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Roles of FEN1 in tumor biology: Mechanisms, therapeutic implications, and emerging strategies

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ABSTRACT

Flap endonuclease 1 (FEN1), a multifunctional, structure-specific nuclease critical for DNA replication and repair, has emerged as a pivotal player in tumor biology. Multiple mutations and genetic polymorphisms in FEN1 are linked to cancer predisposition and genomic instability across various malignancies. Furthermore, aberrant overexpression of FEN1 correlates with tumor initiation, aggressive progression, and poor prognosis in diverse cancers. Accumulating evidence demonstrates that suppressing FEN1 expression or activity sensitizes cancer cells to conventional therapies (chemotherapy and radiotherapy), molecularly targeted agents, and emerging immunotherapies, such as chimeric antigen receptor T-cell (CAR-T) therapy, suggesting its broad utility in overcoming treatment resistance. Additionally, developing small-molecule FEN1 inhibitors and synthetic-lethal interactions between FEN1 and additional DNA-repair genes could guide the development of precision combination therapies. By exploiting FEN1's unique substrate recognition properties, early-stage cancers can be detected via liquid biopsy or protein-focused assays. Collectively, this review underscores FEN1 as a promising biomarker and a multifaceted target for cancer interception and treatment, while also emphasizing the need for further mechanistic exploration and translational validation of FEN1-directed strategies.

1. Introduction

The survival and proliferation of cells are fundamentally dependent on the maintenance of genomic stability. Disruptions in genomic homeostasis have been associated with the development and progression of tumors (Shen et al., 2005). DNA repair enzymes play a crucial role in maintaining genomic stability. Flap endonuclease-1 (FEN1), a member of the radiation sensitive 2 family (RAD2) family of structure-specific nucleases. Current evidence suggests that FEN1 performs vital functions in various DNA repair and metabolic processes, including Okazaki fragment maturation and base excision repair (BER), through its three major nuclease activities: flap endonuclease activity, 3gap endonuclease activity, and exonuclease activity (Bambara et al., 1997; Lieber, 1997; Liu et al., 2004; Liu et al., 2009). First, the endonuclease activity of FEN1 enables the removal of primers and 5′ flap DNA structures generated during lagging strand synthesis. Furthermore, FEN1 efficiently excises 5′ flap structures generated by DNA polymerase δ/ε during BER (Shen et al., 2005; Zheng et al., 2005). During apoptosis, FEN1 contributes to apoptotic DNA fragmentation through its 5′ exonuclease activity and gap endonuclease activity (Kim et al., 2000; Liu et al., 2004; Zheng et al., 2005), ensuring normal DNA metabolism in cells. Besides, FEN1 is involved in resolving replication fork stalling and maintaining telomere stability, further underscoring its importance in DNA metabolic processes (Kim et al., 2000; Parrish et al., 2003; Warbrick et al., 1998;

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Zheng et al., 2005). Through these diverse nuclease activities, FEN1 plays a vital role in preserving genomic stability and preventing malignant transformation of cells. Moreover, when mutations, genetic polymorphisms, and abnormal expression occur, FEN1 plays a role in the development and advancement of tumors in different organs through various mechanisms, as outlined in this review.

Beyond this, we also highlight recent conceptual and technological breakthroughs involving FEN1 that are reshaping its diagnostic and therapeutic potential. For example, novel platforms have been developed for the highly sensitive and quantitative detection of FEN1 activity. These include nanodetection platforms, aptamer-based signal amplification systems, and clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 12a-based (CRISPR/Cas12a-based) methods capable of detecting activity at the single-molecule level (Cui et al., 2023; Meng et al., 2024; Zhang et al., 2024). These advances herald a new era for early cancer diagnostics. Furthermore, synthetic lethality interactions between FEN1 and other proteins, such as breast cancer gene 1 (BRCA1), exonuclease 1 (EXO1), DNA-dependent protein kinase catalytic Subunit (DNA-PKcs), and TIMELESS, could offer new therapeutic strategies for cancers(Andronikou et al., 2024; Saldanha et al., 2024; Zhang et al., 2022).

This review aims to synthesize the role of Flap Endonuclease 1 (FEN1) in tumorigenesis, drug resistance, and novel diagnostic approaches. A systematic literature search from January 1990 to March 2025 identified 507 articles from PubMed/MEDLINE and 673 from Web of Science Core Collection. Following a rigorous screening process, 97 studies met the inclusion criteria (Fig. 1). Based on the synthesized evidence, we discuss the significance of FEN1 as a promising biomarker and therapeutic target. Finally, we suggest that future research should prioritize delineating the specific mechanisms of FEN1 in tumorigenesis and progression across diverse cancer types.

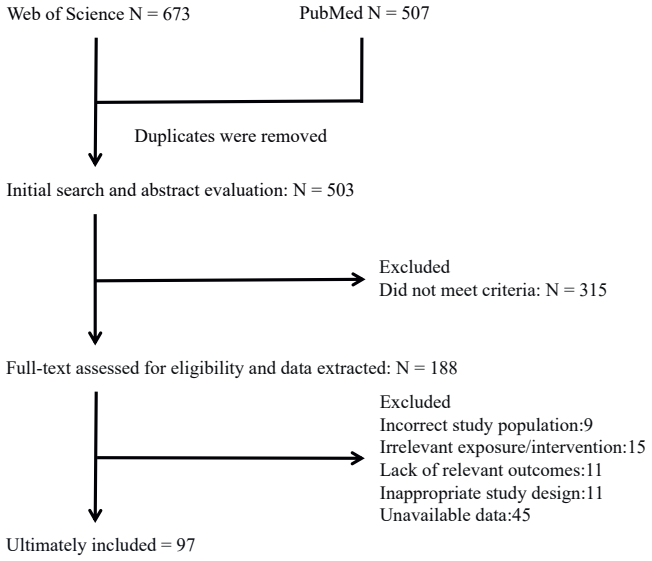

Fig. 1. PRISMA flow diagram detailing the systematic identification and screening of included studies. The initial search across PubMed/MEDLINE and Web of Science Core Collection (1990-March 2025) retrieved 507 and 673 records, respectively, using a comprehensive search strategy for FEN1 and cancer. After duplicate removal and screening, 97 studies were included. The primary reasons for excluding studies during the full-text assessment were: incorrect study population, irrelevant exposure/intervention, lack of relevant outcomes, inappropriate study design, and unavailable data.

2. The association of FEN1 with tumorigenesis and tumor progression

2.1. The role of FEN1 mutations and genetic polymorphisms in tumor susceptibility and genomic instability

Mutations or polymorphisms in FEN1 have been associated with increased mutation rates and a higher risk of tumorigenesis, highlighting its potential role in genomic instability–driven cancer development (Kunkel et al., 1997). Notable mutations identified in the FEN1 gene include the E160D mutation observed in nude mice, as well as the A159V, E359K, and L209P mutations reported in human studies (Chung et al., 2015; Sun et al., 2017; Zheng et al., 2011a; Zheng et al., 2007). These mutations are visually summarized in Fig. 2. In addition, the genetic polymorphisms of FEN1, including -69G/A (rs174538) and 4150 G/T (rs4246215), can determine its enzymatic activity and influence tumor incidence (Chen et al., 2013; Liu et al., 2012).

2.1.1. FEN1 mutation

The FEN1 E160D mutation in nude mice serves as the first animal model of FEN1 mutations (Zheng et al., 2007). This specific mutation significantly reduced the gap endonuclease and exonuclease activities of FEN1, resulting in an increased spontaneous mutation rate in cells and the accumulation of nondigested DNA fragments in apoptotic cells. Therefore, the nude mice carrying this mutation were more prone to developing tumors, chronic inflammatory diseases, and autoimmune disorders. In humans, somatic mutations in the FEN1 gene, such as I39T, P151L, A159V, and R245W, have also been identified in several human tumor types, including lung cancer, melanoma, esophageal cancer, breast cancer (BC), and kidney cancer (Zheng et al., 2007). Like E160D, these mutations have also been shown to impair FEN1's gap endonuclease and exonuclease activities while retaining its flap endonuclease function. Although the overall mutation frequency of FEN1 in human tumors is relatively low (approximately 4 %), some variants such as A159V were found at a frequency of 3 %–15 % in certain tumor samples. The findings imply that it is yet to be confirmed whether these mutations in humans can elicit the same pathological effects seen with E160D in mice.

The FEN1 gene mutation F343A/F344A in mice involves replacing phenylalanine at positions 343 and 344 with alanine, also known as FFAA. This mutation reduces FEN1 nuclease activity and interferes with its interaction with proliferating cell nuclear antigen (PCNA), blocking Okazaki-fragment maturation and causing massive DNA breakage that triggers Chk1-dependent G2/M arrest and tetraploid aneuploidy (Zheng et al., 2011a). This chain of events eventually boosts the chances of malignant transformation in the cells involved. Notably, the FFAA mutation was artificially introduced in mice to investigate the biological significance of the FEN1–PCNA interaction, and it has not been reported in human populations to date.

A previous study identified the E359K mutation in the FEN1 gene, which substitutes glutamate with lysine at position 359 (Chung et al., 2015). This mutation impairs its gap endonuclease activity and its interaction with Werner syndrome protein, resulting in an inability to process bubble-like structures at DNA ends, decreased telomere stability, increased DNA replication stress, and the occurrence of various types of chromosomal aberrations, which leads to a higher rate of malignant transformation. Notably, the E359K mutation was reported in a heterozygous state in a patient with a family history of breast and uterine cancers; however, no further pedigree analysis was performed (Chung et al., 2015). This suggests that current evidence linking the E359K variant to human cancer susceptibility remains extremely limited. Therefore, the primary translational significance of the E359K germline mutation lies in cancer risk prediction for families carrying this variant, although its population-wide allele frequency and independent validation in other cohorts are yet to be established.

