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REVIEW

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Impact of glycolysis enzymes and metabolites in regulating DNA damage repair in tumorigenesis and therapy

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Abstract

Initially, it was believed that glycolysis and DNA damage repair (DDR) were two distinct biological processes that independently regulate tumor progression. The former metabolic reprogramming rapidly generates energy and generous intermediate metabolites, supporting the synthetic metabolism and proliferation of tumor cells. While the DDR plays a pivotal role in preserving genomic stability, thus resisting cellular senescence and cell death under both physiological and radio-chemotherapy conditions. Recently, an increasing number of studies have shown closely correlation between these two biological processes, and then promoting tumor progression. For instance, lactic acid, the product of glycolysis, maintains an acidic tumor microenvironment that not only fosters cell proliferation and invasion but also facilitates DDR by enhancing AKT activity. Here, we provide a comprehensive overview of the enzymes and metabolites involved in glycolysis, along with the primary methods for DDR. Meanwhile, this review explores existing knowledge of glycolysis enzymes and metabolites in regulating DDR. Moreover, considering the significant roles of glycolysis and DDR in tumor development and radio-chemotherapy resistance, the present review discusses effective direct or indirect therapeutic strategies targeted to glycolysis and DDR.

Keywords Glycolysis, DNA damage repair, Genomic stability, Tumor, Resistance

Background

Distinct from normal tissue cells, solid tumor cells have a tendency to utilize glycolysis to produce ATPs (adenosine triphosphates) rather than aerobic respiration, even in the presence of oxygen-rich conditions, which is widely known as the "Warburg effect" [1, 2]. Multiple factors are believed to responsible for this phenomenon. Primarily, solid tumor cells generally initiate glycolysis to fulfill the hypoxic and energy shortage tumor microenvironment (TME), and the alteration of signaling pathways and glycolysis related enzymes making tumor cells tend to utilize glycolysis to metabolize glucose. In addition, the ability of tumor cells to uptake glucose is more than ten times that of normally differentiated cells, and glycolysis possess a shorter while faster metabolic pathways than that of oxidative phosphorylation [3]. Besides providing ATPs for tumor cells, glycolysis can also generate various intermediate metabolites for nucleotide, protein as well as fatty acid metabolisms [3, 4]. As the product of glycolysis lactic acid gradually acidifies the TME, which in turn disrupting the immune environment and extracellular matrix, and therefore advancing and exacerbating the migration and invasion ability of tumors [5–7]. Deprivation of glycolysis by inhibiting glucose transporter proteins (Gluts) and glycolysis related proteins induce apoptotic cell death in several kinds of cancer cells [8–10]. Although there are still conflicting aspects, the

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alteration of glycolysis can modulate autophagy, which is generally considered as a pro-survival mechanism. Moreover, increasing investigations indicate glycolysis play a role in modulating DNA damage and DNA damage repair (DDR). For instance, several glycolysis enzymes promote the DDR upon both chemotherapy agents and radiation [8, 9, 11, 12], and the glycolysis metabolites function in reducing the reactive oxygen species (ROS) thereby reducing the probability of DNA damage [13, 14]. In addition, cellular senescence, characterized by metabolic deregulation and macromolecular damage causing genomic instability, arises as a stress response to diverse stimuli. Gorgoulis et al. emphasized the necessity of elucidating the mechanisms underlying cellular senescence, revealing the crucial involvement of DNA damage responses and protein stress in initiating senescence, frequently accompanied by metabolic shifts towards glycolysis [15, 16]. Therefore, the metabolic reprogramming of glycolysis in tumor cells not only promotes the progression of tumors, but also resists the efficacy of radiochemotherapy. In the current review, we will discuss the impact of glycolytic pathways on DDR, and their roles in regulating tumor progression and therapy.

The primary process of glycolysis

Glycolysis represents the initial enzymatic degradation process of glucose within eukaryotic cells, during which a single glucose molecule degrades into two pyruvate molecules and releases two ATP molecules. Glycolysis is recognized as a primitive and fundamental means of energy acquisition, serving as the common metabolic pathway for glucose catabolism. Subsequently, pyruvate will be metabolized by the oxidative phosphorylation process to generate carbon dioxide and water, and release a large amount of ATP under aerobic conditions. However, under hypoxia and mitochondrial dysfunction conditions, pyruvate is enzymatically converted to lactic acid by lactate dehydrogenase (LDH). This transformation relies on NADH (nicotinamide adenine dinucleotide reduced form) as a hydrogen donor, and then regenerates NAD^+ (nicotinamide adenine dinucleotide) during the process. Therefore, lactic acid serves as a valuable indicator for monitoring glycolytic activity.

As shown in Fig. 1, glycolysis process comprises ten reactions that can be segregated into two distinct stages: the preparatory phase for fermentation and the subsequent energy-releasing stage [17, 18]. The preparatory phase of glycolysis comprises five key reactions. 1) Glucose is converted to glucose-6-phosphate (G6P) by hexokinase (HK), an irreversible process consuming an ATP molecule. This reaction activates glucose molecules and ensures the intracellular glucose is effectively captured, and therefore prevents its efflux of the cell. 2) G6P is isomerized to fructose-6-phosphate (F6P) by phosphoglucose isomerase (PGI), while this reaction is reversible. 3) F6P is converted to fructose-1,6-bisphosphate (F1,6BP) by 6-phosphofructo-1-kinase (PFK-1), an irreversible step requiring an ATP. Meanwhile, F6P can be reversible catalyzed to fructose-2,6-bisphosphate (F2,6BP) by 6-phosphofructo-2-kinase (PFK-2), which plays an important role in regulating glycolysis by modulating the activity of PFK-1. 4) F1,6BP is reversible transformed into glyceraldehyde-3-phosphate (GA3P) and dihydroxyacetone phosphate (DHAP) by aldolase. 5) DHAP is reversible isomerized to GA3P by triosephosphate isomerase (TPI), as it can't be utilized by glycolysis. During this preparatory phase, one glucose molecule is converted into two GA3P and consumes two ATP molecules.

The following five reactions constitute the energy-releasing stage. 6) GA3P is dehydrogenated by glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in the presence of inorganic phosphate (Pi) to produce 1,3-diphosphoglycerate (1,3-BPGA), and simultaneously reduce 1 molecule of NAD^+ to NADH. 7) Under the catalysis of phosphoglycerate kinase (PGK), 1,3-BPGA is converted to 3-phosphoglycerate (3-PGA) and generates the first ATP molecule. 8) 3-PGA is converted to 2-PGA under the action of phosphoglycerate mutase (PGAM). 9) 2-PGA undergoes dehydration to generate phosphoenolpyruvate (PEP) by enolase. These four reactions are all reversible. 10) With the help of pyruvate kinase (PK), PEP transfers phosphate groups to ADP, and then generates pyruvate and ATP. This is the second ATP generated during glycolysis. As one glucose molecule is converted into two GA3P, so totally four ATP molecules and two NADH molecules are generated during the energy-releasing stage, and the total reaction of glycolysis is shown in Fig. 1. For detailed information on the agonists and antagonists of glycolytic-related enzymes, please refer to the following literatures [2, 17, 18], and we will not delve into them further here.

