

RAD51 recombinase: biology, regulation, and therapeutic targeting

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ABSTRACT

Accurate repair of DNA double-strand breaks (DSBs) is essential for maintaining genomic integrity. RAD51, the core recombinase in homologous recombination, plays central roles in repairing DNA damage and protecting stalled replication forks. In normal cells, RAD51 helps maintain genomic integrity; however, in cancer, its overexpression often supports replication-stress tolerance, as well as resistance to chemotherapy, radiotherapy, and PARP inhibitors. RAD51 is tightly controlled at multiple levels, including transcriptional, post-transcriptional, and post-translational regulation, which together shape its activity in different biological contexts. This review summarizes the structural features of RAD51, its regulatory networks, and its roles in human disease, with particular emphasis on cancer progression and treatment resistance. Currently available RAD51 inhibitors, their mechanisms of action, and the main challenges that still limit clinical translation are discussed. Together, current findings indicate that RAD51 is a key genome maintenance factor and a promising therapeutic target in precision oncology.

Keywords: RAD51, Homologous recombination, DNA repair, RAD51 inhibitors, Synthetic lethality

1. INTRODUCTION

Cells continually face endogenous and exogenous DNA-damaging insults. Endogenous threats arise from intrinsic cellular processes, including replication errors and reactive oxygen species (ROS) generated during metabolism. Exogenous sources include ultraviolet radiation, ionizing radiation, and various chemical carcinogens [1]. In response, cells activate the DNA damage response (DDR), which enforces cell-cycle checkpoints and allows for repair; when the damage is beyond repair, apoptosis is often triggered [2]. Among all forms of DNA lesions, double-strand breaks (DSBs) are among the most severe threats to genomic stability. To counteract DSBs, eukaryotic cells rely primarily on two evolutionarily conserved repair pathways: homologous recombination (HR) and non-homologous end joining (NHEJ) [3]. NHEJ, initiated by rapid binding of the Ku heterodimer to DNA ends, achieves rejoining without the need for a homologous template. NHEJ is active throughout the cell cycle and is particularly dominant in G1 phase, when sister chromatids are absent [4]. In contrast, HR is a high-fidelity pathway that uses the sister chromatid as a template to restore the original DNA sequence. HR involves end

resection; generation of 3' single-stranded DNA (ssDNA) overhangs; loading of RAD51 onto ssDNA by mediators such as Breast Cancer Susceptibility Protein 2 (BRCA2); homology search and strand invasion; DNA synthesis; and resolution of Holliday junction recombination intermediates [5]. Because of its strict dependency on a sister chromatid template, HR is restricted primarily to the S and G2 phases of the cell cycle, and is particularly suited for repairing replication-associated DSBs.

RAD51, the core recombinase in HR, catalyzes strand invasion. After DSB resection, RAD51 is loaded onto ssDNA in a BRCA2-dependent manner and assembles into a helical nucleoprotein filament (Figure 1A). This filament then searches for homologous sequences and promotes pairing with duplex DNA. Subsequently, in strand invasion, the duplex is locally unwound, and base pairing between the invading strand and its complement leads to the formation of a displacement loop (D-loop) (Figure 1B) [6]. Beyond DSB repair, RAD51 plays a key role during replication stress: it stabilizes stalled replication forks by forming protective filaments on DNA, thereby limiting access of nucleases such as Meiotic Recombination 11 (MRE11) and preventing fork degradation [7]. This protective function is further supported

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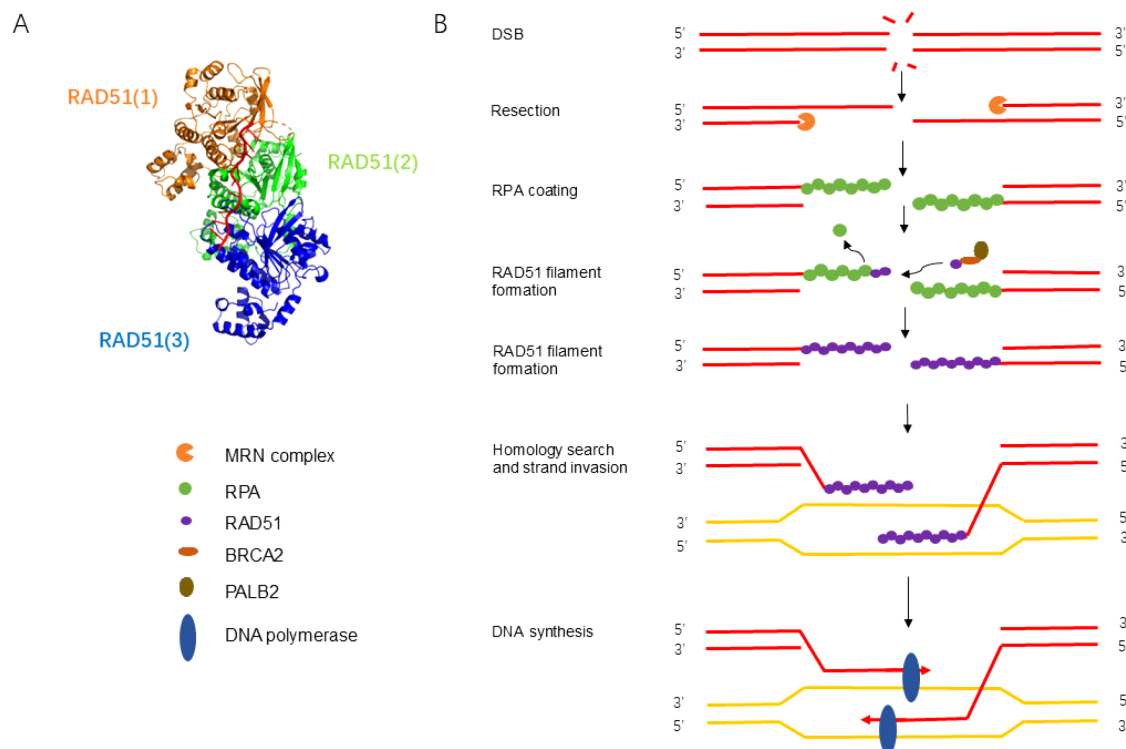


Figure 1 | RAD51-mediated HR repair and nucleoprotein filament structure.

