Oncogene c-Myc: From molecular mechanism to targeted therapy (Review)

JIANJUN LU[1*], JING ZHU[2*], LIQIONG ZHANG[2*], XIANG ZHENG[3], SHAN YANG[3], YATONG SANG[3], MINGLI YANG[3] and YU TANG[3]

[1]Department of Pathology, Suzhou Ninth People's Hospital, Suzhou, Jiangsu 215200, P.R. China; [2]Yunnan Key Laboratory of Breast Cancer Precision Medicine, Academy of Biomedical Engineering, Kunming Medical University, Kunming, Yunnan 650000, P.R. China; [3]Department of Genetics, School of Basic Medicine, Zunyi Medical University, Zunyi, Guizhou 563000, P.R. China

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Abstract. c-Myc, a member of the MYC family, is an extensively studied proto-oncogenic transcription factor that plays crucial roles in various biological processes of tumor cells, including proliferation, cell cycle regulation, DNA damage repair, metabolic reprogramming, differentiation and genomic maintenance. Furthermore, in cancer therapeutics, c-Myc may serve as a key factor influencing targeted drug efficacy and tumor drug resistance. This review comprehensively summarizes the structural characteristics of c-Myc and its roles and key molecular mechanisms across various malignancies, as well as current strategies for c-Myc-targeted therapies and related clinical trials. Additionally, the existing challenges in c-Myc research are discussed and future research directions are being outlined. The synthesis aims to provide novel insights for fundamental research, offer new perspectives for precision cancer therapy in clinical practice and ultimately bring renewed hope for cancer treatment.

Contents

Correspondence to: Dr Mingli Yang or Dr Yu Tang, Department of Genetics, School of Basic Medicine, Zunyi Medical University, Basic Medical Sciences Building, 1 Road of Campus, Xinquan New District, Zunyi, Guizhou 563000, P.R. China
E-mail: yangmingli_1982@126.com
E-mail: tangyu199612@163.com

*Contributed equally

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1. Introduction

The global incidence of cancer continues to rise annually, remaining a major health challenge worldwide (1). According to the latest estimates from the International Agency for Research on Cancer, 2022 witnessed nearly 20 million new cancer cases [including non-melanoma skin cancers (NMSCs)] and 9.7 million cancer-related deaths (including NMSCs) (2). Epidemiological projections indicate that approximately one in five individuals will develop cancer during their lifetime, with about one in nine men and one in 12 women succumbing to the disease (3). Current therapeutic strategies for cancer patients primarily include surgical resection, radiotherapy, chemotherapy and small-molecule targeted therapies. Unlike conventional chemotherapy that indiscriminately kills cancer cells, targeted therapies disrupt specific oncogenic pathways to inhibit cancer-cell replication and proliferation while minimizing damage to normal tissues. However, limitations persist, including a scarcity of actionable therapeutic targets and the emergence of drug resistance during treatment (4-6). Consequently, there is an urgent need to identify novel therapeutic targets and elucidate mechanisms underlying treatment resistance in oncology research.

Transcription factors are critical regulatory proteins that govern gene expression by binding to specific DNA sequences, thereby precisely controlling transcriptional processes (7). These proteins typically comprise two functional domains: A DNA-binding domain [e.g., zinc fingers or helix-loop-helix (HLH) motifs] that recognizes conserved sequences in promoters or enhancers, and an activation/repression domain that recruits RNA polymerase or histone-modifying complexes to initiate or suppress transcription (8). Their spatiotemporal specificity enables selective activation in distinct cell types or developmental stages, orchestrating cellular differentiation, metabolic regulation and stress responses (9). Investigations into transcription factor networks not only reveal disease mechanisms but also provide theoretical foundations for

targeted therapies. As central hubs of gene regulatory networks, they hold significant potential in synthetic biology and cellular reprogramming (10).

Among these, the myelocytomatosis oncogene (MYC) family (including c-Myc, N-Myc and L-Myc) represents a pivotal group of transcription factors regulating cell proliferation and differentiation. These proteins share a conserved basic HLH leucine zipper (LZ) domain (11). By forming heterodimers with MYC associated factor X (MAX) proteins, they specifically bind E-box sequences (CACGTG) in target gene promoters, modulating the transcriptional activity of ~15% of human genes (12). Under physiological conditions, MYC proteins coordinate cell cycle progression, metabolic reprogramming (e.g., enhanced glycolysis and glutaminolysis) and ribosome biogenesis to promote tissue development and regeneration, while simultaneously suppressing differentiation signals through antagonism of mother against decapentaplegic (MAD)/MAX network transcriptional repressor (MNT) family transcription factors (13).

The pathogenesis and progression of cancer involve a multi-step, multi-stage process driven by genetic alterations. Studies have revealed that aberrant activation of MYC family genes (e.g., through chromosomal translocations, gene amplification or dysregulation of upstream signaling pathways) is a hallmark of numerous cancers, with c-Myc overexpression observed in ~70% of human malignancies (14). Dysregulated c-Myc expression is closely associated with cancer initiation and progression (15). Research demonstrates that c-Myc regulates >15% of the human genome and orchestrates transcription mediated by all three RNA polymerases (I, II and III), directly influencing 2,000-4,000 target genes. This broad regulatory capacity has earned c-Myc the designation of a 'master gene regulator' (16,17).

c-Myc is aberrantly activated in diverse hematological malignancies, including leukemia (18), lymphoma (19) and multiple myeloma (20), and solid tumors, such as pancreatic ductal adenocarcinoma (21), non-small cell lung cancer (NSCLC) (22), SCLC (23), hepatocellular carcinoma (24), prostate cancer (25) and breast cancer (26). Mechanistically, c-Myc drives tumorigenesis through multiple pathways: Promoting cell proliferation (27), suppressing apoptosis (28), reprogramming metabolism (29), inducing angiogenesis (30) and modulating cancer stem cell maintenance (31). Beyond cell-autonomous effects, c-Myc also remodels the tumor microenvironment (TME) and facilitates immune evasion (26,32). These findings collectively position c-Myc as a pivotal therapeutic target in the era of molecular oncology.

In conclusion, given the direct correlation between the dysregulation of c-Myc and the development of tumors, this review summarizes the latest progress in c-Myc research and systematically examines the three core issues of c-Myc research: i) c-Myc, as a transcription factor, lacks a typical drug-binding pocket and is difficult to be directly targeted; furthermore, it performs essential physiological functions in normal cells and systemic inhibition is prone to cause toxicity; ii) c-Myc is embedded in redundant and dynamic transcriptional regulatory networks, with complex mechanisms, making it difficult to validate the targets and challenging to meet the requirements of clinical translation for predictability and controllability; iii) the function of c-Myc is significantly influenced by tissue type, genetic background and microenvironment, limiting the applicability of broad-spectrum intervention strategies. In response to these issues, four complementary research paths were summarized: i) Inhibiting the dimerization of c-Myc/Max; ii) targeting key co-factors such as transcription domain associated protein (TRRAP) and bromodomain protein 4 (BRD4), to indirectly regulate c-Myc-dependent transcriptional programs; iii) using degradation mechanisms to eliminate c-Myc; iv) combining with immunotherapy and stress pathways. Additionally, in the discussion, the c-Myc research related to personalized medicine, proteolysis-targeting chimeras (PROTAC) technology and nano-delivery is outlined, clarifying the feasible steps for the transformation of basic discoveries into therapeutic applications, providing a concise and operational reference for targeting c-Myc.