Among all the catalytic enzymes participated in glycolysis, HK, PFK-1 and PK function as the rate-limiting enzymes [2, 17]. As PFK-1 characters the lowest catalyze activity, thus serving as the gatekeeper for glycolysis. Its activity is effectively allosteric inhibit by citrate, ATP, as well as its catalytic product F1,6BP, while ructose-2,6-bisphosphate (F2,6BP) potently aggregates its activity [3]. Cellular F2,6BP is synthetized by 6-phosphofructo-2-kinase (PFK-2) from F6P. Notably, PFK-2 simultaneously catalyze the inverse reaction, the hydrolysis of F2,6BP to F6P, thus exhibiting phosphatase activity and being referred to as fructose-2,6-bisphosphatase (FBPase-2). Although not directly involved in the glycolysis process, PFK-2 is widely approved to be a crucial modulator of the glycolysis process. In addition, there are also

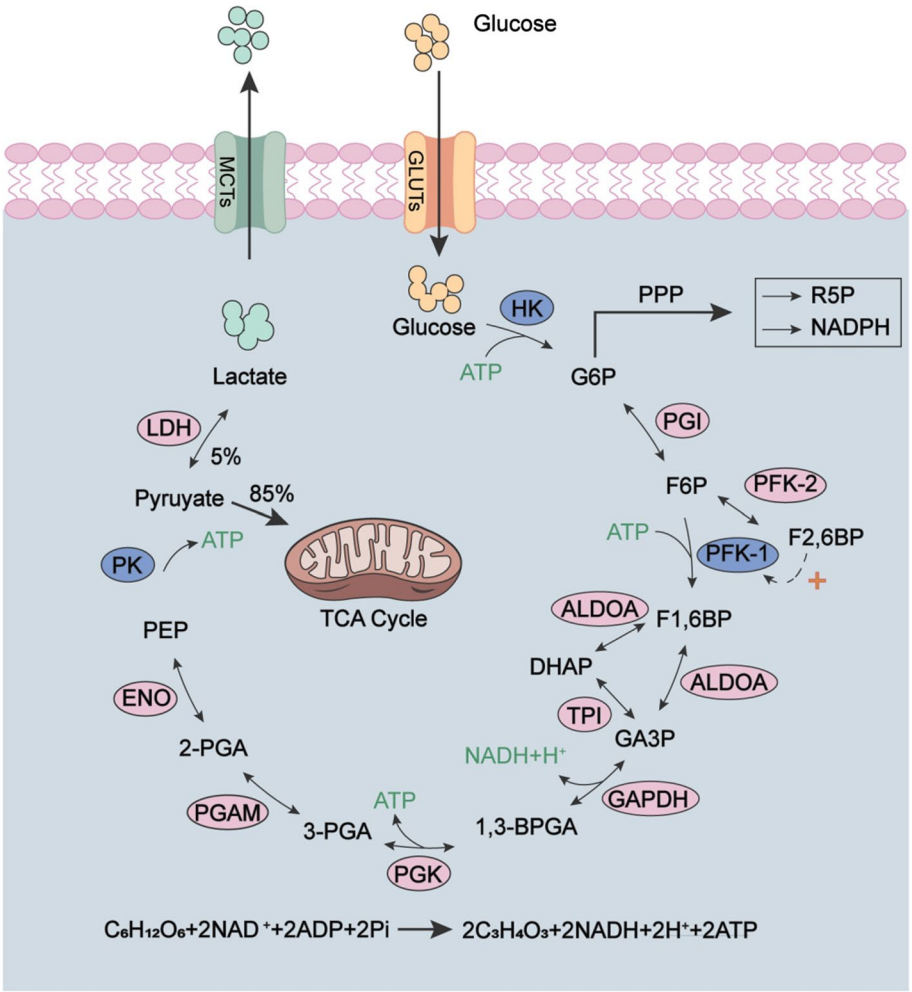


Fig. 1 Schematic diagram of glycolysis process. Enzymes: GLUTs (glucose transporter proteins), HK (hexokinase), PGI (phosphoglucose isomerase), PFK-1 (6-phosphofructo-1-kinase), PFK-2 (6-phosphofructo-2-kinase), ALDOA (aldolase A), TPI (triosephosphate isomerase), GAPDH (glyceraldehyde-3-phosphate dehydrogenase), PGK (phosphoglycerate kinase), PGAM (phosphoglycerate mutase), ENO (enolase), PK (pyruvate kinase), LDH (lactate dehydrogenase), MCTs (monocarboxylate transporters). Glycolytic intermediates: G6P (glucose-6-phosphate), F6P (fructose-6-phosphate), F2,6BP (fructose-2,6-bisphosphate), F1,6BP (fructose-1,6-bisphosphate), GA3P (glyceraldehyde-3-phosphate), DHAP (dihydroxyacetone phosphate), 1,3-BPGA (1,3-bisphosphoglycerate), 3-PGA (3-phosphoglycerate), 2-PGA (2-phosphoglycerate), PEP (phosphoenolpyruvate), NADH (nicotinamide adenine dinucleotide reduced form), NAD^+ (nicotinamide adenine dinucleotide). Abbreviation: PPP (pentose phosphate pathway), TCA cycle (Krebs cycle), NADPH (nicotinamide adenine dinucleotide phosphate, reduced form), R5P (ribulose-5-phosphate). The overall reaction equation for the glycolysis process was shown

other proteins closely related to the glycolytic pathway, such as Glut, MCTs (monocarboxylate transporters) and LDH. Prior to the commencement of the glycolytic pathway, glucose is transported from the extracellular to the intracellular by trans-membrane Glut, which is widely expressed in nearly all cells. LDH converts pyruvate and NADH to lactic acid and NAD^+, therefore leading to the acidic tumor microenvironment (TME), which can promote tumor invasion and angiogenesis [19]. Interestingly, lactic acid can participate in the occurrence and development of tumors as a carcinogenic factor [5, 20]. Moreover, it negatively regulates the function and metabolic growth of immune cells, ultimately achieving "immune escape" and avoiding surveillance by immune checkpoints [21].

Primary mechanisms of DDR in eukaryotic cells

Upon stimulation by external and internal environment factors, such as exogenous chemical carcinogens, ultraviolet, ionizing radiation, endogenous chemical carcinogens, and oxidative stress, normal cells generally undergo DNA base mutations/damage, DNA inter-strand crosslinks, DNA strand breaks and/or chromosomal variations [22]. Among all the DNA

damage mechanisms, DNA double-strand break (DSB) is the relatively serious mechanism, which need timely and appropriate repair. Otherwise, cells will emerge cell cycle arrest or even develop into cell death, or introduce mutations and chromosomal translocations, making the cell prone to either senescence or tumorigenesis [23–25]. For cancer cells, DNA damage and its repair are important therapeutic targets, such as radiotherapy, alkylating agents and platinum based drugs, etc. As shown in Fig. 2, cell fate is determined by the balance of DNA damage and its repair. Massive DNA damage, when left unrepaired or subject to incorrect repair processes that substantially affect cellular function, can give rise to genomic instability, ultimately culminating in phenomena such as cell death, tumorigenesis, senescence, or metabolic reprogramming. Apart from causing damage to the DNA within chromosomes, mtDNA (mitochondrial DNA) is susceptible to attacks by endogenous damaging factors, such as ROS, resulting in dysfunction of the mitochondrial respiratory chain [26, 27]. In eukaryotic cells, homologous recombination repair (HRR) and non-homologous end joining (NHEJ) are frequently discussed and investigated for DSB repair. Several mechanisms are utilized for mismatch and single-strand break (SSB) repair, including DNA direct repair (DR), mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER).

HRR and NHEJ

HRR possess a high fidelity repair mechanism, which predominantly occurs in the S and G2 stages of the cell cycle, mainly because the sister chromatids function as template is spatially close during this period. Therefore, although this type of HRR can be error-free, the actual occurrence rate of it in cells is not high. In some cases, non-sisters chromatids can also be used as templates for HRR, which may lead to point mutations or gene conversions at injury sites [28]. NHEJ does not require homology and repairs damages at any phase of the cell cycle, however, this repair method inevitably leads to the deletion of DNA bases in the vast majority cases. HRR and NHEJ share both competitive and complementary relationships, as plasmid DNA with DSB could be repaired by either method in cells, and either defect would lead to the enrichment of another method [28, 29]. Although the NHEJ proteins are recruited to DSB more rapidly than HRR proteins, both sets of factors are present at the DSB during significant period [30]. In fact, several proteins are involved in both HRR and NHEJ processes, such as BRCA1/2 (breast cancer susceptibility proteins 1/2), DNA-PK (DNA-dependent protein kinase), ATM (Ataxia telangiectasia mutated kinase), Rad50, Rad18, H2AX, PARP-1, etc. [28, 31, 32]. The significant enhancement in γ-H2AX (phosphorylation of H2AX at Ser139) is one of the typical biomarker for DSB, which is widely used for DSB detection in scientific investigation. When DSB are aroused, H2AX is