The FEN1 L209P mutation has been associated with the development

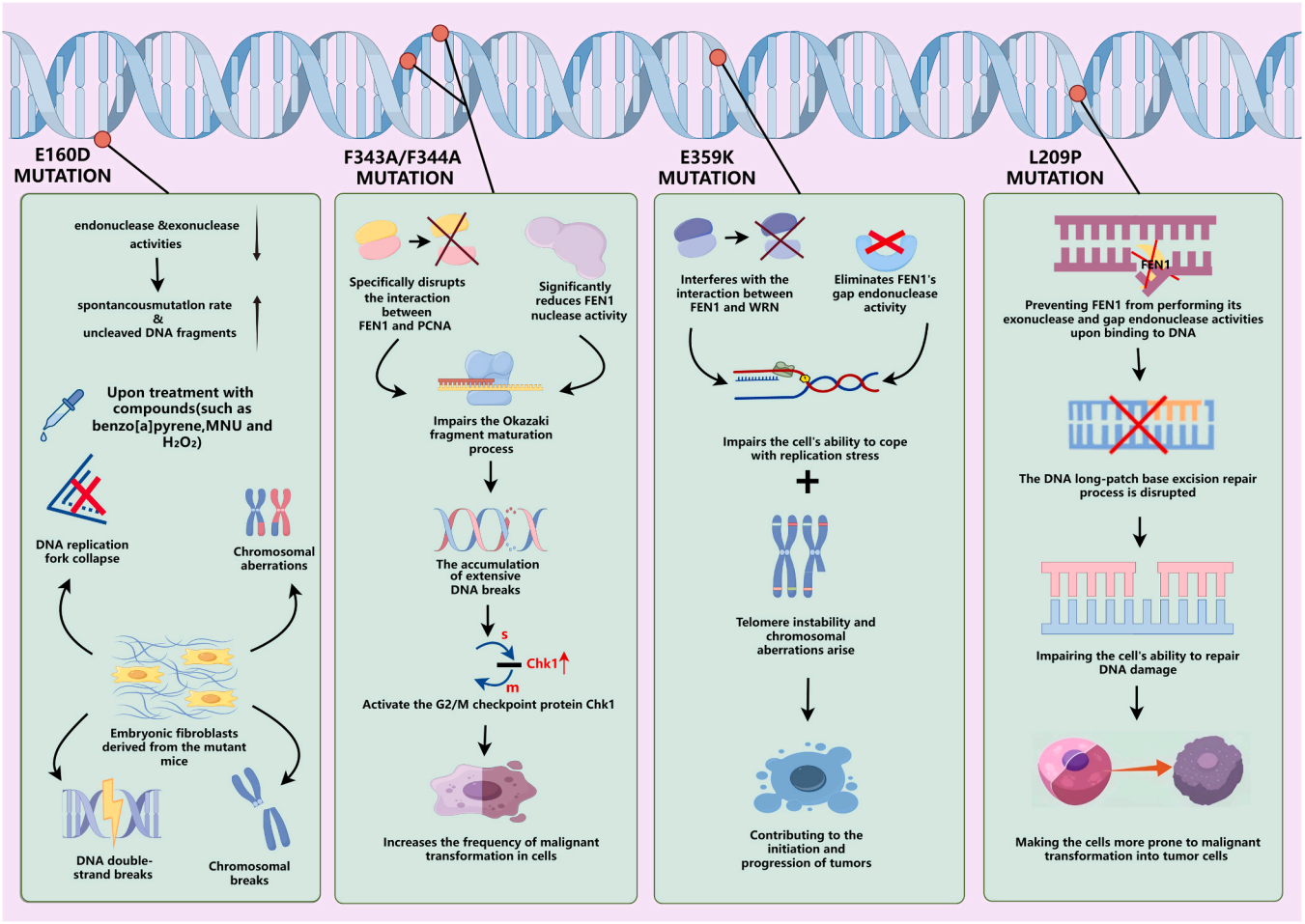

Fig. 2. Flap endonuclease 1 (FEN1) mutations associated with cancer predisposition and genomic instability. The panel shows, from left to right, the FEN1 E160D, F343A/F344A, E359, and L209 mutation sites. Mutations at these distinct sites can disrupt different enzymatic activities of FEN1, leading to abnormalities during DNA or chromosomal replication, thereby increasing susceptibility to tumorigenesis.

of human colorectal cancer (CRC) (Sun et al., 2017). Researchers predict that the active center of FEN1 consists of two magnesium atoms, identified as M1 and M2. The mutation L209P is expected to disturb the side-chain interactions involving L209 and S187/L183, which may result in the helix near the 179–187 amino acids losing its stability and becoming more flexible. The interactions between D179/D181 and the M2 metal atom could eventually be disrupted, preventing its exonuclease and gap endonuclease activities upon binding to DNA. As a result, the DNA long-patch base excision repair (LP-BER) process was interrupted, which in turn led to decreased genomic stability and increased the likelihood of tumorigenic transformation (Sun et al., 2017). The L209P mutation is reported based on TCGA data. The study functionally characterizes it but does not independently replicate its association with cancer in a separate cohort. It is not a common polymorphism, and its reporting in a single study means the evidence is still preliminary regarding population-level risk. The L209P mutation demonstrates a dominant-negative effect, impairing long-patch base excision repair and promoting genomic instability. This suggests a potential role in tumorigenesis, and cells harboring this mutation showed increased sensitivity to DNA-damaging agents like 5-FU, hinting at a possible pharmacogenomic application. However, this remains to be validated clinically.

2.1.2. Genetic polymorphisms

The genetic polymorphisms of FEN1 can determine its enzymatic activity and influence tumor incidence. Among the most studied polymorphisms are the -69G/A (rs174538), located in the promoter region of the FEN1 gene, and the 4150 G/T (rs4246215), situated in the 3´untranslated region (Chen et al., 2013; Liu et al., 2012). The genetic polymorphisms at these two loci affect enzymatic activity, which is associated with susceptibility to various tumors, such as gliomas, BC, gastric cancer (GC), lung cancer, liver cancer, CRC, and Wilms tumor (Rezaei et al., 2016; Zheng et al., 2011b; Zhu et al., 2018).

These variants are relatively common in Chinese populations, with minor allele frequencies of the –69 A and 4150 T alleles ranging from 36.0 % to 45.8 % across independent cohorts(Gao et al., 2014; Rezaei et al., 2016). Furthermore, the two single nucleotide polymorphisms (SNPs) exhibit strong linkage disequilibrium ($D' > 0.95$; $r^2 > 0.85$), suggesting they may jointly influence FEN1 expression and cancer risk. The A allele of the rs174538 locus serves as a protective factor that reduces tumor occurrence. Likewise, the T allele at the rs4246215 location is linked to a decreased risk of tumor formation. In vitro studies using luciferase assays after transient transfection have demonstrated that the presence of the A allele at rs174538 or the T allele at rs4246215 could significantly suppress the risk of developing digestive system tumors (Yang et al., 2009). However, contrasting findings have emerged from other studies. For instance, individuals with the GA or AA genotypes at the FEN1 rs174538 locus who were exposed to polycyclic aromatic hydrocarbons exhibited a higher mutation rate in exons 19 and 21 of the epidermal growth factor receptor (EGFR) gene compared to those with the GG genotype (Chen et al., 2021).

2.2. FEN1 overexpression linked to tumor development and progression

FEN1 plays a pivotal role in tumor initiation and progression by promoting replication fork restart, suppressing spontaneous breaks, and maintaining persistent DNA-protein crosslinks, thereby contributing to genomic instability (Becker et al., 2018; Jimeno et al., 2017). Furthermore, existing research has reported elevated expression levels of FEN1 in various tumor cells and tissue specimens, including those derived from BC, GC, ovarian cancer (OC), cervical cancer, lung cancer, and prostate cancer (Li et al., 2019; Zheng et al., 2011b). In this section, we will provide an overview of the pro-tumorigenic functions of FEN1 across various cancer types. The key clinicopathological correlations of FEN1 overexpression are systematically summarized in Table 1. Furthermore, we have summarized the mechanisms involving FEN1 and the experimental models used across different tumor tissues and cell lines in Table 2.These observations are visually summarized in Fig. 3.

3. The role of FEN1 in anti-tumor treatments

3.1. Suppressing FEN1 expression to enhance tumor cell sensitivity to chemotherapy

Previous studies have shown that FEN1 expression was upregulated in fibroblasts of nude mice under prolonged exposure to toxic drugs (Christmann et al., 2005). In DT40 chicken cells, the knockout of FEN1 resulted in heightened sensitivity to alkylating agents and oxidizing agent (Matsuzaki et al., 2002). Since tumor resistance mechanisms are often associated with the loss of genomic stability and activation of DNA damage repair pathways in tumor cells, the aforementioned findings have significantly heightened researchers' interest in investigating FEN1's potential involvement in tumor drug resistance and radiotherapy resistance, yielding numerous confirmed findings (Nickoloff et al., 2022). The role of FEN1 in resistance to various therapies is illustrated in Table 3 and Fig. 4.

3.1.1. Platinum-based agents

FEN1, as an important DNA repair protein, is often upregulated following the administration of platinum-based drugs, contributing to resistance to these agents (Zhu et al., 2019). During the formation of

Table 1
Clinicopathological Correlations of FEN1 Overexpression in Human Cancers.