2. The transcription factor c-Myc

c-Myc, encoded by the human chromosomal locus 8q24, is a 439-amino-acid oncoprotein characterized by a C-terminal DNA-binding domain and an N-terminal transactivation domain (TAD) (33). The C-terminal region contains a 100-residue LZ motif that mediates heterodimerization with its LZ partner MAX, enabling DNA binding to gene promoters (Fig. 1) (34). As a member of the Myc family, which also includes N-Myc and L-Myc, c-Myc shares high homology with its paralogs but exhibits distinct expression patterns (35). While c-Myc is ubiquitously expressed in proliferating cells and tightly regulated at genetic, protein and mRNA levels, N-Myc and L-Myc display more restricted spatiotemporal expression during cellular and tissue development (36).

The N-terminal TAD (residues 1-143) is an intrinsically disordered domain critical for c-Myc's transcriptional activation and biological activity (37). Comprising MB0, MBI and MBII subdomains, the TAD contains canonical phosphorylation sites (e.g., S62 and T58) that regulate c-Myc stability via phosphorylation cascades (38,39). MBII (residues 129-143), the most extensively studied subdomain, serves as a hub for key protein interactions and is indispensable for c-Myc's oncogenic potential (39). Adjacent to this region, the MBIIb subdomain (residues 226-270) features a proline (P), glutamic acid (E), serine (S) and threonine (T)-rich 'PEST' motif involved in stability regulation independent of ubiquitination (40). The MBIII subdomain modulates protein stability and enhances cellular transformation, whereas MBIV exhibits context-dependent variability in transformation assays (41).

The C-terminal LZ domain (residues 357-439) facilitates nuclear localization and dimerization with MAX. This heterodimer binds E-box sequences (CACGTG) in target gene promoters via disulfide bonds, initiating transcriptional activation (42,43) (Fig. 1).

Collectively, c-Myc's structural architecture enables its dual role as a transcriptional activator and repressor, coordinating critical cellular processes such as transcription (44), translation (45), chromatin remodeling (46) and proteostasis (47). A study revealed that c-Myc binds nearly all active promoters and enhancers, regulating genes essential for cell growth (48). Under physiological conditions, c-Myc expression is tightly controlled at transcriptional, post-transcriptional

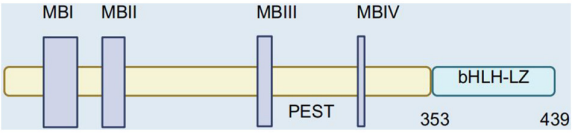

Figure 1. Structure of c-Myc. c-Myc protein contains an unstructured N-terminal transcription regulatory domain and a nuclear localization signal, and the C-terminus contains a bHLH-Zip domain. The C-terminal bHLH-LZ domain (residues 357-439) facilitates nuclear localization and dimerization with MAX. This heterodimer binds E-box sequences (CACGTG) in target gene promoters via disulfide bonds, initiating transcriptional activation. bHLH-Zip, basic helix-loop-helix leucine zipper; MAX, MYC associated factor X.

and post-translational levels. However, dysregulation via chromosomal translocations, insertional mutagenesis or gene amplification leads to oncogenic c-Myc accumulation. This drives metabolic reprogramming to sustain rapid tumor cell proliferation, ultimately fueling cancer initiation and progression (49,50).

3. c-Myc abnormalities in cancer

Cancer is a complex and heterogeneous disease driven by dysregulated oncogene expression, which disrupts the homeostasis of oncogenic or tumor suppressor signaling pathways (51,52). Studies have shown that abnormal c-Myc expression, observed in most malignant tumors, plays a key role in tumorigenesis as it controls critical cellular processes (53,54). However, the oncogenic function of c-Myc is not uniform; its upstream regulatory mechanisms, dominant downstream effector networks and ultimate clinical significance exhibit profound 'context dependence' across different cancer types. This specificity stems from the unique genetic background, microenvironment and driving signals of each cancer type, causing c-Myc to play different roles in tumor progression.

For instance, in breast cancer, the abnormal activation of c-Myc is often closely related to hormone signaling and post-transcriptional regulation, with its function strongly pointing towards metabolic reprogramming, maintenance of stem cell characteristics and treatment resistance (5). c-Myc enhances VEGF expression by stimulating the translation of VEGF mRNA, highlighting its role in mediating the interaction between cancer cells and the TME (55,56). Elevated estrogen levels are associated with c-Myc expression, especially in estrogen receptor (ER)-positive patients, where there is a mutual dependence between estradiol and c-Myc. c-Myc is considered a classic estrogen-induced gene in breast cancer cells. Knockdown of insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) reduces the stability of c-Myc mRNA, while its ectopic expression enhances the stability of c-Myc mRNA under normoxic conditions (57). Hypoxia-induced long non-coding RNA KB-1980E6.3 recruits IGF2BP1 to stabilize c-Myc mRNA, thereby promoting self-renewal and stemness maintenance in breast cancer (57). High c-Myc expression significantly enriches cancer stem cells (CSCs) (58). Diclofenac inhibits the proliferation of triple-negative breast cancer (TNBC) by down-regulating c-Myc, reducing glucose uptake and inhibiting glycolysis (59). c-Myc lies downstream of the lysine methyltransferase 2D (KMT2D)-histone H3 lysine 4 mono-methylation (H3K4me1)-Y-box binding protein (YBX1) axis; its expression in TNBC is suppressed upon KMT2D or YBX1 knockdown. c-Myc or SENP1 re-expression rescues the proliferation and migration in KMT2D/YBX1-deficient TNBC cells (60). Methyltransferase-like protein 3 stabilizes the c-Myc/WD repeat-containing protein 5 (sWDR5) interaction through a methylation-independent mechanism, enhancing c-Myc's transcriptional activity on glycolytic genes and promoting the development of TNBC (61). 3-Bromopropionic acid inhibits the growth of TNBC by downregulating c-Myc, suppressing glycolysis (lactate production, ATP synthesis and hexokinase activity) and inducing mitochondrial apoptosis (62,63). Overexpression of protein arginine methyltransferase 1 (PRMT1) is associated with upregulation of c-Myc in TNBC, where PRMT1 stabilizes c-Myc to promote tumor progression and confer resistance to olaparib. Targeting PRMT1 can enhance the sensitivity to olaparib (64). The above studies demonstrate the specific role of c-Myc in breast cancer, particularly in the aggressive subtype TNBC, as a core node of treatment resistance and a key executor of metabolic reprogramming. By contrast, in pancreatic cancer, c-Myc more often functions as an integration hub downstream of oncogenic signaling pathways (such as KRAS), with its primary role being to drive metabolic reprogramming and construct an immunosuppressive barrier in response to the nutrient-poor microenvironment. In pancreatic cancer, c-Myc directly binds to the fibroblast growth factor binding protein 1 (FGFBP1) promoter to drive its expression. The F-Box and WD repeat domain containing 7 (Fbw7)/c-Myc axis regulates FGFBP1 levels, and inhibiting c-Myc can suppress angiogenesis and tumor progression (65). c-Myc cooperates with programmed cell death 1 (PD-1), and inhibiting c-Myc can enhance PD-1 checkpoint blockade (66). c-Myc upregulates CD47 transcription, enabling pancreatic cancer cells to evade immune phagocytosis through the CD47-signal regulatory protein α (SIRPα) interaction. Blocking CD47 can enhance the infiltration of CD8+ T cells and macrophages and inhibit tumor growth (67,68). The mucin 5AC, oligomeric mucus/gel-forming (MUC5AC)/β-catenin/c-Myc axis promotes glutamine/glutamate metabolism, pyrimidine biosynthesis and gemcitabine resistance by upregulating MUC1/hypoxia-inducible factor (HIF)-1α and glycolysis (69,70). CD36 inhibits β-catenin/c-Myc signaling by proteasomal degradation of glypican-4 (GPC4), thereby suppressing glycolysis and tumor growth. Ectopic GPC4 reactivates β-catenin/c-Myc signaling in colorectal cancer, suggesting that targeting GPC4 may overcome treatment resistance and tumor stem cell characteristics (71). Overexpression of c-Myc induces epithelial-mesenchymal transition in chemotherapy-resistant cancer-associated fibroblasts and secretion of exosomal microRNA (miR)-106b, while exosome inhibitors can reverse gemcitabine resistance (72). Circular RNA PDK1 acts as a scaffold for the ubiquitin conjugating enzyme E2 O ubiquitin ligase and forms a ternary complex with bridging integrator 1 (BIN1) to induce BIN1 degradation, thereby relieving its inhibition on c-Myc transcriptional activity and promoting pancreatic cancer growth, metastasis and glycolysis (73). This reveals a specific network of c-Myc in pancreatic cancer that integrates metabolism, immune microenvironment and treatment resistance. In

