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Review Article

Exploiting replication stress for synthetic lethality in MYC-driven cancers

Yuan Zhang[1,2*], Meng Ye[1,2*], Xin Luan[1,2#], Zhe Sun[2#], Wei-Dong Zhang[1,3#]

[1]School of Pharmacy, Guangdong Pharmaceutical University, Guangzhou 510006, Guangdong, China; [2]Institute of Interdisciplinary Integrative Medicine Research, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China; [3]School of Pharmacy, Second Military Medical University, Shanghai 200433, China. [*]Equal contributors. [#]Co-corresponding authors.

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Abstract: The oncoprotein MYC, overexpressed in more than 70% of human cancers, plays a pivotal role in regulating gene transcription and has long been recognized as a promising target for cancer therapy. However, no MYC-targeted drug has been approved for clinical use, largely due to the lack of a well-defined druggable domain and its nuclear localization. MYC-overexpressing cancer cells exhibit increased replication stress, driven by factors such as elevated replication origin firing, nucleotide depletion, replication-transcription conflicts, and heightened reactive oxygen species (ROS) production. Simultaneously, MYC activates compensatory mechanisms, including enhanced DNA repair, checkpoint-mediated cell cycle regulation, and metabolic reprogramming, to mitigate this stress and support cell survival. Interfering with these compensatory pathways exacerbates replication stress, leading to synthetic lethality in MYC-driven cancer cells. In this review, we summarize recent advances in leveraging replication stress to achieve synthetic lethality in MYC-driven cancers. Furthermore, we discuss current strategies targeting replication stress, highlighting new opportunities for the development of therapies against MYC-driven malignancies.

Keywords: MYC, synthetic lethality, DNA replication stress

Introduction

MYC is an attractive yet undruggable target in cancer therapy

The oncoprotein MYC, overexpressed in over 70% of human cancers, serves as a key regulator of gene transcription and is a powerful driver of malignant transformation [1]. In non-malignant cells, MYC protein level is tightly controlled by various mechanisms to ensure proper cellular functions [2]. However, in many human cancers, these regulatory mechanisms are often dysregulated, leading to the upregulation of MYC [1]. This results in the uncontrolled cell proliferation and tumorigenesis. The dysregulation of MYC is primarily attributed to the following reasons: 1) Genetic amplification: This is a common mechanism for MYC activation in many solid tumors. The MYC gene is most frequently amplified in ovarian cancer (64%), esophageal cancer (45.3%), squamous cell lung cancer (37.2%), and breast cancer (30%) [3]; 2) Gene translocation: MYC gene translocation is predominantly present in hematological malignancies. In Burkitt lymphoma, MYC gene is moved next to the immunoglobulin gene locus, leading to its overexpression and contributing to cancer development. Besides the predominant immunoglobulin gene locus translocation (80%), MYC gene can also translocate to the kappa light chain locus (15%) or to the lambda light chain locus (5%) to promote cancer development [4]; 3) Altered signaling pathways: Activating mutations in signaling pathways like WNT-β-catenin, RAS, and PI3K can regulate MYC expression and stability [5-8] (**Figure 1**).

The oncogenic potential of MYC has been demonstrated through various mouse tumor models. Tissue-specific MYC overexpression driven by transgenic constructs with distinct regulatory elements represents one of the most thoroughly studied transgenic models of malignancy. For example, in the Eμ-Myc mouse model,

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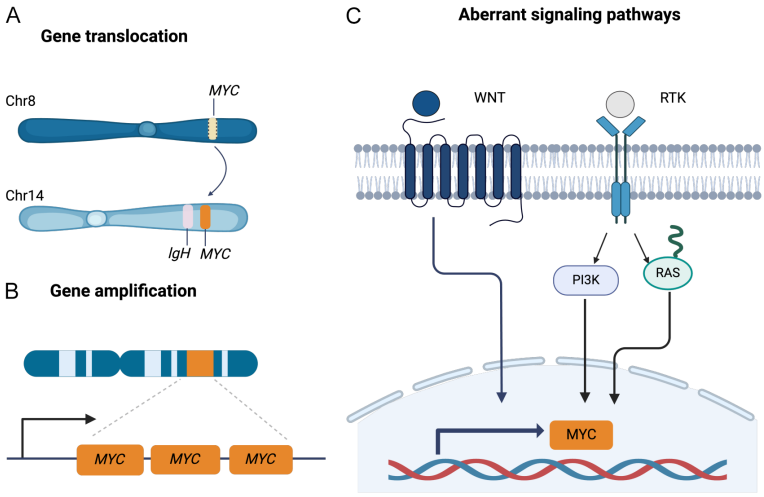

Figure 1. Mechanisms of MYC Dysregulation in Human Cancers. A. Gene Translocation: For example, the MYCgene translocases from chr8 to the IgH on chr14, thereby enhancing MYC expression. B. Gene Amplification: Amplification of the MYC gene leads to a significant increase in its expression. C. Aberrant Signaling Pathways: Activating mutations in upstream regulatory pathways, such as WNT/β-catenin, RAS, and PI3K, can regulate MYC transcription levels and protein stability, resulting in the overexpression of the MYC oncogene. Abbreviations: chr8, chromosome 8; chr14, chromosome 14; IgH, immunoglobulin heavy chain; WNT, Wingless-type MMTV integration site; RAS, rat sarcoma viral oncogene; PI3K, phosphatidylinositol 3-kinase; RTK, receptor tyrosine kinase.

MYC overexpression in B cells under the control of the immunoglobulin heavy chain enhancer leads to B-cell lymphoma, mimicking human Burkitt lymphoma [9]. Similarly, in the MMTV-Myc model, MYC overexpression driven by the MMTV promoter leads to mammary tumors, providing a model for breast cancer studies [10]. In the Probasin-Myc model, MYC overexpression in the prostate under the probasin promoter induces prostate cancer [11]. Conversely, the silence of MYC expression can significantly inhibit tumor growth and even induce tumor regression. For instance, in Tet-off MYC models of liver cancer and osteosarcoma, MYC silencing has been shown to trigger tumor regression and promote differentiation [12, 13]. In an APC-deficient model of intestinal tumors, intestine-specific MYC knockout markedly suppresses tumorigenesis in the small intestine [14]. Therefore, targeting MYC is an attractive therapeutic intervention for cancer therapy.