(A) Trimeric structure of the RAD51–ssDNA nucleoprotein filament (PDB: 5H1B). Three consecutive RAD51 protomers, RAD51(1), RAD51(2), and RAD51(3), are shown in cartoon representation, assembled around single-stranded DNA (red). This filament is a key intermediate in HR, and it supports homology search and strand invasion during accurate DSB repair. (B) Schematic representation of RAD51-mediated HR repair. After induction of a DSB, DNA ends undergo 5′–3′ resection by the MRE11–RAD50–NBS1 (MRN) complex, thus generating 3′ ssDNA overhangs. These ssDNA regions are rapidly coated by replication protein A (RPA), which prevents degradation. RAD51 is then loaded onto ssDNA in a process mediated by BRCA2 and partner and localizer of BRCA2 (PALB2), thereby displacing RPA and forming a nucleoprotein filament. The RAD51 filament subsequently searches for homology and promotes strand invasion into the intact sister chromatid, thus generating a D-loop. This intermediate provides a template for DNA synthesis and restoration of the damaged sequence.

by findings regarding RAD51 paralogs, including the BCDX2 complex [8], and additional regulators such as GRB2, which stabilizes RAD51–DNA interactions by modulating its ATPase activity [9].

Within the broader DDR network, RAD51 acts as an effector rather than a sensor. Its activity is coordinated by upstream signaling pathways and is controlled primarily by the apical kinases ataxia-telangiectasia mutated (ATM) and ataxia-telangiectasia and Rad3-related (ATR). ATM is activated mainly by DSBs, whereas ATR responds to replication stress and ssDNA. Once activated, these kinases phosphorylate downstream targets including p53, CHK1, and CHK2, and consequently establish cell-cycle checkpoints and create conditions that permit HR to proceed (Table 1) [10, 11]. In this framework, ATM and ATR function as signal transducers, whereas RAD51 directly executes repair through strand exchange. This division of labor ensures that HR is tightly coupled to the cell-cycle stage and DNA damage context.

Although HR is essential for genome maintenance, it is frequently dysregulated in cancer. RAD51

is upregulated in many tumors, thus enhancing the capacity to repair DNA damage, and decreasing sensitivity to chemotherapy and radiotherapy [12, 13]. Elevated RAD51 activity also increases cancer cells' tolerance to replication stress associated with rapid proliferation, thus promoting both therapeutic resistance and genomic instability [14]. RAD51 has therefore emerged as a promising therapeutic target to sensitize tumors to DNA damage agents or to exploit synthetic lethal interactions.

2. RAD51 STRUCTURE AND EXPRESSION REGULATION

RAD51 comprises several functional domains: an N-terminal lobe domain (NLD), a core ATPase domain, DNA-binding loops, and flexible linker regions that together support DNA recognition and filament dynamics [15]. Cryo-electron microscopy and biochemical studies have revealed that the NLD mediates chromatin interactions: Lys64 and Lys70 are

Table 1 | Functional comparison of RAD51 versus apical DNA damage signaling kinases.

Functional category	RAD51	ATM	ATR
Primary role	HR effector (executes repair)	Signal transducer	Signal transducer
Biochemical function	Catalyzes strand invasion and exchange	Phosphorylates p53, CHK2, etc.	Phosphorylates CHK1.
Damage type sensed/repaired	DNA double-strand breaks (post-resection)	DNA double-strand breaks	Replication stress; single-stranded DNA
Key interacting proteins	BRCA2, PALB2, and RAD51 paralogs	MRN complex	ATRIP and TOPBP1

critical for nucleosome binding and interaction with the N-terminus of histone H4, and this interaction may help recruit RAD51 to chromatinized DNA breaks [16]. The ATPase cycle regulates filament conformation: ATP binding stabilizes an active, extended filament with high ssDNA affinity, whereas hydrolysis of ATP to ADP yields a compressed, inactive state and promotes dissociation [17].

RAD51 expression is tightly regulated at multiple levels, particularly at the transcriptional and post-transcriptional stages. Numerous transcription factors directly bind the *RAD51* promoter and positively regulate its expression. These include the epithelial-mesenchymal transition (EMT)-associated transcription factors ZEB1 and Slug/Snai2 [18], zinc finger protein 131 (ZNF131) [19], C-terminal binding protein 1 (CtBP1) [20], chromodomain helicase DNA-binding protein 4 (CHD4) [21], and Forkhead box M1 (FOXM1) [22]. In contrast, negative regulators such as interferon regulatory factor 1 (IRF1) [23], E2F transcription factor 7 (E2F7) [24], and tumor protein p53 [25] suppress RAD51 transcription and consequently attenuate HR. Some of these regulatory events are associated with DNA damage signaling. For example, DNA damage activates poly(ADP-ribose) polymerase (PARP), which in turn recruits the chromatin remodeler amplification in liver cancer 1 (ALC1) and creates a more accessible chromatin environment conducive to EMT-TF binding to the RAD51 promoter. Similarly, ZNF131 binds the RAD51 promoter through its zinc finger domain and cooperates with BTB domain and CNC homolog 1 (BACH1) in activating transcription, supporting HR, and contributing to resistance to radiotherapy and chemotherapy. CtBP1 also directly activates RAD51 transcription in breast cancer, whereas its knockdown decreases RAD51 expression, impairs formation of DNA repair foci, and sensitizes cells to cisplatin.

At the post-transcriptional level, the microRNA-34 (miR-34) family, including miR-34a-5p, miR-34b-5p, and miR-34c-5p, targets the RAD51 3'-UTR, and consequently represses translation and/or promotes mRNA degradation [26]. This layer of regulation helps fine-tune RAD51 abundance and maintain appropriate repair activity under various cellular conditions.

3. RAD51 POST-TRANSLATIONAL MODIFICATIONS

3.1 Ubiquitination

RAD51 protein abundance and activity are largely controlled by the ubiquitin-proteasome system, in which multiple E3 ubiquitin ligases participate. The role of ubiquitin protein ligase E3A (UBE3A), which was originally associated with global genome nucleotide excision repair, has recently been extended to HR, on the basis of evidence that it directly interacts with and ubiquitinates RAD51 [27, 28]. Early mitotic inhibitor 1 (EMI1) promotes cytoplasmic ubiquitination and degradation of RAD51, thereby inhibiting its nuclear translocation and HR activity [29]. Tripartite motif-containing 36 (TRIM36) also binds RAD51; accelerates its ubiquitin-dependent degradation; and leads to impaired DNA repair, increased radiosensitivity, and decreased tumor growth [30].