Cancer Type	FEN1 Alteration	Key Clinicopathological Correlations	Specimen	Cohort Size	Clinical Endpoint
Breast Cancer	Overexpression (mRNA) (Berfelde et al., 2024)	Not mentioned	TCGA database (tissue) & Cell Lines ((T-47D, MCF7, BT-474, SK-BR-3, BT-20, MDA-MB-468, MDA-MB-231, and BT-549)	Gene expression: Tumor: 7569, Normal: 242, Metastatic: 82 Survival analysis: 1879 patients	↓OS
	Overexpression (mRNA & Protein)(Abdel-Fatah et al., 2014)	High grade ($P = 4.89 \times 10^{-57}$); High mitotic index ($P = 5.25 \times 10^{-28}$); Pleomorphism ($P = 6.31 \times 10^{-19}$); ER/PR negativity ($P = 9.02 \times 10$–35); Triple-negative phenotype ($P = 6.67 \times 10^{-21}$)	Tumor tissue	Training: 128; Test: 249; Validation: 1952 (mRNA) ER-: 568; ER+ : 894 (Protein)	↓disease specific survival (DSS)
Gastric Cancer	Overexpression (mRNA) (Zhao et al., 2021)	Correlated with older age ($P = 0.031$) ; High expression associated with favorable prognosis ($P = 0.0048$)	TCGA database (tissue)	375 tumor, 32 normal (TCGA);	↓OS
	Overexpression (mRNA & Protein)(Wang et al., 2014)	Degree of differentiation ($P = 0.027$); Lymphatic metastasis ($P = 0.001$); Tumor size ($P = 0.026$); TNM stage ($P = 0.020$)	Tumor tissues and cell line (SGC-7901)	42 paired tumor/normal tissues	Suggests a poor prognosis
Liver Cancer	Overexpression (mRNA & Protein) (Li et al., 2019)	Tumor size ($P = 0.047$); Metastasis status ($P = 0.013$)	Tumor tissue	34 patients (tissue analysis	↓OS and disease-free survival (DFS)
	Overexpression (mRNA) (Li et al. 2019)	Tumor grade ($P < 0.05$) ; Pathological stage ($P < 0.05$) ; Plasma AFP level ($P < 0.05$	TCGA database (tissue)	365 patients	↓OS
Cholangiocarcinoma	Overexpression (mRNA & Protein) (Yuwei et al., 2024)	Not mentioned	Tumor tissues	30 patients	↓DFS
Pancreatic Cancer	Overexpression (Protein) (Isohookana et al., 2018)	Not mentioned	Tumor tissues	102 patients	↓DFS, OS, and relapse-free survival
Ovarian Cancer	Overexpression (mRNA) (Abdel-Fatah et al., 2014)	High grade ($P = 0.009$); High FIGO stage ($P = 0.046$); Large residual tumor ($P = 0.034$)	Tumor tissues	156 patients	↓DFS and DSS
Lung Cancer	Overexpression (mRNA & Protein) (Zhang et al., 2018)	Poor differentiation ($P = 0.012$); Ki-67 expression ($r = 0.485$, $P < 0.01$) Poor survival when combined with Ki-67 ($P = 0.016$)	Tumor tissues	mRNA: 83 paired samples; IHC: 136 cases	↓OS
	Overexpression (mRNA & Protein) (He et al., 2017b)	Clinical stage (Spearman correlation, $P = 0.021$)	Tumor tissues	Not specified in corrigendum	↓OS
Neuroblastoma	Overexpression (mRNA) (Wang et al., 2024a)	Tumor cell stemness (mRNAsi, R=0.77, $P < 0.0001$); Enhanced proliferation, invasion, and cell cycle progression (Experimental validation, $P < 0.01$)	Tumor tissues and cell line (SH-SY5Y)	Bulk RNA-seq: 498 (GSE49710), 223 (E-MTAB-8248); Single-cell: 160,847 cells (16 patients)	↓OS and event-free survival

Table 2
Summary of FEN1 Molecular Mechanisms and Experimental Models in Various Cancers.

Cancer Type	Specimen	supporting pathway
Breast Cancer	(Zeng et al., 2019) - Cell lines：MCF-7 and MDA-MB-231 - MCF-7 xenograft models	- **DNA Replication & Repair**: Central role in DNA metabolism. - **Epigenetic Regulation / DNA Methylation**: Forms a FEN1/PCNA/DNMT3a complex to promote methylation of the miR-200a promoter. - **miRNA Silencing**: Mediates hypermethylation and downregulation of miR-200a-5p. - **Oncogenic Signaling (MET/EGFR)**: Downregulation of miR-200a leads to increased expression of its targets, MET and EGFR, activating downstream PI3K/AKT and MAPK/ERK pathways to promote cell proliferation.
	(Wu et al., 2024) - Cell lines：MDA-MB-231 and MCF-7 - MDA-MB-231 xenograft models	- **STAT3 Signaling**: Promotes phosphorylation/activation of STAT3, enhancing cell migration, invasion, and metastasis. - **NF-κB Pathway**: Its transcription is upregulated by NF-κB/p65. - **EMT & Metastasis**: Regulates EMT markers (increases N-cadherin, decreases E-cadherin) and upregulates MMP2/9. - **Cell Proliferation & Tumor Growth**: Enhances cell viability, colony formation, and in vivo tumor growth.
Oral Tumour	(Li et al., 2023) - Cell lines：SCC15 and WSU-HN6 - SCC15 xenograft models	**Ferroptosis Inhibition** (Inhibits lipid peroxidation and ferroptotic cell death via the FTX/FEN1/ACSL4 axis).
	(Wang et al., 2023) - Cell line：Cal-27 -Tumor tissues - Cal-27 xenograft models	**Immunomodulation** (Regulates immunosuppressive phenotypes PD-L1 and HLA-DR via the IFN-γ/JAK/STAT-1 signaling pathway).
Liver Cancer	(Wang et al., 2024) - TCGA-LIHC database - Cell lines：Bel-7402 and Hep-3B - Tumor tissues	- **Cell Cycle Regulation** (Promotes G2/M transition via Cdc25C/CDK1/Cyclin B1). - **DNA Replication & Repair** (Implicated via its known nuclease function, essential for genomic stability).
	(Li et al., 2019) - Cell lines：SMMC-7721, MHCC97-H, and HCCLM3 - Tumor tissues - Mouse xenograft model	- **EMT (Epithelial-Mesenchymal Transition)** (Promoted via TGFβ1/miR-140–5p axis). - **TGF-β Signaling Pathway** (FEN1 is a downstream effector).
	(Bian et al., 2022) - Cell lines：SK-HEP1 and HepG2, Hep3B, and Huh7 - Tumor tissues - HepG2 xenograft model	- **p53 Signaling Pathway** (Inactivated via USP7/MDM2 axis, promoting degradation of p53). - **Ubiquitin-Proteasome System** (FEN1 stabilizes MDM2 by recruiting USP7).
	(Peng et al., 2024) - Cell lines: Huh7 and MHCC-97H; CD133 + liver cancer stem cells (LCSCs) - Tumor tissues - Mouse xenograft model	- **Cancer Stemness** (Enhances stemness properties in LCSCs). - **SUMOylation Post-Translational Modification** (Stabilized by SUMO2, antagonizing proteasomal degradation).
Cholangiocarcinoma (Yuwei et al., 2024)	- Cell lines: HUCCT1 and QBC939 -Tumor tissues	- **Wnt/β-catenin Signaling** (Mediates EMT and tumor progression). - **DNA Damage Repair** (Induces repair to maintain genomic stability). - **Glycolytic Metabolism** (Promotes aerobic glycolysis/ Warburg effect).
Ovarian Cancer (Zhao et al., 2021)	Cell lines: SKOV-3 and OVCAR-3	- **DNA Replication & Repair** (Okazaki fragment maturation, DNA repair, interaction with PCNA). - **Cell Cycle Progression** (Promotes G1/S transition, regulates cyclin D1/CDK2). - **Cancer Cell Proliferation & Invasion** (Enhances colony formation, migration, and invasion; regulates MMP2/ MMP9/Cox-2).
Lung Cancer	(He et al., 2020) - Cell lines：A549 and H460 - Tumor tissues - A549 xenograft models	**DNA Damage Repair & Drug Resistance** (Maintains DNA repair capacity and chemoresistance; post-translationally regulated by PRMT1-mediated arginine methylation for protein stability)
	(Zhu et al., 2019) - Cell lines：A549 and H460 - A549 xenograft models	- **AKT/NF-κB Signaling & Drug Resistance** (Transcriptionally upregulated by the AKT/NF-κB pathway to enhance DNA repair and confer resistance to DNA-damaging agents). - **DNA Replication & Repair** (Core component of LP-BER pathway; critical for Okazaki fragment maturation and genome stability maintenance).
Neuroblastoma (Wang et al., 2024a)	- Cell line: SH-SY5Y—— Single-cell: 160,847 cells (16 patients);	- **Cell Cycle Regulation** (Promotes S phase entry, prevents G2/M arrest) - **DNA Replication & Repair** (Okazaki fragment maturation, DNA repair) - **Tumor Cell-Stroma Communication** (Modulates MIF-(CD74 +CXCR4) & PTN-NCL axes); - **Apoptosis Regulation** (Inhibits mitochondrial apoptosis pathway); - **Cellular Invasion** (Enhances invasive capacity)

cisplatin resistance in lung adenocarcinoma cells, the drug induces sustained activation of AKT/NF-κB/p65, which can directly bind to the FEN1 promoter, resulting in its continuous transcriptional upregulation (Zhu et al., 2019). However, when AKT activity is inhibited, leading to the downregulation of FEN1, DNA damage accumulates, causing increased apoptosis and significantly reducing cisplatin resistance. Similarly, in glioblastoma and GC cells, the inhibition of FEN1 expression promoted apoptosis and enhanced tumor cell sensitivity to cisplatin (Nikolova et al., 2009; Xie et al., 2016).

