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REVIEW

The Effect of Myc Inhibition Combined with the Synergistic Effect of Photothermal, Photodynamic and Radiotherapy in Tumor Treatment

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Abstract: Photothermal therapy, photodynamic therapy, and radiotherapy offer the potential for precise tumor ablation with minimal adverse reactions. Myc is an oncogene that plays a critical role in cell growth and tumor development by regulating processes such as cell proliferation, differentiation, apoptosis, and metabolism. It is widely expressed in human cancers and is recognized as one of the potential targets for cancer therapy. Recent studies on the mechanism of Myc suggest that inhibiting its expression can delay cancer onset and progression. With the development of medical technology, photothermal therapy utilizes the photothermal conversion properties of nanomaterials to transform light energy into local high temperatures, thereby ablating tumor cells; photodynamic therapy relies on the synergistic action of photosensitizers, light, and oxygen to generate cytotoxic reactive oxygen species that destroy the structure of tumor cells; radiotherapy uses high-energy rays to precisely damage the DNA double-strands of tumor cells and induce free radical damage. All three therapies have demonstrated unique advantages and remarkable efficacy in the field of cancer treatment, offering new treatment options and survival hopes for cancer patients. Meanwhile, they have also propelled the continuous advancement of cancer treatment from traditional models towards more precise and minimally invasive approaches. In this review, we summarize the principles of photothermal, photodynamic therapy and radiotherapy and their related roles in tumor treatment with Myc inhibitors. We hope this review will provide new sights into cancer treatment related to the Myc gene.

Keywords: photothermal therapy, photodynamic therapy, radiotherapy, Myc, Myc inhibitor, combination therapy

Introduction

The Myc gene is one of the most studied proto-oncogenes, and is associated with the formation, maintenance and progression of various cancers.[1–3] More importantly, Myc is highly expressed in human cancers, and the research into its expression and function could bring new opportunities for tumor treatment. The Myc oncogene family consists of MYC, MYCN, and MYCL, all of which are major drivers of human tumorigenesis. Dysregulation of any member's expression can lead to different malignancies.[4] Myc activation through bromodomain proteins may be inhibited by drug-like molecules, thereby suppressing tumorigenesis.[5] The inhibition of c-Myc expression by small hairpin RNA or bromodomain can achieve inhibition of leukemia initiating cell activity which has been validated in mouse leukemia model.[6] Therefore, Myc has shifted from being considered "undruggable" to an "attractive" target for cancer therapy. However, the complex protein structure of Myc still poses a significant challenge for the development and optimization of Myc inhibitors.[7] It is necessary to find more effective direct or indirect inhibitors of Myc.

Myc inhibitors can be classified into the following categories: 1) blocking Myc transcription: Bromodomain and extraterminal (BET) domain inhibitors, G-quadruplex stabilizers; 2) impairng Myc translation: Antisense oligonucleotides

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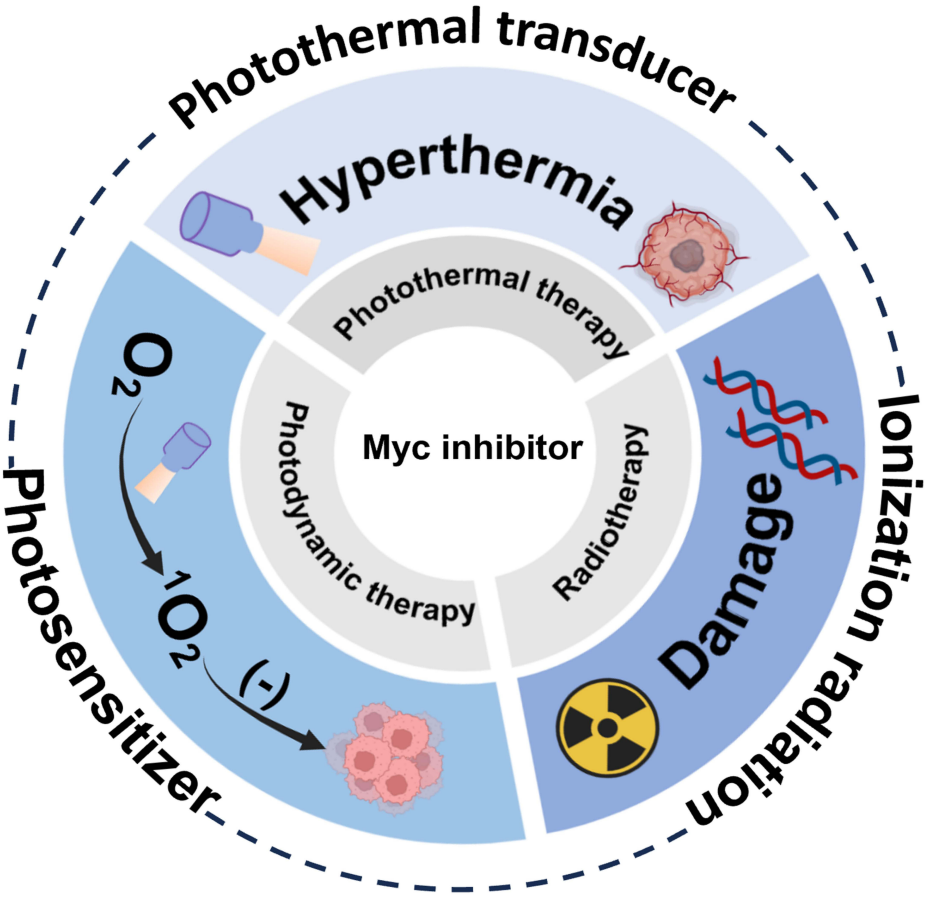
Graphical Abstract



(ASOs), siRNA/shRNA such as in a clinical trial sponsored by Dicerna, which used Myc RNAi (DCR-Myc) for solid tumors, multiple myeloma, or lymphoma treatment;[8] 3) inhibitors of Myc dimerization and DNA binding: small molecules such as KJ-Pyr-9, MYCi975, EN4, KSI-3716, etc.[9] Myc inhibitors interfere with the interaction between Myc and MAX while simultaneously decreasing the stability of the Myc protein. This dual interfere of Myc inhibitors can significantly suppress the global expression of Myc target genes, curtails the proliferation of Myc-dependent cancer cells, and restrains tumor growth in vivo.[10] Currently, BET inhibitors have exhibited remarkable efficacy in preclinical models and have demonstrated superior antitumor activities in clinical trials of hematological malignancies like leukemia and lymphoma.[10] For example, the BET inhibitor BRD4 blocks tumor progression in two ways: on the one hand, it inhibits cancer cell proliferation by directly downregulating c-Myc; on the other hand, it hinders the communication and interaction between cancer cells and the tumor microenvironment, thereby restricting tumor expansion.[11] KSI-3716 has shown efficacy in mouse bladder cancer models.[11] KJ-Pyr-9 can interfere with the growth of human tumor cell xenografts of Myc-dependent transcriptional programs and might cross the blood-brain barrier.[12] BET domain inhibitors (BETis) such as micellar JQ1 (mJQ1) can bind to BRD2/4 and prevent BRD4 from binding to acetylated histones within the Myc site, thereby reducing the expression of Myc superfamily members.[4,13] Because of its unique properties, Myc inhibitors not only can inhibit cancer cells when used alone but also exhibit advantages in enhancing the efficacy and reducing the side effects of anticancer treatment.[14,15] The combination of Myc inhibitors with chemotherapy drugs such as vincristine, ATO, cisplatin, doxorubicin, and 5-fluorouracil can achieve a synergistic enhancement of the anti-cancer effect, providing a stronger impetus for cancer treatment.[16,17] This indicates that Myc inhibitors in combination with other therapeutic modalities can

augment tumor suppression. Recently, more Myc inhibitors have been utilized in clinical trials and we list them in Table 1. Myc inhibitors (such as MRT-2359, OMO-103, Sepantronium Bromide, ZEN-3694, etc.) are in Phase I or phase I/II.