other types of malignant tumor, the regulation and function of c-Myc also have their unique characteristics. c-Myc transcriptionally activates colon cancer-associated transcript-1, which in turn enhances c-Myc expression in cervical cancer through Wnt/β-catenin signaling (74-76). c-Myc binds to the growth differentiation factor 15 (GDF-15) promoter to drive its expression, and GDF-15 indirectly activates c-Myc, which is associated with the progression and metastasis of cervical cancer (77-79), suggesting a unique positive feedback loop in gynecological tumors. In bladder cancer, c-Myc is a downstream target of the NF-κB pathway, and Rab23 promotes cell proliferation and invasion by activating NF-κB (80). X-linked Inhibitor of Apoptosis Protein stabilizes c-Myc by inhibiting glycogen synthase kinase 3β (GSK-3β)-mediated Thr58 phosphorylation (81). miRNA-451 directly targets the 3'-UTR of c-Myc to inhibit the migration and invasion of bladder cancer (82), demonstrating the specificity of regulation at different levels. In hematological malignancies and certain types of solid tumor, the stability regulation and direct transcriptional activation mechanisms of c-Myc are particularly prominent, making its function more akin to a direct oncogene-driven event. In chronic myeloid leukemia, overexpression of cancerous inhibitor of protein phosphatase 2A stabilizes c-Myc by inhibiting protein phosphatase 2A-mediated dephosphorylation, thereby driving blast crisis (83). Notch homolog 1 (Notch1) directly transcribes and activates c-Myc to stimulate the proliferation of leukemia cells (84-86). In SCLC, histone deacetylase (HDAC)7 promotes tumorigenesis by regulating the acetylation and nuclear transport of β-catenin, upregulating c-Myc and Exportin 1 (XPO1). XPO1 inhibitors show enhanced efficacy in SCLC models with high HDAC7 expression (87). Dual mouse double minute 2 homolog (MDM2)/XPO1 inhibition increases nuclear p53 levels, suppresses MYC transcription and induces apoptosis in tumor protein (TP)53 wild-type acute myeloid leukemia (AML), with cells expressing high levels of c-Myc showing greater sensitivity (88). These studies indicate that interventions targeting c-Myc protein stability, transcriptional complexes or nuclear transport may have specific therapeutic potential in such cancers.

In summary, c-Myc is not a single-function pan-cancer driver but a transcriptional regulatory hub that exerts its effects depending on the specific TME and molecular background. The downstream biological effects triggered by its abnormal activation, including metabolic reprogramming, maintenance of stem cell characteristics, immune evasion and treatment resistance, vary significantly among different cancer types. This variation stems from the cancer-type-specific combinations of upstream regulatory mechanisms (such as hormone signaling, kinase pathways, RNA-binding proteins or epigenetic modifications) and core effector pathways (such as glycolysis, Wnt/β-catenin, CD47-SIRPα or NF-κB). Therefore, systematically dissecting the dominant regulatory nodes and functional output profiles of c-Myc in various malignant tumors will help develop more cancer-type-adapted intervention strategies. For example, targeting the ER-c-Myc axis or the IGF2BP1-mRNA stability pathway in ER-positive breast cancer; combining inhibition of CD47 or FGFBP1 downstream of c-Myc in pancreatic cancer; and using dual MDM2/XPO1 inhibition to induce c-Myc downregulation in TP53 wild-type AML. Such precision intervention approaches based on mechanistic heterogeneity will significantly enhance the clinical feasibility and patient benefit of c-Myc-targeted therapy.

4. The molecular mechanisms underlying c-Myc's roles in cancer progression

c-Myc is one of the most frequently dysregulated transcriptional regulators in tumorigenesis. Its oncogenic effect stems from the coordinated regulation of multiple malignant biological processes rather than the activation of a single pathway. It upregulates cell cycle-related genes by binding to E-box sequences, driving continuous proliferation and enhancing ribosome biogenesis and protein translation. To meet the demands of rapid proliferation, it simultaneously promotes glycolysis and glutaminolysis to provide energy and biosynthetic precursors. In the DNA damage response, it exhibits dual regulation: On the one hand, it exacerbates genomic instability, and on the other hand, it maintains basic repair capacity to ensure cell survival. Additionally, it remodels the TME by regulating immune checkpoint molecules, angiogenic factors and matrix remodeling enzymes. It also activates stem cell-related genes and inhibits differentiation, endowing cells with self-renewal, heterogeneity and treatment resistance. These functions are integrated by c-Myc and are interdependent, forming a complete oncogenic program (Fig. 2).

c-Myc and cell cycle regulation. The c-Myc oncoprotein stimulates the cell cycle via three primary mechanisms: Upregulating cyclins and cyclin-dependent kinase (CDKs), downregulating CDK inhibitors (p15, p21 and p27), and accelerating G1-to-S phase transition (89). Dysregulated c-Myc activity drives uncontrolled proliferation, a hallmark of tumorigenesis (90). c-Myc knockout reduces Cell division cycle 25A (Cdc25A) expression, diminishes cyclin B1/Cdc2 activity, enhances radiation-induced G2/M arrest and sensitizes LNCaP cells to ionizing radiation (91). Beyond activating cyclins and CDKs, c-Myc promotes cell cycle progression by impairing 'braking' proteins. For example, p27 requires phosphorylation at Thr-187 for recognition and ubiquitination by the SCF-S-phase kinase associated protein 2 (SKP2) complex (89). c-Myc facilitates p27 degradation by the following mechanisms: i) Inducing Skp2 expression (92,93), ii) activating Cdk2 via cyclin upregulation (94), and iii) activating Cdk1 (89,95). In lymphoma and osteosarcoma cells, c-Myc inhibition upregulates p21, inducing G2/M arrest (14,96).