Recent studies have shown that various drugs could increase the

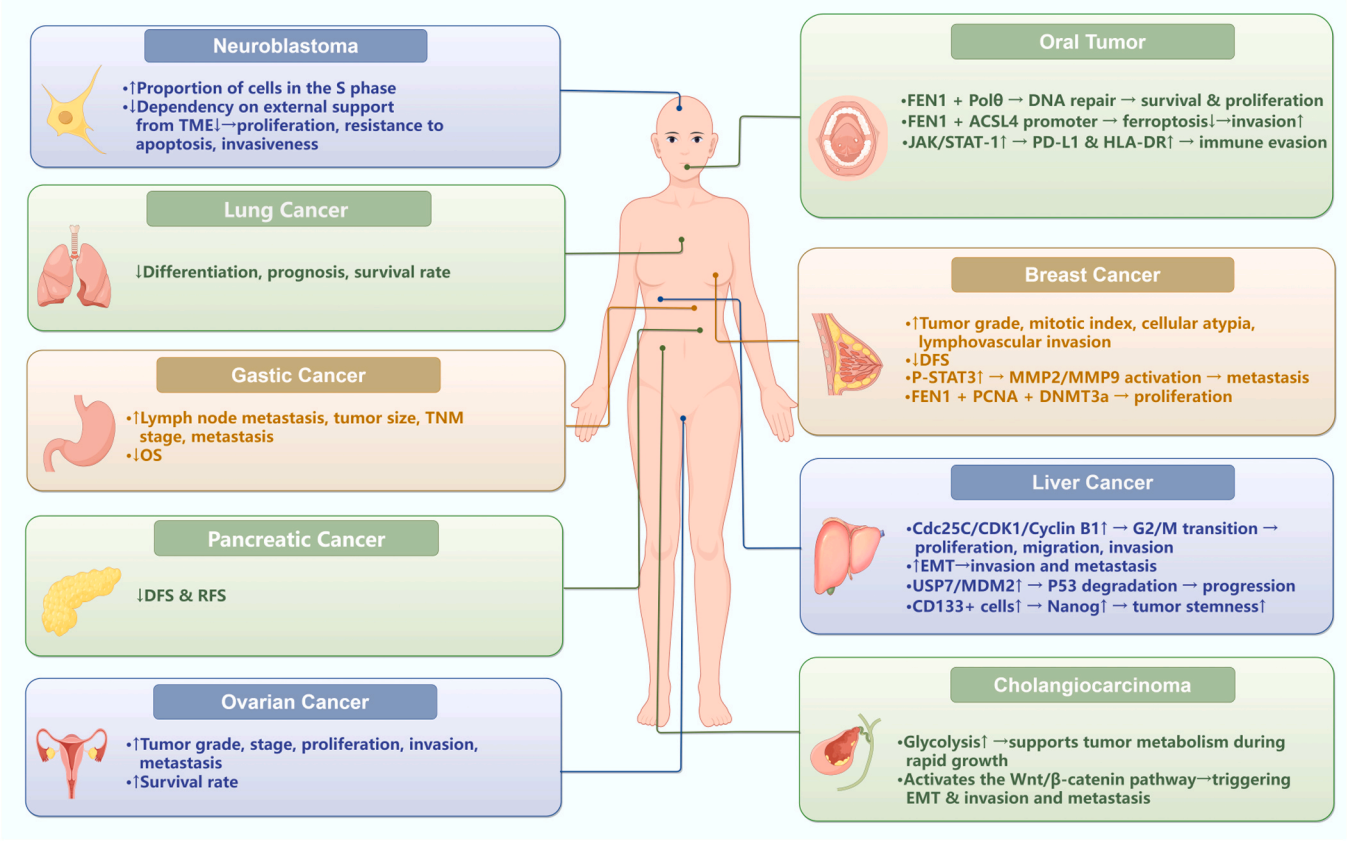

Fig. 3. Aberrant FEN1 expression linked to tumor development and progression. FEN1 is upregulated in the listed tumors—including neuroblastoma, lung cancer, and gastric cancer—and promotes tumorigenesis via various signaling pathways.

sensitivity of tumor cells to cisplatin by inhibiting FEN1 expression. Metformin, a classic antidiabetic drug, has been found to downregulate FEN1 expression, inhibit the BER pathway, impair the DNA damage repair capacity of head and neck squamous cell carcinoma cells, and enhance their sensitivity to cisplatin (Shanchun et al., 2023). Similarly, in ER-positive BC cells, letrozole has been found to reduce FEN1 expression through an ERK/Elk-1-dependent mechanism (Zeng et al., 2017). This reduction increases the sensitivity of aromatase-overexpressing BC cells to cisplatin.

The involvement of FEN1 in oxaliplatin resistance is also noted. In CRC cells, lowering the levels of Myeloid Ecotropic Viral Integration Site 1, a negative regulatory protein, resulted in higher expression of FEN1 (Li et al., 2022). By enhancing the DNA repair capacity of CRC cells, FEN1 facilitates the repair of DNA damage induced by oxaliplatin treatment, thereby reducing apoptosis. Consequently, the high expression of FEN1 promotes the development of oxaliplatin resistance.

3.1.2. *Doxorubicin*

Research on miRNAs involved in DNA damage response and tumorigenesis partly revealed the role of FEN1 in doxorubicin (DOX) resistance. Most often, miRNAs are thought to act as negative regulators of gene expression (Hu et al., 2017). miRNAs targeting FEN1 follow the same pattern. In BC cells, miR-140 was found to suppress FEN1 expression by binding to the FEN1 promoter region, thereby hindering tumor DNA repair and increasing sensitivity to DOX (Lu et al., 2020). Moreover, high levels of insulin-like growth factor 1 receptor have also been found in osteosarcoma cells, which could suppress FEN1 expression by downregulating the tumor-suppressing miRNA miR-610, thereby enhancing cancer cell sensitivity to DOX (Dong et al., 2023).

3.1.3. *Paclitaxel*

Paclitaxel, as an important drug in the adjunctive treatment of various cancers, it occupies a pivotal and irreplaceable role among antitumor therapies. However, after paclitaxel treatment, the expression of FEN1 increased in BC, prostate cancer, and cervical cancer cells (Wang et al., 2015). This upregulation reduced DNA damage caused by chemotherapy drugs and significantly increasing cancer cell resistance to paclitaxel.

3.1.4. *Camptothecin*

Irinotecan and topotecan are pentacyclic alkaloids derived from Camptotheca acuminata and have been approved for clinical cancer treatment (Li et al., 2017). However, the clinical use of irinotecan and topotecan is limited due to side effects, such as diarrhea and the development of drug resistance. Recent studies have shown that the application of FEN1 inhibitors could significantly enhance the sensitivity of tumor cells, including those derived from prostate, breast, and lung cancers to irinotecan and topotecan (Wu et al., 2022). This heightened sensitivity is mediated by the induction of mitochondrial membrane potential loss and the accumulation of reactive oxygen species (ROS), which subsequently promotes cell apoptosis.

3.1.5. *5-Fluorouracil*

5-FU-based chemotherapy is a key approach for treating CRC, but it comes with systemic toxicity, limited effectiveness, lack of selectivity, and resistance issues. Current studies on CRC cells indicate that FEN1 expression is elevated in 5-FU-resistant CRC cell lines, which play a role in 5-FU resistance linked to APC mutations (Das et al., 2014).

3.1.6. *Temozolomide*

Temozolomide (TMZ) is a lipophilic agent that readily crosses the

Table 3
Mechanisms and models of FEN1 in Cancer Therapy Response.

Therapy Class		Tumor type	Specimen (Cell Line, PDX, in vivo)	Mechanism of FEN1 involvement	Quantitative assessment
Chemotherapy	Platinum-based agents	Lung cancer (Zhu et al., 2019)	Cell line: A549 Model: A549 xenograft models	The AKT/NF-κB axis confers cisplatin resistance by transcriptionally upregulating FEN1 to enhance LP-BER.	None
		Gastric cancer (Xie et al., 2016)	Cell line: SGC-7901	Cisplatin sensitization by FEN1 silencing via impaired DNA repair and mitochondrial apoptosis.	None
		Breast cancer (Zeng et al., 2017)	Cell line：BT474	FEN1-mediated trastuzumab resistance via HER activation and ERα potentiation.	None
		colorectal cancer (CRC) (Li et al., 2022)	Cell lines: HCT116, SW480, Caco2, and HCT8 Model: HCT116 xenograft models Clinical samples: pairs of CRC tissues and adjacent normal tissues	Oxaliplatin resistance and CRC tumorigenesis promoted via the ELFN1-AS1/MEIS1/FEN1 axis and enhanced BER repair.	None
	Doxorubicin (DOX)	Glioblastoma(Lu et al., 2020)	Cell lines：MCF-7, MDA-MB-231, T47D, Beap37, and MCF-7/ADR In vivo model: MCF-7 and MB231 Xenograft models	miR-140 suppresses FEN1 expression to hinder DNA repair and sensitize cells to DOX.	None
		Osteosarcoma (Dong, S. et al., 2023)	Cell lines: MG-63, U20S, and 143B In vivo mdel: 143B Xenograft models	Enhanced DOX sensitivity via the miR-610/FEN1 axis.	Bliss method
	Paclitaxel	Breast cancer (Wang et al., 2015)	Cell lines: MCF-7 and MDA-MB-231 Clinical samples: 268 paraffin-embedded breast cancer tissues	Paclitaxel resistance in breast cancer via YY1-mediated FEN1 upregulation and enhanced BER repair.	None
	Camptothecin (CPT)	Prostate Cancer	Cell lines：PC3 and DU145 In vivo model: PC3 xenograft models	Combining FEN1 inhibitor (SC13) and CPT overcomes chemoresistance by blocking BER-induced apoptosis via DSB accumulation in p53-mutant cells.	None
	5-Fluorouracil (5-Fu)	Colorectal Cancer (Das et al., 2014)	Cell lines：HCT-116, LOVO, and HT-29	FEN1 downregulation sensitizes cells to 5-FU by inhibiting LP-BER.	None
	Temozolomide (TMZ)	Lung cancer (He et al., 2020)	Cell lines: A549 and H460	PRMT1-mediated methylation stabilizes FEN1 against proteasomal degradation, promoting DNA repair and driving resistance to chemotherapy.	None
		Colorectal Cancer (Panda et al., 2009)	Cell lines: HCT116 (MMR-deficient) and HCT116 +ch3 (MMR-proficient)	TMZ resistance overcome by targeting FEN1 (Asp181) to disrupt BER and induce lethal DNA damage.	None
Targeted drugs	Trastuzumab	Breast cancer (Zeng et al., 2017)	Cell Line: BT474	FEN1 confers trastuzumab resistance by enhancing HER/ERα signaling, and its knockdown reverses this resistance.	None
CAR-T therapy		Ovarian cancer Breast cancer Cervical cancer (Dong, Y. et al., 2023)	Cell lines：HeLa, MCF-7, SKOV-3 and HEK293T In vivo model: HeLa xenograft models	FEN1 inhibition promotes CAR-T cell recruitment and tumor killing via the BER/cGAS-STING/chemokine axis	None
Radiotherapy		Cervical cancer (Li et al., 2019)	Cell Line: HeLa In vivo model: HeLa xenograft models	FEN1 inhibition confers radiosensitization through BER disruption, accumulation of unrepaired DNA damage, genomic instability, and activation of mitochondrial apoptosis.	None