F-box DNA helicase 1 (FBH1), a UvrD family helicase containing an F-box motif, functions as part of the SKP1-CUL1-F-box (SCF) E3 ligase complex. FBH1 ubiquitinates RAD51 at Lys58 and Lys64, and is critical for replication fork stability [31, 32]. Ring finger and WD repeat domain 3 (RFWD3) catalyzes polyubiquitination of RAD51, thereby weakening its affinity for ssDNA and facilitating its dissociation from repaired DNA sites [33]. In contrast, the deubiquitinase ubiquitin C-terminal hydrolase L3 (UCHL3) removes ubiquitin chains from RAD51, thus preserving its functional state and promoting its interaction with BRCA2, thus supporting efficient recruitment to DSBs and maintaining genomic stability [34]. Together, these ubiquitin-dependent switches are critical for balancing RAD51 activity during replication and repair.

3.2 Phosphorylation

Phosphorylation events modulate RAD51 filament dynamics and interaction partners. CHK1 phosphorylates RAD51 at threonine 309 (Thr309); inhibition of CHK1 (e.g., UCN-01) decreases Thr309 phosphorylation and sensitizes cells to replication stress [35]. Polo-like kinase 1 (Plk1) phosphorylates RAD51 at serine 14 (Ser14), thereby priming adjacent threonine 13 (Thr13) for subsequent phosphorylation by casein kinase 2 (CK2). This sequential phosphorylation promotes RAD51 interaction with Nijmegen Breakage Syndrome Protein

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1 (NBS1), thereby enhancing its focal accumulation at DNA damage sites and ensuring precise HR repair [36]. In addition, tyrosine phosphorylation (at residues including Tyr315 and Tyr54), mediated by Mesenchymal-Epithelial Transition factor (c-MET) and Abelson Tyrosine-Protein Kinase 1 (c-Abl), influences RAD51 oligomer stability and its interaction with partner proteins. In contrast, phosphatases such as EYA transcriptional coactivator and phosphatase 4 (EYA4) selectively dephosphorylate RAD51 at sites such as Tyr315, thereby modulating its repair function [37–39].

3.3 SUMOylation and lactylation

After DNA damage, TOP1-binding arginine/serine-rich protein (TOPORS) mediates SUMOylation of RAD51 at Lys57 and Lys70. This process is tightly controlled by ATM, which phosphorylates TOPORS at Thr515 and consequently enhances its interaction with RAD51. SUMOylated RAD51 exhibits enhanced recruitment to damage sites and facilitates HR [40]. Beyond canonical repair regulation, RAD51 SUMOylation at Lys57 by small ubiquitin-like modifier 1 (SUMO1) is a signaling event that enhances the transcriptional activity of Specificity Protein 1 (Sp1), upregulates Golgi phosphoprotein 3 (GOLPH3), and ultimately contributes to cisplatin resistance in colon cancer cells [41]. More recently, lysine lactylation (e.g., at Lys73 by KAT2A/GCN5) has been reported to increase HR efficiency and to be associated with cisplatin resistance in ovarian cancer, in a novel metabolic–epigenetic interface in RAD51 regulation [42].

4. RAD51 IN HUMAN DISEASE

4.1 Roles of RAD51 in cancer

4.1.1 Roles of RAD51 in malignant progression of tumors. As the core executor of HR, RAD51 is indispensable in repairing DSBs and stabilizing stalled replication forks. In a pan-cancer bioinformatics study including 33 cancer types, RAD51's diagnostic and prognostic value has been systematically evaluated [43]. RAD51 was found to be significantly overexpressed in 28 cancer types (Figure 2), 15 of which achieved diagnostic AUC values exceeding 0.9 indicating strong diagnostic potential. Survival analyses further associated elevated RAD51 expression with poor overall survival (OS) in 11 cancer types, particularly glioma, in which RAD51 levels closely correlated with tumor grade and patient outcomes. Notably, in nine of these cancer types, the survival difference between RAD51 high- and low-expression groups remained statistically significant. Functional enrichment analyses consistently linked RAD51 to cell-cycle progression and DNA repair pathways. In addition, RAD51 expression negatively correlated with the predicted immunotherapy response in several tumor types. For example, patients with thyroid carcinoma, lung adenocarcinoma, liver hepatocellular carcinoma, glioma, or kidney renal clear cell carcinoma who had lower RAD51 expression

were more likely to respond to immune checkpoint blockade therapy.

Beyond DNA repair, RAD51 influences tumor progression by promoting EMT, migration, and invasion (Figure 3). According to clinical data, RAD51 expression is higher in lymph node and brain metastases than primary tumors, and increases with tumor stage. Consistently, RAD51 depletion markedly suppresses distant colonization of the lung, liver, and bone in vivo without significantly affecting primary tumor growth [44]. Loss of the transcription factor SIM2, or mutation of its phosphorylation site (Ser115Ala), impairs RAD51 recruitment to DNA damage sites, decreases HR efficiency, increases genomic instability, and enhances tumor invasion and metastasis [45]. In esophageal squamous cell carcinoma, RAD51 promotes EMT through the p38/Akt/Snail signaling axis, thereby increasing migration, invasion, and tumorigenicity in vivo [46]. In prostate cancer, RAD51 inhibition suppresses cell migration and decreases EMT markers such as vimentin; this process is regulated by an EGFR–Erk1/2–Akt–RAD51 signaling cascade that drives tumor invasiveness [47]. In oral squamous cell carcinoma, elevated RAD51 expression further facilitates tumor progression by affecting cell adhesion-related functions that are critical for invasion and metastasis [48].

RAD51 has also been implicated in tumor metabolic reprogramming. In pancreatic cancer, RAD51 increases hypoxia-inducible factor-1 α (HIF-1 α) protein levels and upregulates key glycolytic enzymes, including glucose transporter 1 (GLUT1), hexokinase 2 (HK2), and lactate dehydrogenase A (LDHA), thereby enhancing aerobic glycolysis and promoting tumor progression, chemotherapy resistance, and radiotherapy resistance (Table 2) [62]. Notably, combination treatment with the glycolysis inhibitor 2-deoxyglucose with the RAD51 inhibitor DIDS produces synergistic antitumor effects [63]. Mechanistically, 2-deoxyglucose depletes intracellular ATP by blocking glycolysis, thereby weakening RAD51-mediated DNA repair and sensitizing tumor cells to RAD51 inhibition. In esophageal squamous cell carcinoma, epigenetic regulation further links RAD51 to immune evasion. The histone demethylase KDM1A removes the repressive H3K9me2 mark from the RAD51 promoter, thus leading to RAD51 upregulation. Increased RAD51 then suppresses NF- κ B-dependent pro-inflammatory cytokines, such as IL-6 and IL-1 β , and attenuates STING-mediated antitumor immune responses, particularly in stromal tumor-infiltrating lymphocytes [64]. In contrast, RAD51 inhibition induces cytoplasmic dsDNA accumulation, activates cGAS–STING signaling, upregulates immune checkpoint molecules, and promotes the infiltration of peripheral blood mononuclear cells into tumor tissue [65].