Despite the potential of targeting MYC, several conceptual and practical challenges have resulted in its classification as "undruggable" [15]. These challenges include the absence of well-defined binding pockets within MYC proteins and concerns about possible "on-target" toxicity affecting normal tissues [16]. The latter concern has been somewhat mitigated by sophisticated in vivo genetic modeling studies utilizing the dominant negative MYC peptide Omomyc, which has demonstrated the possibility of a therapeutic window for targeting MYC effectively [17]. These observations are further supported by the identification of the small molecule MYCi975, which disrupts the formation of MYC/MAX dimers and has shown good tolerability in vivo [18]. In addition to disrupting MYC/MAX dimer formation, various alternative strategies have been explored to address the challenges of targeting MYC. These approaches generally fall into five categories: 1) inhibiting MYC transcription, 2) blocking MYC mRNA translation, 3) destabilizing MYC protein, and 4) limiting MYC's access to its downstream gene targets. These strategies have been thoroughly reviewed in other articles [19]. Beyond these approaches, synthetic lethality-based strategies for treating MYC-driven cancers have gained increasing attention in recent years, offering promising avenues for therapeutic development.

Leveraging synthetic lethality to target MYC

The concept of synthetic lethality (SL) originally arose from studies in Drosophila [20, 21] and yeast [22, 23] models. It was first described in Drosophila as a recessive lethal phenomenon [21], classically defined as: the inactivation of either one of two genes alone has little effect on cell viability, but simultaneous inactivation of both genes leads to cell death (**Figure 2**). Approximately twenty years ago, Hartwell first proposed that synthetic lethal interactions could be exploited to identify new anticancer drug targets [24]. Hartwell and his successor Kaelin further suggested that applying the concept of synthetic lethality could lead to the discovery of new targets for cancer therapy, wherein one member of the synthetic lethal pair is a gene product with a cancer-specific mutation,

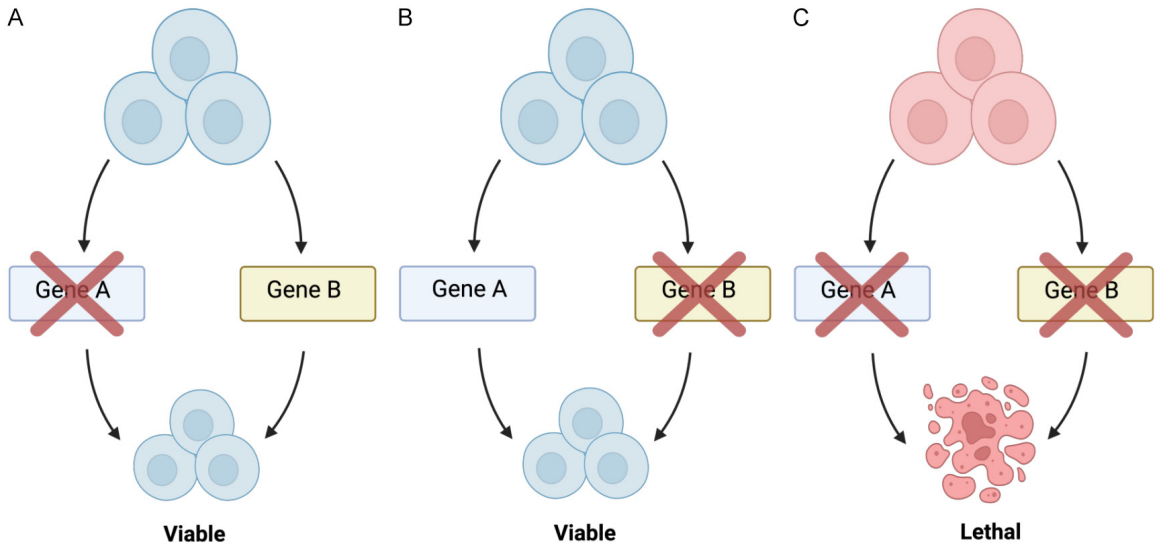

Figure 2. The concept of synthetic lethality. The inhibition or loss of either gene A or gene B alone is viable (A and B), but the simultaneous inhibition or loss of both genes is lethal (C). The red cross symbol in the figure represents inhibition or loss.

and the other member is a potential drug target [25].

The most classic example of a synthetic lethal gene pair is the inhibition of poly (ADP-ribose) polymerase (PARP) in BRCA-deficient tumors. PARP is an enzyme involved in the repair of single-strand breaks (SSBs) in DNA via the base excision repair (BER) pathway [26]. Breast Cancer Gene 1 (BRCA1) and Breast Cancer Gene 2 (BRCA2) are key players in the homologous recombination (HR) repair pathway, which repairs double-strand breaks (DSBs) in DNA [27, 28]. In cells with functional BRCA, these DSBs would normally be repaired by HR. However, in BRCA-mutant cells, HR repair is compromised, leaving the cells unable to fix the DSBs created by PARP inhibition [29]. The accumulation of unrepaired DSBs ultimately leads to genomic instability, cell cycle arrest, and cell death. PARP inhibitors have been approved for the treatment of BRCA-mutated ovarian, breast, and pancreatic cancers, becoming the first clinically applied synthetic lethality-targeted therapies [30].

In MYC-driven cancers, two primary categories of vulnerabilities have been identified. The first encompasses mechanisms that directly regulate MYC, including proteins involved in controlling MYC expression, stability, and functional activity [31-33]. The second category includes downstream pathways activated by MYC, which play MYC essential roles in driving tumorigenesis and sustaining rapid cancer cell proliferation [34, 35]. Activation of these pathways imposes various cellular stresses on the cancer cells, such as metabolic strain, replication stress, and proteotoxicity [33, 36, 37]. To adapt and survive, cancer cells trigger specific stress response mechanisms that counteract these MYC-induced stresses, thereby maintaining cellular viability and promoting tumor progression [33, 38]. These stress response pathways create potential therapeutic vulnerabilities in MYC-driven cancers, presenting promising targets for the development of novel synthetic lethal strategies. Among the various stresses triggered by MYC, DNA replication stress is particularly prominent. It manifests as replication fork stalling, accumulation of DNA damage, and genomic instability, which are critical consequences of MYC overexpression and offer potential avenues for therapeutic intervention [39]. In this review, we will outline recent progress in utilizing replication stress to achieve synthetic lethality in MYC-driven cancer cells. Additionally, we will discuss current strategies targeting replication stress, aiming to present new opportunities for the treatment of MYC-related cancers.