blood-brain barrier and is primarily used against tumors by inducing DNA damage and promoting programmed cell death (Lee, 2016). Inhibition of FEN1 nuclease activity using specific FEN1 inhibitors could block the LP-BER pathways, thereby increasing the cytotoxicity of TMZ in CRC cells (Panda et al., 2009). In lung cancer cells, PRMT1-mediated arginine methylation stabilized FEN1 (He et al., 2020). Downregulation of PRMT1 leads to a loss of FEN1 protein stability, accumulation of DNA damage, and enhanced sensitivity of tumor cells to TMZ. These findings collectively suggest that FEN1 may influence DNA repair pathways related to TMZ resistance, thereby modulating tumor cell sensitivity to TMZ.

3.2. Targeting FEN1 to enhance tumor cell sensitivity to targeted drugs

Over the past three decades, targeted therapies have significantly advanced cancer treatment by improving specificity and reducing systemic toxicity. In HER2-positive BC, trastuzumab has markedly improved patient survival, yet its therapeutic response is limited, with objective response rates observed in less than 30 % of patients. Recent studies have found that Trastuzumab exposure induces FEN1 upregulation in a time- and dose-dependent manner, while FEN1 knockdown significantly enhances trastuzumab-induced inhibition of proliferation and promotes apoptosis in HER2-overexpressing BC cells (Zeng et al., 2017). Mechanistically, FEN1 contributes to trastuzumab resistance by sustaining HER receptor signaling and enhancing ERα transcriptional activity. Therefore, targeting FEN1 may serve as a promising strategy to overcome trastuzumab resistance and improve clinical outcomes in HER2-positive BC (Zeng et al., 2017).

3.3. Blocking FEN1 to increase tumor cell sensitivity to CAR-T therapy

CAR-T therapy has demonstrated remarkable therapeutic effects in hematologic cancers. Nonetheless, the intricate nature and positioning of solid tumors in the body present several challenges for CAR-T-cell therapy (Lieber, 1997), including the toxicity associated with CAR-T cells, antigen escape and diversity, and the immunosuppressive nature of the TME (Rafiq et al., 2020). When FEN1 inhibitors are combined with CAR-T cell therapy, they induce the accumulation of

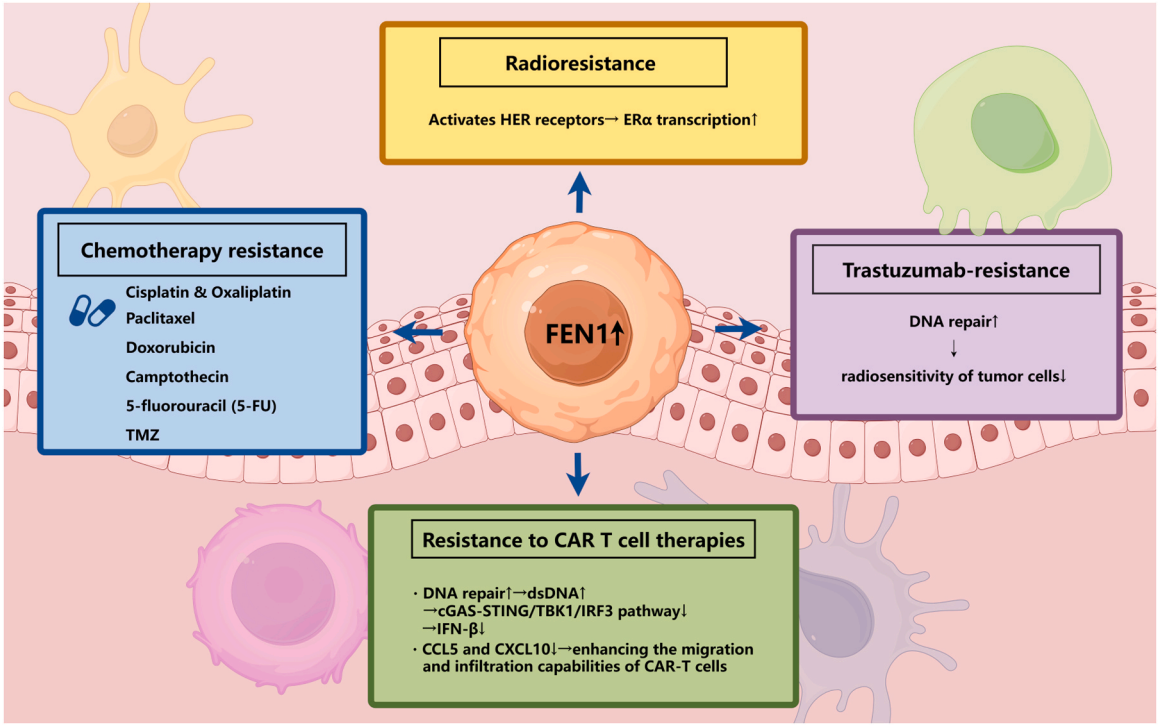

Fig. 4. The role of FEN1 in anti-Tumor treatments. Suppressing FEN1 expression to enhance tumor cell sensitivity to chemotherapy (Cisplatin, Oxaliplatin, Paclitaxel, Doxorubicin, Camptothecin, 5-fluorouracil, and Temozolomide), Trastuzumab, CAR-T therapy, and radiotherapy.

double-stranded DNA in tumor cells by inhibiting DNA repair, which activates the cyclic GMP-AMP synthase-stimulator of interferon genes/TANK-binding kinase 1/interferon regulatory factor 3 (cGAS--STING/TBK1/IRF3) signaling pathway (Dong et al., 2023). This activation promotes the secretion of immune molecules such as Interferon-beta (IFN-β), enhancing anti-tumor immune responses. Furthermore, FEN1 inhibitors modulate the TME by inducing the secretion of C-C motif chemokine ligand 5 (CCL5) and C-X-C motif chemokine ligand 10 (CXCL10), thereby enhancing the migration and infiltration capabilities of CAR-T cells (Dong et al., 2023). The combination of FEN1 inhibitors and CAR-T cell therapy significantly suppressed tumor growth, demonstrating strong synergistic effects.

3.4. Blocking FEN1 to enhance tumor cell sensitivity to radiotherapy

Significant progress has been made in radiotherapy over the past three decades. It has been reported that after radiation exposure, FEN1 expression was further upregulated in HeLa cells and BC cells (Li et al., 2019). Nevertheless, the application of FEN1 inhibitors could increase the radiosensitivity of tumor cells by inhibiting DNA repair. Further studies are needed to determine the role of FEN1 in radiotherapy resistance.

4. Research on targeting FEN1

4.1. Diagnosis

Both the analysis of multi-omics data through protein-protein interaction networks and various in vivo and in vitro experimental results collectively suggest that FEN1 may act as a molecular biomarker for different cancer types (Basic et al., 2021). It holds significant clinical application potential in tumor diagnosis and prognosis assessment. The key evidence supporting its biomarker potential is comprehensively summarized in Table 4.

4.1.1. Locating base triplet structures resulting from single nucleotide polymorphisms

As a key enzyme in the DNA strand synthesis process, FEN1 can precisely recognize overlapping base triplet structures resulting from SNPs and specifically detect base mutations within a wild-type background (Ma et al., 2024). Utilizing this capability, two methods have been developed that are highly sensitive for real-time tracking of tumor growth and treatment response.

The first approach uses FEN1 as a specific recognition element to precisely recognize the three-base overlap caused by SNPs and to cut the 5′ flap of the downstream probe, thereby initiating the catalytic hairpin assembly reaction to produce fluorescence signals for SNP detection (Zhang et al., 2024). This technology utilizes streptavidin-biotin complexes for magnetic probe separation, avoiding false positives and enhancing detection reliability. This technique has demonstrated remarkable sensitivity in identifying Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations and may be used to detect SNPs in human cancer cells, facilitating the advancement of more precise early diagnostic tools for diseases (Zhang et al., 2024).