In summary, c-Myc is a central oncogenic transcription factor regulating cell cycle progression. As a MYC family member, it forms heterodimers with MAX to bind E-box sequences (CACGTG) in target gene promoters, directly controlling ~15% of human genes (97). c-Myc drives G1/S transition by upregulating cyclin D and CDK4/6, activating E2F transcription and suppressing CDK inhibitors (e.g., p21, p27), thereby sustaining proliferative signaling (93,98).

c-Myc and DNA damage repair. c-Myc influences DNA damage response (DDR) mechanisms, fostering genomic instability (99). By interacting with repair proteins, c-Myc modulates cellular responses to genotoxic stress, underscoring its potential as a therapeutic target for enhancing DNA-damaging

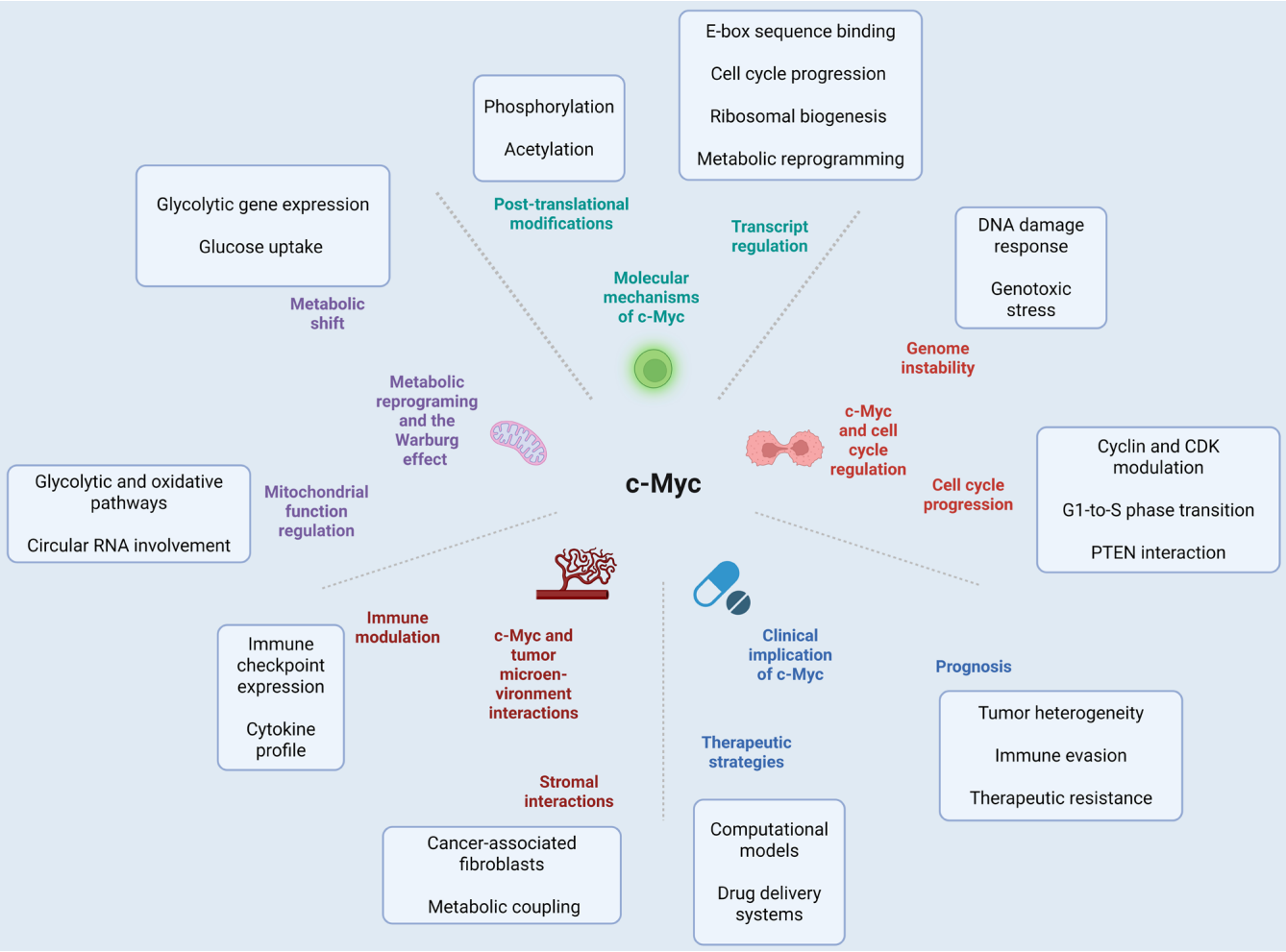

Figure 2. The molecular mechanisms underlying c-Myc's roles in cancer progression. Post-translational modifications, such as phosphorylation and acetylation, modulate c-Myc stability, localization and activity, influencing its ability to regulate downstream oncogenic pathways. Studies revealed that autophagy can either suppress or promote tumor growth, further highlighting c-Myc's adaptive role in maintaining oncogenic phenotypes under microenvironmental stress. Additionally, c-Myc governs therapeutic resistance and metabolic adaptation. PTEN, phosphatase and tensin homolog; CDK, cyclin-dependent kinase.

agents (100). c-Myc binds promoters of DNA double-strand break (DSB) repair genes [e.g., Nijmegen Breakage Syndrome 1 (NBS1), X-Ray Repair Cross Complementing 6, Rad5-like protein (Rad5)1, breast cancer type 2 susceptibility protein, Rad50 double-strand break repair protein, DNA repair and recombination protein Rad54 and DNA-dependent protein kinase catalytic subunit (DNA-PKcs)], regulating their expression (100). Inhibiting c-Myc-mediated DNA repair induces genomic instability and mitotic catastrophe, sensitizing tumor cells to chemotherapy and radiation (101). In prostate cancer, c-Myc knockout suppresses the homologous recombination (HR) [via NBS1, RAD1 checkpoint DNA exonuclease, structural maintenance of chromosomes 1A] and non-homologous end joining (NHEJ) [via X-ray repair cross complementing 6, protein kinase, DNA-activated, catalytic subunit, polynucleotide kinase 3'-phosphatase] pathways, enhancing radiosensitivity (101). In embryonal rhabdomyosarcoma, c-Myc inhibition activates intrinsic apoptosis, exacerbates DSB damage and impairs DNA-PKc (NHEJ) and RAD51 (HR) recruitment, increasing radiosensitivity (102). c-Myc also regulates mismatch repair (MMR) gene expression. MMR corrects base mismatches and insertion-deletion loops, ensuring replication fidelity (103-105). Silencing MutL homolog 1 (MLH1) and MutS homolog 2 (MSH2), core MMR proteins, disrupts post-radiation mismatch correction, sensitizing cells to apoptosis (106,107). In melanoma, c-Myc downregulation suppresses MLH1/MSH2 and activates p53-independent apoptosis, enhancing γ-radiation sensitivity (108). In breast cancer, c-Myc amplification synergizes with HR deficiency to drive poly ADP-ribose polymerase inhibitor resistance (109).