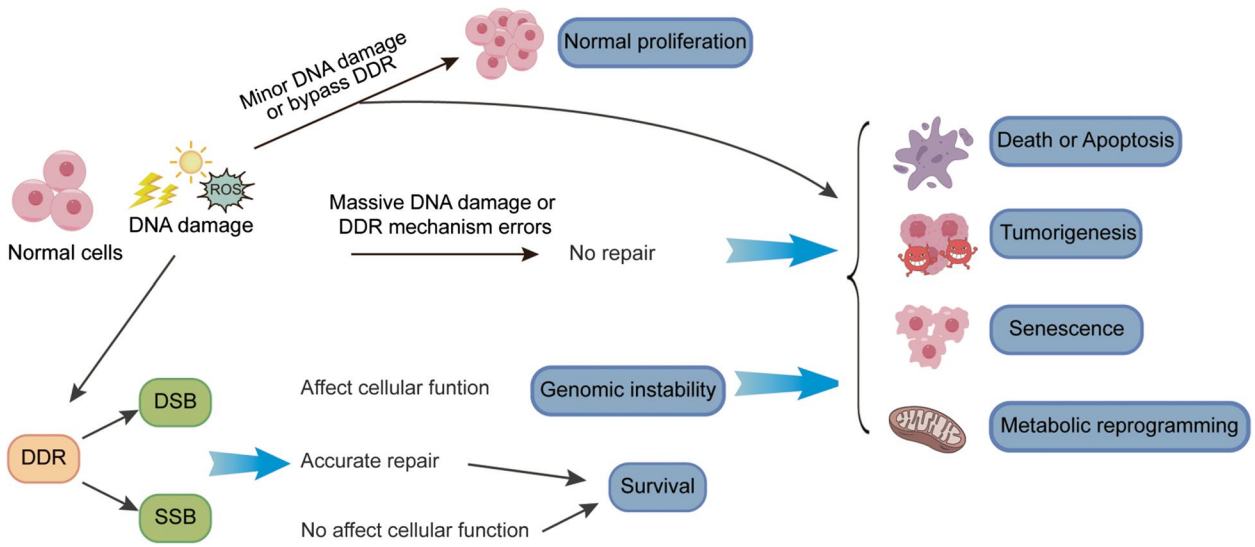


Fig. 2 Cell fate is determined by the balance of DNA damage and its repair. External and internal environmental factors can elicit diverse forms of DNA damage. While some injuries exert minimal impact on cells, others, coupled with inadequate/unsuitable DNA repair, may result in cell cycle arrest, cell death, mutations, and chromosomal translocations, ultimately fostering senescence or tumorigenesis. Under optimal or nearly optimal repair conditions, cells have the capacity to recuperate to relatively normal states and successfully conclude their predetermined life cycle, maintaining genomic stability and ensuring proper cellular function. The delicate balance between DNA damage and its repair thus plays a pivotal role in determining the ultimate fate of cells

rapidly phosphorylated by PI3K-related kinases, including ATM, DNA-PK and ATR (ataxia telangiectasia and Rad3-related kinase), which then amplify DNA damage signal and recruit functional proteins for DDR, such as MDC1 [33, 34]. However, former studies indicated that γ-H2AX is not indispensable for HRR and NHEJ, as its absence failed to block the HRR and NHEJ [33, 35, 36]. The role of γ-H2AX in DDR can be referenced here [33].

During the HRR (Fig. 3A), the MRN complex (MRE11-Rad50-NBS1) acts as a DSB sensor and participates in the initial phase upon DNA damage. This complex rapidly recruits to DSB ends via Rad50, and then resects the end of broken DNA via MRE11 with the help of BRCA1 to generate 3'-end ssDNA (single-strand DNA), RPA covers and stabilizes these single chain regions. Generally, ATM is stabilized by DNA-PK and existed in an inactivated dimer form. NBS1 recruits and disrupts the dimer form of ATM, which then transformed to activate form by auto-phosphorylation at S1981, S367 and S1893 sites [37]. Subsequently, activated ATM anchors at the DSB and catalyzes the phosphorylation of downstream effectors, such as H2AX. With the help of Rad54 and BRCA2, the recombinase Rad51 is recruited to the DSB site and replaced RPA [38]. After disconnecting from BRCA2, Rad51 polymerized and forms a filament nearby the ssDNA, and then the ssDNA-Rad51 filament enters the template and forms D-loop intermediates to complete the HRR [39].

When it comes to NHEJ (Fig. 3B), the Ku70-Ku80 heterodimer is the first factor binding to DSB in NHEJ pathway in most cases. On the one hand, the abundant Ku70-Ku80 heterodimer have a high affinity for binding to DSB ends and therefore preventing its excessive excision. On the other hand, the Ku70-Ku80 heterodimer recruit DNA-PK and Artemis nuclease to the DSB ends, both of them play a role in DNA end processing. The end processing of DNA includes nucleotide addition, modification and excision, which is necessary for the following DNA repair and the reason for NHEJ prones to cause genome rearrangement. Once the DNA-PK is recruited, it is activated by auto-phosphorylation, and phosphorylates other targets including H2AX [40–42]. Subsequently, XRCC4, XLF (XRCC4-like factor) and DNA ligase IV anchor to the DSB ends and perform break sealing. Besides the canonical NHEJ pathway above, there is an alternative NHEJ (alt-NHEJ) pathway functions independent of Ku70-Ku80. During this process, the MRN complex assists in processing the DSB ends [28, 43], and then PARP-1, XRCC1 and DNA ligase III are utilized to rejoining the break ends. This pathway requires 5–25 bp micro-homology and characters slow efficiency [44]. For those looking forward to further understanding HRR and NHEJ proteins and detailed processes, please refer to the following literatures [28, 31].

In addition, another mechanism based on DSB is SSA (Single Strand Annealing), which belongs to the homologous directed repair mechanism. It uses homologous repeat sequences on the DSB flank for repair, and the process of ligation is often prone to errors due to the removal of DNA repeat sequences. Unlike HRR, SSA does not require chain invasion and donor sequence; therefore it does not require RAD51 support [45]. In addition, the RAD52-RPA complex participates in the core response of SSA, making RAD52 a highly valuable therapeutic target in homologous recombination deficient BRCA1 or BRCA2 deficient cells [46].

For DNA SSB

This intricate mechanism for DNA SSB repair involves several steps and a myriad of proteins, ensuring the accurate restoration of damaged DNA. Initially, DNA damage is detected by a network of sensor proteins, such as poly(ADP-ribose) polymerase (PARP), which recognizes SSB [47]. Upon detecting an SSB, PARP-1 swiftly localizes to the damage site and activates its catalytic function, using NAD^+ as a substrate to synthesize poly(ADP-ribose) (PAR) polymers [48, 49]. This process, known as PARylation, serves as a vital signaling mechanism that orchestrates the recruitment of various DNA repair factors to the site of damage [48, 49]. Besides, PARP-1's PARylation activity can influence chromatin structure, promoting a more relaxed state that facilitates access of repair enzymes to damaged DNA. This chromatin remodeling function is crucial for efficient DNA repair, as it ensures that repair factors can reach and repair damage within the tightly packed chromatin.

One of the primary repair mechanisms is base excision repair (BER), which addresses damaged bases (Fig. 3C) [50]. This process commences with the recognition and excision of the damaged base by DNA glycosylases, like uracil-DNA glycosylase (UDG), forming an apyrimidinic (AP) site. Subsequently, AP endonucleases, like APE1, cleave the DNA backbone at the AP site, creating a single-nucleotide gap. This gap is then filled in by DNA polymerase β, which utilizes the intact DNA strand as a template. Finally, DNA ligase III, aided by XRCC1, seals the nick, completing the BER process. In cases where the damage is more extensive or the BER pathway is overwhelmed, the cell may resort to the more comprehensive nucleotide excision repair (NER) mechanism (Fig. 3D) [51]. NER recognizes a wider spectrum of lesions, including bulky adducts and UV-induced damage. The NER process can be divided into two sub pathways: Global Genome NER (GG-NER) and Transcription Coupled NER (TC-NER) (only GG-NER will be discussed below).