MYC-induced replication stress: mechanisms, consequences, and cellular responses

The mechanisms

MYC overexpression induces replication stress through several interconnected mechanisms related to its ability to drive aggressive cell pro-

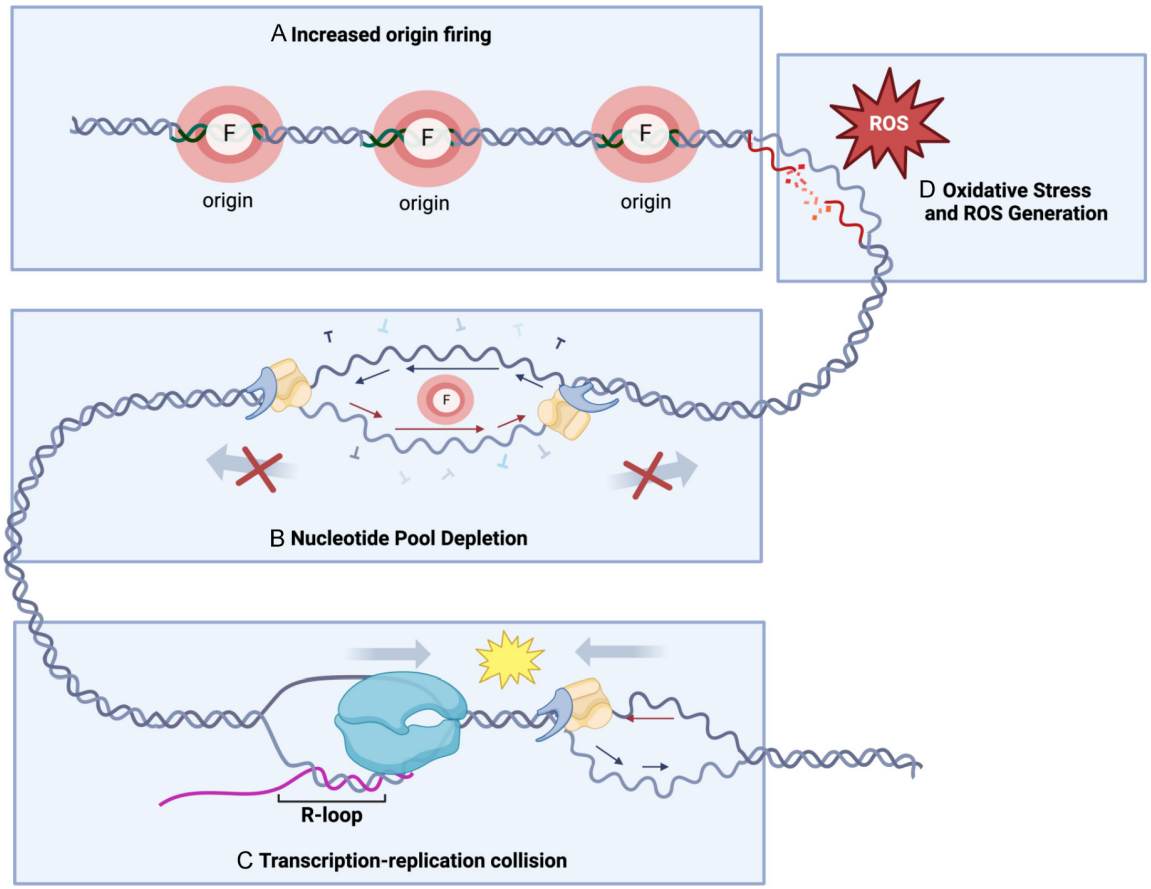

Figure 3. Mechanisms of MYC-induced replication stress. Replication stress arises from both endogenous and exogenous obstacles that affect DNA replication. A. Increased activation of replication origins, caused by the activation of the MYC oncogene. B. Nucleotide pool depletion, insufficient nucleotide supply caused by the excessive replication demands driven by MYC, leading to uncontrolled S-phase entry in the context of nucleotide pool depletion, which may impair DNA replication and block replication fork progression. C. Collisions between replication and transcription, which hinder DNA replication progression by generating DNA topological stress and forming persistent R-loops. D. Oxidative stress and ROS production, resulting from the metabolic reprogramming induced by MYC, leading to elevated ROS that damage DNA double strands. A-D. These figures illustrate the DNA molecule (blue strand), replication origins (indicated by pink circles labeled with the letter F and the green strand), DNA double-strand breaks (red strand), and replication forks consisting of helicase enzymes (blue) and polymerase enzymes (yellow). RNA polymerase is depicted in green, and newly synthesized RNA molecules are shown as purple strands. For simplicity, the pre-replicative complex and replication bodies are omitted. Red arrows indicate the direction of continuous DNA synthesis on the leading strand, while blue arrows represent the direction of discontinuous DNA synthesis on the lagging strand. Red crosses denote interference with DNA replication.

liferation and deregulate key cellular processes (**Figure 3**). These mechanisms include the following.

Increased replication origin firing: MYC overexpression drives the activation of a greater number of replication origins, even during S phase, as a strategy to sustain rapid DNA synthesis and cell proliferation [40]. It has been shown that MYC is not only a transcription factor but also directly involved in the regulation of DNA replication. Specifically, MYC interacts with the pre-replicative complex and localizes to early sites of DNA synthesis, contributing to the activation of replication origins [41] (**Figure 3A**). By increasing the number of replication initiation sites, MYC ensures that sufficient genomic material is replicated within a shorter time frame, supporting the high proliferation demands of MYC-driven cancer cells. However, this excessive origin firing places strain on the replication machinery by increasing competition for essential replication factors and limiting the availability of nucleotide pools [42]. The consequence is

often stalled or collapsed replication forks, as the replication process becomes less efficient and prone to errors under such stress. Stalled forks can lead to DNA breaks if not properly resolved, thereby introducing DNA damage and further exacerbating replication stress within the cell [43].

Nucleotide pool depletion: MYC activates the transcription of genes involved in nucleotide biosynthesis to meet the demand for rapid DNA synthesis in highly proliferative cells [44]. This activation includes pathways such as purine and pyrimidine synthesis [45], which are essential for supplying the building blocks for DNA replication. However, even with enhanced nucleotide biosynthesis, the demand induced by MYC overexpression can outstrip the cell's capacity to maintain adequate nucleotide levels. When nucleotide pools become insufficient, DNA replication slows, resulting in stalled replication forks as the replication machinery waits for the supply to catch up [46] (**Figure 3B**). These stalled forks are highly susceptible to collapse if unresolved, which can lead to double strand breaks and chromosomal instability.