With the development of modern cancer therapeutic methods, photothermal therapy, photodynamic therapy and radiotherapy have played an important role in cancer treatment and exhibit strong anti-tumor effects.[18–20] These treatment methods utilizing light, heat, radiation effects on tumor location within a certain scope, and then achieve antitumor effect. Photothermal therapy (PTT) utilizes the photothermal effect of photothermal transduction agents (PTAs) which collect energy in the light and convert it into heat. The increase in temperature in the photothermal agent (PTAs) is mainly caused by localized surface plasmon resonance (LSPR). When the photothermal agent (such as noble metal nanoparticles or certain semiconductor materials) is exposed to light of a specific wavelength, the collective oscillation of surface electrons (LSPR) occurs, converting the absorbed light energy into heat energy, thereby achieving a local increase in temperature.[21] This causes the temperature of the surrounding environment to increase and triggers cancer cell death. For instance, high temperature can cause damage to vascular endothelial cells and thrombosis, block the blood supply to tumors, exacerbate hypoxia and nutrient deficiency in cancer cells, and synergistically enhance the killing effect.[22] In addition, high temperature can enhance the exposure of antigens on the surface of tumor cells, potentially triggering immunogenic cell death and providing a basis for combined immunotherapy.[23] More importantly, Yang et al discovered that the combination of photothermal therapy (PTT) and Myc inhibitors can further suppress residual cancer cells and restrain tumor metastasis.[24] Similar to PTT, in photodynamic therapy (PDT), photosensitizers (PS) transfer the energy of light. When PS is activated by light of a certain wavelength, it induces the generation of reactive oxygen species which can lead to tumor ablation.[25] For example, G4-forming sequences located in the untranslated regions of cancer-related genes (RAS and Myc) can be used as photosensitizers for cancer photodynamic therapy.[26] With its low toxicity and high safety, PDT is widely employed in the treatment of solid tumors such as bladder, esophageal, skin and breast tumors.[19] In recent years, a large number of studies have shown that photodynamic therapy (PDT) combined with anti-vascular endothelial growth factor (VEGF) therapy can effectively inhibit tumor growth, providing a new idea for tumor treatment.[27,28] A research into photoimmunotherapy has revealed that when Myc inhibitor-JQ1 is combined with PDT, it can effectively inhibit the expression of c-Myc and PD-L1, thereby successfully thwarting the PDT-mediated immune escape. The synergistic action of this combination therapy significantly boosts the overall effectiveness of the treatment by acting on multiple targets concurrently.[29] Radiotherapy makes use of ionizing radiation (such as X-rays, electron beams, etc.) to form charged particles that deposit energy in tissues and cells. Ionizing radiation energy can damage cellular genetic material or cause genetic changes and kill cancer cells.[30] And radiotherapy has become a growing consensus that radiotherapy can improve the response rate and overall efficacy of immunotherapy. Wu et al summarized

Table 1 Summary of Clinical Trials of Myc Inhibitors Published on the NIH Website by April 2024 (https://clinicaltrails.gov)

Clinical Trials ID	Study Start	Drug	Sponsor	Study Status	Study Phase
NCT04309968	2020-04	SYHA1801	CSPC ZhongQi Pharmaceutical Technology Co., Ltd. (Tianjin, China)	Unknown status	Phase I
NCT04808362	2021-04	OMO-103	Peptomyc S.L. (Barcelona, Spain)	Terminated	Phase I/II
NCT05100251	2021-10	WBC100	Zhejiang University (Zhejiang, China)	Recruiting	Phase I
NCT04840589	2022-02	BET Bromodomain Inhibitor ZEN-3694	National Cancer Institute (NCI)	Recruiting	Phase I/Ib
NCT04896073	2022-03	Minnelide	National Cancer Institute (NCI)	Recruiting	Phase II
NCT05546268	2022-10	MRT-2359	Monte Rosa Therapeutics, Inc (Arizona, United States)	Recruiting	Phase I/II
NCT05263583	2022-12	Sepantronium Bromide	Cothera Bioscience, Inc (Beijing, China)	Recruiting	Phase II
NCT06059001	2023-08	OMO-103	Peptomyc S.L. (Barcelona, Spain)	Recruiting	Phase I/Ib
NCT05950464	2023-12	BET Bromodomain Inhibitor ZEN-3694	National Cancer Institute (NCI)	Recruiting	Phase I/Ib

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the preclinical mechanisms by which radiotherapy enhanced anti-tumor immune responses and recently updated clinical trial results.[31] In addition, radiotherapy can down-regulate the expression of Myc during the tumor treatment, and the combination of radiotherapy and Myc inhibitors have a significant inhibitory effect on tumors.[32] Since Myc inhibitors, such as BETi, has a regulatory role of the immune mechanisms, including checkpoint inhibitors, immune cells and cytokines, etc. And Myc inhibitors have great prospect in joint physical therapy to treat cancer.[33] PTT, PDT, and immunotherapy have demonstrated excellent efficacy in inhibiting tumor progression.[19,34,35] The above physical treatments have a great correlation with the immune response. More importantly, immunotherapy has shown enormous potential in anti-tumor therapy, which can reactivate the human body immune response against tumor cells.[36,37] When combined with PTT, PDT and radiotherapy, immunotherapy may provide promising prospects for cancer treatment.

Previous reviews of photothermal, photodynamic and radiation therapy mainly have primarily focused on their development processes. In the recent review of PTT and PDT, researchers prefer to elaborate from the perspective of materials. Liu et al summarized various inorganic and organic nano photothermal transducers (PTAs) and described some strategies to strengthen PTT effects.[38] Ji's review provided a general overview of the emerging nanomedicines for PDT-driven tumor immunotherapy.[34] Wang et al designed an intelligent PdH@MnO_2/Ce6@HA (PHMCH) yolk-shell nanoplatform to combine gas therapy with photothermal therapy (PTT) and photodynamic therapy (PDT) for synergistic antitumor effects. These three therapies work together to attack tumor cells through different mechanisms, achieving precise treatment of melanoma and effective protection of normal tissues.[39] Regarding Myc inhibitors, reviews focused on its development, different regulation modes and their clinical prospects for cancer treatment.[9,40,41] But there are limited reviews highlighting the application of Myc inhibitors in photothermal therapy, photodynamic therapy and radiotherapy. Therefore, we summarize the application of Myc inhibitors combined with photothermal therapy, photodynamic therapy and radiotherapy in the treatment of tumors in this review (Figure 1). We aim to provide a novel way for the preclinical treatment of tumors through combination therapy.