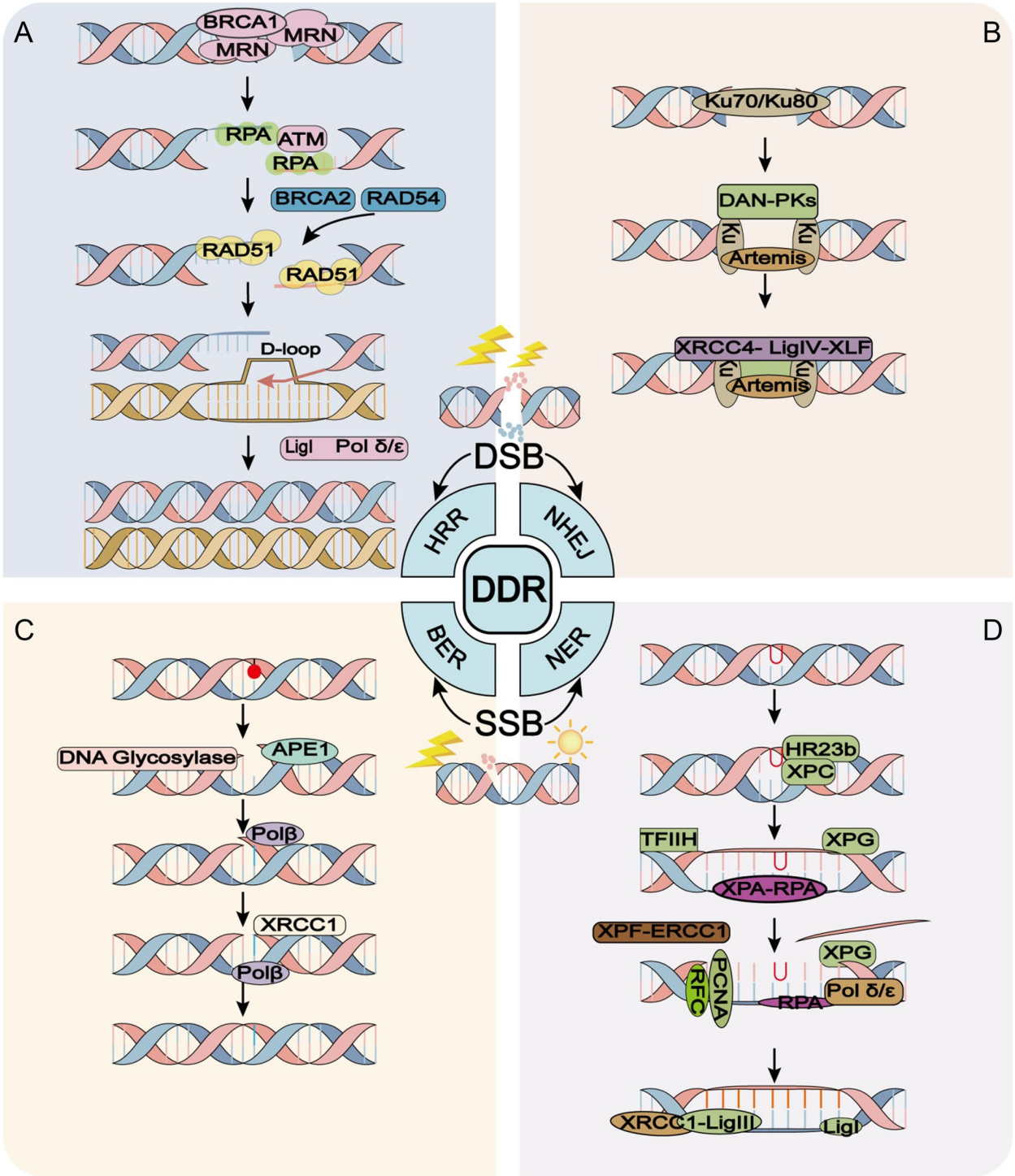


Fig. 3 Brief schematic models of common DNA damage repair pathways. DNA double-strand break (DSB) and single-strand break (SSB) represent two prevalent and critical forms of DNA damage, and numerous repair pathways have been studied extensively. **A** and **B** In the case of DSB, homologous recombination repair (HRR) and non-homologous end joining (NHEJ) are commonly employed repair methods. HRR boasts a high-fidelity repair mechanism, whereas NHEJ frequently results in the deletion of DNA bases in the majority of instances. **C** and **D** For SSB, base excision repair (BER) and nucleotide excision repair (NER) are frequently utilized repair methods. BER is relatively straightforward, whereas NER is more intricate

The process involves excision of the damaged DNA segment (typically 22–30 nucleotides) by endonucleases, followed by gap-filling by polymerase δ or ε and ligation by DNA ligase I or III. After XPC complex recognizes damage, XPA-RPA confirms and stabilizes the damage, followed by endonucleases cutting DNA at the 5 'and 3' ends of the damage. DNA polymerase δ or ε and ligase I or III are responsible for filling and connecting, while XPG, XPF, TFIIH, etc. promote the process of NER [52, 53]. Moreover, when DNA replication encounters SSB, the cell employs a specialized mechanism called post-replication repair (PRR), often mediated by error-prone trans-lesion synthesis (TLS) polymerases like polymerase η [54]. TLS allows DNA replication to bypass the damage site, albeit with a risk of introducing mutations.

Glycolytic enzymes in regulating DNA damage

Former studies show that DNA damage and repair processes exert profound effects on cellular metabolism. DNA lesions can disrupt metabolic pathways, while efficient DNA repair mechanisms are crucial for restoring metabolic homeostasis and ensuring cell survival. The intricate interplay between DNA integrity and metabolism underscores the importance of maintaining genomic stability for overall metabolic health. During the tumorigenesis process, extensive DNA damage and repair may be important factors leading to metabolic reprogramming [55, 56]. Conversely, glycolysis, particularly the activity of glycolytic enzymes, plays a role in modulating DDR mechanisms. These enzymes can influence the availability of metabolites and energy necessary for DNA repair processes, impacting the cell's ability to respond to and recover from DNA damage. Therefore, while DNA damage and repair can affect glycolysis, glycolytic enzymes also play a crucial role in influencing DDR mechanisms.

HK2

As the first rate-limiting enzyme in glycolysis, HK, particularly isoform 2 (HK2), emerges as a multifaceted player in cellular responses to DNA damage, albeit with indirect mechanisms. It has been established that HK2 localizes to the DNA in acute myeloid leukemia and normal hematopoietic stem and progenitor cells, where it contributes to maintaining stemness [12]. This unusual subcellular localization suggests that HK2 may participate in nuclear processes beyond its canonical role in glycolysis. By modulating gene expression or interacting with chromatin-associated proteins 53BP1 and Rad51, HK2 could influence the cellular response to DNA damage, potentially enhancing survival and proliferation under stressful conditions [12]. In embryonal rhabdomyosarcoma, hyperactive AKT1 signaling promotes tumor progression and DNA repair [57]. By increasing glucose uptake and flux through the glycolytic pathway, hyperactive AKT1 enhances the cell's metabolic flexibility, allowing it to withstand DNA damage and continue proliferating. Therefore, HK2 inhibitors could represent a promising therapeutic strategy to sensitize cells to DNA-damaging agents [57]. Similarly, inhibiting HK2 kinase can reverse DNA damage repair in NSCLC cells regulated by CAFs and increase radiation sensitivity [58]. Loss of BRCA1 in ovarian cancer cells initiates a metabolic shift towards glycolysis [59]. This metabolic reprogramming, driven by HK2 and other glycolytic enzymes, provides ovarian cancer cells with the energy and biosynthetic intermediates necessary to withstand chemotherapy and progress towards malignancy. Therefore, targeting glycolytic pathways, particularly HK2, may present a promising opportunity for chemoprevention [59]. 3-Bromopyruvate, a glycolytic inhibitor, regulates the status of glycolysis and modulates the sensitivity of human hepatocellular carcinoma cells to BCNU, a chemotherapeutic agent [60]. This finding underscores the importance of glycolysis in modulating cellular responses to DNA-damaging chemotherapy. By inhibiting HK2 and disrupting glycolysis, 3-Bromopyruvate enhances the efficacy of BCNU, suggesting a potential therapeutic synergy [60]. Meanwhile, 2-DG (2-Deoxy-D-glucose), another inhibitor of HK2, has been shown to modulate cellular sensitivity to DNA-damaging agents, such as radiation and chemotherapy, underscoring the intricate connection between glycolysis and DNA damage responses [61]. Beyond cancer, HK2 and glycolysis have also been implicated in neurodegenerative diseases such as Alzheimer's disease [62]. Here, biological sex and DNA repair deficiencies drive systemic metabolic remodeling and brain mitochondrial dysfunction, which are closely tied to glycolysis and HK2 activity. Although the direct link between HK2 and DNA damage in Alzheimer's disease remains to be fully elucidated, this research highlights the broader implications of glycolytic dysregulation in disease pathogenesis [62].