Collisions between replication and transcription: MYC-driven cells often have elevated transcriptional activity [47], especially for genes involved in growth and proliferation. This elevated transcription enhances cell growth but also increases the likelihood of replication-transcription collisions. When replication and transcription machinery operate simultaneously on the same DNA template, the risk of collisions rises significantly, particularly in regions of high transcriptional activity [48] (**Figure 3C**). These collisions hinder the progress of the replication fork, creating physical obstacles that can stall the replication machinery and induce fork collapse [49]. Such replication-transcription conflicts are recognized as potent sources of replication stress, as the stalled forks often fail to resume proper replication, leading to DNA damage and genomic instability.

Oxidative stress and ROS generation: MYC-induced metabolic reprogramming shifts cellular metabolism toward increased glycolysis and mitochondrial respiration [38], both of which are major sources of reactive oxygen species (ROS) [50]. Elevated ROS levels can damage cellular macromolecules, including DNA [51] (**Figure 3D**). Oxidative damage to DNA disrupts the stability and progression of replication forks, as oxidized bases and DNA strand breaks interfere with the continuity of DNA synthesis [52]. This oxidative stress exacerbates replication stress by making replication forks more prone to stalling and collapse. Furthermore, persistent oxidative damage can overwhelm the DNA repair systems, particularly in MYC-overexpressing cells that may have already compromised repair capacities, leading to cumulative genomic instability [53].

The consequences, and cellular responses

Although unrestricted activation of MYC can induce intense replication stress, cells cope with MYC-induced replication stress through several key stress response mechanisms. These pathways work to stabilize replication forks, repair DNA damage, and allow cells to complete replication and survive despite high levels of stress.

Activation of the ATR-CHK1 pathway: The ataxia telangiectasia and Rad3-related protein (ATR)/checkpoint kinase 1 (CHK1) pathway plays a central role in the replication stress response, which is triggered by the formation of single-stranded DNA (ssDNA) during replication stress or DNA repair [54]. ATR kinase is recruited to ssDNA sites by ATR-interacting protein (ATRIP) and is activated with the assistance of cofactors such as claspin and topoisomerase II binding protein 1 (TopBP1) [55]. Activated ATR initiates downstream signaling by activating CHK1, which transduces DNA damage response (DDR) signals to facilitate various effector functions, including activation of S phase and G2 phase checkpoints, regulation of replication fork progression, nucleotide synthesis, and antiapoptotic signaling [56-58]. In MYC-dependent tumor cells, persistent replication stress continuously activates the ATR/CHK1 pathway, thereby preventing catastrophic genomic instability [41]. This pathway stabilizes stalled replication forks, supports their restart, and enforces cell cycle checkpoints to allow time for repair [54]. When replication forks stall due to replication stress, ssDNA accumulates and becomes coated with replication protein A (RPA), creating a platform for the recruitment of DDR responders such as ATR and CHK1 [59]. This recruitment activates signaling pathways that lead to cell cycle arrest, stabilization or resolution of stalled forks, and the eventual restart of DNA replication [60].

Enhanced DNA damage repair (DDR) pathways: MYC-overexpressing cells exhibit upregulation of DNA damage repair pathways, including homologous recombination (HR) and non-homologous end joining (NHEJ), to efficiently repair double-strand breaks (DSBs) arising from replication fork collapse [61]. MYC directly regulates the expression of multiple DSB repair genes by binding to their promoter regions, as demonstrated by Luoto et al. These genes include *RAD51, RAD51B, RAD51C, XRCC2, RAD50, BRCA1, BRCA2, DNA-PKcs, XRCC4, Ku70,* and *DNA ligase IV* [62]. By enhancing the transcription of these key repair factors, MYC strengthens the DDR and promotes genomic stability in cancer cells. Conversely, inhibition of MYC expression leads to reduced levels of ataxia-telangiectasia mutated (ATM) and DNA-dependent Protein Kinase, Catalytic Subunit (DNA-PKcs), which diminishes DSB repair capacity [63].

Upregulation of nucleotide biosynthesis: MYC overexpression promotes nucleotide biosynthesis by upregulating key enzymes across multiple metabolic pathways, including the folate cycle and pentose phosphate pathway (PPP) [31]. In the folate cycle, MYC enhances the expression of enzymes that generate one-carbon units, which are essential for purine and thymidine synthesis [64]. These one-carbon units facilitate the production of nucleotides, directly supporting DNA and RNA synthesis [65]. Meanwhile, MYC also activates the PPP, which provides ribose-5-phosphate, a precursor for nucleotide synthesis, as well as nicotinamide adenine dinucleotide phosphate (NADPH), which is essential for redox balance and biosynthetic reactions [66, 67]. The concerted upregulation of these pathways leads to increased deoxynucleotide triphosphate (dNTP) pools, enabling MYC-driven cells to sustain high rates of DNA synthesis, meet the demands of rapid cell division, and alleviate replication stress [68]. This increased supply of nucleotides helps to avoid replication fork stalling and DNA damage, thereby supporting genomic integrity and cellular proliferation [69]. Through these adaptations, MYC-overexpressing cells maintain a continuous supply of nucleotides, supporting their aggressive growth and survival.

Upregulation of WRN helicase: The Werner Syndrome RecQ-like Helicase (WRN) protein, which is often upregulated in MYC-overexpressing cells, helps resolve unusual DNA structures, such as G-quadruplexes and other secondary structures that can form in regions of high transcription and replication stress [70, 71]. WRN stabilizes stalled replication forks and promotes fork restart, reducing the likelihood of fork collapse and subsequent DNA damage. By facilitating the resolution of these structures, WRN supports continuous DNA replication and limits the accumulation of DNA damage [72]. MYC transcriptionally regulates WRN, suggesting a positive feedback mechanism that provides additional protection against topological stress during S phase by increasing WRN helicase expression levels, thus promoting efficient cell proliferation [71].

Reactive oxygen species (ROS) detoxification mechanisms: MYC-driven metabolic reprogramming leads to elevated reactive oxygen species (ROS) levels [31, 73], a byproduct of enhanced mitochondrial activity and metabolic flux [74]. While ROS can drive DNA damage and contribute to genomic instability, MYC-overexpressing cells adapt by activating several antioxidant pathways to neutralize excess ROS. One major pathway involves the synthesis of glutathione (GSH), a key intracellular antioxidant that detoxifies ROS and protects against oxidative damage [75]. MYC-driven cancers often increase the expression of enzymes involved in GSH biosynthesis, such as glutamate-cysteine ligase, to maintain a robust antioxidant defense [76]. Additionally, MYC-overexpressing cells can activate the Nuclear Factor (erythroid-derived 2)-like 2 (NRF2) pathway [77], which regulates the expression of various antioxidant genes, including those involved in NADPH production [78]. NADPH serves as a crucial reducing agent for regenerating, thereby sustaining antioxidant capacity [79]. Through these adaptive mechanisms, MYC-overexpressing cells mitigate ROS-induced damage, maintain redox balance, and support their high proliferative and metabolic demands.