Discussion

The Inhibitory Effect of Myc Inhibitors Combined with Photothermal Therapy on Tumors

Photothermal therapy (PTT) is another type of cancer treatment compared to chemotherapy, radiotherapy, and surgical treatments. With the development of photothermal materials, this therapeutic approach has great potential for clinical translation. PTT converts light energy into heat, triggering the ablation of tumor. PTT can prompt a portion of the activated T lymphocytes to differentiate into memory T cells, which are able to monitor and defend against tumor recurrence over an extended period, augmenting the long-term anti-tumor efficacy. Collectively, these mechanisms endow PTT with potent anti-tumor capabilities.[42] Li et al reported that hyperthermia can enhance the uptake of immune effectors and reduce hypoxia-related immunosuppression by increasing tumor perfusion and reoxygenation, and can also increase the transport and effector function of immune cells, as well as increase pro-inflammatory factors.[2,43] Baronzio's review introduced that hyperthermia can enhance antigen presentation and promote anti-tumor immune response and proposed that hyperthermia can be used as an innate immune enhancer.[44] Oei et al reported that hyperthermia can alleviate the DNA repair system, which may enhance DNA-targeted anti-tumor therapy or promote tumor neoantigen production.[45] Additionally, photothermal agents (PTAs) plays a crucial role in PTT. Mediated by PTAs, PTT produces hyperthermia, which activates the body's immune response leading to cell death and tumor suppression. Various types of PTAs have been synthesized such as inorganic nanomaterials, organic dyes and polymer.[46] In addition, the therapeutic efficacy of PTT can be improved by using nanocarrier delivery systems. A research team designed a BRD4-targeting photothermal agent (PTJQ) that, under low-power-density laser irradiation, specifically binds to the bromodomain of BRD4, induces protein degradation, disrupts BRD4's structure, and inhibits its transcriptional regulatory function. This process effectively blocks the transcriptional activation of Myc and BCL-2 oncogenes, thereby suppressing tumor growth.[47] The development of nanoparticle medicine has made PTT a potential minimally invasive treatment for solid tumors. For example, the researchers prepared a nanomaterial by coating the cell membranes of hybrid red blood cells (RBCS) and B16-F10 melanoma cells with hollow copper sulfide nanoparticles (NP) loaded with doxorubicin (DOX) to produce DCuS@[RBC-B16] NP. This research is then

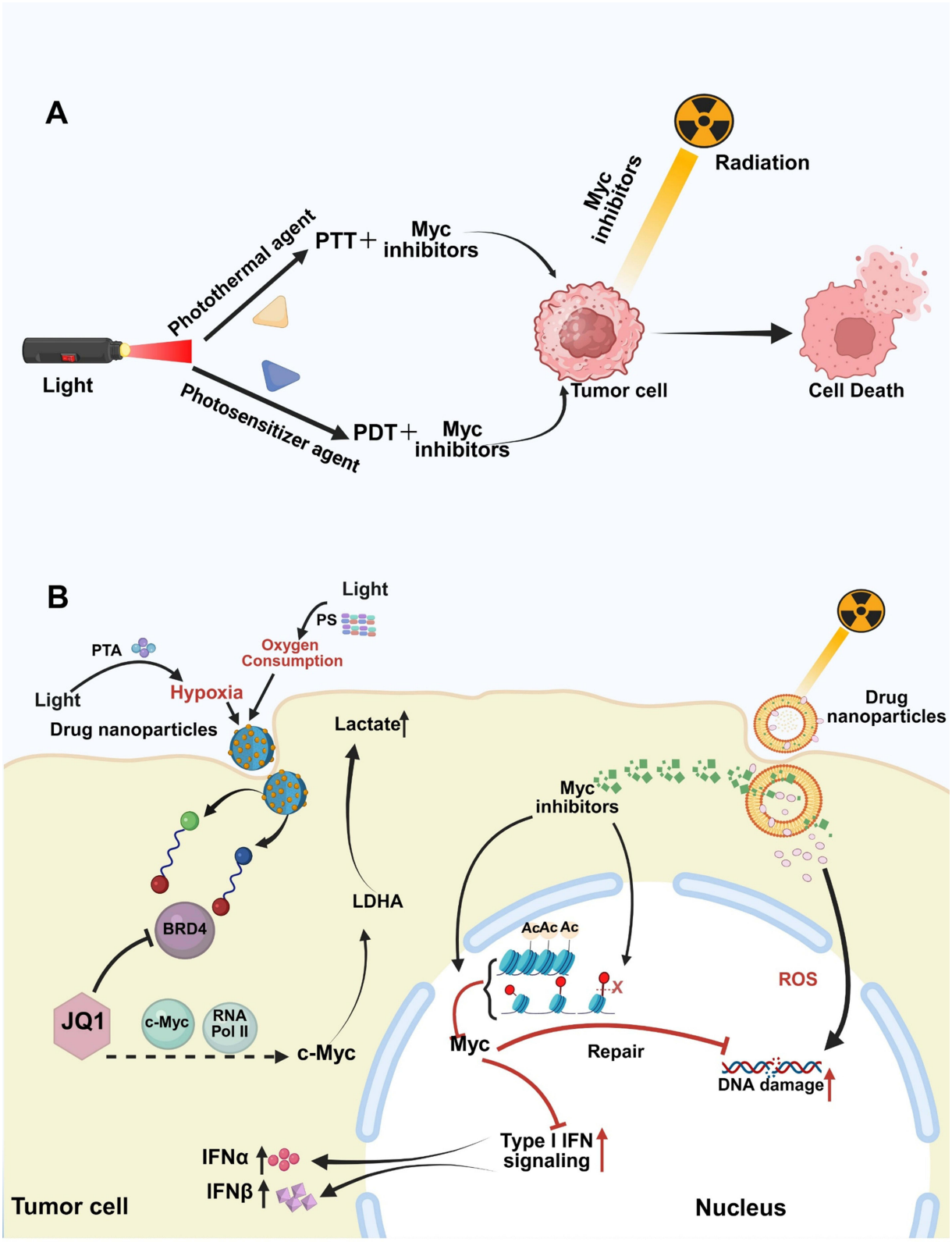

Figure 1 A schematic diagram of PTT, PDT, and radiation therapy in combination with Myc inhibitors for the treatment of tumors. (**A**) When Myc inhibitors are combined with physical therapy, they can exert a powerful inhibitory effect. (**B**) When physical therapy is combined with Myc inhibitors, they can work synergistically to exert anti-tumor effects. For instance, under irradiation with specific wavelengths of light, the photosensitizer is activated and undergoes a photochemical reaction with oxygen in the tumor microenvironment, generating cytotoxic substances such as singlet oxygen which leads to tissue hypoxia and thereby destroys the tumor cells. The combined use of radiotherapy and Myc inhibitors in treating tumors can achieve this effect through DNA damage and the Type I signaling pathway, significantly enhancing anti-tumor efficacy. Note: The conversion of PTT photosensitizers to Hypoxia and the increased oxygen consumption caused by PDT photosensitizers (PS) are marked in red. Created in BioRender. OeO, (**C**) (2025) https://BioRender.com/xqft4n5.