4.1.2 Targeting RAD51 to enhance tumor radiosensitivity. Although radiotherapy remains a cornerstone of cancer treatment, its efficacy is often limited by intrinsic

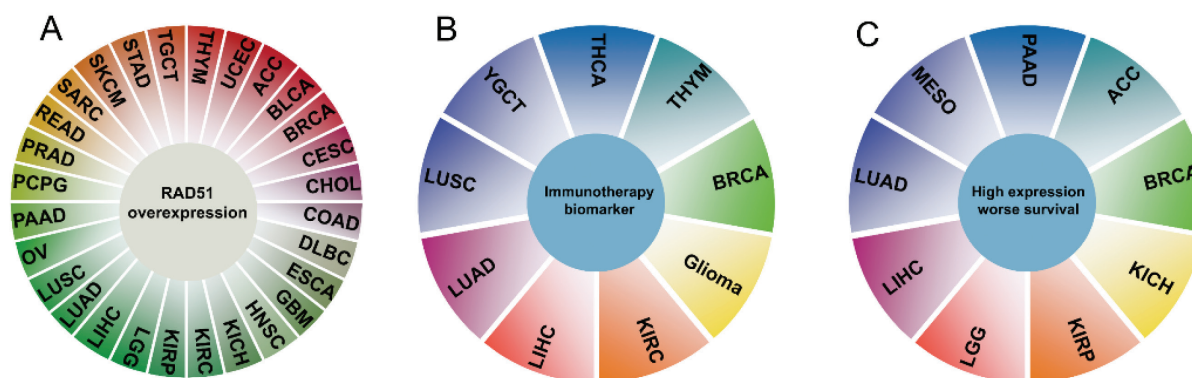


Figure 2 | Pan-cancer analysis of RAD51 expression and clinical relevance.

(A) RAD51 is significantly overexpressed in 28 cancer types, including adrenocortical carcinoma (ACC), bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), cholangiocarcinoma (CHOL), colon adenocarcinoma (COAD), diffuse large B-cell lymphoma (DLBC), esophageal carcinoma (ESCA), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), brain lower grade glioma (LGG), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), ovarian serous cystadenocarcinoma (OV), pancreatic adenocarcinoma (PAAD), pheochromocytoma and paraganglioma (PCPG), prostate adenocarcinoma (PRAD), rectal adenocarcinoma (READ), sarcoma (SARC), skin cutaneous melanoma (SKCM), stomach adenocarcinoma (STAD), testicular germ cell tumors (TGCT), thymoma (THYM), and uterine corpus endometrial carcinoma (UCEC). (B) Significant survival differences have been found between high versus low RAD51 expression in nine cancer types: ACC, BRCA, KICH, KIRP, LGG, LIHC, LUAD, MESO, and PAAD. (C) RAD51 has predictive value for immunotherapy in the following nine cancer types: BRCA, glioma, KIRC, LIHC, LUAD, LUSC, TGCT, thyroid carcinoma (THCA), and THYM.

or acquired radioresistance. As a central HR protein, RAD51 plays a key role in the radiation response and is therefore an attractive radio-sensitization target. RAD51 overexpression has been associated with radioresistance in multiple tumor models, whereas pharmacologic inhibition by B02 sensitizes cells to irradiation [49–51]. RAD51 also exerts cytoprotective effects in the cytoplasm by interacting with glutathione peroxidase 4 (GPX4) and ferritin heavy chain 1 (FTH1), thereby limiting ROS accumulation and ferroptosis and further strengthening radioresistance [49].

Targeting upstream regulators can also increase radiosensitivity. The cyclin-dependent kinase 2 (CDK2) inhibitor milciclib downregulates RAD51, prolongs γ -H2AX persistence, and induces cell-cycle arrest and apoptosis in radioresistant HCT116 and DLD-1 cells [66]. In addition, F-box only protein 22 (FBXO22) promotes RAD51 expression through FOXM1, whereas FBXO22 knockdown enhances radiosensitivity; findings that this effect is reversed by RAD51 overexpression have confirmed that RAD51 is a critical downstream effector in FBXO22-mediated radioresistance [67].

4.1.3 Targeting RAD51 to overcome chemotherapy resistance. RAD51 contributes to resistance against DNA-damaging chemotherapeutic agents, including cisplatin, mitomycin C, and bleomycin, by enhancing HR repair. Accordingly, RAD51 inhibition restores chemosensitivity in multiple tumor models [68]. In oral squamous cell carcinoma cells with high RAD51 expression, the RAD51 inhibitor B02 significantly enhances cisplatin

cytotoxicity; therefore, RAD51 blockade can counteract chemotherapy resistance [69].

Mechanistically, RAD51 overexpression increases HR repair ability and allows tumor cells to efficiently repair chemotherapy-induced DSBs and maintain survival. In contrast, suppression of RAD51 impairs DNA repair, and leads to accumulation of unrepaired lesions and subsequent cell death. Therefore, tumors with low RAD51 expression generally have elevated chemotherapy sensitivity. For example, in advanced high-grade serous ovarian carcinoma, high RAD51 expression is strongly associated with diminished sensitivity to platinum-based neoadjuvant chemotherapy, elevated likelihood of platinum resistance and relapse, and significantly attenuated progression-free survival and OS [70]. In glioblastoma, shRNA-mediated knockdown of RAD51 markedly increases temozolomide sensitivity, as shown by decreased viability and increased apoptosis [71].

Several upstream factors regulate RAD51 expression or stability and consequently influence chemosensitivity. Kin17 DNA and RNA binding protein (KIN17) increases RAD51 levels and protects cells against oxaliplatin-induced DNA damage; Jun activation domain-binding protein-1/COP9 signalosome complex subunit 5 (JAB1/COPS5) upregulates RAD51 through a p53-dependent mechanism; and Nucleolar and Spindle-Associated Protein 1 (NUSAP1) stabilizes RAD51 in chronic lymphocytic leukemia, whereas its inhibition sensitizes cells to fludarabine and ibrutinib [52–54]. Iron metabolism also affects RAD51 activity and chemotherapy sensitivity. In ovarian cancer, iron downregulates DNA polymerase θ