Exploiting replication stress to target MYC-driven cancer

Exploiting replication stress provides a powerful approach to selectively target MYC-driven cancers. Overexpression of MYC increases DNA replication demand, thereby heightening the likelihood of transcription-replication conflicts and placing substantial strain on the replication machinery. This frequently leads to replica-

tion fork stalling and genomic instability. To maintain genome integrity and survival, MYC-overexpressing tumor cells engage multiple compensatory pathways: they enhance DNA repair mechanisms to resolve DNA damage, finely regulate cell cycle checkpoints to prevent catastrophic errors, alleviate transcription-replication conflicts to maintain replication fork progression, and upregulate nucleotide biosynthesis to replenish the nucleotide pools depleted by excessive replication demands. In addition, these cells also adapt their metabolic environment and manage reactive ROS levels, indirectly influencing replication fidelity and cellular viability. Disrupting any of these supportive systems can tip the balance towards catastrophic replication failure and cell death. As summarized in **Table 1**, key vulnerabilities directly linked to replication stress - such as DNA repair factors, cell cycle checkpoint regulators, transcription-replication conflict modulators, and nucleotide synthesis enzymes - offer strategic points of intervention to intensify replication stress and selectively eliminate MYC-driven tumor cells.

Targeting DNA repair machinery

When MYC-overexpressing tumor cells face replication stress, replication fork stability and DNA repair mechanisms become crucial defenses. These tumor cells rely on multiple DNA repair pathways to cope with the DNA damage caused by excessive replication pressure. Therefore, targeting these repair mechanisms can selectively kill MYC-driven tumor cells through synthetic lethality.

The *WRN* gene encodes the Werner Syndrome RecQ-like Helicase (WRN) protein, a member of the RecQ family DNA helicases that resolves topologically unfavorable DNA structures arising during the S phase [70]. By alleviating replication stress, WRN prevents the accumulation of DNA damage in MYC-overexpressing cells. In contrast, loss of WRN function in these cells leads to increased DNA damage at sites of active replication, making WRN a critical vulnerability [71]. This concept has been validated in vivo: in tissue-specific transgenic mice expressing MYC in B lymphocytes, loss-of-function mutations in WRN significantly delayed tumorigenesis. Similarly, in xenograft models of human cancer cell lines with high MYC expression, silencing WRN led to pronounced growth inhibition [80]. These findings highlight WRN as a potential therapeutic target for MYC-driven tumors.

The failure of replication fork protection mechanisms in MYC-overexpressing tumors exacerbates replication stress, which can lead to the accumulation of DNA damage, including single-stranded DNA (ssDNA) and double-strand breaks (DSBs) [81]. Replication fork stalling, often triggered by replication stress, activates the ATR-CHK1 signaling pathway to stabilize the fork and facilitate repair of ssDNA damage [43]. However, when replication forks collapse, they can cause more severe DNA damage, such as double-strand breaks, which require alternative repair mechanisms, including homologous recombination (HR) and non-homologous end joining (NHEJ) [82]. As MYC-driven cancer cells become heavily reliant on these DNA repair pathways to cope with both ssDNA and DSBs, disrupting these repair mechanisms creates critical vulnerabilities. Targeting these repair pathways can selectively impair the survival of MYC-driven tumors, exploiting their dependence on efficient DNA repair under replication stress.

The ATR-CHK1 pathway serves as a critical responder to replication stress and single-strand DNA (ssDNA) damage in MYC-overexpressing tumors. By stabilizing replication forks and activating the DNA damage response, ATR-CHK1 mitigates the effects of excessive replication stress and maintains genomic stability [41]. Inhibiting the ATR-CHK1 pathway exacerbates DNA damage and replication stress, ultimately leading to selective cell death in MYC-driven tumors [83]. Studies have demonstrated that MYC-driven tumors exhibit high sensitivity to ATR and CHK1 inhibitors [84-87]. For instance, in mouse models of ATR-Seckel syndrome, reduced ATR expression completely suppressed the development of MYC-driven lymphomas and pancreatic tumors induced by replication stress [84]. Similarly, targeted inhibition of CHK1 using RNA interference or small-molecule inhibitors successfully induced apoptosis in MYC-overexpressing B-cell lymphoma models both in vitro and in vivo [85, 86]. In neuroblastomas with MYCN amplification, sustained CHK1 activation is closely associated with tumor sensitivity to CHK1 inhibitors [87]. CHK1 inhibitors disrupt replication fork progression, induce S-phase apoptosis, and further validate

Table 1. Key vulnerabilities and therapeutic targets for exploiting replication stress in MYC-driven tumors

Target/Pathway	Mechanism of Action	Main phase	Vulnerability in MYC-driven Cells	Reference
DNA repair factors				
WRN	Resolves replication stress-induced DNA structures	S-phase	Inhibition increases DNA damage and replication stress	[71, 80]
ATR-CHK1	Stabilizes replication forks, repairs ssDNA damage	Replication stress	Inhibition destabilizes replication forks and exacerbates DNA damage	[84-87]
DNA-PKcs	Repairs DSBs via NHEJ	DSB repair	Inhibition blocks DSB repair and causes genomic instability	[88]
RAD51	Promotes HR-mediated DSB repair	S/G2-phase	Inhibition disrupts HR repair and intensifies replication stress	[90, 95]
Sam68 (with RAD51)	Regulates PARP activity	DNA damage response	Inhibition impairs DNA repair and PARP activity	[91]
Cell cycle checkpoint regulators				
CHK1/WEE1	CHK1 stabilizes replication forks; WEE1 regulates G2/M transition	S-phase, G2/M checkpoint	Disruption of replication checkpoints increases DNA damage	[100]
Aurora A/B	Regulate spindle formation, centrosome function, and cytokinesis	M-phase (mitosis)	Impairment of mitotic processes causes chromosomal instability	[104]
TPX2	Mediates spindle assembly and ensures accurate chromosome segregation	M-phase (mitosis)	Loss of function disrupts spindle integrity and mitotic progression	[106]
SUMOylation (SAE1/2)	Modulates protein stability and activity under replication stress	Entire cell cycle	Destabilization of cell cycle regulators and repair proteins	[111]
Transcription-Replication Conflict Modulators				
Exosome complex	Maintains transcription elongation and resolves transcription-replication conflicts	S-phase	Inhibition disrupts transcription elongation and replication fork progression	[114]
TOP1	Resolves DNA supercoiling stress and regulates R-loop formation	S-phase	Inhibition increases R-loop accumulation and replication stress	[115]
CDK12	Regulates transcription and DNA repair, preventing DSBs from conflicts	S-phase, DNA damage response	Loss or inhibition increases transcription-replication conflicts and genomic instability	[116]
Nucleotide synthesis enzymes				
PRPS2	Catalyzes the production of PRPP, essential for purine synthesis	S-phase	Loss reduces nucleotide synthesis, impairing proliferation	[119]
IMPDH1/2	Catalyzes the rate-limiting step in guanine nucleotide synthesis	S-phase	Inhibition blocks proliferation, induces S-phase arrest	[44]
CTPS1	Catalyzes CTP synthesis, supports DNA replication and repair	S-phase	Inhibition causes nucleotide shortage and replication stress	[120]