FEN1-aided recombinase polymerase amplification (RPA), the second approach, merges FEN1-catalyzed invasive reactions with RPA by disabling RPA enzymes before invasive reactions, designing brief RPA primers, and changing the conditions for invasive reactions (Ma et al., 2024). This method is specific for mutations present at an abundance as low as 0.01 % in blood, with results available in 40 min. Utilizing this approach, a new portable device powered by batteries and equipped with dual-channel fluorescence detection has been developed to assist in real-time liquid biopsy, offering clinicians a potential method for gene typing or mutation-guided personalized medicine in emergency situations or resource-limited areas.

4.1.2. Aptamer-based signal amplification system

Combining FEN1's nuclease activity with aptamer-based signal amplification holds significant potential for clinical applications in tumor tissue analysis. An example is the target-activated T7 transcription circuit (Zhang et al., 2023). In this detection mechanism, FEN1 cuts

Table 4
Summary of FEN1-Based Tumor Detection Methods.

Method Name	Analytical Performance (LoD, Dynamic Range)	Matrix	Cross-reactivity	Turnaround Time	Head-to-head Comparison (vs. ddPCR/NGS)	Clinical Validation Status
Hairpin-empowered invasive reaction combined with CHA cascade for SNP detection (Zhang et al., 2024)	- LoD: 0.36 fM for mutant target (MT) - Dynamic Range: 1 fM – 100 pM for MT; 1 %–100 % mutation abundance	Human cancer cell lines (PANC-1, HCT-116, A549, HeLa, 293 T); soybean leaf genomic DNA; human serum	High specificity; tested against single-base and multi-base mismatches; minimal interference from wild-type and mismatched sequences	~3 h (2 h for FEN1 cleavage + 30 min for CHA)	Not directly compared with ddPCR/NGS; results consistent with sequencing for soybean and human cell genotyping	No clinical validation
FEN1-aided RPA (FARPA) for cfDNA mutation detection (Ma et al., 2024)	- LoD: 5 copies for mutants; 0.01 % mutation abundance - Dynamic Range: 0.01 %–100 % mutation abundance	Plasma (cfDNA); oral swabs (for genotyping)	High specificity; minimal interference from wild-type background and biological matrices (e.g., BSA, DNase I, DMEM)	~40 min for liquid biopsy (including cfDNA extraction); ~15 min for genotyping from oral swabs	100 % agreement with NGS for 20 cfDNA samples; 100 % agreement with pyrosequencing for 43 gDNA samples	Validated with clinical samples but not approved
T7 transcription circuit-mediated signal amplification for FEN1 activity (Zhang et al., 2023)	- LoD: 1.75×10^{-6} U/μL - Dynamic Range: 1.0×10^{-4} to 1.0×10^{-2} U/μL	Cell extracts (e.g., HeLa, A549, MRC-5 cell lines)	High selectivity; tested against non-specific nucleases (e.g., Exo I, *Eco*RV, *Pvu*II, *Nru*I) with no significant response	~3.5 h (estimated from experimental steps: FEN1 cleavage 40 min, extension 30 min, transcription 90 min, DNase I 10 min, DSN digestion 40 min)	Not compared with ddPCR/NGS; sensitivity compared with other FEN1 assays (e.g., gold nanostar-based, graphene oxide-based)	No clinical validation
Synergistic DNA walker powered by endogenous APE1 and FEN1 for dual-mode biosensing (Meng et al., 2024)	- LoD (Fluorescence): 0.01 U mL^{-1} - LoD (Electrochemical): 0.002 U mL^{-1} - Dynamic Range (Fluorescence): 0.01–10 U mL^{-1} (linear), 0.01–500 U mL^{-1} (detectable) - Dynamic Range (Electrochemical): 0.01–50 U mL^{-1} (linear)	Serum; cell lysates (MCF-7, HEK-293T)	High specificity; tested against UDG, EXO I, EXO III; minimal cross-reactivity	~2.5–3.5 h (including walker reaction and HCR)	Not compared with ddPCR/NGS; validated in spiked serum and cell lysates	No clinical validation
In situ DNA walker for AND-gate imaging of TE and FEN1 activities (Wang et al., 2024b)	- LoD: 0.01 U for FEN1; 6 HeLa cell extracts for TE - Dynamic Range: 0.03–1.2 U for FEN1; 10^2–10^5 HeLa cell extracts for TE	Living cells (e.g., HeLa, MCF-7, SKBR3 cell lines)	High selectivity; tested against non-specific enzymes (e.g., Bst 2.0 DNA polymerase, T4 DNA ligase, Vent DNA polymerase, Exo I, NLBsRNBI, Splint R ligase, Exo III) with no significant response	~4 h for imaging in cells (time to maximum signal)	Not directly compared with ddPCR/NGS; results consistent with Protein Atlas database and previous studies	No clinical validation
Double-wing switch nanodevice-mediated primer exchange reaction for the activity analysis of FEN1 (Chen et al., 2023)	LoD: 0.55 mU Dynamic Range: 0.001–8 U	Cell lysates (nuclear/ cytoplasmic), human serum	Specific to FEN1	~2 h (including PER and ThT binding)	Not compared with ddPCR/NGS	No clinical validation/ approval – tested on spiked serum and cell lysates
Label-free and low-background FEN1 sensing based on cleavage-induced ligation of bifunctional dumbbell DNA and in-situ signal readout (Zeng et al., 2023)	LoD: 0.007 U/mL Dynamic Range: 0.01–2.5 U/mL	Human serum, cell lysates (HeLa, MCF-7, A549, 293 T)	High specificity; negligible response to BSA, ALP, GOx, APE1, Exo I/III, T4 ligase	~3 h (including cleavage, ligation, exonuclease digestion, CuNPs formation)	Not compared with ddPCR/NGS	No clinical validation/ approval – tested on spiked serum and cell lysates
Ligase detection reaction amplification-activated CRISPR-Cas12a for single-molecule counting of FEN1 (Wang et al., 2024)	LoD: 1.31×10^{-8} U Dynamic Range: to 16 U (8 orders)	Breast cancer tissues, human cell lines (MCF-7, HeLa, A549, LO2)	No significant response to Lambda Exo, Exo III, BSA, T4 DNA ligase	~2–3 h (including LDR, Exo I digestion, Cas12a cleavage, and single-molecule counting)	Not compared with ddPCR/NGS	No clinical validation/ approval – tested on limited clinical samples (5 cancer vs. 5 healthy)

the 5' flap of the DNA complex probe with double flaps, resulting in either a notched double-stranded DNA or a free 5' flap single-stranded DNA with a 3'-OH end. When T7 RNA polymerase is introduced, it triggers an efficient T7 transcription amplification reaction, resulting in the production of a significant quantity of RNA aptamers. These RNA aptamers then bind to specific fluorescent dyes, significantly enhancing the fluorescent signal. This method allows for the effective detection of extremely low concentrations of FEN1 while offering vital information about tumor growth and progression.

4.1.3. Nanodetection platforms

In recent years, DNA walker-based nanodetection platforms have emerged, offering new possibilities for the highly sensitive detection of cancer biomarkers. A dual-mode biosensor based on DNA walkers has been developed, leveraging the synergistic action of two endogenous cellular enzymes, apurinic/apyrimidinic endonuclease 1 (APE1) and FEN1, to drive DNA walker movement on DNA-functionalized Au nanoparticles (Meng et al., 2024). In the fluorescence mode, the DNA walker movement, initiated by APE1 and driven by FEN1, generates a strong signal across a concentration range of 0.01–500 U mL^{-1}, demonstrating excellent linearity between 0.01 and 10 U mL^{-1}. In the electrochemical mode, the integration of an upstream DNA walker with a downstream hybridization chain reaction dual signal amplification strategy further improves APE1 detection sensitivity, extending the linear range to 0.01–50 U mL^{-1}. This dual-mode biosensor not only significantly boosts detection sensitivity but also demonstrates strong specificity and anti-interference properties, effectively distinguishing between cancerous and normal cell lysates.

Additionally, DNA walker-based nanoparticles allow for the real-time tracking of FEN1 activity within tumor cells. An in situ tracking system employing a DNA walker for AND-gate logic imaging of telomerase (TE) and FEN1 activities in live cells utilizes a fluorescence signal-trigger mechanism to sensitively detect the simultaneous presence and dynamic activity of FEN1 and TE (Wang et al., 2024b). FEN1 cleaves specific DNA structures for precise replication, and TE elongates telomeres for stability. Using AND-gate DNA walker technology allows for real-time monitoring of this crucial mechanism, offering a way to study the roles of FEN1 and TE in tumor development and to screen for potential anticancer drugs.

In addition to DNA walker-based nanoparticle platforms, other methods such as nanospheres, nanoparticles, and Nano Firework technologies have been developed to detect FEN1 expression in tumor cells, thereby contributing to early cancer diagnosis (Chen et al., 2023; Zeng et al., 2023). For the rapid and label-free evaluation of FEN1 activity in tumor cells and serum samples, a technique using a double-wing switch nanodevice for primer exchange is designed (Chen et al., 2023). This method utilizes FEN1 to cleave the 5′ flap fragment, thereby activating the primer exchange reaction. This process generates a large number of telomeric repeat fragments that, in conjunction with the Thioflavin T dye, produce a fluorescence signal. This enables highly sensitive detection of FEN1 activity.

Detecting FEN1 activity can also be achieved through an innovative method that uses cleavage-induced ligation of bifunctional dumbbell DNA and copper nanoparticles for in-situ signal readout (Zeng et al., 2023). In this process, FEN1 cleaves the 5′ flap, and T4 DNA ligase subsequently joins the cleaved fragment to form a closed double-stranded DNA structure, which is resistant to exonuclease digestion and serves as a template for generating fluorescent copper nanoparticles (CuNPs). FEN1 activity is indicated by the fluorescence signal from the CuNPs. The novel application provides fresh avenues for FEN1's participation in cancer diagnostics and treatment.