PFK-2/PFKFB3

Although serving as the gatekeeper for glycolysis, the role of PFK-1 in DNA damage and DDR is still uncovered. However, robust researches revealed that PFK-2 plays essential roles in regulating DNA damage and DDR. Among all four isoforms of PFK-2/FBPase-2, PFKFB3 (6-phosphofructo-2-kinase/ fructose-2,6-bisphosphatase isoform 3) characters the highest ratio (> 700) of kinase/phosphatase activity. Generally, it's highly expressed in rapidly proliferation cells, and its activity and expression are induced by various cellular signals, such as hypoxia, growth factor and hormone. Moreover, an increasing

number of studies indicate its involvement in regulating nuclear damage and repair processes, although its roles remain controversial.

Da et al. emphasized PFKFB3's potential as a prognostic and tumor microenvironment biomarker in human cancers, and its expression is correlated with several signaling pathways, including cell cycle and DNA damage response [63]. Moreover, Xiao et al. reported that PFKFB3 inhibition induced cell death and synergistically enhanced chemosensitivity of both carboplatin and cisplatin in endometrial cancer cells by enhancing DNA damage as well as reducing RAD51 expression [8]. Our former study reported that blocking the necroptosis pathway attenuated PFKFB3 inhibitor-induced cell viability loss and genome instability in colorectal cancer cells, suggesting that PFKFB3 inhibition may enhance the efficacy of chemotherapy by exacerbating DNA damage [9]. Inhibiting either PFKFB3 or TIGAR individually led to an elevation in DNA damage in HeLa cells, and the phenotypic effect was notably more pronounced in cells deficient with both proteins [64]. Interestingly, PFKFB3 knockdown increased the AKT-mTOR activity in this research, which is distinct from most studies [64].

Gustafsson et al. found that targeting PFKFB3 radiosensitized cancer cells and suppressed HRR, a crucial DNA repair pathway [65]. Shi et al. reported that inhibiting PFKFB3 hinders the growth of hepatocellular carcinoma by disrupting DNA repair mechanisms via AKT signaling, implicating AKT as a mediator of PFKFB3's effects on DNA repair and cancer progression. This study highlights the complexity of signaling networks involved in PFKFB3's function and underscores the potential for targeting multiple pathways to achieve therapeutic benefit [66]. Ninou et al. showed that PFKFB3 inhibition sensitizes cancer cells to DNA crosslinking chemotherapies by suppressing Fanconi anemia repair, further emphasizing PFKFB3's role in regulating specific DNA repair pathways [67]. Recently, Sun et al. reported that PFKFB3 translocate to sites of DNA damage induced by oxidative stress, facilitating DNA repair processes through its interaction with the MRN-ATM signaling pathway [68]. Meanwhile, they also point out that PFKFB3 is involved in regulating the process of cellular senescence [68].

Importantly, PFKFB3's effects on DNA damage and repair are not uniform across all cell types and contexts. While inhibition of PFKFB3 often enhances DNA damage and sensitizes cancer cells to therapeutic interventions, its role in other type cells can be more nuanced. In Fanconi anemia hematopoietic stem cell, p53-TIGAR axis suppresses glycolysis and therefore reduced DNA damage, while ectopic expression of PFKFB3 resisted p53-TIGAR mediated metabolic reprogramming [69]. Although they failed to monitor the role of PFKFB3 in modulating DNA damage, it is highly likely that PFKFB3 promotes DNA damage under these conditions, highlighting the need for a careful assessment of PFKFB3's function in different cellular environments. Another study unveiled that p53 orchestrates DNA repair and nucleotide synthesis by repressing PFKFB3 expression, thereby fostering the pentose phosphate pathway and leading to a more efficacious DDR mechanism [70]. In these studies, PFKFB3 may play a negative role in regulating DDR.

PKM2

Among the primarily four isoforms of PK mammalian cells, PKM2 (pyruvate kinase muscle 2 isoform) is highly expressed in cancer cells and functions as a master regulator of cancer reprogramming. Beyond, despite potential contradictions, previously studies have indicated that PKM2 is implicated in regulating cellular senescence, potentially due to variations in cell type and PKM2 forms [71, 72]. The upregulation of PKM2, along with its altered subcellular localization, has been correlated with multiple hallmarks of cancer, such as perpetual proliferative signaling, evasion from apoptosis, the activation of invasion and metastasis pathways, and the deregulation of energetic metabolism. PKM2 exists in two forms in tumors: a tetramer that promotes glycolysis, fueling tumor energy metabolism, and a dimer that enters the DNA to regulate gene expression, activating Wnt signaling pathways and influencing DDR. This morphological switch is vital for tumor survival, growth, and adaptation. Additionally, although its involvement in regulating nuclear damage and the subsequent repair processes is recognized, the precise mechanisms by which it functions in these pathways continue to be a topic of ongoing discussion and research.

PKM2 directly interacts with p53, and disrupts p53's phosphorylation by ATM. As a result, the expression of PKM2 confers a proliferative advantage to tumor cells when confronted with DNA damaging stimuli [73]. In non-small cell lung cancer (NSCLC) cells, inhibition of PKM2 triggers a cascade of events, including the upregulation of p53, ROS production, DNA damage, and downregulation of PARP-1, while its overexpression attenuates the DNA damage, mitochondrial fission, and cell viability loss aroused by agent [74, 75]. Knockdown of PKM2 enhances the radiosensitivity of cervical cancer cells, and enhanced the p-ATM and γ-H2AX, suggesting that PKM2 may confer resistance to radiation-induced DNA damage [76]. Upon DNA damage induced by radiation, PKM2 interact with FACT complex (SPT16 and SSRP1), and the pyruvate produced by PKM2 directly bind to SSRP1, therefore enhancing FACT-mediated chromatin loading of γ-H2AX. This promotion of γ-H2AX's

chromatin loading facilitates DNA repair and tumor cell survival [77]. Downregulation of PKM2 by siRNA or small molecular inhibitor enhances the effects of olaparib, a PARP-1 inhibitor, by amplifying the p-ATM and γ-H2AX levels, and PKM2 inhibition disrupts the nuclear accumulation of BRCA1, thereby compromising the cell's ability to effectively repair DNA damage by HRR [78]. Another study also uncovered that ATM phosphorylates PKM2 at T328 site, and pT328-PKM2 promotes HRR-mediated DNA DSB repair by phosphorylating CtIP at T126 site, enhancing CtIP recruitment to DSB and facilitating DNA end resection [79].

The abovementioned researches indicate that PKM2 inhibits DNA damage and promotes DDR, however, there are also some studies suggest that PKM2 plays a completely opposite role. For instance, Xia et al. demonstrated nuclear PKM2 interacts with H2AX and then phosphorylates it at S139 site, and depletion of PKM2 reduces the level of γ-H2AX under DNA damage conditions [80]. Another study indicated PKM2 binds to DDB2 (DNA Damage-Binding Protein 2), a critical component of the NER pathway that specifically recognizes UV-induced DNA damage, and this interaction impairs the efficient assembly of the NER complex and consequently compromise the cell's ability to repair UV-induced DNA damage. However, this study claimed PKM2 negatively correlates with cell survival upon UV irradiation, which is inconsistent with the general perspective [81].

Other glycolytic enzymes

As for several other glycolytic enzymes, such as PGI, TPI, PGK, and enolase may indirectly impact DNA damage through metabolic alterations, but their direct regulating of DNA damage has not been well established yet. While PGAM has been suggested to modulate the DNA damage response, there is a paucity of conclusive experimental data to definitively support this assertion [82].

