is a significant barrier to effective GBM treatment [147, 148]. Although TMZ remains the first-line therapy, less than 20% of the administered dose crosses the BBB, necessitating high doses that lead to unnecessary systemic side effects. One promising approach to overcoming poor drug delivery to GBM is the use of DDS to enhance drug absorption and therapeutic efficacy while minimizing toxicity to surrounding healthy tissues [149]. However, the concentration of TMZ in cerebrospinal fluid remains low, prompting efforts to optimize delivery efficiency by exploring alternative administration methods. While these techniques have shown promising results in animal models, they have not yet achieved significant breakthroughs in clinical trials [150-152]. In recent years, numerous studies have focused on strategies to overcome the BBB in GBM [153, 154]. Nanoparticles offer great potential for drug delivery, and utilizing them to transport therapeutic agents across the BBB into GBM tissues appears to be an ideal solution [155]. One notable example is the use of gold@copper selenide nanoparticles (Au@Cu2-xSe NPs), which were the first reported nanoparticles designed to function as autophagy inhibitors, thereby enhancing the efficacy of radiotherapy in GBM. These nanoparticles inhibit autophagy flux, leading to increased ubiquitination of Rad51 and its subsequent degradation by proteasomes, ultimately preventing DNA repair in damaged tumor cells [156]. Nanoparticles have also been employed to deliver small interfering RNA (siRNA) to GBM with promising outcomes. For instance, the nanomaterial ECO(1-aminoethylimino[bis(*N*-oleoylcysteinylaminoethyl) propionamide]) has effectively delivered siRNA targeting DDR proteins ATM and DNA-PKcs, selectively radiosensitizing tumor cells and improving therapeutic efficacy. In a GBM xenograft model, the combination of this siRNA delivery system with radiotherapy significantly improved survival rates [157]. Another nanoparticle-

based system has been developed to deliver siRNAs targeting MGMT, effectively sensitizing GBM cells to TMZ by overcoming resistance associated with MGMT-mediated DNA repair. Sequential administration of this siRNA-loaded nanoparticle and TMZ shows promise in improving GBM patient outcomes [158]. Despite these advances, significant breakthroughs in the application of novel DDS specifically targeting DDR pathways for GBM remain elusive.

Current clinical progress of DDR inhibitors

In the following section, we will review ongoing or recently concluded clinical trials for various DDR-targeting kinases to highlight their potential in GBM therapy.

PARP inhibitors are currently the only DDR-targeting drugs approved for clinical use, with six available on the market. Pamiparib, a highly selective and BBB-permeable PARP1 inhibitor, is among those approved and is currently being tested in several clinical trials for additional indications and combination therapies for GBM (Table 1). Beyond Pamiparib, next-generation PARP1 inhibitors such as Saruparib and AZD9574 are in clinical development. These

Table 1 Selected small molecule inhibitors of DDR

Compound	Target	Status	NCT number
Olaparib	PARP1/2/3	Approved	NCT05188508, NCT03991832, NCT03561870, NCT03212742, NCT03233204, NCT03212274, NCT02974621, NCT05432518, NCT01390571
Niraparib	PARP1/2	Approved	NCT06258018, NCT05406700, NCT05297864, NCT05076513, NCT06388733, NCT04221503
Rucaparib	PARP1/2/3	Approved	NCT03318445
Talazoparib	PARP1/2/3	Approved	NCT04740190
Fluzoparib	PARP1/2	Approved	NCT02575651
Pamiparib	PARP1/2	Approved	NCT03150862, NCT04614909, NCT03914742, NCT03749187
Veliparib	PARP1/2	Phase Ⅲ	NCT00770471, NCT00946335, NCT02152982, NCT01514201
Senaparib	PARP1	Phase Ⅲ	NCT04822961, NCT04434482, NCT05262842, NCT05269316
Saruparib	PARP1	Phase Ⅰ/Ⅱ	NCT05938270, NCT06120491, NCT06380751, NCT05489211
AZD9574	PARP1	Phase Ⅰ/Ⅱ	NCT05417594
VX-984	DNA-PK	Phase Ⅰ	NCT02644278
Nedisertib	DNA-PK	Phase Ⅰ	NCT02516813, NCT02316197, NCT03770689, NCT04555577, NCT04533750, NCT05687136, NCT03724890
AZD7648	DNA-PK	Phase Ⅰ/Ⅱ	NCT03907969, NCT05116254
CC-115	DNA-PK	Phase Ⅱ	NCT01353625, NCT02833883, NCT02977780
AZD1390	ATM	Phase Ⅰ	NCT03215381, NCT05182905, NCT03423628, NCT05678010, NCT05116254, NCT04550104
Lartesertib	ATM	Phase Ⅰ	NCT04882917, NCT05396833
Berzosertib	ATR	Phase Ⅰ/Ⅱ	NCT02589522, NCT04802174