4.1.4. CRISPR/Cas system

The CRISPR/Cas12a-based FEN1 quantification detection technology has demonstrated significant potential for clinical applications (Cui et al., 2023; Ding et al., 2022; Wang et al., 2024). Initially, a dumbbell DNA structure featuring a 5' flap must be created, after which FEN1 triggers the trans-cleavage activity of Cas12a (Cui et al., 2023). Alternatively, the ligase-dependent reaction could generate a double-stranded DNA template that activates the CRISPR-Cas12a system, releasing a fluorescent signal and enabling the quantitative assessment of FEN1 activity (Wang et al., 2024). In a different approach, FEN1's enzymatic activity directly triggered DNA cleavage, activating the nuclease activity of Cas12a to amplify the detection signal (Ding et al., 2022). These cutting-edge methods supported extremely sensitive detection at the single-molecule level and provided efficient tools for early cancer detection, diagnosis, and the development of FEN1-targeted therapies.

Collectively, the FEN1-based methodologies summarized herein demonstrate exceptional potential for tumor diagnosis and monitoring, showcasing high sensitivity, specificity, and innovative detection mechanisms. Nevertheless, it is crucial to recognize that none of these methods have undergone comprehensive clinical validation or received regulatory approval to date. To bridge this gap between promising research and clinical application, a structured and rigorous development path is required. Key steps forward include prospective clinical cohorts, CLIA-Grade assay development, Head-to-Head comparisons, matrix expansion, and regulatory pathways. These steps will help translate these innovative FEN1-based detection methods into clinically viable tools for tumor diagnosis and monitoring.

4.2. FEN1 inhibitors

Recognizing the essential function of FEN1 in DNA processes and its role in cancer, many research organizations are beginning to focus on developing inhibitors for FEN1 (Lam et al., 2006; Wang et al., 2014). There is considerable proof that suppressing FEN1 expression can make cells more sensitive to DNA-damaging agents (Xin et al., 2020).

4.2.1. N-hydroxy urea compounds

Hydroxyurea-based compounds were recognized as effective and selective FEN1 inhibitors in preliminary screening studies. Four N-hydroxy urea compounds—Compound #2, Compound #8, Compound #16, and Compound #20—demonstrated significant effects in multiple tumor models (Exell et al., 2016; Xin et al., 2020; Yang et al., 2022). For instance, Compound #8 could block FEN1's ability to cleave the 5′ ends of Okazaki fragments, it prevents the timely repair of unprocessed gaps during DNA replication, leading to replication fork collapse (Yang et al., 2022). This collapse increases the sensitivity of tumor cells to both endogenous and exogenous DNA damage, such as that caused by chemotherapy and radiotherapy, thus impairing their survival capacity.

Compound #20 has demonstrated that it enhances the sensitivity of lung and BC cells to DNA-damaging agents such as cisplatin and arsenic trioxide (He et al., 2017a; Xin et al., 2020). Furthermore, the FEN1 inhibitor SC13 is a derivative of Compound#20, incorporating a pyrrolo [3,2-*d*]pyrimidine group to increase drug permeability (He et al., 2016). SC13 is found to interfere with DNA replication and repair in BC cells, inhibiting cell proliferation and inducing chromosomal instability, ultimately leading to cell death.

4.2.2. NSC-281680

Currently, the majority of FEN1 inhibitors are designed to target critical amino acids located within the protein's active site. For instance, researchers have identified the compound NSC-281680 through computational molecular docking, which specifically interacted with the aspartic acid residue at position 181 of FEN1 (Panda et al., 2009), thereby blocking its binding pocket. Subsequent in vitro studies revealed that NSC-281680 could inhibit the endonuclease activity of FEN1 and enhance the cytotoxic effects of TMZ in colon cancer cells.

4.2.3. FEN1i

Through high-throughput screening, a series of potent FEN1

inhibitors have been identified and synthesized, including PTPD (3-hydroxy-5-methyl-1-phenylthieno[2,3-*d*]pyrimidine-2,4(1 H,3 H)-dione) and structurally related analogs, all exhibiting nanomolar-level inhibitory activity and favorable pharmacological potential (Yang et al., 2022). In cisplatin-resistant ovarian cancer cells, such as A2780cis and PEO4, these inhibitors significantly enhance cisplatin-induced cytotoxicity, characterized by increased DNA double-strand breaks, G2/M phase cell cycle arrest, and elevated apoptosis (Mesquita et al., 2021). Furthermore, in breast cancer 2 (BRCA2)- or POLβ-deficient ovarian cancer cells, FEN1 inhibitors trigger synthetic lethality (SL), highlighting their potential in precision oncology.

4.2.4. Other inhibitors

In addition to the previously discussed FEN1 inhibitors with clearly defined molecular structures and active sites, several natural plant extracts have also demonstrated the ability to inhibit FEN1 expression in tumor cells. For example, gallic acid, a naturally occurring polyphenolic compound, has been found to downregulate FEN1 gene expression, impairing the ability of BC cells to repair DNA damage (Velaiyan et al., 2024). Another compound, myricetin (3, 3′, 4′, 5, 5′, 7-hexahydroxyflavone cannabiscetin), a flavonoid, has been identified as a FEN1 inhibitor and showed heightened sensitivity to FEN1 overexpression in CRC (Ma et al., 2019). Although the extracts of the aforementioned natural plants demonstrated clear inhibitory effects on FEN1, the specific targets and mechanisms remain incompletely understood. Further research is needed to fully elucidate their potential therapeutic applications in cancer treatment.

The article outlines the antitumor properties of FEN1 inhibitors, which have been proven only in lab and animal studies. Although FEN1 inhibitors exhibit potential for clinical application, their translation into clinical practice requires substantial further investigation and validation.

4.3. Synthetic lethality

Cancer cells with defects in one DNA repair pathway often develop multiple overlapping and complementary repair mechanisms, which increases their dependence on alternative pathways for survival and proliferation. This poses difficulties for clinical treatment (Ray Chaudhuri et al., 2016). Synthetic Lethality is strictly defined as a genetic interaction where concomitant perturbation of two genes (e.g., via dual CRISPR-knockout or siRNA-knockdown) results in cell death, whereas perturbation of either gene alone does not. Focusing on DNA repair for SL presents an innovative approach for personalized cancer treatment. The clinic has seen the realization of this concept's promise: The interaction between poly(ADP-ribose) polymerase (PARP) inhibition and deficiencies in recombination genes like BRCA1 or BRCA2 has become a standard in personalized oncology (O'Neil et al., 2017). However, to date, only one SL-based therapeutic has been implemented in clinical practice. Therefore, identifying new SL targets with potential clinical applications is significant for cancer treatment. Research on yeast genetic interactions has shown that the FEN1 gene interacts with more genes than any other (Guo et al., 2020). These interactions include several genes involved in the homologous recombination (HR) pathway, such as BRCA2. This section provides a detailed overview of these interactions. To systematically summarize the key findings, Table 5 presents the functional genomic and experimental models that profile FEN1 synthetic lethality.

4.3.1. BRCA 2

PARP inhibitors like olaparib, niraparib, and rucaparib have demonstrated efficacy in maintenance therapy for OC patients with BRCA mutations; however, over 40 % of these patients did not respond to PARP inhibitor treatment (Audeh et al., 2010). Research indicates that ovarian tumors with low levels of BRCA2 and FEN1 are associated with better survival rates than those with low BRCA2 and high FEN1. BRCA2 functions as a tumor suppressor and is key to the HR repair pathway of DNA double-strand breaks, in addition to being essential for replication fork stability (Fradet-Turcotte et al., 2016). In BRCA2-mutant OC cells, FEN1 contributes to BER and other repair mechanisms that act as an alternative to HR, enabling cell survival (Patel et al., 2021). However, when FEN1 is also deficient in BRCA2-mutant tumor cells, there is a marked accumulation of DSBs, increased S-phase arrest, and enhanced apoptosis. Similar observations have been reported in BC, CRC, prostate cancer, and lung cancer cells (Guo et al., 2020; Mesquita et al., 2021). Thus, reducing FEN1 expression in cells

Table 5
Functional Genomic and Experimental Models Profiling of FEN1 Synthetic Lethality.

Partner	CRISPR/ siRNA Genetics	Chemical Genetics	Epistasis Mapping	Cells	Validated In Vivo	Tumor characteristics	Predictive Biomarkers for Trials
FEN1 BRCA2 (Guo et al., 2020)	siRNA	C8 (FEN1 inhibitor)	Based on S. cerevisiae synthetic lethality networks, where RAD27 (FEN1 homolog) had numerous SL interactions with HR genes (e.g., RAD51, RAD52).	- BRCA2-deficient (PEO1,DLD1 BRCA2-/- colorectal) - BRCA2-proficient (PEO4, OV-90, OVCAR-3)	Mouse xenograft models	BRCA2 mutations	BRCA2 mutation
FEN1 EXO1(Andronikou et al., 2024)	siRNA	LNT1 (EXO1/ FEN1 inhibitor	BRCA2-dependent	KB2P1.21, KP3.33, and DLD-1 BRCA2	No	BRCA2-deficient; PARG-deficient; p53-deficient	PARG loss; BRCA2 mutation
FEN1 DNA-PKcs (Zhang et al., 2022)	siRNA	sc-13 inhibitor NU-7441 inhibitor	Synthetic lethal with DNA-PKcs loss; acts via BRCA1/RAD51/WRN Synthetic lethal with FEN1 loss; complementary to HR pathway	M059K, M059J and U251	Mouse xenograft models	DNA-PKcs-deficient glioma	Low DNA-PKcs activity ; high FEN1 expression
FEN1 TIMELESS (Saldanha et al., 2024)	siRNA	LNT1 Auxin-inducible degron (AID) system	Essential for backup Okazaki fragment (OF) processing, particularly when canonical FEN1/LIG1 pathway is compromised. Canonical Okazaki fragment processing pathway; synthetic lethal with loss of TIM-PARP1 interaction or TIMELESS function.	U2OS, HEK293T, HCT116	No	TIM-deficient	TIM-deficient

lacking BRCA2 might result in SL, highlighting FEN1 as a promising target for SL-based cancer therapies in BRCA2-deficient tumors.