Collectively, c-Myc-driven DDR dysregulation (observed in ~40% of c-Myc-driven tumors) creates 'synthetic lethality' vulnerabilities (e.g., with p53 loss), offering therapeutic opportunities (e.g., ATR inhibitors) (110,111). These findings highlight c-Myc's dual role in accelerating tumorigenesis and modulating therapy sensitivity, emphasizing the need to dissect its regulatory mechanisms for combination therapy development.

c-Myc and metabolic reprogramming in the Warburg effect. Metabolic reprogramming, particularly the Warburg effect (aerobic glycolysis), supports biosynthetic demands and rapid proliferation in cancer (112). c-Myc drives this shift by enhancing glycolytic gene expression and glucose uptake (113).

Non-coding RNAs (e.g., miR-181d) stabilize c-Myc, further promoting glycolysis and oncogenic signaling (114). c-Myc also balances mitochondrial glycolysis and oxidative phosphorylation to sustain tumor growth (115). Circular RNA ECE1 regulates the c-Myc/thioredoxin interacting protein axis, exemplifying its role in metabolic reprogramming (e.g., in osteosarcoma) (116). Lactate shuttling between tumor and stromal cells reflects c-Myc-driven cooperative metabolism within the TME (117). In nasopharyngeal carcinoma, c-Myc mediates latent membrane protein 1 (LMP1)-induced hexokinase 2 (HK2) upregulation, enhancing glycolysis. HK2 knockdown radiosensitizes LMP1-overexpressing cells (118). c-Myc also governs glutamine metabolism by increasing glutamine transporters and glutaminase expression, promoting glutaminolysis (119,120). Enhanced glutamine metabolism confers radioresistance via G2/M checkpoint override (121), nucleotide synthesis (122) and redox balance modulation (123). These findings suggest targeting c-Myc-mediated metabolic pathways (e.g., glucose/glutamine metabolism) may improve radiosensitivity.

In summary, c-Myc-driven metabolic reprogramming (the Warburg effect) is a hallmark of cancer. Deciphering its molecular underpinnings opens avenues for metabolic intervention strategies.

c-Myc TME interactions. c-Myc shapes the TME by regulating immune evasion, angiogenesis and stromal crosstalk (124,125). It alters immune checkpoint expression (e.g., PD-L1, CD47) and cytokine profiles, enabling immune escape. Senescent cells in the TME secrete pro-inflammatory factors, further promoting tumor growth (26). c-Myc directly binds programmed cell death ligand 1 (PD-L1) and CD47 promoters to enhance their transcription (126-128). c-Myc knockout downregulates PD-L1/CD47, boosting anti-tumor immunity, while PD-L1/CD47 overexpression rescues c-Myc loss-induced growth suppression (127). c-Myc inhibition reduces mitochondrial reactive oxygen species (ROS) in hypoxic cells, diminishing ROS-mediated Fe^{2+}-to-Fe^{3+} conversion, thereby activating prolyl hydroxylase to degrade HIF-1α (129). In endometrial cancer, c-Myc silencing suppresses HIF-1α, enhancing radiosensitivity. HIF-1α overexpression reverses this effect, implicating c-Myc in radioresistance via HIF-1α stabilization (130).

These findings position c-Myc as a master regulator of both intrinsic tumor proliferation and TME remodeling. Targeting the c-Myc-TME axis (e.g., combined with anti-angiogenics or immune checkpoint inhibitors) may enhance therapeutic efficacy, though its dynamic complexity warrants further exploration for precision strategies.

c-Myc and CSCs. CSCs, with self-renewal and tumor-initiating capacities, drive cancer progression (131). c-Myc maintains CSC stemness by directly activating pluripotency genes [Nanog homeobox (NANOG), octamer-binding transcription factor 4, SRY-box transcription factor 2(SOX2)] and modulating the Wnt/β-catenin, Notch and Hippo pathways, while suppressing differentiation signals (e.g., miR-34a) (132-137). The arginyl-tRNA synthetase-mitotic arrest deficient 1 like 1 fusion gene promotes nasopharyngeal carcinogenesis and chemoradioresistance by activating the Far upstream element binding protein 1/c-Myc axis, inducing CSC-like properties (138). In T-cell acute lymphoblastic lymphoma, c-Myc binds the HIF-2α promoter, sustaining CSC self-renewal via Nanog and SOX2 (139). Triptolide (C1572), a natural compound, selectively depletes therapy-resistant CSCs in TNBC by degrading c-Myc via the proteasome. c-Myc knockout mimics this effect, inducing CSC senescence (140). In conclusion, c-Myc also drives CSC plasticity through epigenetic remodeling (e.g., DNA demethylation), conferring adaptive advantages (141). As a central node in CSC regulatory networks, c-Myc represents a promising target for eradicating tumor recurrence.

Overall, c-Myc-driven tumorigenesis is a highly integrated biological process. The cell cycle progression, metabolic reprogramming, DNA damage response, TME remodeling and stem cell characteristics it regulates are not independent of each other but form a functionally interconnected and multi-feedback-regulated network. In this network, continuous proliferation is the core phenotype, and metabolic reprogramming and adaptive regulation of the DNA damage response jointly support the maintenance of this phenotype. The biosynthetic demands triggered by c-Myc's acceleration of the cell cycle are met by its simultaneous activation of glycolysis and glutaminolysis programs; the corresponding metabolites (such as acetyl-CoA and α-ketoglutarate) can serve as substrates for epigenetic modifications, feeding back to enhance c-Myc's transcriptional activity and the stemness features it induces. Meanwhile, the replication stress and ROS accumulation caused by rapid proliferation and metabolic activities trigger genomic instability. c-Myc selectively regulates homologous recombination, mismatch repair and other pathways, allowing for limited genetic variation accumulation under the premise of ensuring basic cell survival, thereby influencing the evolutionary trajectory of tumors. c-Myc also shapes an immunosuppressive microenvironment by upregulating immune checkpoint molecules and angiogenic factors, providing protection for the above-mentioned intrinsic oncogenic programs; its activation of stem cell-related genes helps maintain tumor heterogeneity, invasion potential and treatment resistance. Therefore, c-Myc is a core regulatory hub coordinating multiple oncogenic functions. This systemic feature suggests that targeting a single downstream effector molecule is susceptible to network compensation mechanisms; in contrast, directly interfering with c-Myc protein itself (such as through protein degradation or transcriptional inhibition), or jointly blocking multiple key functional outputs (such as metabolic intervention combined with immune checkpoint blockade), may more effectively disrupt the oncogenic steady state it drives (Fig. 2).