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used in combination imaging of melanoma, photothermal therapy (PTT), and chemotherapy.[48,49] The assembly of radioactive substances and light activation, along with image-guided light therapeutics in accurately identifying disease sites, can enhance the efficacy of PTT therapy and reduce side effects.[50] When PTT combined nanoplatforms could increase the therapeutic efficacy of malignant Michigan Cancer Foundation-7 (MCF-7) cells.[51] Sweeny et al reported that Prussian blue nanoparticles, an organic photothermal agent, were used to achieve combined photothermal and immune therapy against neuroblastoma.[48] Henderson et al investigated the interaction between photodynamic therapy (PDT) and hyperthermia through tumor regrowth and in vitro and in vivo cloning assay.[49] The occurrence and development of tumors are highly correlated with the physiological state of the tumor microenvironment (TME). Tumor cell death will produce tumor related antigen and then can appear the expression of antigen-presenting cells (APCs). However, these reactions cannot to effectively activate dendritic cells and T cells in TME.

The oncogene Myc is dysregulated in all kinds of human tumors and is a vital collection of multiple oncogenic signaling pathways and immune microenvironment. For example, On the one hand, Myc promotes the expression of immunosuppressive factors, and on the other hand, it inhibits the expression of immune activation regulators.[50] The treatment of Myc targets can provide potential clues for tumor therapy. A study has demonstrated that the BRD4 inhibitor NHWD-870 can suppress the expression of c-Myc and significantly inhibits the growth of multiple cancer cells originating from solid tumors. Due to the issue of efficacy and drug resistance, most BET inhibitors in clinical use, such as GSK525762, CPI-0610, OTX-015 and others, has similar structure to JQ1 which exhibit good preliminary effects on hematological malignancies.[52–54] As an emerging therapy, PPT therapy can effectively eliminate cancer cells and accurately target tumor.[40] However, monotherapy with PTT often fails to trigger sufficient therapeutic effects, which may result in incomplete elimination of tumor cells or lead to tumor recurrence and distant metastasis. Photothermal treatment in combination with other therapies can enhance overall treatment outcomes. For example, PTT combined with chemotherapy can eliminate cisplatin-resistant tumor models;[40] Researchers have developed a γ-PGA-based hydrogel system that combines photothermal therapy (PTT) with chemotherapy to enhance drug release in a controlled manner for improved cancer treatment. This will pave the way for future applications in precision oncology.[55] PTT in combination with gene therapy in recent times, an increasing number of studies have shown that photothermal therapy can also achieve synergistic effects;[56] Photothermal therapy combined with surgical treatment can more comprehensively remove tumor.[57] Additionally, PTT can also induce massive tumor cell death and trigger immune responses, including the redistribution and activation of immune effector cells and the transformation of memory T lymphocytes.[58] Hence, when Myc inhibitors combined therapy with PTT can make the cytotoxic T lymphocyte activation induced strong immune memory effect significantly, and restrain BRD4-c-Myc axis to inhibit the growth of triple-negative breast cancer (TNBC) in mice.[59] Althoff et al certified that JQ1, as a Myc inhibitor, caused a significant reduction in tumor cell viability and induced apoptosis to inhibit the proliferation of transplanted tumors.[60] "EN4" is another novel compound which directly targets c-Myc in cells, prevents c-Myc DNA binding and reduces its transcriptional activity, thereby down-regulating the transcriptional target and hindering tumorigenesis.[52] "EN4" off targeting might cause serious side effects, leading to nonselective inactivation and proliferation of normal cells.[53] When attaining localized photothermal therapy (PTT), gastric cancer stem cell therapy and nanoliposomes co-loaded with IR780 photosensitizer (designated Nano-EN-IR@Lip) can rapidly kill tumor cells and prevent tumor recurrence.[24] Those approach exhibits excellent biocompatibility, thermal ablation and tumor inhibition.[24] We briefly outline the combination of PTT and Myc inhibitors for the treatment of tumors (Figure 2).

A recent study showed that by nano-assembling palmitoyl-bioconjugated acetyl-coenzyme-A (called "siNozyme"), which co-delivers anti-c-Myc siRNA and aldehyde, achieving growth inhibition of approximately 90% of human melanoma.[54] Nam et al suggested that PTT in combination with a therapeutic dose of adriamycin can cause to bust antitumor responses and eliminate the primary and secondary tumors. In their work, they fabricated a core-shell nanostructure with a core of a spiky Au NP in a dopamine shell (SGNP@PDAs) which can enhance the photothermal stability of spiky Au NPs under laser irradiation. In CT26 tumor model, PTT via SGNP@PDAs alone resulted in 75% regression of most solid tumors, a 4-fold increase CD8+ T cell responses compare to control group, and induction of antitumor immunity.[56] However, mild PTT alone usually cannot activate the immune response and prevent tumor metastasis. Ge et al designed a photothermal agent, copper sulfide@ovalbumin (CuS@OVA), which can optimize the tumor microenvironment (TME) and active an adaptive immune response to restrain tumor growth and metastasis in a mouse melanoma model. In addition, the release of copper ions from acidic TME promoted the M1 polarization of

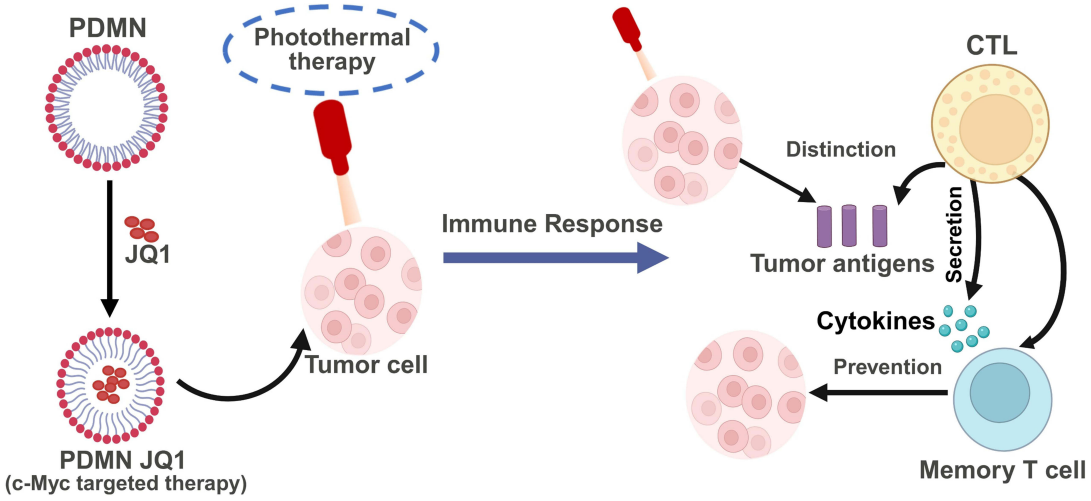

Figure 2 Schematic illustration of Myc inhibitors combined therapy with PTT. Created in BioRender. OeO, (C) (2025) https://BioRender.com/mr3m6ka.

tumor-associated macrophages.[57] The combination of PTT and Myc inhibitors demonstrated great potential for cancer treatment. In Table 2, we list the inhibitors utilized in the synergistic therapy of photothermal therapy and Myc inhibitors in recent researches. Cancer nano-therapy is developing rapidly to seek better ways to treat cancer. In order to reduce side effects, nanostructured lipid carriers (NLC) appeared in the late 1990s, it is mainly claimed to improve the solubility of drug and enhance drug delivery and sustain the release of drug-loaded.[61]

Nevertheless, PTT offers advantages such as it can accurately target the tumor to minimize the damage to the surrounding healthy tissue.[38] Several challenges need to be addressed before photothermal therapy (PTT) can be applied clinically. Firstly, the limited tissue penetration may hinder effective tumor ablation beyond the light irradiation range.