Abbreviations: WRN, Werner Syndrome RecQ-like Helicase; ATR/CHK1, ataxia telangiectasia and Rad3-related protein/checkpoint kinase 1; DNA-PKcs, DNA-dependent Protein Kinase, Catalytic Subunit; RAD51, RAD51 recombinase; Sam68, Src-associated in mitosis, 68 kDa; CHK1/WEE1, checkpoint kinase 1/WEE1 G2 checkpoint kinase; TPX2, Targeting Protein for Xklp2; SAE1/2, SUMO-activating enzyme subunit 1/2; Top1, Topoisomerase 1; CDK12, cyclin-dependent kinase 12; PRPS2, phosphoribosyl pyrophosphate synthetase 2; IMPDH1/2, inosine monophosphate dehydrogenase1/2; CTPS1, CTP synthase 1; ssDNA, single-stranded DNA; DSBs, double-strand breaks; HR, homologous recombination; NHEJ, non-homologous end joining; PARP, poly(ADP-ribose) polymerase; PRPP, phosphoribosyl pyrophosphate; CTP, cytidine triphosphate.

the therapeutic potential of targeting the ATR-CHK1 pathway.

Double-strand break (DSB) repair mechanisms, such as homologous recombination repair (HR) and non-homologous end joining (NHEJ), are essential for the survival of MYC-driven cancer cells, which face substantial genomic instability caused by replication stress [39]. Targeting these repair pathways presents a promising therapeutic strategy to induce synthetic lethality in MYC-overexpressing tumors. MYC overexpression induces significant DSBs, forcing tumor cells to rely heavily on HR and NHEJ for genome stability [88-91]. DNA-PKcs is a critical component of the NHEJ pathway, which repairs DSBs in a rapid but error-prone manner [92]. Inhibiting DNA-PKcs not only impairs NHEJ repair but also significantly reduces the efficiency of DSB repair and somatic recombination. Studies have shown that targeting DNA-PKcs decreases the viability of MYC-overexpressing small cell lung cancer cells, demonstrating its therapeutic potential [88]. Homologous recombination repair (HR) is a high-fidelity mechanism for repairing DSBs and is heavily dependent on RAD51 recombinase (RAD51) [93]. RAD51 is frequently overexpressed in various cancers and plays a critical role in homologous recombination repair, particularly during mitosis, where it responds to increased replication stress [94]. In triple-negative breast cancers (TNBC) with MYC amplification, RAD51 is upregulated, making these cells highly dependent on HR for survival [95]. Due to increased replication stress and DNA damage, these cells are highly dependent on RAD51-mediated homologous recombination repair (HR), making them more susceptible to disruptions in DNA repair pathways [96]. Combining MYC inhibition with PARP inhibitors resulted in a synthetic lethality effect in MYC-driven TNBC cells [90].

Furthermore, combining RAD51 inhibition with targeting other DNA repair proteins, such as Sam68, offers additional therapeutic potential for MYC-driven cancers [91]. Sam68 (Src-associated in mitosis, 68 kDa) is an RNA-binding protein that plays a critical role in regulating RNA splicing and DNA damage repair [97]. In stem cell-like cancer cells, high MYC expression relies on Sam68 to maintain efficient DNA repair. Inhibiting Sam68 disrupts PARP poly (ADP-ribosylation), leading to cell death [91]. However, cancer cells partially counteract Sam-68 inhibition by upregulating RAD51. Therefore, the dual inhibition of Sam68 and RAD51 further impairs DNA repair and significantly reduces cancer cell viability. This approach highlights the potential of combining multiple DNA repair pathway targets as a therapeutic strategy to exploit the vulnerabilities of MYC-driven cancers.

Targeting cell cycle regulation

MYC-driven tumors exhibit enhanced dependency on cell cycle regulation due to their high replication stress and genomic instability. Targeting key regulatory nodes in the cell cycle, such as replication checkpoints (e.g., CHK1/WEE1), mitotic regulators (e.g., Aurora A/B and TPX2), and the SUMOylation pathway involved in protein dynamics, can effectively exacerbate replication stress and induce tumor cell death.

In MYC-overexpressing tumors with high replication stress, checkpoint kinase 1(CHK1) and WEE1 G2 checkpoint kinase (WEE1) are two critical checkpoint regulators. CHK1 activates the ATR pathway during the S phase, stabilizing replication forks and delaying cell cycle progression to alleviate replication stress [98]. WEE1 regulates the G2/M checkpoint by inhibiting cyclin-dependent kinase 1(CDK1) activity, preventing DNA-damaged cells from prematurely entering mitosis [99]. In a neuroblastoma model with MYCN amplification, pharmacological inhibition of both CHK1 and WEE1 synergistically impairs neuroblastoma cell growth in vitro. This combination treatment strategy directly targets the adaptive response to replication stress in MYC-driven tumors and offers a potent therapeutic option [100].