5. c-Myc and tumor therapy

As a transcription factor, c-Myc plays a central role in cell proliferation, differentiation and metabolism by regulating downstream gene expression. Its aberrant activation is implicated in >70% of human cancers (44). However, c-Myc has long been considered an 'undruggable' target due to the lack of a well-defined binding pocket, its reliance on protein-protein interactions, and its nuclear localization, which complicates therapeutic targeting. Additionally, c-Myc

is frequently activated via amplification rather than mutation in most tumors, and its inhibition may disrupt normal cellular functions, leading to severe toxicity (13,54). Recent advances in protein engineering, RNA technology and artificial intelligence have revitalized efforts to target MYC, with multiple inhibitors now in clinical trials, offering new hope for cancer therapy (36). Below, current c-Myc-targeted strategies and clinical progress are discussed.

Targeted therapeutic strategies for c-Myc. As a typical intrinsically disordered protein, c-Myc exhibits high dynamics and lacks a stable tertiary structure. Coupled with its strict nuclear localization property, this poses significant scientific challenges for targeted intervention: The extended and conformationally diverse protein surface makes it difficult to form deep and clear small molecule binding sites, severely limiting the design of traditional inhibitors; furthermore, the nuclear membrane barrier further restricts the effective delivery of candidate drugs to the target site. Therefore, current research and development strategies have systematically shifted towards an indirect intervention mode based on mechanistic understanding, aiming to dismantle the oncogenic function of c-Myc from multiple dimensions. This transformation needs to be understood in the broader context of the evolution of the target biology paradigm-compared to traditional kinase targets, c-Myc lacks a clear active groove at the structural level, and its protein-protein interaction interface exhibits a dynamic flat characteristic, making it difficult to provide high-affinity small-molecule binding sites; in terms of the mechanism, it does not rely on catalytic activity, so the 'enzyme activity inhibition' strategy (such as blocking ATP binding) cannot be adopted, and instead, it must interfere with its dynamic assembly processes such as dimerization, DNA binding and cofactor recruitment; in terms of design thinking, the 'occupation-driven' classic model is largely ineffective, breakthroughs are concentrated on 'function-driven' (such as blocking MYC/MAX) or 'elimination-driven' (such as PROTAC degradation, RNA interference) approaches, with the core logic shifting from 'inhibition' to 'elimination'; in the clinical transformation aspect, although there are a large number of kinase inhibitors approved for market, direct small molecule inhibitors for c-Myc have not yet achieved success, highlighting the necessity and challenge of the paradigm shift. This comparison aims to illustrate that the latest progress in the c-Myc field (such as degraders and RNA therapies) not only represents technological iteration but also represents a fundamental evolution of the drug design concept for 'undruggable' targets.

At the level of transcriptional complexes, c-Myc must form a heterodimer with MAX to specifically recognize and bind to the E-box sequence (5'-CACGTG-3') in the promoter region of target genes, thereby initiating the expression of downstream oncogenes (142,143). Thus, targeting the protein-protein interaction interface or interfering with its DNA binding ability has become a key path to block oncogenic signaling, and such strategies (such as OMO-103) have been proven not only to inhibit tumor cell proliferation but also to down-regulate the expression of c-Myc-driven immunosuppressive molecules (such as PD-L1), potentially reversing the immune microenvironment (143). At the level of protein homeostasis regulation, c-Myc has an extremely short half-life (~20-30 min), and its ubiquitin-proteasome-dependent degradation is precisely regulated by a phosphorylation cascade-phosphorylation of serine 62 (S62) mediated by ERK, CDK or JNK can enhance its stability, while subsequent phosphorylation of threonine 58 (T58) by GSK-3β triggers recognition by E3 ubiquitin ligases such as FBW7, ultimately leading to proteasomal degradation (144). Based on this, small molecule compounds (such as 361 and 975) can accelerate the clearance of c-Myc by promoting T58 phosphorylation or inhibiting S62 modification (66), and this clearance at the protein level is thought to simultaneously relieve c-Myc's transcriptional drive on multiple immune checkpoints. More advanced strategies rely on PROTAC technology to achieve controlled degradation: Currently, they mainly fall into three categories-the first is 'indirect targeting', which targets key transcriptional co-factors of c-Myc, such as bromodomain and extra terminal domain (BET) family protein BRD4 (which recruits c-Myc to chromatin by recognizing histone acetylation marks and is a core co-factor for c-Myc transcriptional activation). Several BRD4-PROTACs based on JQ1 or OTX015 (such as ARV-825) have entered preclinical studies and have been shown to significantly downregulate c-Myc expression through efficient degradation of BRD4, potentially relieving multiple inhibitions on the immune system; the second is 'direct targeting'-molecules such as AU-15330 developed by Aurigene aim to bind to the c-Myc/Max dimer interface and recruit mental retardation E3 ligase, which has been confirmed in preclinical models to induce endogenous c-Myc degradation and is currently in the in-depth validation stage, with its potential for combination with immunotherapy being highly anticipated; the third is an exploratory 'RNA-PROTAC fusion strategy', which involves designing small-molecule ligands that specifically recognize specific secondary structures of c-Myc mRNA (such as G-quadruplexes in the 5'UTR region) as 'warheads', and then coupling them with E3 ligase ligands to construct bifunctional molecules. This strategy is still in the early stage of concept validation (145,146). At the level of transcriptional regulation, given that the c-Myc promoter is rich in super-enhancers and highly dependent on epigenetic cooperation, targeting the upstream transcriptional machinery is also an effective alternative approach: BET bromodomain inhibitors (such as JQ1 and OTX015) weaken the anchoring of BRD4 at the c-Myc promoter and its recruitment of the transcriptional elongation complex by blocking BRD4's recognition of acetylated histones (147-149). These inhibitors have shown potential for synergy with anti-PD-1/PD-L1 therapies in preclinical studies; CDK7/9 inhibitors (such as KB-0742) directly inhibit the phosphorylation of RNA polymerase II and transcriptional elongation, thereby globally suppressing c-Myc mRNA synthesis (150), and may also sensitize to immunotherapy by reducing the expression of immune checkpoint molecules (150). In terms of RNA-level intervention, RNA interference technology also shows significant value: Small interfering RNA (siRNA) requires a delivery system (such as lipid nanoparticles or GalNAc conjugation) to enter cells. The representative drug DCR-MYC (developed by Dicerna, using the proprietary GalXC™ delivery technology) is an intravenous siRNA designed to specifically silence MYC mRNA; antisense oligonucleotides (ASO) are single-stranded

DNA/RNA molecules that mainly inhibit translation through RNase H-mediated mRNA degradation or steric hindrance. Although AZD4785 (developed by Ionis/AstraZeneca, targeting KRAS mRNA) does not directly act on c-Myc, its clinical success strongly validates the feasibility of ASO technology in targeting 'undruggable' oncogenic transcripts. ASOs targeting c-Myc have demonstrated efficacy in preclinical models and silencing c-Myc can reshape the tumor immune microenvironment, but still faces challenges in *in vivo* delivery efficiency and nucleic acid stability; short hairpin RNA is usually delivered by viral vectors (such as lentivirus or adeno-associated virus) and processed into siRNA in cells. Currently, it is more commonly used in gene therapy research and cell therapy (for example, in the modification of chimeric antigen receptor-T cells to knockdown c-Myc to enhance their *in vivo* persistence). At the level of stress pathway synergy, overexpression of c-Myc can lead to a sharp increase in protein synthesis load, imbalance in ribosome biogenesis and intensified endoplasmic reticulum stress, making tumor cells specifically dependent on pathways such as the unfolded protein response (UPR). Therefore, combined targeting of key nodes in the UPR (such as inositol-requiring enzyme 1 or protein kinase R-like endoplasmic reticulum kinase) can significantly amplify the apoptotic signals induced by c-Myc inhibition, achieving a synergistic anti-tumor effect (151,152).