Continued

Compound	Target	Status	NCT number
Ceralasertib	ATR	Phase Ⅲ	NCT05514132, NCT05450692, NCT05061134, NCT04417062, NCT05582538, NCT04699838, NCT02264678, NCT03682289, NCT03801369, NCT04704661, NCT03878095, NCT04090567, NCT03579316, NCT03334617, NCT03833440
Elimusertib	ATR	Phase Ⅰ/Ⅱ	NCT03188965, NCT04616534, NCT04576091, NCT04535401, NCT04491942, NCT04267939, NCT04514497
Gartisertib	ATR	Phase Ⅰ	NCT02278250, NCT02278250
Camonsertib	ATR	Phase Ⅰ/Ⅱ	NCT04972110, NCT05566574, NCT05405309, NCT04855656, NCT04497116
Adavosertib	Wee1	Phase Ⅱ	NCT03579316, NCT03668340, NCT03385655
Azenosertib	Wee1	Phase Ⅱ	NCT05198804, NCT04814108, NCT05128825, NCT04158336, NCT04833582, NCT05743036, NCT04516447, NCT04972422, NCT05682170
Debio-0123	Wee1	Phase Ⅰ/Ⅱ	NCT05109975, NCT03968653, NCT05815160, NCT05765812
GSK-3326595	PRMT5	Phase Ⅱ	NCT04676516, NCT03614728, NCT02783300
AMG-193	PRMT5	Phase Ⅰ/Ⅱ	NCT05094336
MRTX-1719	PRMT5	Phase Ⅰ/Ⅱ	NCT05245500
TNG908	PRMT5	Phase Ⅰ/Ⅱ	NCT05275478
PF-06939999	PRMT5	Phase Ⅰ	NCT03854227
PRT-543	PRMT5	Phase Ⅰ	NCT03886831
Onametostat	PRMT5	Phase Ⅰ	NCT03573310
CYT0851	RAD51	Phase Ⅰ/Ⅱ	NCT03997968
Amuvatinib	RAD51	Phase Ⅱ	NCT01357395
Prexasertib	CHK1	Phase Ⅱ	NCT04023669
BBI-355	CHK1	Phase Ⅰ	NCT05827614
CCT245737	CHK1	Phase Ⅰ/Ⅱ	NCT02797964, NCT02797977
GDC-0425	CHK1	Phase Ⅰ	NCT01359696
GDC-0575	CHK1	Phase Ⅰ	NCT01564251
LY2880070	CHK1	Phase Ⅱ	NCT02632448, NCT05275426
PEP07	CHK1	Phase Ⅰ	NCT05659732, NCT05983523

inhibitors were designed by AstraZeneca to avoid toxicity associated with PARP2 inhibition. Although both are PARP1-selective, AZD9574 specifically developed for its low efflux activity and superior BBB penetration. AZD9574 is currently being evaluated in a Phase I clinical study (CERTIS1; NCT05417594) [159, 160]. Veliparib, another PARP inhibitor capable of crossing the BBB, has also been explored for GBM treatment, but its clinical progress has been slow (NCT00770471). Despite hundreds of clinical trials involving PARP inhibitors, many have yet to receive approval for GBM treatment. ATM inhibitors are less advanced in clinical development, with most still in Phase I or II trials. Recently, the ATM inhibitor AZD1390 entered Phase I trials. This compound is an optimized version of AZD0156 with improved BBB penetration. A clinical trial is currently underway for recurrent and newly diagnosed WHO Grade 4 glioma patients (NCT05182905; Table 1). Compared with ATM inhibitors, ATR inhibitors show more promise, with several compounds advancing through clinical trials. Among these, ceralasertib stands out as the only ATR inhibitor to reach Phase III trials. Ceralasertib, a modified version of AZD20 specifically optimized for BBB penetration, has demonstrated efficacy in preclinical GBM models [161]. Multiple clinical trials are currently assessing its effectiveness across different cancer types. CC-115 is a dual DNA-PK/mTOR inhibitor that can cross the BBB and is currently under investigation in GBM patients. Its toxicity and efficacy are being evaluated, particularly in combination with CDK4/6 and EGFR inhibitors [162].

Future Perspectives

The DDR network in the human body is intricate and tightly regulated, with various proteins coordinating to maintain genomic integrity during cellular processes. These DDR-related proteins play a crucial role in detecting and repairing DNA damage, ensuring genome stability, and enabling the body to withstand multiple forms of stress encountered daily. However, these protective mechanisms also benefit cancer cells, allowing them to rapidly proliferate and develop drug resistance. As a result, targeting DDR-related proteins has emerged as a powerful strategy for selectively inhibiting cancer cell growth. The success of PARP inhibitors in treating BRCA1/BRCA2-mutant tumors has firmly established the feasibility of this approach, inspiring confidence among researchers and driving the development of additional DDR-targeting therapies. To date, PARP inhibitors are the only DDR-targeting drugs that have been successfully brought to market, while other inhibitors, such as those targeting ATR and DNA-PK, are still in clinical trials. Table 1 summarizes the approved PARP inhibitors and other DDR inhibitors currently under clinical evaluation. The strategy behind these inhibitors is consistent: they selectively exploit the DNA repair mechanisms of tumor cells, sparing normal tissues from collateral damage. Following the significant progress made with PARP inhibitors, there is growing optimism that similar approaches targeting other DDR components could yield equally promising results.

GBM is the most lethal primary brain tumor of the CNS, characterized by a low median survival rate even after aggressive treatment. Current GBM therapy typically involves surgical resection followed by radiation and adjuvant chemotherapy. However, the effective delivery of therapeutic agents to the CNS is severely hindered by the BBB, which limits drug penetration to the tumor site. Despite the challenges faced in developing DDR inhibitors for GBM, their potential therapeutic benefits are significant. A deeper understanding of DDR pathways could help elucidate the role of key DDR targets in mediating responses to chemotherapy and radiotherapy, ultimately supporting the development of DDR inhibitors as viable treatment options for GBM. In conclusion, while DDR inhibitors have encountered several challenges in GBM therapy, ongoing research continues to advance our understanding of these mechanisms.

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