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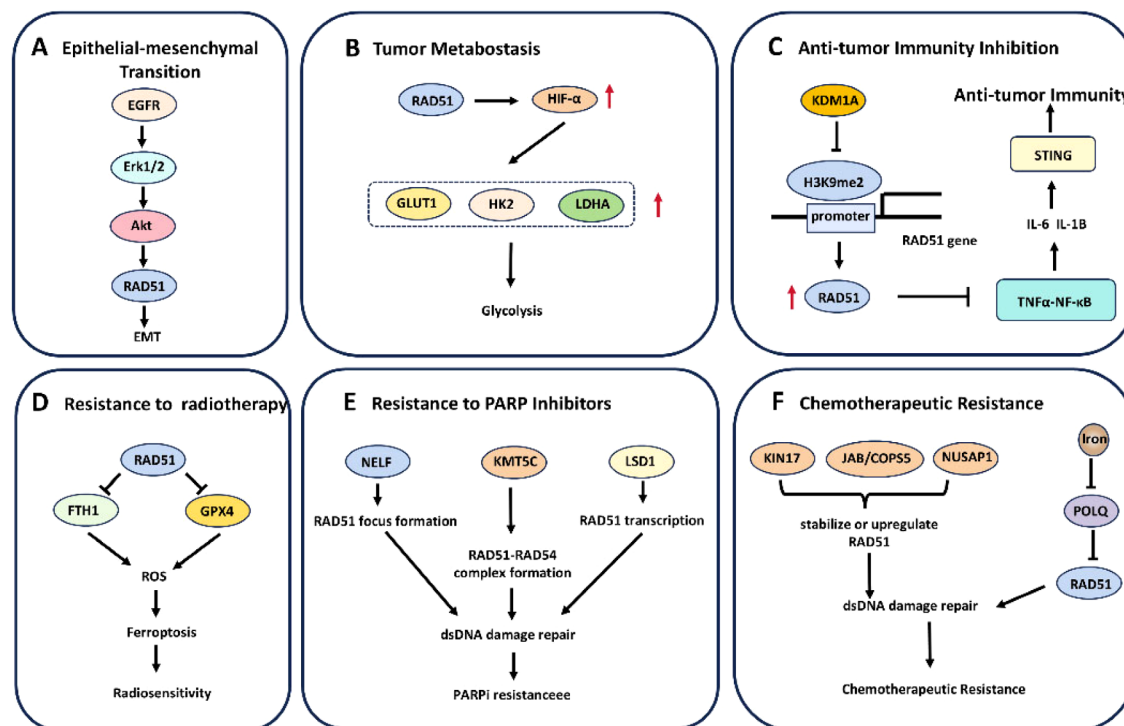


Figure 3 | Multifaceted roles of RAD51 in tumor progression and therapeutic resistance.

Schematic overview of how RAD51 contributes to EMT; metabolic reprogramming; immune evasion; and resistance to radiotherapy, chemotherapy, and PARP inhibitors. (A) EGFR-driven ERK1/2–AKT signaling upregulates RAD51 and promotes EMT and cell motility. (B) RAD51 enhances HIF-1 α expression and glycolytic gene programs (GLUT1, HK2, and LDHA), thus supporting aerobic glycolysis. (C) KDM1A-mediated removal of H3K9me2 activates RAD51 transcription, and subsequently suppresses NF- κ B-dependent cytokines (e.g., IL-6 and IL-1 β) and dampens STING-dependent anti-tumor immunity. (D) Cytoplasmic RAD51 interacts with GPX4 and FTH1, thereby limiting ROS accumulation and ferroptosis, and contributing to radioresistance. (E) KMT5C facilitates RAD51–RAD54 complex formation, thus enhancing HR and PARP inhibitor resistance; LSD1 further promotes RAD51 transcription, whereas NELF depletion impairs BRCA1 recruitment and RAD51 focus formation, thereby sensitizing cells to PARP inhibition. (F) KIN17, JAB1/COP55, and NUSAP1 sustain RAD51 expression and consequently drive chemoresistance. In ovarian cancer, iron depletion induces POLQ nuclear translocation, thus alleviating RAD51 suppression, restoring HR, and reinforcing chemoresistance.

Table 2 | Roles of RAD51 in tumor treatment resistance.

Key role of RAD51	Mechanism/regulation	Reference
Drives radioresistance	Upregulated in resistant tumors; inhibits ferroptosis via GPX4/FTH1; targeted by CDK2/FBXO22	[49–51]
Drives chemoresistance	Promotes DNA repair; regulated by KIN17, JAB1, NUSAP1, iron metabolism, and the tumor microenvironment	[52–54]
Mediates PARPi resistance	Enhanced expression/activity via epigenetic regulators (KMT5C and LSD1) and other factors (NELF and KIAA1529)	[55–59]
Influences drug sensitivity	Downstream of AKT in osimertinib response	[60]
Facilitates immune evasion	RAD51 inhibitor treatment induces PD-L1 expression	[61]

(POLQ) and promotes its nuclear translocation, thereby alleviating POLQ-mediated suppression of RAD51, restoring HR, and contributing to platinum resistance. In contrast, iron chelation or knockdown of FTH1/FTL maintains POLQ–RAD51 colocalization, inhibits RAD51-dependent repair, increases DNA damage, and sensitizes cells to platinum drugs [72]. The tumor microenvironment also participates in RAD51-mediated drug

resistance. In gastric cancer, mesenchymal stem cell–conditioned medium induces programmed death-ligand 1 (PD-L1), which in turn promotes RAD51 expression and nuclear accumulation, enhances DNA repair, and increases cisplatin resistance [73].

4.1.4 RAD51-mediated PARP inhibitor resistance. PARP inhibitors (PARPi) selectively target tumors with HR

defects by exploiting synthetic lethality, and have shown marked efficacy in cancers with BRCA1/2 mutations. However, acquired and intrinsic PARPi resistance remains a major obstacle in a substantial proportion of patients. Increasing evidence suggests that epigenetic regulators and signaling pathways promote PARPi resistance by modulating the expression or activity of the HR effector RAD51 [55]. For example, in hepatocellular carcinoma, the methyltransferase lysine methyltransferase 5C (KMT5C) enhances RAD51–RAD54 complex formation, thereby improving HR efficiency and conferring PARPi resistance [56]. Lysine-specific demethylase 1 (LSD1) directly binds the RAD51 promoter and activates its transcription; accordingly, genetic depletion or pharmacologic inhibition of LSD1 decreases RAD51 and BRCA1/2 expression, induces an HR-deficient phenotype (decreased RAD51 foci and increased DSBs), and restores sensitivity to PARPi such as olaparib in originally insensitive tumor cells [57]. Similarly, depletion of the negative elongation factor (NELF) complex impairs BRCA1 recruitment to DSB sites, decreases BRCA1 and RAD51 focus formation, and sensitizes cells to PARP inhibition [58]. In ovarian cancer, KIAA1529 has also been shown to upregulate RAD51 through Aurora-A signaling and subsequently confer PARPi resistance [59]. Collectively, these findings position RAD51 as a central node in PARPi resistance and suggest that targeting its regulatory network might help overcome therapeutic failure.