In summary, although the above strategies take different paths, they are complementary and work in concert, collectively forming a multi-level targeted network covering transcription, translation, protein homeostasis and stress response, systematically dismantling the oncogenic program driven by c-Myc. This provides a solid, diverse and translational scientific basis for breaking through the long-held perception of c-Myc as 'undruggable'. It is particularly worth emphasizing that the combination of these c-Myc-targeting strategies with immune checkpoint inhibitors is emerging as a highly promising new direction for overcoming immune therapy resistance and converting 'cold tumors' into 'hot tumors'. The exploration in this area is ongoing. Collectively, these multi-pronged strategies provide innovative avenues to overcome c-Myc's 'undruggability'.

Clinical trial progress. At present, the clinical intervention strategies targeting c-Myc mainly include direct inhibition, functional interference, epigenetic regulation, protein degradation and indirect transcriptional inhibition (Table I). These explorations not only reflect the continuous efforts to target this core oncogene but also systematically reveal the multiple challenges it faces in terms of biological regulatory complexity and drug development feasibility. A careful analysis of the clinical outcomes of each strategy provides an important basis for subsequent rational drug design (153).

G-quadruplex stabilizers such as CX-3543 can inhibit c-Myc transcription by stabilizing specific DNA secondary structures in the c-Myc promoter region and preventing transcription factor binding. Although CX-3543 showed promising antitumor activity in early clinical trials in neuroendocrine tumors, poor pharmacokinetic properties, unacceptable dose-limiting toxicity and unsatisfactory clinical efficacy led to the termination of clinical trials. Its research and development work was terminated. The specific reasons are as follows: i) The pharmacokinetic profile of CX-3543 was a fatal flaw in its clinical development. Studies have shown that the drug has a high systemic clearance (rapid elimination from the body), making it difficult to maintain blood drug concentrations within the effective therapeutic window. In order to achieve the target inhibition effect, patients need frequent intravenous injection (such as once a day or multiple times a week), which not only seriously affects patient compliance, but also increases the risk of complications such as infection and phlebitis. ii) In the phase II study, CX-3543 showed severe retinal toxicity (e.g., retinal pigment epithelial cell damage, visual field defects), and the incidence of toxicity increased with increasing doses. This toxicity was 'dose-limiting' (i.e., could not be avoided by dose adjustment) and could not be mitigated by dose reductions, ultimately preventing treatment continuation. Retinal toxicity is an important safety hazard of anticancer drugs, especially for patients with long-term use, which may lead to permanent vision impairment. Therefore, regulatory agencies have a low tolerance for retinal toxicity. iii) Although CX-3543 showed inhibition of c-Myc pathway and ribosome reconstitution in multiple cell models (e.g., tumor cell lines and animal transplanted tumors), the objective response rate of CX-3543 in phase II clinical trials (for a variety of solid tumors, e.g., neuroendocrine tumors and lymphomas) was low (well below the prespecified response threshold). This impractical dosing regimen, combined with the observed dose-limiting retinal toxicity in patients, resulted in an unacceptable benefit-risk ratio that did not meet regulatory criteria for further clinical advancement (ClinicalTrials.gov no, NCT00780663) (153-156). This finding suggests that the discontinuation of CX-3543 was not due to a single factor but rather to a combination of pharmacokinetic, safety and efficacy failures. Therefore, the development and use of c-Myc inhibitors should be further explored. At the same time, the specific recognition and effective targeting of nuclear DNA structures by small molecules still face significant limitations in pharmacokinetics and delivery efficiency. Antisense oligonucleotides (such as INX-3280) degrade c-Myc mRNA through an RNase H-dependent pathway. Although the proof-of-concept study in AML was discontinued, it confirmed the feasibility of RNA-level targeting (157,158); current research and development efforts are focused on improving the tumor-targeting delivery efficiency, serum stability and cellular uptake of nucleic acid drugs. OMO-103 (Omomyc) is a small protein that can penetrate the cell membrane and inhibit the formation of c-Myc/MAX heterodimers by competitively binding to MAX. It has shown good safety in phase I/II trials for metastatic pancreatic ductal adenocarcinoma and osteosarcoma, and can reduce c-Myc activity in tumor tissues, inhibiting proliferation and migration (159,160). Its potential synergistic value lies in the possible alleviation of the c-Myc-driven immunosuppressive microenvironment, but attention should be paid to the immunogenicity risk of peptide drugs, the difficulty of large-scale production processes, and the tissue distribution and target occupancy in solid tumors after systemic administration. OTX-2002 is an mRNA-based lipid nanoparticle delivery system designed to induce epigenetic silencing at the c-Myc gene locus. In early clinical trials for hepatocellular carcinoma (NCT05497453), it was observed that c-Myc expression was downregulated and tumor growth was inhibited (161);

Table I. Clinical trial information of drugs targeting c-Myc.

Category	Drug name	Mechanism of action	Indication	Clinical trial phase	Results/status	(Refs.)
Direct c-Myc suppression	CX-3543	Stabilizes G-quadruplex structures in the c-Myc promoter, blocking transcription factor binding	Neuroendocrine carcinoma	Early-phase trials	Trials halted but provided insights into gene structure modulation	(153-156) NCT00780663
	INX-3280	Antisense oligonucleotide binds to c-Myc mRNA, triggering RNase H degradation	Acute myeloid leukemia	Early-phase trials	Discontinued but validated RNA-level interference strategies	(157,158)
c-Myc functional interference	OMO-103 (Omomyc)	Competes with MYC associated factor X (MAX) to form inactive heterodimers, blocking c-Myc-MAX-DNA interaction	Metastatic pancreatic ductal adenocarcinoma, osteosarcoma	Phase I/II	Reduced tumor c-Myc levels, inhibited proliferation/migration; safe; completion expected in 2026	(159-161) NCT04808362 NCT06059001 NCT06650514
Epigenetic modulators	OTX-2002	Lipid nanoparticle-delivered mRNA therapy targeting c-Myc epigenetic regulation (histone/DNA methylation)	Hepatocellular carcinoma & solid tumors	Early-phase trials	Reduced c-Myc expression, suppressed tumor growth/metastasis	(162) NCT05497453
c-Myc degraders	WBC100	Targets c-Myc nuclear localization signals to induce protein degradation	c-Myc-positive advanced solid tumors	Phase I	Well-tolerated, reduced tumor c-Myc levels; preliminary efficacy observed	(162) NCT05100251
Other targeted agents c-Myc transcriptional activation	JQ1 (BET inhibitor)	Inhibits BET protein binding to acetylated histones, blocking c-Myc transcriptional activation	Multiple cancers	Early-phase trials	Demonstrated antitumor activity across cancers, offering new therapeutic options	(161,162)

BET, bromodomain and extra terminal domain.

its long-term application requires further assessment of off-target epigenetic editing risks, organ selectivity of the nanoparticle carrier and potential immune activation effects. WBC100 promotes the proteasomal degradation of c-Myc by interfering with its nuclear localization signal and has shown acceptable safety and target inhibition activity in phase I trials for c-Myc-positive advanced solid tumors (162); its clinical translation potential depends on the depth, duration and tolerance of the therapeutic effect, and related mechanism studies will also help guide the development of more precise protein degradation strategies. BET inhibitors (such as JQ1) indirectly inhibit c-Myc transcription by blocking the binding of coactivators such as BRD4 to acetylated histones. Early clinical data show that they have broad-spectrum anti-tumor activity (147,149); however, the first-generation compounds are limited by hematological toxicity (such as thrombocytopenia) due to insufficient target selectivity, which has driven the exploration of highly selective second-generation inhibitors and combination therapy regimens.