Table 2 Outline of Synergistic Therapy of PTT, PDT and Radiotherapy with Myc Inhibitors

Therapy			Reference
Photothermal Therapy	**Photothermal Transduction Agents**	**Myc inhibitor**	
	PDMNs	JQ1	23,41
	IR780	EN4	43,44,45
Photodynamic Therapy	Photosensitizers	Myc inhibitor	
	Nanoparticles	BRD4i (JQ1)	69-71,25
	G4 ligands	G4 motifs	60,74-76
Radiotherapy	Radiosensitizer	Myc inhibitor	
	Enzyme-responsive mJQ1	BRD4i (JQ1)	16.18, 21
	PWAI	5-Aza	28,101–105

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Additionally, Other drawbacks of PTT also exist such as the relatively inefficient delivery of PTAs in tumors, heating in tumor areas could lead to normal tissues damage and the overexpression of heat shock proteins in some cancers could cause PTT resistance.[38] Zhu et al reported that proper laser dosage can determine the optimal treatment duration after PTAs treatment of the tumor.[62] However, the complex protein structure of Myc still poses a significant challenge for the clinical application of Myc inhibitors. Omomyc, a promising small molecule Myc inhibitor, is in pre-clinical stage. In short, Myc inhibitors can be used as a targeted therapy method in combination with PPT, showing a strong inhibitory effect on tumor treatment. For example, the combination of EN4 and JQ1 with PTT treatment can halt the progression of tumors.[24,59] This combination therapy provides a new perspective for the current precision treatment of cancer. At present, clinical trials of Myc inhibitors combined with PTT has not been reported.

The Tumor Suppression via Combined Myc Inhibition and Photodynamic Therapy

Photodynamic therapy (PDT) is a rapidly developing treatment created in the last century and is considered as a minimally invasive cancer treatment.[63] PDT uses photosensitizers to induce photochemical reactions that release free oxygen radicals and reactive oxygen species, thereby can eradicate tumor cells.[64] In some types of cancer, such as breast cancer,[65,66] colorectal cancer,[67,68] pancreatic cancer[69] and bile duct cancer,[69] patients treated with PDT have excellent therapeutic effect. In 1994, PDT was approved in Japan as a radical approach for superficial esophageal cancer.[70] PDT has demonstrated excellent long-term treatment outcomes compared with esophagectomy. In United States PDT was used in the palliative treatment of patients with Barrett's esophageal dysplasia and symptomatic obstructive esophageal cancer.[71] The PDT also include type I and type II photothermal reaction, which can destroy the cancer and stimulate immune reaction. Type I reaction produces free radicals and free radical anions (eg, O_2•−HO•). Type II reaction produces singlet oxygen ($^1O_2$). These two mechanisms can occur concurrently, leading to excessive production of reactive oxygen species (ROS) in cancer and cellular toxicity.[26] Low levels of ROS plays an important role in maintaining cell homeostasis.[72] However, an imbalance between ROS generation and detoxification may leave cells with high ROS content, generating oxidative stress. The oxidative could damage cellular components (eg, proteins, lipids, and DNAs), apoptosis, or necrosis, and may promote oncogenic mutations.[73] PDT can cause inflammation, innate immunity, adaptive immunity, and has anti-vascular effects. PDT also can stimulate neutrophils, macrophages and lymphocytes proliferation of immune cells. The stimulated cells can rapidly infiltrate into the tumor tissue, then cause specific immune response to tumor.[74–76] In general, PDT plays a dual role in tumor tissue ablation. On one hand, it directly exerts toxic effects on tumor cells, leading to their damage. On the other hand, it can inflict damage on the tumor vasculature.[74] Wu et al constructed a novel nanoplatform combining innate immune activator Astragaloside III (As) and the PDT reagent chlorine e6 (Ce6) (As + Ce6) @MSNs-PEG. Under the induction of PDT photosensitizer Ce6, it can effectively induce the apoptosis of tumor cells, improve the infiltration of immune cells into the tumor, and showed good tumor penetration and good synergistic immunotherapy effect on CT26 tumor.[77] Other studies showed that PDT can enhance anti-tumor immunity and strengthen the immunogenicity toward tumor.[78] This anti-tumor immunity depends on the activation of antigen presenting cells (APCs). In recent times, an increasing number of studies have revealed that the combination of photodynamic therapy (PDT) with other treatment modalities yields more favorable anti-tumor outcomes and can diminish the incidence of adverse side effects. Yuan and his research team harnessed a nanoparticle platform-supported photosensitizer in conjunction with PD-L1 blockade therapy, thereby enhancing the therapeutic efficacy for CRC.[79] The research devised an anoxic-responsive nanoscale Covalent Organic Framework (COF) nanoplatform tailored for hypoxia-activated cascade chemotherapy and photodynamic therapy. This innovative platform enables programmed hypoxia-triggered cascade chemotherapy, which enhancing the therapeutic efficacy in tumor treatment.[80] In brief, the combination of PDT with other therapeutic modalities can integrate diverse treatment mechanisms, thereby accomplishing a concerted assault on tumors, augmenting anti-cancer efficacy, and contributing to the deceleration of the disease progression in patients. In addition, some researchers designed a new small-molecule light therapy agent, PDI-TN. During PDT, with imaging technology, the distribution changes of photosensitizers within the pathological tissue, the generation of ROS, as well as the morphological alterations of the pathological tissue were observed. Thereby, the treatment plan could be adjusted promptly to minimize the damage to normal tissue.[81]