During DSB repair, disruption of the HR pathway compromises accurate repair of DNA lesions and leads to genomic instability. This deficiency not only contributes to tumor initiation and progression, but also creates a therapeutic vulnerability. RAD51 is a core recombinase in the HR pathway, and the formation of RAD51 nuclear foci at DNA damage sites is widely considered to provide a functional readout of HR competence [74, 75]. Accordingly, assessment of RAD51 focus formation after DNA damage can serve as a biomarker for HR deficiency and has important implications in predicting PARPi sensitivity, guiding treatment selection, and clarifying resistance mechanisms.

4.1.5 Other combination strategies involving RAD51 inhibitors. EGFR inhibitors are cornerstone treatments for selected non-small cell lung cancer subtypes [76]. In non-small cell lung cancer cells, RAD51 expression is an important determinant of sensitivity to osimertinib. Osimertinib itself downregulates RAD51 by inhibiting the AKT pathway, and RAD51 inhibition further enhances its antitumor activity [60]. Tumor cells, by exploiting the high PD-L1 expression on T cells, engage PD-1, and subsequently suppress antitumor immunity and promote immune escape [77, 78]. Recent studies have shown that RAD51 inhibition increases PD-L1 expression on tumor cell surfaces. More importantly, combining RAD51 inhibition with PD-L1 blockade elicits stronger T cell-mediated tumor killing than either monotherapy alone [61]. RAD51 inhibition might therefore

sensitize tumors to immune checkpoint blockade by reshaping PD-L1-dependent immune interactions.

4.2 RAD51 and Fanconi anemia

Fanconi anemia (FA), the most common inherited bone marrow failure syndrome, is characterized by congenital anomalies, progressive pancytopenia, and predisposition to malignancy [79]. It is caused by biallelic pathogenic variants in any one of at least 22 known FA-associated genes (designated *FANCA* through *FANCW*), which collectively constitute the FA/BRCA DNA repair pathway. RAD51 (designated *FANCR*) occupies a notable position within this pathway. Unlike most FA genes, which follow autosomal recessive inheritance, *FANCR*/RAD51-related disease shows autosomal dominant inheritance, wherein heterozygous missense variants are sufficient to cause FA through a haploinsufficiency mechanism [80]. As the terminal effector of the FA/BRCA pathway, RAD51 mediates HR-based repair of DNA DSBs and stabilizes stalled or collapsed replication forks. These functions are essential for genome maintenance, and their disruption underlies the FA phenotype [81].

4.3 RAD51 and congenital mirror movements

Congenital mirror movement disorder (CMM) is a rare autosomal dominant neurodevelopmental condition (with ~50% penetrance) characterized by involuntary symmetric hand movements that impair bimanual coordination and daily functioning [82]. *RAD51* has been identified as a causative gene for CMM [83]. The incomplete penetrance of heterozygous *RAD51* mutations in CMM has been hypothesized to reflect a mechanism of somatic strand-specific imprinting and selective sister chromatid segregation. During a critical asymmetric cell division in early brain development, RAD51-dependent selective segregation of epigenetically distinct sister chromatids establishes contralateral motor circuits. In *RAD51* heterozygotes, impaired selective chromatid segregation leads to random distribution; consequently, approximately half of heterozygotes develop normal circuitry, whereas the other half exhibit homolateral wiring that produces mirror movements [84].

5. SMALL-MOLECULE INHIBITORS OF RAD51

Given its central role in HR and its frequent upregulation in aggressive tumors, RAD51 has emerged as an attractive therapeutic target. By supporting DNA repair and tolerance to replication stress, RAD51 contributes to resistance against radiotherapy, chemotherapy, and PARP inhibitors. Accordingly, pharmacological inhibition of RAD51 offers a rational strategy to sensitize tumor cells to DNA-damaging agents and to overcome acquired resistance. In the past decade, small-molecule inhibitors have increasingly been developed to target distinct functional aspects of RAD51, including its DNA-binding activity, oligomerization, ATPase function, and interaction with key partners such as BRCA2.

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5.1 Inhibitors targeting the RAD51–DNA interaction

High-throughput screening has identified 4,4'-diisothiocyanostilbene-2,2'-disulfonic acid (DIDS) as a potent inhibitor of RAD51-mediated strand exchange (Table 3). DIDS directly binds RAD51, interferes with its interaction with DNA substrates, and ultimately blocks key steps of HR [85]. B02 is a widely used RAD51 inhibitor that disrupts RAD51–DNA binding. By preventing RAD51 association with both ssDNA and dsDNA, B02 impairs nucleoprotein filament assembly, decreases recruitment to DNA damage sites, and compromises HR. Consequently, it enhances the cytotoxicity of DNA crosslinking agents such as cisplatin and mitomycin C, and it has shown synergistic activity with PARP inhibitors in multiple preclinical models [86]. Structural optimization of B02 has yielded more potent analogues, including the quinazolinone derivative compound 17 with improved affinity for RAD51. Compared with B02, compound 17 more effectively suppresses RAD51 focus formation and enhances radiosensitivity in triple-negative breast cancer cells [103].

Nitro-oleic acid (OA-NO₂) represents a covalent class of RAD51 inhibitors. OA-NO₂ alkylates Cys319, a residue involved in the RAD51–ABL1 interaction, thereby decreasing RAD51 affinity for ssDNA and impairing Tyr315 phosphorylation-dependent signaling [87]. In addition to inhibiting HR, OA-NO₂ exerts broader anti-tumor effects including suppression of tumor cell migration and invasion via modification of IKKβ and p65, and disruption of proteasome function, thus inducing endoplasmic reticulum stress and apoptosis [88]. OA-NO₂ enhances the efficacy of PARP inhibitors, chemotherapy, and radiotherapy in preclinical models. Although early clinical studies in non-oncologic settings (e.g., kidney disease, asthma, and pulmonary hypertension) have suggested a favorable safety profile, its electrophilic nature prompts concerns regarding off-target effects, particularly with long-term, high-dose use [89]. A derivative, CP-8, demonstrates improved antitumor activity and selectivity, and has been found to effectively suppress tumor growth in triple-negative breast cancer models, as both a monotherapy and a combination therapy with talazoparib, with minimal toxicity to normal cells and no evident systemic toxicity in vivo [104].