Aldolase, particularly Aldolase A and B, exhibits complex roles in regulating DNA damage. Aldolase A has been shown to promote radioresistance by upregulating glycolysis post-irradiation, providing metabolic intermediates for DNA repair pathways [83, 84]. Specifically, it facilitates the activity of DNA-PKcs and ATM kinases, which are critical for DSB repair [85]. In contrast, by impairing DNA MMR mechanisms, Aldolase B contributes to the accumulation of DNA damage, ultimately triggering apoptosis in colorectal cancer cells [86].

GAPDH, usually used as the internal reference, are unveiled to involve in the cellular response to DNA damage. In DNA damaged Saccharomyces cerevisiae cells, the peptide derived from GAPDH secreted into the microenvironment can enhance cell survival [87]. Its phosphorylation mediated by Src kinase regulates its nuclear translocation, enhancing resistance to DNA damage in mammalian cells [88]. Furthermore, GAPDH expression is modulated by natural flavonoids like naringin, which aids in DNA repair by facilitating NER machinery, thereby mitigating UVB-induced DNA damage [89]. Moreover, GAPDH interacts with chromatin-associated proteins and other enzymes, to sustain nucleotide salvage pathways critical for DNA repair under stress conditions [90, 91]. Interestingly, GAPDH's overexpression protects against neurovascular degeneration following retinal injury, highlighting its potential therapeutic implications in mitigating DNA damage-related disorders [92]. Conversely, its inappropriate nuclear accumulation can lead to non-apoptotic cell death, a phenomenon mitigated by CIB1 through AKT and ERK signaling [93]. Studies also indicate that GAPDH can physically interact with DNA repair enzymes, such as apurinic/apyrimidinic endonuclease I (APE1), facilitating the protection of cells against oxidant-induced DNA damage [94, 95]. Ferreira E et al. further underscores the necessity of GAPDH for efficient repair of cytotoxic DNA lesions in bacteria, suggesting a conserved function across species [96]. Conversely, pyruvate, a metabolic intermediate closely tied to GAPDH function, can mitigate cell stress and genotoxicity, underscoring the therapeutic potential of modulating GAPDH-related pathways in response to DNA damage [97].

Beyond these enzymes directly involved in the glycolysis process, there are also some other proteins intimately related to glycolysis, such as hypoxia inducible factor (HIF). As a transcription factor, HIF activates genes encoding key enzymes involved in the glycolytic pathway, including HK2, PFKFB3, PKM2 and LDH [98, 99]. By upregulating these glycolytic proteins, HIF promotes glucose uptake, accelerates glucose breakdown, and enhances lactate production, thereby providing energy for cells in oxygen-deprived environments. This adaptation to hypoxia is particularly evident in cancer cells, where HIF-mediated glycolysis supports tumor growth, invasion, and metastasis [100]. Furthermore, HIF can also directly regulate DDR, with evidence suggesting its involvement in modulating the expression of genes critical for DNA repair mechanisms [101–103]. Here, we will not further summary the roles of these proteins in regulating DNA damage.

Glycolytic intermediate metabolites in regulating DNA damage

Intermediate metabolites generated during glycolysis are also involved in the pentose phosphate pathway (PPP), thereby they can indirectly influence DNA damage through this mechanisms. In the PPP, G6P is converted into 6-phosphogluconolactone, which further leads to the generation of NADPH (nicotinamide adenine

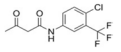
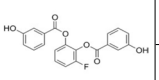
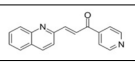
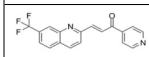
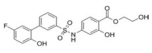
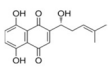
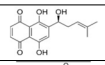
dinucleotide phosphate, reduced form) and ribose-5-phosphate (R5P). NADPH functions as an important antioxidant within cells, maintaining the reduced state of glutathione (GSH) and protecting cells against oxidative stress damage [104], which is one of the triggering factors of DNA damage. GSH functions as a fundamental antioxidant in preserving intracellular redox equilibrium. By eliminating ROS, it safeguards cells against oxidative stress. Moreover, GSH holds a vital position in regulating various modes of cell death during cancer therapy by altering ROS concentrations, underscoring its importance in cellular redox regulation and disease mechanisms. Beyond this mechanism, several studies have also clarified some other mechanisms. Li et al. reported that nuclear F1,6BP directly interacts with HMGB1 (High Mobility Group Box 1), disrupting its association with chromatin and thereby inhibiting HMGB1's ability to support DNA repair processes [105]. Therefore, F1,6BP sensitizes cancer cells to chemotherapy-induced DNA damage, thereby inhibiting tumor growth and enhancing the efficacy of chemotherapeutic agents. The relationship between pyruvate and DNA damage is an area of active research that has uncovered several intriguing connections, and it has been shown to play a role in modulating cellular responses to DNA damage in various ways. In glioblastoma cells, pyruvate facilitates the γ-H2AX loading to chromatin mediated by the FACT complex, therefore promotes the efficient initiation of DNA repair and resulting in the radiation resistance of these cells [77]. Another study showed that pyruvate can act as a precursor for GSH biosynthesis through oxidative metabolism in hepatocellular carcinoma cells, which is an important antioxidant that protects against oxidative stress-induced DNA damage [106]. Meanwhile, pyruvate dehydrogenase 1α (PDHE1α) orchestrates the rapid conversion of pyruvate into acetyl-CoA (acetyl-coenzyme A), a vital step in supporting local chromatin acetylation during the critical phase of DNA damage repair. This enzymatic process fosters the development of relaxed chromatin configurations, thereby enhancing the accessibility of essential repair factors and ultimately facilitating the efficient restoration of DNA integrity [107].

During glycolysis, the key substrate and product directly involved in energy generation are NAD^+ and NADH, respectively. NADH is a critical cofactor in cellular respiration, which functions as an electron carrier, transferring electrons through the electron transport chain, ultimately leading to the production of ATP, the cell's energy currency. Moreover, NADH exists in a reduced state and can reduce intracellular ROS levels, thereby reducing the occurrence of DNA damage. However, there are indications from certain studies that NADH might contribute to the process of DNA damage by mediating oxidative stress [13, 14]. Numerous research endeavors have underscored the pivotal role of NAD^+ in the intricate mechanisms of DNA damage repair, notably by serving as an essential cofactor for PARP enzymatic activity. PARP enzymes employ NAD^+ as their substrate to mediate the attachment of ADP-ribose moieties from NAD^+ onto acceptor proteins, notably histones and chromatin-bound proteins in proximity to DNA lesions. The PARylation process serves as a crucial signaling mechanism, expediting the recruitment of DNA repair proteins to the site of damage and fine-tuning their functional properties, thereby significantly enhancing the overall efficiency and effectiveness of the DNA repair process [108]. Moreover, NAD^+ plays a pivotal role in orchestrating protein–protein interactions vital for DNA repair. Age-related declines in NAD^+ levels have been implicated in the accumulation of DNA damage and the progression of aging [109]. Further researches have shown that restoring NAD^+ levels through supplementation effectively enhances the repair mechanisms of DNA damage incurred by radiation, oxidative stress, as well as the natural aging process [110, 111]. In summary, NAD^+ plays a direct role in DNA repair processes, particularly through PARP-1 activation, while NADH's primary contribution is indirect, through maintaining cellular energy levels essential for DNA repair and other cellular functions.

Tumor therapeutic agents targeting glycolysis cells. Chemotherapeutics such as cisplatin and doxorubicin, and radiation induce and DNA damage

DNA damage is a well-established mechanism to trigger cell death in cancer DNA lesions, activating cellular stress responses that can culminate in apoptosis. Targeting DNA repair pathways, such as PARP inhibitors in BRCA-mutated tumors, further exacerbates DNA damage and enhances therapeutic efficacy. Recently, the exploration of therapeutic agents targeting glycolysis and DNA damage has garnered significant attention in the scientific community, particularly within the realm of oncology research. This approach leverages the unique metabolic features of cancer cells, which often rely heavily on aerobic glycolysis for energy production, alongside targeting DNA integrity, a fundamental aspect of cell survival. Multiple inhibitors of glycolytic enzymes have been investigated, including Glut [112–114], HK2 [115–120], PFK-2 [8, 9, 65, 67], PKM2 [74, 78, 121–123] and LDH [124] (Table 1). These inhibitors have shown promising antitumor effects in preclinical models, demonstrating reduced proliferation and induction of apoptosis in cancer cells.