With the development of nano-drug delivery systems, drug therapy combined with photodynamic therapy (PDT) can effectively inhibit Myc gene expression in tumor cells. Therefore, Myc inhibitors combined with PDT therapy provides a potential for anti-tumor therapy. Researches showed that the Myc proto-oncogene is a gene product involved in the transcriptional regulation of a variety of genes that are essential for cellular programs required for normal and tumor cell growth and proliferation.[82] In recent times, an increasing number of studies have revealed that the combination of photodynamic therapy (PDT). For instance, BRD4 inhibitors such as JQ1 is one of the Myc inhibitors, which can block c-Myc transcription and inhibit glycolysis.[29] At the same time, JQ1 were shown to down-regulate Myc and inhibit tumor growth of Myc activation in multiple animal models.[83–85] G4 motifs are secondary DNA structure which can either positively or negatively regulate gene expression.[86] When G4 motifs is stabilized, resulting in decreased expression of Myc.[87,88] Using in photosensitizers, G4 ligands can be selectively accumulated in tumors to reduce their side effects on normal cells and enhance anti-tumor efficacy.[26] PDT can induce inflammatory cells and promote cell apoptosis, which is an effective treatment. Hexaminolevulinate (HAL) is a hexyl ester of aminolevulinic acid (ALA) with a higher lipophilicity and also is a promising compound for PDT therapy. Cekaite et al demonstrated that c-Myc expression in Jurkat cells could be down-regulated by HAL-PDT.[89] Ruhdorfer et al also reported that ALA-PDT treatment of A-431 cells could down-regulate the c-Myc gene.[79] In a novel mechanism of the response of rectal cancer cells to photodynamic therapy, PDT can reduce c-Myc expression in CRC cells.[80] Compared with the single treatment of PDT, the combination of PDT and Myc inhibitor can increase the sensitivity of tumor cells to PDT and produce multi-target synergistic effect to enhance the anti-cancer effect. This provides a more effective plan for future cancer treatment, which is expected to improve patient prognosis and quality of life and promote the development of precision therapy. Sun et al demonstrated a supramolecular prodrug nanoplatform that co-delivers a prodrug containing the bromodomain protein 4 inhibitor (BRD4i) JQ1 and a photosensitizer for combined photoimmunotherapy in pancreatic cancer. Theses nanoparticles included adamantine-conjugated heterodimers of JQ1, pyropheophorbide a (PPa) and cyclodextrin-grafted hyaluronic acid (HA-CD). They found that PDT can improve the immunogenicity of tumor cells, promote the infiltration of cytotoxic T lymphocytes into the tumor, and enhance the effect of immunotherapy.[29] We make a schematic diagram based on this research regarding the combination therapy of PDT with Myc inhibitors. PDT mediated by photosensitizer initiates ICD of tumor cells, activates the CTLs and causes tumor regression. At the same time, BRD4i JQ1 could impede the transcription of the downstream genes of the c-Myc signaling pathway and c-Myc, including HK-2 and LDHA (Figure 3). dBET6 is a BRD4 degrader based on PROTAC technology, which can effectively and continuously degrade BRD4 protein, thereby exerting anti-tumor effects and immune regulatory effects. When combined with PDT, it can inhibit the progression and metastasis of breast cancer. These studies indicate that compared with single treatment modalities, combination therapy has great advantages in cancer treatment.[81] The combined use of multiple therapies can enhance the antitumor effect and improve the killing ability of drugs. At present, there are still few studies on the combined use of Myc inhibitors and PDT. Both can produce powerful antitumor effects. However, whether their combination can achieve a dual antitumor effect still needs to be studied by researchers. Those study showed that combination therapy had an extremely advantage in cancer treatment compared with single treatment approaches. Combined treatment of a variety of synergy can improve the antitumor activity and at the same time also can increase the drug killing ability. We listed recent study of combination therapies of photodynamic therapy and Myc inhibitors in Table 2.

Over the past decades, photodynamic therapy (PDT) had made great progress in cancer treatment and had been widely used as a physical therapy in clinical practice. However, photodynamic therapy exists some drawbacks. Such as, due to the insufficient light penetration, it can only be used for the treatment of superficial tumors.[90] Besides, when the oxygen concentration is not high enough in the medium, the photodamage is reduced or even no photodynamic reaction occurs at all.[91] Currently, one of the biggest disadvantages of PDT is the phototoxic reaction, which can be manifested as pain, erythema and edema. One large study about the patients of receiving PDT over 5 years showed that 92% of subjects bore pain, 89% patients occurred erythema and 80% endured oedema.[92] Therefore, more attention should be paid to novel photosensitizers to reduce the side effects of PDT in the future. Recent research on Myc inhibitors has also been greatly developed, and many Myc inhibitors have been used in clinical trials. Bromodomain Inhibitor ZEN-3694is in phase I/Ib clinical trials. However, there are currently few clinical trials on PDT combined with Myc inhibitors, and researchers need to further explore the best cancer treatment.

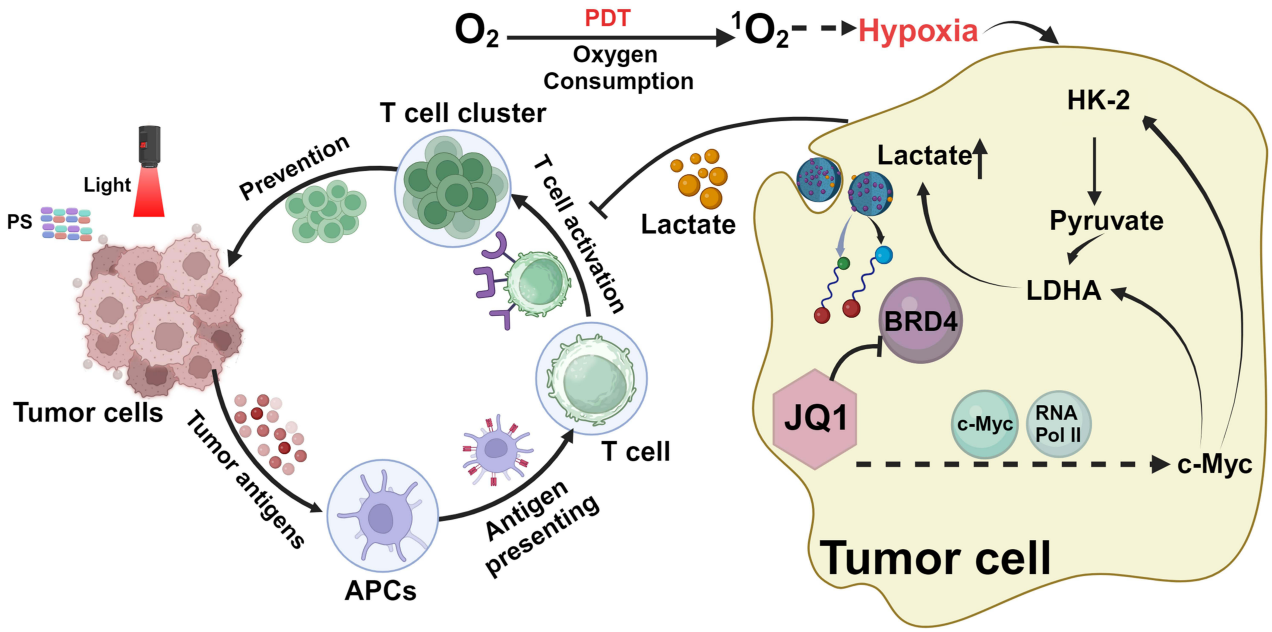

Figure 3 Mechanism diagram of Myc inhibitors combined with PDT for tumors. The main mechanism by which photodynamic therapy inhibits tumors is that photosensitizers, when irradiated with light of specific wavelengths, generate reactive oxygen species such as singlet oxygen, thereby causing tissue hypoxia. These reactive oxygen species can directly kill tumor cells and induce immunogenic cell death, which in turn activates the immune response to inhibit tumor growth. The red text indicates photodynamic therapy and photosensitizer-induced hypoxia. Created in BioRender. OeO, (C) (2025) https://BioRender.com/e8co039.