Natural products have also yielded RAD51 inhibitors. Halenaquinone, isolated from marine sponges, binds RAD51 and blocks the interaction of RAD51 or RAD51–ssDNA complexes with dsDNA, thus decreasing radiation-induced RAD51 focus formation without affecting initial ssDNA binding [90, 91]. Similarly, the sulfonated dye Chicago Sky Blue inhibits RAD51-mediated strand exchange and D-loop formation in a dose-dependent manner by preventing RAD51 binding to ssDNA, independently of ATP hydrolysis [92].

5.2 Inhibitors targeting RAD51 oligomerization

Targeting RAD51 oligomerization offers an alternative approach to disrupt filament assembly. Representative

compounds include IBR2 and RI-1. IBR2 binds the RAD51 oligomerization interface, and subsequently blocks polymerization and HR activity. It also promotes RAD51 degradation via the ubiquitin–proteasome system, thereby decreasing RAD51 protein levels. Functionally, IBR2 inhibits the proliferation of Ba/F3 cells bearing the Thr315Ile mutation and has shown synergistic effects with imatinib in K562 xenograft models, thus suggesting potential for overcoming drug resistance [93]. Further structural optimization led to the development of IBR120, a more potent and selective inhibitor. Its R-configuration and optimized conformational geometry are key determinants of activity. IBR120 exhibits broad anticancer effects across multiple cell lines while maintaining low toxicity toward normal epithelial cells [105].

RI-1 acts through a different mechanism by covalently modifying Cys319 at the monomer–monomer interface, thereby disrupting RAD51 oligomerization and impairing nucleoprotein filament assembly without affecting upstream RPA binding [94]. This selectivity enables RI-1 to potentiate the cytotoxicity of DNA-damaging agents. However, because its chloromaleimide moiety functions as a Michael acceptor, it exhibits irreversible binding, limited stability, and potential off-target effects. Replacement of the reactive group with a methoxyphenyl substituent generates RI-2, which lacks Michael acceptor reactivity, and therefore exhibits improved stability and retains potent inhibitory activity against RAD51 [106].

5.3 Inhibitors targeting the ATP-binding pocket or D-loop formation

EN7883 and EN9632 are two novel classes of compounds that target the ATP-binding pocket of RAD51 [95]. Both have been found to decrease HR efficiency in a dose-dependent manner in DR-GFP assays at low micromolar concentrations, without inducing significant G2/M arrest. Structural modeling suggests distinct binding modes: EN7883 forms hydrogen bonds with residues in the Walker A motif via its imidazole ring, whereas EN9632 engages a broader hydrophobic pocket and interacts with residues such as Lys133 and Glu322 through its carbonyl and sulfonyl groups, respectively. Another class of inhibitors targets a later step in HR. The compound RI(dI)-2 selectively blocks RAD51-mediated D-loop formation, a critical step in strand invasion, without significantly affecting nucleoprotein filament assembly or RAD51 focus formation. This mechanism effectively suppresses HR and enhances tumor cell sensitivity to ionizing radiation [96].

5.4 Inhibitors targeting the RAD51–BRCA2 interaction

RAD51 activity depends on its interaction with BRCA2, which loads RAD51 onto ssDNA through BRC repeats and consequently initiates filament assembly [107].

Table 3 | Small-molecule inhibitors targeting RAD51.

Inhibitor	Structure	Target	In vitro IC ₅₀ /binding affinity	Reference
DIDS		Inhibition of RAD51–ssDNA binding	D-loop assay: 1–10 μ M	[85]
B02		Inhibition of RAD51–dsDNA binding	D-loop assay: 27.4 μ M	[86]
Nitro-oleic acid		Cys 319	Cancer cell lines IC ₅₀ : 5–30 μ M	[87-89]
Halenquinone		Inhibition of RAD51–dsDNA binding	MOLT-4 cell line IC ₅₀ : 1.44 mM	[90, 91]
Chicago Sky Blue		Inhibition of RAD51–ssDNA binding	Strand exchange assay: 0.4 μ M	[92]
IBR2		Inhibition of polymerization	Cancer cell lines IC ₅₀ : 11–16 μ M	[93]
RI-1		Disruption of oligomerization	Cancer cell lines IC ₅₀ : 20–40 mM	[94]
EN7883		ATP-binding site	–	[95]
RI(dl)-2		Inhibition of D-loop formation	D-loop assay: 11.1 μ M	[96]
7m		FxxA-binding pocket	K _D : 1.3 μ M	[97]
CAM833		FxxA-binding pocket	K _D : 366 nM	[98]
4d		RAD51–BRCA2 protein–protein interaction	ELISA: EC ₅₀ 16 μ M	[99]
Compound 7		BRC4 binding site	ELISA: EC ₅₀ 19 μ M	[100]
Compound 46		RAD51–BRCA2 protein–protein interaction	ELISA: EC ₅₀ 28 μ M	[101]
RB-1	Ac-sWLTX-NH2	RAD51–BRCA2 protein–protein interaction	K _D : 9.24 nM	[102]

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Disrupting this interaction effectively inhibits HR, overcomes PARPi resistance, and expands synthetic-lethality approaches [107]. Structure-guided approaches have identified several small molecules targeting the RAD51–BRCA2 interface. Scott et al. have developed tryptophan-derived fragments targeting the FxxA pocket of RAD51 and, through structure–activity relationship optimization, identified compound 7m with markedly improved affinity [97]. Biophysical studies have confirmed that 7m competitively occupies the FxxA site and disrupts RAD51–BRCA2 binding. CAM833 also targets this pocket and decreases RAD51 focus formation while increasing γ -H2AX levels, in agreement with HR inhibition [98].

Other chemotypes include dihydroquinolinone–pyrazoline derivatives. Compound 4d binds a complementary hydrophobic pocket on RAD51 and forms stabilizing interactions, including a salt bridge with Arg250 and a hydrogen-bond network via its core heteroatoms. Functional assays have confirmed its ability to disrupt the RAD51–BRCA2 interaction [99]. RS-35d, sharing a similar scaffold, additionally inhibits DDR kinases such as ATM, ATR, and DNA-PK, thus inducing a “within-pathway” synthetic lethality effect that can overcome PARPi resistance in BRCA2-mutant pancreatic cancer cells [108].

Additional inhibitors include N-acyl hydrazones (e.g., compound 7) and pyrazolo[1,5-a]pyrimidines (e.g., compound 46). Representative compounds bind RAD51 at sites overlapping with BRCA2 interaction regions and act synergistically with PARP inhibitors such as

talazoparib in inducing DNA damage and apoptosis [100, 101]. Peptide inhibitors have also shown promise: RB-1 binds RAD51 with high affinity and achieves potent inhibitory activity in multiple renal cancer cell lines, with favorable stability and minimal toxicity in vivo, thereby supporting its potential for further development [102].