Table 1 Glycolysis inhibitors targeting DNA damage as potential anti-cancer drugs [8, 9, 65, 67, 74, 78, 112–124]

Name	Targeted enzyme	Structural formula	DNA Damage	Damage Repair	Concentration apply (μM)	Function	Reference
Fasentin	Glut		Not Mention	Not Mention	25	Stimulation of glycolysis by di-nitro phenol conferred resistance to radiation-induced DNA damage and cell death, whereas fasentin mitigated this effect.	112
WZB117			Not Mention	Not Mention	25	A single treatment with WZB117 do not elicit DNA damage, however, when combines with an ATR inhibitor, it synergistically induces DNA damage and apoptosis.	113
			Increase	Arouse HR and NHEJ, possible feedback effect induced by DNA damage	30	MK-2206, a potent allosteric Akt inhibitor, exhibites a synergistic effect with WZB117 in inhibiting growth, inducing DNA damage, and triggering apoptosis in breast cancer cells when combined.	114
2-DG	HK2		Reduce	Reduce	5000	It decreases reactive oxygen species produced by metabolic activity and diminishes the levels of p-ATM and γ-H2AX.	115
			Not Mention	Reduce	5000	At high concentrations, 2-DG inhibits DNA repair and enhances the manifestation of radiation damage. Conversely, low concentrations of 2-DG do not inhibit DNA repair and decrease in the frequency of micronuclei formation.	116
			Increase	Not Mention	700	The combination of metformin and 2-DG enhances DNA damage, DNA adduct formation, intracellular reactive oxygen species levels, alteration of mitochondrial membrane potential, and increases apoptosis.	117
3-Bromopyruvate			Increase	Not Mention	10 μg/mL	It mitigates the hyperactive oxygen metabolism of tumor cells and alleviates tumor hypoxia, ultimately enhancing radiation-induced DNA damage.	118
			Increase	Reduce	4 μg/mL	It enhances DNA damage in radiation therapy and diminishes energy supply while interfering with protein biosynthesis, thereby reducing the capacity for DNA damage repair.	119
			Increase	Reduce	10	It reduces ATP levels by inhibiting glycolysis, thereby inducing DNA damage and impeding DNA repair.	120
PFK-15	PFK-2		Increase	Arouse DNA damage repair, possible feedback effect induced by DNA damage	5	It induces DNA damage, apoptosis and necroptosis cell death.	9
PFK-158			Increase	reduce HR repair	5	It combines with carboplatin or cisplatin, demonstrates strong synergistic antitumor activity. It downregulates the upregulation of RAD51 expression induced by these chemotherapeutics and enhanced the DNA damage.	8
KAN0438757			Increase	reduce HR repair	10	PFKFB3 rapidly translocates to ionizing radiation-induced nuclear foci in a manner dependent on MRN-ATM-γH2AX-MDC1 and co-localizes with proteins involved in DNA damage and HRR.	65
			Increase	Reduce Fanconi Anemia Repair	10	It sensitizes cancer cells to platinum drugs, including treatment-resistant cancer cells by increasing DNA damage and reduce sensitizes cancer cells to platinum drugs.	67
Shikonin	PKM2		Increase	Not Mention	0.3	When combined with NCT-503, it exhibited significant anti-cancer effects by inducing G2/M cell cycle arrest, DNA damage, and apoptosis.	74
			Increase	Reduce	4~8	It increases DNA damage, decreases the expression of BRCA1 and PKM2, and synergizes with olaparib to reduce cell growth, colony formation, and migration, while inducing apoptosis.	78
			Increase	Not Mention	4~10	It induces MLKL activation and chromatinolysis in glioma cells, accompanied by the nuclear translocation of AIF and the presence of γ-H2AX.	121
			Increase	Arouse DNA damage repair, possible feedback effect induced by DNA damage	6	It facilitates the nuclear translocation of AIF and the formation of γ-H2AX, leading to the induction of necroptosis.	122
Alkannin			Increase	Arouse DNA damage repair, possible feedback effect induced by DNA damage	0.75	Sublethal doses of alkannin induce ROS elevation and oxidative DNA damage, and blocking DNA repair with the PARP inhibitor olaparib markedly synergized with alkannin to yield synergistic cytotoxicity	123
Galloflavin	LDH		Not Mention	Not Mention	30	It has no cytotoxicity effect on its own, but it enhances the DNA damage caused by Cisplatin and reduces its repair.	124

The combination of glycolysis inhibitors and DNA damaging agents presents a compelling therapeutic strategy, and their synergistic effects have sparked a surge of interest in exploring the underlying mechanisms and optimizing these combinations for clinical application (Fig. 4). One such advancement lies in the understanding of how glycolysis inhibition modulates the tumor's redox status. Cancer cells often exhibit elevated levels of ROS due to their altered metabolism. Glycolysis inhibitors, by disrupting ATP production and the associated antioxidant defenses, can exacerbate oxidative stress, making cancer cells more susceptible to DNA damage. For instance, studies have shown that PKM2 inhibitor treatment increases intracellular ROS levels, induces DNA damage and ROS-dependent apoptosis [74].

Another emerging area of research focuses on the interaction between glycolysis inhibition and epigenetic modifications. Epigenetic regulators, such as histone deacetylases (HDACs), play crucial roles in maintaining chromatin structure and gene expression. Recent evidence suggests that glycolytic metabolism influences chromatin structure by modulating HDAC activity, either directly through metabolic intermediates or indirectly via changes in HDAC expression and regulation. This crosstalk between metabolism and epigenetics represents a crucial layer of regulation that fine-tunes cellular responses to environmental cues and maintains

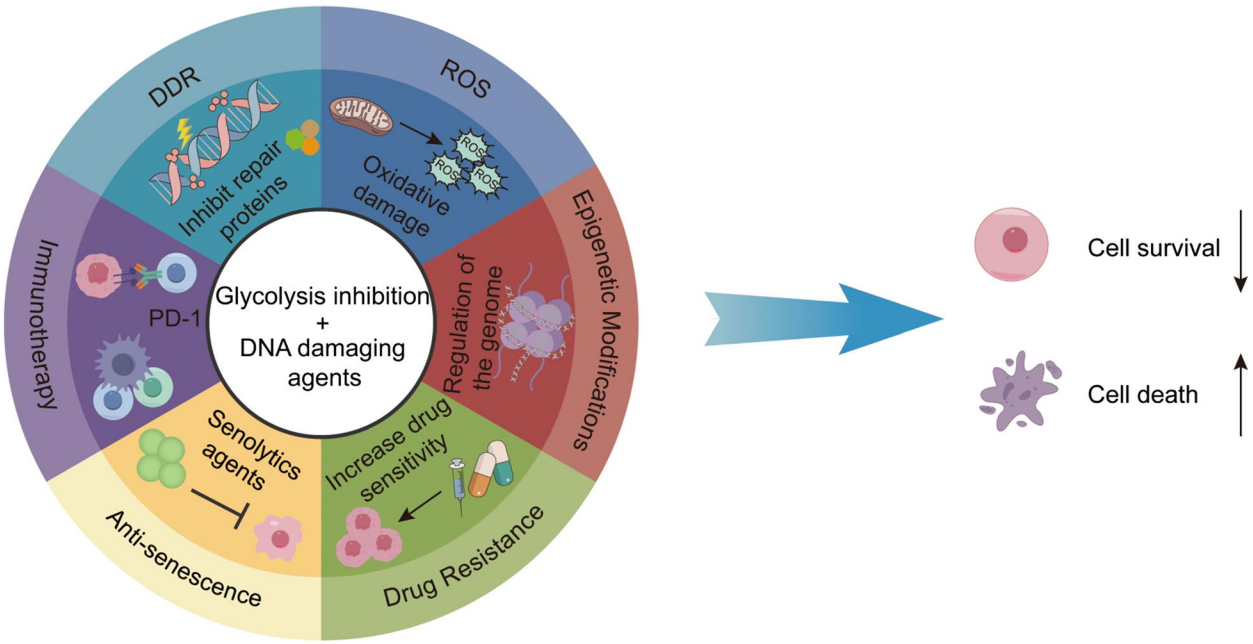


Fig. 4 Mechanism of glycolysis inhibition & DNA damage in tumor therapy. DDR: DNA damage repair; ROS: reactive oxygen species. The combination of glycolysis inhibitors and DNA damaging agents constitutes a highly persuasive therapeutic approach, with their synergistic effects potentially attributed to the following mechanisms: 1) diminishing the efficacy of DDR; 2) elevating intracellular ROS levels; 3) modifying epigenetic patterns; 4) overcoming drug resistance by disrupting survival pathways; 5) resisting cellular senescence mechanisms that promote survival; and 6) enhancing the immune system's capabilities

homeostasis. Inhibiting glycolysis leads to chromatin condensation, hindering DNA repair and enhancing cancer cells' sensitivity to DNA-damaging drugs, suggesting a novel therapeutic strategy for cancer treatment [125].