Aurora A and Aurora B are key mitotic regulators that are closely associated with replication stress commonly observed in MYC-overexpressing tumors. Aurora A primarily regulates spindle formation and centrosome function [101], while Aurora B is involved in proper chromosome alignment, kinetochore-microtubule attachment, and cytokinesis [102]. Under replication stress, cells face additional pressure on spindle function and chromosome segregation. Aberrant functions of Aurora A and Aurora B further exacerbate defects in chromosome alignment and segregation, leading to chromosomal abnormalities or polyploidy [103]. Studies have shown that selective Aurora kinase inhibitors,

by inhibiting the activity of Aurora A and B, can induce mitotic arrest, polyploidy formation, and apoptosis in MYC-driven lymphomas [104]. Similarly, Targeting Protein for Xklp2 (TPX2), a crucial mitotic regulator, is a key mediator of spindle assembly. Under replication stress, enhanced TPX2 function is vital for maintaining spindle integrity and ensuring accurate chromosome segregation [105]. MYC reprograms TPX2 expression to ensure proper chromosome segregation under replication stress conditions. Depletion of TPX2 impairs mitotic progression, induces cell death, and inhibits tumor growth [106].

The SUMOylation pathway is an essential regulatory mechanism for maintaining protein function and cell cycle homeostasis under replication stress. During replication stress, SUMOylation regulates the stability and activity of several key proteins, including Aurora A, Aurora B, TPX2, and other DNA damage repair proteins [107-110]. SAE1 (SUMO-activating enzyme subunit 1) and SAE2 (SUMO-activating enzyme subunit 2) are critical enzymes in the SUMOylation pathway, responsible for activating SUMO proteins and mediating the SUMOylation of target proteins. In MYC-driven tumors, where replication stress levels are elevated, SUMOylation plays a particularly important role in regulating the function of key proteins and maintaining cell cycle balance [111]. Mouse models have demonstrated that SAE2 is essential for the growth of MYC-dependent tumors. Gene expression analysis of human breast cancers with high MYC expression revealed that lower levels of SAE1 and SAE2 in tumors are associated with longer disease-free survival in patients [111].

Targeting transcription-replication conflicts

MYC-driven tumor cells typically exhibit excessive proliferation, accompanied by globally elevated transcription levels [112]. The excessive transcriptional activity conflicts with the DNA replication process, leading to replication fork stalling and accumulation of DNA damage, which in turn triggers replication stress [113]. This replication stress exacerbates the dependency of MYC-overexpressing tumors on factors regulating transcription-replication conflicts, making it a critical vulnerability of tumor cells. Therefore, targeting these regulatory factors can selectively kill MYC-dependent tumor cells through synthetic lethality mechanisms [114-116].

One example is the targeting of the exosome complex to inhibit the proliferation of neuroendocrine tumor cells with MYCN amplification. The exosome complex, a 30-50 exonuclease complex, functions in MYCN-driven tumor cells during the S phase by recruiting exonucleases to maintain efficient transcription elongation and prevent transcription-replication conflicts, thus promoting the rapid proliferation of neuroendocrine tumor cells. Based on this mechanism, targeting the exosome complex presents a potential therapeutic strategy for MYCN-amplified neuroendocrine tumors, which can suppress tumor cell proliferation and induce lethality [114]. Additionally, MYC overactivation leads to the accumulation of R-loops, which represent another vulnerability in tumor cells. R-loops form when RNA hybridizes with the DNA template strand, causing localized DNA unwinding. During this process, Topoisomerase 1 (TOP1) plays a critical role [117]. TOP1 alleviates the supercoiling stress of DNA and regulates the formation of R-loops, making it an effective therapeutic target. Both genetic and pharmacological studies have shown that TOP1 inhibitors selectively reduce the in vivo growth of MYC-transformed tumors, demonstrating their potential therapeutic effects [115]. Finally, cyclin-dependent kinase 12 (CDK12) plays an essential role in preventing transcription-replication conflicts and maintaining genomic stability. In MYC-driven cancers, CDK12 regulates transcription and DNA repair processes, preventing double-strand breaks caused by transcription-replication conflicts. However, loss or inhibition of CDK12 exacerbates these conflicts, leading to increased genomic instability. This provides theoretical support for targeting CDK12 as a cancer therapy, particularly in MYC-driven tumors [116].

Targeting nucleotide synthesis pathways

MYC supports cancer cell proliferation and survival by facilitating multiple anabolic processes. Several genes involved in de novo purine and pyrimidine synthesis pathways are directly targeted by MYC [45]. For example, MYC directly upregulates the transcription of phosphoribosyl pyrophosphate synthetase 2 (PRPS2), inosine monophosphate dehydrogenase1/2 (IMPDH1/2) [44, 68]. PRPS2 is the key enzyme in

the purine synthesis pathway, playing an important role in de novo nucleotide synthesis by converting ribose-5-phosphate into phosphoribosyl pyrophosphate (PRPP) [118]. Cunningham and colleagues found that knocking down PRPS2 has a synthetic lethal effect in MYC-overexpressing cells; specifically, the loss of PRPS2 prolongs the survival of transgenic mice with MYC-induced lymphoma [119]. In the P493-6 human Burkitt lymphoma cell line, inhibiting IMPDH activity significantly blocks proliferation induced by MYC activation, resulting in S-phase arrest and increased apoptosis [44]. We recently found a unique function of the rate-limiting nucleotide synthesis enzyme CTP synthase 1 (CTPS1) in the survival of MYC-driven cancer cells. This study identified a novel synthetic lethal strategy to combat MYC-driven cancers by combining CTPS1 inhibitors with ataxia telangiectasia and Rad3-related protein inhibitors, which exploits the inherent vulnerability of MYC-driven tumors to nucleotide shortage and DNA replication stress [120].

Targeting cancer-related energy metabolism

MYC-overexpressing cancer cells exhibit a distinct metabolic profile that supports their high proliferation rates [31]. These cells increase their energy production by upregulating both glycolysis and glutaminolysis, two key pathways that fuel rapid growth [121]. MYC enhances glycolysis by upregulating glucose transporters and glycolytic enzymes [122], which increases glucose uptake and its conversion to pyruvate. Often, this pyruvate is further converted to lactate even in oxygen-rich conditions, a process known as the Warburg effect [123]. This aerobic glycolysis provides not only adenosine triphosphate (ATP) but also essential intermediates for biosynthetic processes, including nucleotide, amino acid, and lipid synthesis [123]. Similarly, MYC-driven cancers show a marked dependency on glutaminolysis [124, 125]. Glutamine serves as a crucial carbon and nitrogen source, fueling the tricarboxylic acid (TCA) cycle and providing substrates for nucleotide biosynthesis, which supports DNA replication and repair in fast-dividing cells [126]. This reliance on both glycolysis and glutaminolysis to meet energy and biosynthetic demands makes MYC-overexpressing cancers particularly sensitive to interventions targeting these metabolic pathways, as disrupting them can exacerbate replication stress and promote tumor cell death [125]. Furthermore, genetic screens have revealed that MYC-driven cancer cells depend on mitochondrial translation regulatory factors to maintain energy metabolism [127, 128]. The loss of these enzymes disrupts mitochondrial respiratory chain complex formation, leading to impaired energy production and inhibited cell growth [129]. Notably, loss of AMPK-related protein kinase 5 (ARK5) leads to a collapse of ATP levels, indicating that mitochondrial damage induces cell death [128]. Mitochondrial dysfunction further exacerbates replication stress because impaired mitochondria cannot effectively support the energy demands of rapidly dividing cells, leading to cell cycle arrest or death [130].