Despite substantial progress, no highly selective RAD51 inhibitor is currently approved for clinical use, and most candidates remain in the preclinical stage. Several challenges limit their development. Covalent inhibitors such as OA-NO₂ lack target specificity because of broad electrophilic reactivity. RI-1 has poor in vivo stability, whereas its derivative RI-2, although more stable, might have diminished potency because of a loss of irreversible binding. In addition, some compounds, such as compound Chicago Sky Blue, display off-target biological activities that prompt potential safety concerns [109]. Future efforts must balance potency, selectivity, and pharmacokinetic properties, and additionally identify the patient populations most likely to benefit from RAD51-targeted therapies.

6. CONCLUSION

RAD51, the central catalytic engine of HR, orchestrates high-fidelity strand exchange and stabilizes replication forks. This review summarized its structural organization, multilayered regulation (transcriptional,

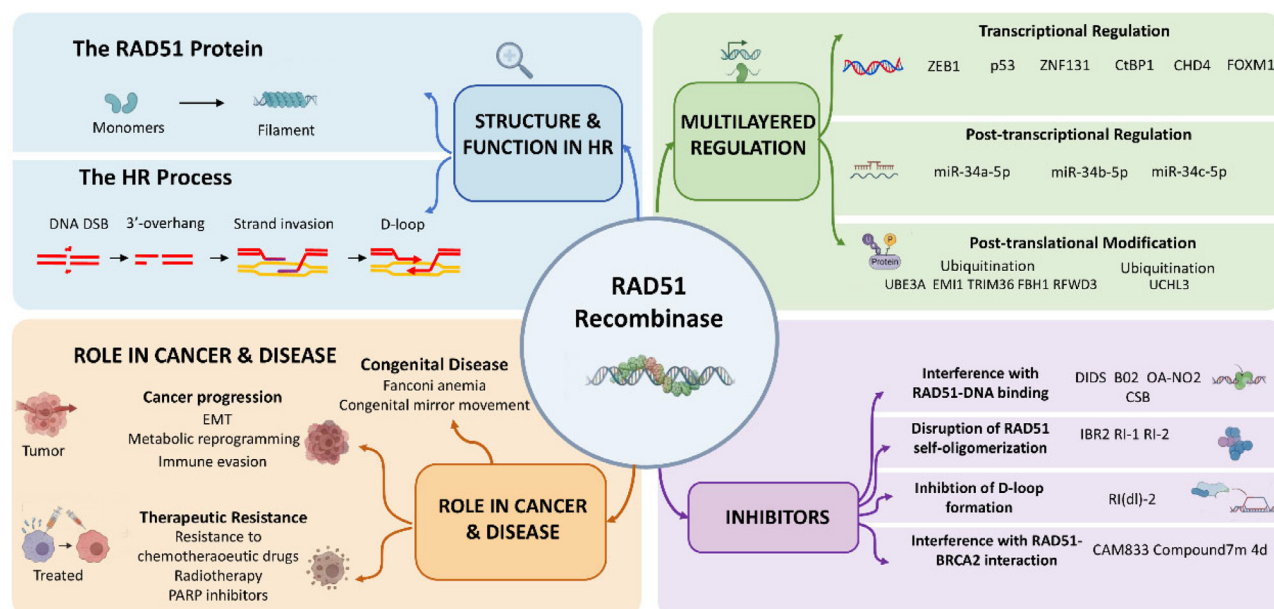


Figure 4 | Multidimensional regulatory network of RAD51 and its functions in cancer and disease.

RAD51 is a core component of the HR repair pathway. Its expression and activity are modulated at the transcriptional, post-transcriptional, and post-translational levels, and ultimately influence cancer development, therapeutic resistance, and the progression of genetic disorders.

post-transcriptional, and post-translational), and context-dependent roles in human disease (Figure 4). Notably, RAD51 exhibits a striking functional duality. Loss-of-function mutations compromise HR and genome integrity, and lead to inherited disorders such as FA and CMM. RAD51 deficiency disrupts replication fork protection and DNA repair in FA, and is proposed to affect asymmetric sister chromatid segregation during neurodevelopment in CMM. In contrast, RAD51 overexpression or hyperactivation is frequently observed in cancer, thus supporting DNA repair; therapeutic resistance; and additional tumor-promoting processes including EMT, metastasis, and metabolic reprogramming. This duality underscores the context-dependent nature of RAD51 as a therapeutic target: its inhibition may be advantageous in tumors with elevated RAD51 activity, whereas its functional restoration might be considered in diseases associated with RAD51 insufficiency.

In oncology, RAD51 has emerged as an attractive yet challenging target. Beyond its canonical role in DNA repair, accumulating evidence suggests that its inhibition can induce replication stress, destabilize replication forks, and lead to cytosolic DNA accumulation, thereby triggering innate immune signaling. These effects support the use of RAD51 inhibitors in HR-proficient tumors and provide a rationale for combining them with PARP inhibitors, DNA-damaging chemotherapy, radiotherapy, or immune checkpoint blockade.

However, the clinical translation of RAD51-targeted therapies remains constrained by the essential role of RAD51 in maintaining genomic integrity in all proliferating cells. Systemic inhibition is therefore likely to lead to on-target toxicity in highly proliferative tissues, including the bone marrow and gastrointestinal epithelium, and might also prompt long-term safety concerns such as secondary malignancies, particularly in younger patients or those requiring prolonged treatment. These limitations highlight the need for strategies that improve tumor selectivity and the therapeutic index. Targeted delivery systems, such as antibody–drug conjugates and nanoparticle-based formulations, may help restrict RAD51 inhibition to tumor cells and mitigate toxicity.

In summary, despite the toxicological challenges associated with targeting a core DNA repair factor, RAD51 remains a compelling candidate for therapeutic intervention, because of its potential to overcome treatment resistance, induce immunogenic stress responses, and synergize with existing therapies. Future efforts should focus on improving selectivity, identifying predictive biomarkers, and optimizing rational combination strategies. Achieving an appropriate balance between efficacy and safety will be critical for translating RAD51-targeted approaches showing preclinical promise into clinically meaningful benefits.

DATA AVAILABILITY STATEMENT

This article is a review article and therefore does not contain original data.

ETHICS STATEMENT

No direct interactions with human or animal subjects were involved. Therefore, ethical approval and informed consent were not required.

AUTHOR CONTRIBUTIONS

ZC: Conceptualization, Writing – original draft, Writing – review & editing. YD: Writing – original draft. LY: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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