Moreover, the use of glycolysis inhibitors in combination therapies may help to overcome drug resistance. Cancer cells that develop resistance to DDR inhibitors or other targeted therapies often do so by activating alternative survival pathways, including those related to metabolism. By blocking glycolysis, these alternative pathways may be compromised, restoring sensitivity to the primary therapeutic agent.

Wang et al. reported that exosomal PKM2 may serve as a promising biomarker and therapeutic target for cisplatin resistance in NSCLC cells, and the PKM2 inhibitor significantly reversed the resistance of cisplatin [11]. Chen et al. conclusively demonstrated that the utilization of LDH inhibitors effectively circumvents chemotherapy resistance by diminishing the efficacy of DNA repair mechanisms. Furthermore, they pinpointed the suppression of lactate production as an encouraging and potentially groundbreaking therapeutic approach for cancer management [124, 126]. Gonzalez et al. demonstrated that mannose inhibits tumor growth and potentiates chemotherapy by competing with glucose for uptake, accumulating as mannose-6-phosphate, and disrupting glucose metabolism in glycolysis, TCA cycle, pentose phosphate pathway, and glycan synthesis. Consequently, it alters Bcl-2 protein levels, rendering cells more susceptible to death [127].

In addition, resisting cellular senescence mechanisms that promote survival represents a novel approach in combined therapies targeting glycolysis and DNA damage. During the process of anti-tumor therapy, cells may activate senescence-related pathways to evade death, resulting in surviving senescent cells that can subsequently lead to treatment failure and tumor recurrence [128, 129]. By modulating glycolysis, a metabolic pathway often deregulated in senescent cells, therapies aim to disrupt the senescent metabolic phenotype, which includes reduced glycolysis and increased autophagy [130]. Simultaneously, DNA damage triggers senescence through the activation of p53 and other senescence-associated signaling pathways, leading to cell cycle arrest and the secretion of senescence-associated secretory phenotype (SASP) factors [131]. Therefore, targeting the DNA damage response, which is activated in senescent cells, can synergize with glycolysis inhibition to mitigate the senescent phenotype. The interplay between glycolysis and DNA damage responses in senescence is bidirectional. Senescent cells exhibit altered glycolysis, which can disrupt the energy supply

necessary for DNA repair, further exacerbating DNA damage and senescence [132]. Conversely, DNA damage can also disrupt glycolysis, leading to metabolic stress and the induction of senescence. By targeting both glycolysis and DNA damage responses, combined therapies aim to reprogram cellular metabolism and DNA repair mechanisms to counteract senescence and promote a more favorable therapeutic outcome in cancer [133, 134].

Finally, the integration of immunotherapy into combined therapies targeting glycolysis and DNA damage is a rapidly evolving field. Immune checkpoint inhibitors, such as anti-PD-1 and anti-CTLA-4 antibodies, have revolutionized cancer treatment by unleashing the immune system's ability to recognize and eliminate cancer cells. Recent studies suggest that glycolysis inhibition can enhance the efficacy of immunotherapy by promoting the infiltration and activation of immune cells within the tumor microenvironment [135, 136]. When coupled with immunotherapy, this synergistic effect can result in more potent antitumor immune responses and ultimately yield better patient outcomes. To overcome challenges such as poor bio-availability and nonspecific toxicity, nanoparticle-based delivery systems have emerged as promising carriers for glycolytic inhibitors and DNA damaging agents. These systems can selectively target tumor tissues, enhancing drug accumulation and reducing off-target effects. For example, polymeric nanoparticles encapsulating 2-DG and doxorubicin have demonstrated enhanced antitumor efficacy in breast cancer [137].

The clinical translation of these combinatorial strategies is actively ongoing, with several promising trials underway. Researchers are exploring various combinations, including glycolysis inhibitors with PARP inhibitors, ATR inhibitors, as well as with standard-of-care chemotherapeutics and radiation. The goal is to identify the most effective and tolerable combinations that can improve patient outcomes and prolong survival. Combination therapies targeting glycolysis and DNA damage pathways offer promising potential to improve treatment outcomes for cancer patients, especially those with resistant or advanced disease. However, further research is needed to optimize dosing schedules, identify predictive biomarkers, and rigorously assess long-term safety and efficacy in clinical trials. The success of these strategies depends on factors such as agent selectivity and potency, timing and sequence of administration, and the specific genetic and metabolic profiles of the cancer. Consequently, a personalized approach to therapy, guided by biomarkers and patient-specific data, is crucial for optimizing these combinatorial strategies and maximizing their clinical benefit.

Prospection

Looking forward, the exploration of the intricate interplay between glycolysis enzymes and metabolites in regulating DNA damage repair represents a promising frontier in tumor therapy. Not only does this relationship govern the cell's ability to repair DNA damage, but DNA damage itself can significantly impact glycolysis, altering the metabolic pathway within cells. By unraveling the intricate molecular mechanisms that orchestrate this bidirectional crosstalk, we can harness this knowledge to develop novel therapeutic strategies that selectively target cancer cells. Future research endeavors should be towards the identification and development of drugs or therapeutic strategies that concurrently target both glycolysis and DNA damage, aiming to achieve a dual-pronged attack on cancer cells. By strategically inhibiting or modulating the activity of these regulators, we aspire to sensitize cancer cells to the effects of DNA-damaging agents, thereby amplifying therapeutic efficacy. This approach could simultaneously disrupt the cancer cell's ability to adapt its glycolytic machinery in response to DNA damage, further compromising its survival. By exploiting this bidirectional relationship, we aspire to amplify therapeutic efficacy while minimizing detrimental impacts on healthy tissues. Moreover, the discovery of predictive biomarkers that correlate with the activity of these glycolytic regulators, as well as their response to DNA damage, could revolutionize personalized medicine. These biomarkers would enable us to tailor therapies not only to the unique characteristics of individual tumors but also to their dynamic responses to DNA damage, ensuring patients receive the most appropriate and effective treatments. As our comprehension of this intricate network deepens, we will gain a more comprehensive understanding of how DNA damage and glycolysis are intertwined, enhancing our ability to harness this knowledge for the benefit of cancer patients. In conclusion, targeting glycolysis and DNA damage in cancer therapy represents a dual-pronged approach with significant therapeutic potential. The combination of these strategies, facilitated by advanced drug delivery systems, holds the key to overcoming treatment resistance and improving clinical outcomes. Ongoing research into the molecular mechanisms underlying these interactions and the development of novel agents will continue to propel this field forward, ushering in a new era of precision oncology.

Conclusion

The interplay between glycolysis and DDR in cancer progression and therapy resistance is summarized. Glycolysis, which is crucial for tumor cell energy production and

proliferation, exhibits a significant correlation with DDR, which is essential for maintaining genomic stability. The review highlights how glycolysis enzymes and metabolites regulate DDR, suggesting a synergistic role in tumor growth. It discusses therapeutic approaches targeting glycolysis and DDR to overcome treatment resistance. By presenting current research status and limitations, the study aims to spur further investigation into these processes. Understanding their interactions is crucial for advancing effective cancer treatment strategies, highlighting their pivotal roles in cancer biology and therapy.

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Authors' contributions
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Data availability
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Declarations

Ethics approval and consent to participate
Not applicable.

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Competing interests
The authors declare no competing interests.

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