In summary, the clinical practice of c-Myc targeted therapy has been continuously accumulating key experiences: Terminated trials have revealed critical bottlenecks in aspects such as target biology, drug delivery and patient selection, while strategies in the clinical development stage need further validation in terms of delivery efficiency, resistance control and long-term safety. Future research should focus on deepening the understanding of translational mechanisms, optimizing subject selection based on molecular typing, prospectively designing combined intervention plans and developing new delivery technologies with greater tissue selectivity to effectively advance c-Myc as a druggable and manageable clinical target. Furthermore, these clinical advancements highlight the potential of c-Myc in the treatment of various cancers. Ongoing research and technological innovations are expected to develop more effective c-Myc targeted drugs, bringing new hope to patients and enriching the scientific basis of precision oncology. It is particularly worth emphasizing that the success of future c-Myc targeted therapies is likely not only due to their direct anti-proliferative effects but also to the synergistic sensitization effects produced by combined strategies such as immunotherapy, opening up new avenues for conquering refractory solid tumors by reshaping the immune microenvironment.

Overall, the successful paradigm of traditional targeted therapy is mainly based on enzyme targets such as kinases with well-defined catalytic domains. These targets typically have stable three-dimensional conformations and deep, conserved ligand-binding pockets, and their functions are highly dependent on enzymatic activities that can be competitively inhibited by small molecules (such as ATP binding), thus supporting rational drug design based on X-ray crystallography or cryo-electron microscopy structures and successfully driving the approval of multiple kinase inhibitors for clinical use. In contrast, c-Myc, as a typical transcription factor, presents fundamentally different scientific challenges for targeting. There are systematic differences between kinases and c-Myc in terms of structural characteristics, functional realization mechanisms and intervention logics: Kinases have rigid, structured active centers, while c-Myc (especially its N-terminal transactivation domain) is an intrinsically disordered protein, lacking a persistent, recognizable hydrophobic binding interface; the oncogenic effect of kinases directly stems from their catalytic activity, and inhibiting this activity can effectively interrupt downstream signal transduction, while the functional realization of c-Myc depends on multiple dynamic processes-including forming heterodimers with MAX, specifically binding to E-box sequences (CACGTG) on DNA, and assembling functional transcriptional complexes with co-regulators such as TRRAP and WDR5, and its oncogenicity is the result of a combination of increased protein expression levels, enhanced complex stability and amplified transcriptional output; therefore, the 'occupation-driven' inhibition strategy for kinases is not applicable to c-Myc. Current promising intervention approaches focus on event-driven strategies, such as recruiting E3 ubiquitin ligases to c-Myc protein or its key co-factors (such as BRD4, WDR5) through PROTAC technology to induce ubiquitination modification and proteasomal degradation; or using RNA interference (siRNA, ASO), targeted protein degradation or transcriptional inhibition to reduce its functional abundance at the mRNA or protein level. These methods do not rely on the recognition of traditional binding pockets but rather weaken the oncogenic function output of c-Myc by regulating protein homeostasis or gene expression. This shift from 'inhibiting activity' to 'regulating abundance and assembly' reflects that drug development targeting transcription factor-like targets is gradually moving towards a new stage with clearer mechanisms and more feasible pathways, and also provides a methodological framework for addressing other 'undruggable' targets.

6. Conclusions and perspectives

c-Myc, as a proto-oncogenic transcription factor, regulates biological processes such as cell proliferation, differentiation and metabolism, and its aberrant activation is implicated in >70% of human cancers. However, several challenges persist in c-Myc research: First, developing targeted therapeutic strategies for c-Myc faces significant hurdles due to its ubiquitous expression in both normal and cancer cells, and direct inhibition strategies have yet to achieve substantial clinical success. Second, while c-Myc expression and activity are regulated by multiple signaling pathways, its precise regulatory network remains incompletely understood, necessitating further elucidation to inform effective therapeutic development. Finally, the context-dependent roles of c-Myc across cancer types-such as promoting proliferation in certain malignancies while suppressing differentiation in others- add complexity to its study. Although the discovery of c-Myc has opened new avenues in cancer research, its intricate regulatory mechanisms and pleiotropic functions pose ongoing challenges. Future studies must prioritize unraveling c-Myc's molecular mechanisms and devising precise therapeutic strategies to overcome its limitations in cancer treatment.

Despite extensive research into c-Myc's role in cancer, its complex regulatory mechanisms and potential therapeutic targets require further exploration. Future directions may include: i) Targeted therapy: Developing small-molecule drugs to directly or indirectly inhibit c-Myc function, such as

by disrupting c-Myc-Max complex formation or blocking its DNA binding; ii) transcriptional co-factor studies: Delving into c-Myc's interactions with transcriptional co-factors to clarify its gene regulatory mechanisms; iii) isoform-specific functions: Investigating functional differences among c-Myc isoforms and their cancer-specific roles; and iv) immunotherapy integration: Exploring c-Myc's role in tumor immune evasion and its potential synergy with immune checkpoint inhibitors. In summary, as a master regulator of cell proliferation and cancer progression, c-Myc's structural and functional features offer critical research avenues. Future efforts should focus on refining targeted therapies and dissecting its roles in the TME and immune evasion to advance cancer treatment.

To date, personalized medicine has emerged as a key focus, as genomic technologies enable tailoring therapies to individual tumor genetic profiles. This approach enhances treatment precision while minimizing adverse effects. Advances in drug delivery systems, particularly nanotechnology-based platforms, improve c-Myc targeting and therapeutic specificity. Novel inhibitors, including peptide-based drugs and PROTACs, represent significant progress in overcoming c-Myc's targeting challenges.

In conclusion, c-Myc is a multifunctional protein with vital biological roles, yet the relationship between its structure and function demands deeper investigation. A comprehensive understanding of its structure, function and interactions will illuminate c-Myc's central role in cellular biology and inspire innovative therapeutic strategies for related diseases.

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Authors' contributions

MY and YT were involved in the conception and design of the study. MY, YT, JL, JZ, LZ, XZ, SY and YS wrote the first draft of the review, while XZ, SY and YS collected the information needed for the review, including references and images. YT revised the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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