Myc Inhibitors Combined with Radiotherapy to Treat Tumor

Radiotherapy is a vital and efficient method to eliminate or control tumors. X-rays, gamma rays and other high-energy photon radiation directly or indirectly effects on the cancer cell and tumor tissue.[93] Direct radiation exposure induces DNA single-strand breaks (SSB) and double-strand breaks (DSB), leading to cell damage and proliferation termination, and even cell necrosis and apoptosis. In the case of indirect radiation effects, ROS production can be induced, which can induce cellular stress and damage to biomolecules, and ultimately change cell signaling pathways.[94] Low-level radiation (LLR) can be used as whole-body or hemi-body radiotherapy. Systemic exposure to LLR (ie, acute absorption ≤ 0.1 Gy or rate ≤0.1 m Gy/min) with long-term irradiation has been shown to inhibit or delay the development of primary and metastatic cancers.[95,96] High-dose-rate radiotherapy has been demonstrated to be efficient in non-melanoma skin cancers treatment, achieving a local control rate of approximately 97% and a cosmetic effect of 94.8% in elderly patients.[97,98] Today, a variety of nano-biomaterials such as Au[99] and MnO2[100] have been widely applied in radiotherapy, and the effect of treating tumors is extremely significant. For example, some nanoparticles such as lactic-co-glycolic acid nanoparticles were synthesized, which can transfer the tumor-specific protein after X-ray stimulation to antigen-presenting cells.[101] Dong et al utilized semiconductor heterojunction structure WO2.9-WSe2-PEG nanoparticles (WSP NPs) and found that the combination of WSP NPs with αPD-L1 resulted in high regression of primary tumors and distant tumors upon X-ray irradiation.[102] In another study, Mn2+ chelated tannic acid-based nanoplatform was utilized to treat tumors by integrating αPD-L1. Compared to the αPD-L1 treated group, combination group of tumor tissue survival rate doubled.[103,104] These results suggest that nano materials combined with radiation therapy can trigger T cell infiltration and improve tumor radiosensitivity.

Tumor radiotherapy is a local treatment method that uses radiation to treat tumors. Radiation resistance occurs in the process of tumor radiotherapy, which is closely related to the prognosis of tumor treatment. Radiation therapy in combination with other treatment modalities also exhibits remarkable advantages and holds significant potential in enhancing therapeutic outcomes. Gong and his team comprehensively reviewed the preclinical and clinical progress achieved in the integration of radiotherapy with PD-1/PD-L1 blockade. They elucidated that the combination of radiotherapy and immunotherapy has the potential to augment the anti - tumor efficacy, opening new avenues for more effective cancer treatment strategies.[105] The combination of multiple methods may become an effective measure for the precise

treatment of tumor. The expression of the Myc gene was correlated with radiotherapy sensitivity. Huang et al investigated that c-Myc can form a feedback network in head and neck squamous cell carcinoma cells to mediate radiosensitivity.[106] In radiotherapy, radiation induces the production of reactive oxygen species (ROS), causing cellular stress, thereby reversing the hypoxic state of the TME. The Myc gene plays a key role in cell proliferation and growth, and has been proven in the occurrence and development of different types of cancer. Chromosomal translocation, genomic amplification, retroviral integration, and mutation can directly activate the Myc proto-oncogene.[107] Myc is also activated by activating other oncogenes (including RAS, SRC, NOTCH[32,108]) or by inhibiting tumor suppressor genes (such as APC) to increase gene expression and/or protein stability.[109] Therefore, the Myc gene is a gene product that is frequently induced during tumor growth. Han et al demonstrated that Myc-targeted therapy enhances tumor immune cell infiltration.[110] Since c-Myc is a hallmark of basal-like breast cancer, which constitutes about 70% of triple-negative breast cancers (TNBC). Thus c-Myc has been proposed as a potential target for triple-negative breast cancer.[111,112] Wang et al developed an ultrasound-responsive spherical nucleic acid targeting c-Myc and PD-L1. After appropriate ultrasonic treatment, the tumor microenvironment is activated, and the proliferation and progression of TNBC are inhibited.[113] This suggests that Myc potential targets in combination with radiation therapy may provide another effective anti-tumor strategy. In tumor-bearing mice B16F10, when Myc inhibitor micellar JQ1 (mJQ1) was combined with radiotherapy, the expression of PD-L1 could be inhibited by increasing the level of cytokines. This can enhance local and systemic anti-tumor immunity activated by cytotoxic T cells, significantly inhibit the growth of B16F10 primary tumors in tumor-bearing mice, and significantly improve the survival of mice.[114] Meanwhile it can improve the activation of CD8+ T cell and induce systemic antitumor immunity to inhibit both primary and distant tumor, therefore extends survival in mice. In addition, epigenetic changes including the DNA methylation and chromatin deacetylation can promote tumorigenesis and cancer progression.[115,116] More importantly, DNA methyltransferase inhibitors (DNMTi) or histone deacetylase inhibitors (HDACi) may epigenetically regulate gene-expression level.[117,118] Cindy et al reported that 5-Aza is a typical DNMTi and is an indirect inhibitor of Myc, which can downregulate Myc gene in few cell lines.[119] Wang et al combined tungsten-based nano-radiosensitizer (PWAI) with Myc inhibitor (5-Aza), which also enhanced the cytotoxicity, proliferation and corresponding immune memory of CD8+T cells.[120] Furthermore, we briefly summarize the mechanisms of radiation therapy combined with Myc inhibitors (Figure 4). These researches revealed that Myc inhibitors with radiation therapy can inhibit tumor cells and activate the immune system. We generalize the combination therapies of radiotherapy and Myc inhibitors of recent studies in Table 2.

Although radiotherapy has been widely used in the treatment of cancer in clinic, it still exists disadvantages. For example, when radiation is utilized in tumors, it can also cause irreversible damage to healthy tissues and the high rate of tumor recurrence after radiotherapy is still unsolved. Therefore, finding a suitable method to treat tumors is still the key point of future research. Several studies on radiotherapy and Myc have shown that Myc gene is associated with radiotherapy resistance and tumor prognosis after radiotherapy.[106,121] Additionally, targeting Myc directly is challenging due to its complex structure. Therefore, alternatives to Myc blockade have been extensively explored to achieve desirable antitumor effects. However, there is a lack of clinical trials on Myc inhibitors combined with radiotherapy so researchers should focus on tumor inhibitors combined with physical therapy in the future.

Summary and Perspective

The development of photothermal therapy, photodynamic therapy and radiotherapy has provided new prospect for the treatment of cancer. However, PTT has inherent limitations, such as shallow light penetration, resulting in incomplete tumor ablation. Yet, when combined with other therapeutic methods, PTT has demonstrated outstanding effects by enhancing drug delivery efficiency, triggering drug release, improving the tumor microenvironment (TME), and inducing the release of tumor-specific antigens.[38] In PDT, photosensitizers can be administered in various ways to trigger apoptosis, necrosis, and ROS production and delay tumor progression.[67] Radiotherapy, when combined other therapeutic method, can observably enhance patients' quality of life, relieve the symptoms, alleviate pain and extend survival.[122] Although these strategies have shown excellent therapeutic potential, they also present a series of challenges.