4.3.2. EXO1

The synergistic interaction between FEN1 and EXO1 has demonstrated a significant SL effect in BRCA2-deficient cells (Andronikou et al., 2024). Due to BRCA2 deficiency impairing HR repair, these cells become more dependent on FEN1 and EXO1 to cope with replication stress and maintain genomic stability. Inhibition of both FEN1 and EXO1 results in the accumulation of unrepaired DNA damage, particularly unprocessed single-strand breaks that evolve into irreparable double-strand breaks, ultimately triggering apoptosis. This SL effect provides an effective therapeutic target for BRCA2-deficient tumors, as simultaneous inhibition of FEN1 and EXO1 amplifies DNA damage, leading to tumor cell death.

4.3.3. DNAPKcs

DNA-PKcs, a key factor in non-homologous end joining (NHEJ)-mediated DNA repair, is implicated in glioma. A notable increase in FEN1 expression is observed in glioma tumors deficient in DNA-PKcs, where FEN1-mediated HR replaces the role of NHEJ (Zhang et al., 2022). FEN1 inhibits MRE11 from extensively degrading nascent strands at arrested replication forks by stabilizing the assembly and loading of BRCA1-RAD51 onto these stalled forks. This aids in HR-mediated DSB repair and facilitates the progression of stalled forks, while also working synergistically with the NHEJ-mediating factor DNA-PKcs to address DNA replication stress. In DNA-PKcs-deficient glioma cells, FEN1 inhibition disrupts the BRCA1/RAD51-mediated HR pathway, creating a synthetic lethal interaction. While deficiency in either FEN1 or DNA-PKcs alone is tolerable, their combined disruption leads to catastrophic replication fork collapse, genome instability, and cell death, revealing a promising therapeutic strategy for this genetic subset of glioma (Zhang et al., 2022).

4.3.4. TIMELESS

TIMELESS (TIM) interacts with PARP1 to coordinate the synthesis of the leading and lagging strands while limiting the exposure of ssDNA, ensuring the smooth progression of DNA replication forks (Saldanha et al., 2024). The rapid loss of TIM or interference with the TIM–PARP1 interaction reduces PARP1 activity behind DNA replication forks, causing an increase in daughter-strand ssDNA gaps and DNA breakage. The effect is worsened when FEN1 activity, which aids in the standard OF maturation process, is lacking, leading to combined fork instability and reduced cell viability. When both FEN1 and the TIM-PARP1 complex are simultaneously inhibited, replication fork stability is compromised, leading to a dramatic increase in DNA damage, ultimately triggering cytotoxicity and SL. The results indicate that targeting both FEN1 and the TIM-PARP1 complex might offer therapeutic benefits and could be a key focus in cancer SL strategies.

5. Clinical translation feasibility and future directions

The compelling data for FEN1 inhibition, summarized in this review, positions it as a promising therapeutic strategy poised for clinical evaluation. To successfully translate this potential into patient benefit, a clear roadmap addressing patient selection, combination strategies, and rational trial design is essential.

FEN1 inhibition is most likely to benefit tumor types with homologous recombination deficiency (HRD), such as ovarian, breast, and prostate cancers, which often harbor BRCA1/2 mutations or other HRD markers. The combination of FEN1 and PARP inhibitors aims to deliver a "dual-strike" on DNA repair. Beyond this strategy, FEN1 inhibitors also hold promise as potent radiosensitizers. Additionally, tumors with high FEN1 expression (e.g., detected via IHC or qPCR) may be more sensitive to FEN1 inhibitors.

The essential role of FEN1 in DNA replication predicts that on-target toxicities will likely mirror those of other DNA-targeting agents. Dose-limiting toxicities are anticipated in rapidly proliferating tissues, primarily manifesting as myelosuppression (neutropenia, thrombocytopenia) and gastrointestinal toxicities (mucositis). Careful dose scheduling, such as intermittent rather than continuous dosing, may help mitigate these effects and widen the therapeutic window.

Initial clinical development should prioritize biomarker-driven trials to efficiently establish proof-of-concept. A window-of-opportunity study design, where a short course of a FEN1 inhibitor is administered to treatment-naïve patients prior to surgery, would provide the most direct evidence of on-target activity by enabling the analysis of pharmacodynamic effects—such as the induction of γH2AX foci and increased DNA damage in tumor tissue—in a pre- and post-treatment setting. Concurrently, the integration of liquid biopsies to monitor dynamic changes in circulating cell-free DNA (cfDNA), offers a powerful, non-invasive tool to complement tissue-based analyses and track early biological response. Furthermore, early-phase clinical trials must incorporate prospective patient stratification based on HRD status and FEN1 expression levels from the outset; this disciplined approach is crucial for validating the synthetic lethal hypotheses in the clinical setting and for identifying the patient populations most likely to derive benefit from this novel therapeutic strategy. Future directions should focus on optimizing FEN1-specific inhibitors, conducting multi-center cohort studies for biomarker validation, and employing adaptive trial designs to accelerate clinical development.

6. Conclusions

In conclusion, FEN1 emerges not merely as a DNA repair enzyme, but as a multifunctional, structure-specific nuclease that serves as a central hub for maintaining genomic integrity. Its critical roles in fundamental processes—such as Okazaki fragment maturation, LP-BER, the resolution of stalled replication forks, and the maintenance of telomere stability—underscore its indispensability. Moreover, FEN1's significant interaction with crucial DNA repair mechanisms like HR and NHEJ makes it a central player in coordinating cellular reactions to replication stress and DNA damage. This central role ultimately dictates cell fate decisions in response to various anti-cancer therapies, influencing outcomes in chemotherapy, targeted therapy, radiotherapy, and immunotherapy by modulating DNA damage repair efficiency and activating immunogenic signaling cascades.

Current studies indicate that FEN1 may serve as a diagnostic or prognostic biomarker in certain types of tumors and is a potential target for anti-cancer therapies. Furthermore, new technologies that target FEN1, such as nanodetection platforms and CRISPR/Cas12a-based methods, are continuously emerging and heralding a new era for early cancer diagnostics. However, the current body of evidence is predominantly characterized by in vitro studies, a lack of randomized clinical data, and uncertainties regarding on-target toxicity. Therefore, future efforts should focus on delineating the specific mechanisms of FEN1 in tumorigenesis and progression across diverse cancer contexts. There is a hopeful anticipation that FEN1 inhibitors will soon enter clinical trials, ultimately offering novel strategies for precision medicine in oncology.

CRediT authorship statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

FEN1	Flap endonuclease-1
RAD2	Radiation sensitive 2 family
CAR-T	Chimeric Antigen Receptor T-cell
BER	Base excision repair
CRISPR/Cas12a	Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated protein 12a
BRCA1	Breast cancer gene 1
EXO1	Exonuclease 1
DNA-PKcs	DNA-Dependent Protein Kinase Catalytic Subunit
CRC	Colorectal cancer
BC	Breast cancer
FFAA	F343A/F344A
PCNA	Proliferating Cell Nuclear Antigen
GC	Gastric cancer
LP-BER	Long-Patch Base Excision Repair
EGFR	Epidermal growth factor receptor
OC	Ovarian cancer
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
DFS	Disease-free survival
OSCC	Oral squamous cell carcinoma
MAPK	Mitogen-Activated Protein Kinase
Elk-1	ETS Like-1 protein
PDPN+ CAFs	Podoplanin-expressing cancer-associated fibroblasts
lncRNA	Long non-coding RNA
ACSL4	Acyl-CoA Synthetase Long-Chain Family Member 4
JAK	Janus kinase
STAT-1	Signal Transducer and Activator of Transcription 1
PD-L1	Programmed Death-Ligand 1
HLA-DR	Human Leukocyte Antigen – DR
Cdc25C	Cell Division Cycle 25 C
CDK1	Cyclin-Dependent Kinase 1
HCC	Hepatocellular carcinoma
SUMO2	SUMOylation via small ubiquitin-like modifier 2
TGFβ1	Transforming Growth Factor Beta 1
USP7	Ubiquitin Specific Peptidase 7
MDM2	Mouse Double Minute 2
AKT	Ak strain transforming
OS	Overall survival
CHOL	Cholangiocarcinoma
TME	Tumor microenvironment
SNPs	Single nucleotide polymorphisms
DOX	Doxorubicin
ROS	Reactive oxygen species
TMZ	Temozolomide
cGAS-STING	Cyclic GMP-AMP synthase-stimulator of interferon genes
TBK1	TANK-binding kinase 1
IRF3	Interferon regulatory factor 3
IFN-β	Interferon-beta
CCL5	C-C motif chemokine ligand 5
CXCL10	C-X-C motif chemokine ligand 10
KRAS	Kirsten rat sarcoma viral oncogene homolog
RPA	Recombinase polymerase amplification
APE1	Apurinic/apyrimidinic endonuclease 1
TE	Telomerase
CuNPs	Copper nanoparticles
SL	Synthetic lethality
BRCA2	Breast cancer 2
PARP	Poly(ADP-ribose) polymerase
HR	Homologous recombination
NHEJ	Non-homologous end joining
TIM	TIMELESS
HRD	Homologous recombination deficiency

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