Exploiting reactive oxygen species vulnerabilities

MYC-overexpressing cells exhibit elevated ROS levels due to enhanced metabolic activity and replication stress [131]. While these cells adapt by activating robust antioxidant defenses to detoxify ROS and maintain redox balance, this adaptation creates a vulnerability: disrupting ROS detoxification or further increasing ROS levels can overwhelm the redox balance, leading to excessive oxidative damage and selective cell death [132, 133]. One way to exploit this vulnerability is by using mitochondrial complex I inhibitors, such as IACS-010759. This inhibitor induces oxidative stress and depletes reduced glutathione (GSH), a key antioxidant, thereby disrupting redox homeostasis and selectively killing MYC-overexpressing cells. Combining IACS-010759 with pro-oxidants, such as high-dose ascorbate, further elevates ROS levels and enhances its therapeutic efficacy in human B-cell lymphoma xenograft models. In addition to directly targeting antioxidant defenses [132], MYC-driven tumors exploit other metabolic adaptations to handle oxidative stress. Specifically, these adaptations target nucleotide pools to counteract oxidative DNA damage. ROS can oxidize free deoxynucleotide triphosphates (dNTPs), disrupting DNA synthesis and compromising genomic stability. To address this challenge, MYC orchestrates two key pathways: the NADPH oxidase 4 (NOX4)-ROS pathway to regulate ROS levels and the polo-like kinase 1 (PLK1)-nudix hydrolase 1 (NUDT1) pathway to sanitize nucleotide pools by removing oxidized dNTPs. Disrupting this delicate balance by targeting NUDT1, a critical enzyme in

nucleotide pool maintenance, induces severe oxidative stress. The NUDT1 degrader LC-1-40 exacerbates nucleotide oxidation, triggers cytotoxicity, and drives tumor regression, presenting a promising strategy to exploit ROS-mediated vulnerabilities in MYC-driven cancers [133].

Conclusion and future perspective

In summary, leveraging replication stress as a synthetic lethal strategy offers a promising therapeutic avenue for MYC-driven cancers. MYC overexpression intensifies replication stress through mechanisms such as enhanced replication origin firing, nucleotide depletion, transcription-replication conflicts, and oxidative damage. MYC-overexpressing cells respond by upregulating stress response pathways, including the ATR/CHK1 checkpoint, DNA repair systems, and nucleotide synthesis pathways, to manage replication stress and maintain genomic integrity. Targeting these compensatory mechanisms exacerbates replication stress and induces synthetic lethality, offering a tumor-selective approach for MYC-driven cancers.

Despite these promising insights, clinical translation of synthetic lethal strategies in MYC-driven cancers are still in its early stages and faces several challenges. The modest clinical benefits observed with single-agent therapies targeting MYC-induced vulnerabilities highlight the need for combination therapies. Issues such as off-target toxicity, especially in highly proliferative normal tissues, and the emergence of drug resistance complicate the development of MYC-directed therapies. Combining synthetic lethal approaches with existing therapies, such as PARP inhibitors, CDK inhibitors, or immune checkpoint blockade, may yield more effective and durable responses. For example, combining PARP inhibitors with ATR or CHK1 inhibitors may produce synergistic effects by simultaneously compromising DNA repair and replication stress response pathways, which could more effectively induce cell death in MYC-driven tumors.

In addition to refining therapeutic combinations, future research should prioritize identifying biomarkers that predict response to replication stress-targeted therapies. Biomarkers, such as replication stress markers, DNA repair deficiencies, or MYC expression levels, could facilitate patient stratification, allowing for more personalized and effective treatment regimens. Developing tools to monitor replication stress in real time, such as imaging or circulating DNA assays, could also support dynamic assessment of treatment efficacy, enabling timely adjustments in therapeutic strategies.

Furthermore, novel screening techniques, such as CRISPR/Cas9-based genome-wide screens, may uncover new synthetic lethal partners for MYC and reveal previously unrecognized therapeutic targets. These discoveries could expand the arsenal of synthetic lethal targets, offering alternatives to current approaches and potentially reducing the risk of drug resistance. High-throughput drug screening of small-molecule inhibitors targeting newly identified MYC-synthetic lethal pairs could also accelerate the development of next-generation therapies.

Another area of opportunity lies in the exploration of the tumor microenvironment's role in MYC-driven replication stress. Interactions between MYC-overexpressing cancer cells and their microenvironment may provide additional therapeutic targets, as immune cells [134], fibroblasts, and stromal cells can influence replication stress and DNA repair mechanisms [135-137]. Immunotherapy, particularly approaches that modulate the immune microenvironment, may complement synthetic lethality by enhancing immune-mediated cell death in MYC-driven cancers.

In conclusion, the concept of synthetic lethality in MYC-driven cancers offers a promising framework for the development of selective and potent cancer therapies. By strategically targeting the replication stress response, DNA repair pathways, and metabolic dependencies unique to MYC-overexpressing cells, we can exploit the inherent vulnerabilities of these cancers. However, achieving clinical efficacy will require overcoming challenges related to toxicity, resistance, and patient heterogeneity. Through continued research and clinical development, synthetic lethality-based therapies hold the potential to transform the landscape of MYC-driven cancer treatment, offering new hope for patients with historically challenging and aggressive tumors.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Wei-Dong Zhang, School of Pharmacy, Second Military Medical University, No. 800 Xiangyin Road, Shanghai 200433, China. E-mail: wdzhangy@hotmail.com; Drs. Zhe Sun and Xin Luan, Institute of Interdisciplinary Integrative Medicine Research, Shanghai University of Traditional Chinese Medicine, No. 1200 Cailun Road, Shanghai 201203, China. E-mail: sunzhe@shutcm.edu.cn (ZS); luanxin@shutcm.edu.cn (XL)

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