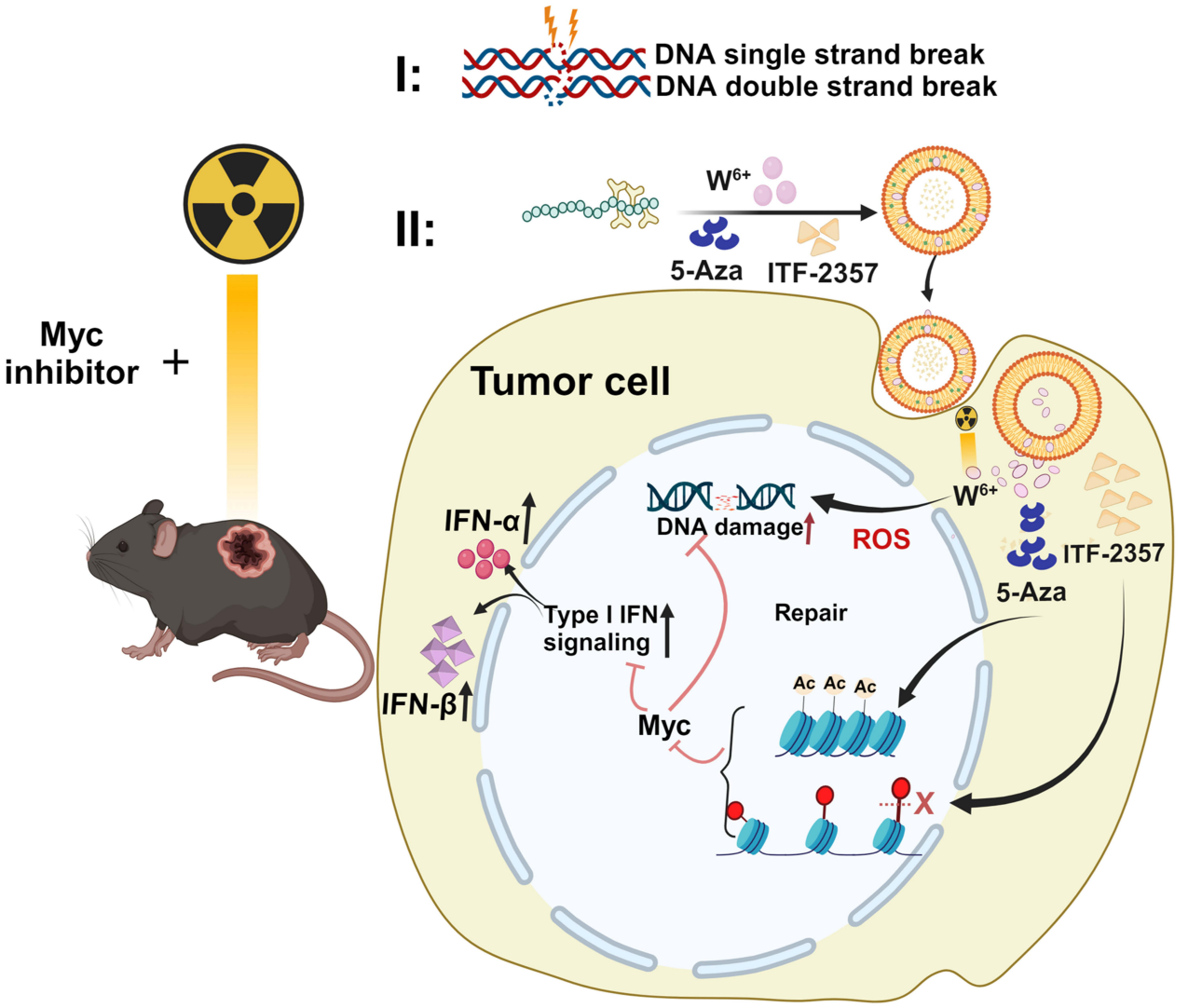

Figure 4 A synthetic routine of radiotherapy and Myc inhibitors for tumor. Myc inhibitors and radiotherapy combine to play a synergistic role in enhancing the killing of tumor cells and regulating the immune response in the tumor microenvironment, thus effectively inhibiting tumor growth. I: The direct radiation from radiotherapy can cause single-strand and double-strand breaks in DNA, thereby inducing cellular damage. II: The combined application of radiotherapy and Myc inhibitors can induce the production of reactive oxygen species (ROS) through indirect radiation effects. This not only triggers cellular stress and damage to biomolecules but also significantly enhances the anti-tumor effect via the Type I signaling pathway. The red text "ROS" stands for Reactive Oxygen Species. Created in BioRender. OeO, C. (2025) https://BioRender.com/gdwdzed.

1. The biocompatibility of nanomaterials in vivo still needs further investigation.
2. The shape and size of nanoparticles can affect the efficiency of drug delivery and also produce some toxic side effects,[123] so the drug delivery efficiency still need to research further.
3. The toxicity of nanomaterials is still controversial and needs further verification.

Previous reviews on PTT, PDT, and radiotherapy have primarily focused on the development of the technologies themselves, including explorations of each therapy's principles and key technological breakthroughs (such as the development of novel photosensitizers, optimization of nanocarriers, and precise regulation of radiotherapy doses). However, they have paid less attention to directions such as the synergistic mechanisms between these therapies and gene regulatory pathways (such as the Myc pathway), integrated analysis of cross-therapy combination strategies, and the clinical translation potential of "target-therapy" combinations, which still require continuous exploration by researchers. Alternatively, gene silencing strategies can also be combined with PTT, enhancing tumor necrosis and sensitivity to the

Table 3 Summary of Photothermal Therapy, Photodynamic Therapy and Radiotherapy in Clinical Trials Published on the NIH Website by April 2024 (https://clinicaltrails.gov)

Therapy	Clinical Trials ID	Study Start	Report Title	Sponsor	Study Status	Study Phase
Photothermal Therapy	NCT00805883	2009-02	MRI Targeted Focal Laser Thermal Therapy of Prostate Cancer Followed by Radical Prostatectomy	University Health Network, Toronto	Completed	Phase I
	NCT01679470	2012-10	Efficacy Study of uroLase Therapy in Subjects with Primary and/or Metastatic Lung Tumors	Nanospectra Biosciences, Inc. (United States)	Terminated	Not Applicable
	NCT03202446	2016-06	Randomized Clinical Trial Evaluating the Use of the Laser-Assisted Immunotherapy (LIT/inCVAX) in Advanced Breast Cancer	Eske Corporation S.A.C (Lima, Pera)	Terminated	Phase III
Photodynamic Therapy	NCT03735095	2020-02	Endobronchial Ultrasound Guided Interstitial Photodynamic Therapy in Treating Patients with Locally Advanced Lung Cancer	Roswell Park Cancer Institute (New York, United States)	Active, not recruiting	Phase I/II
	NCT03678350	2021-09	Light Dosimetry for Photodynamic Therapy with Porfimer Sodium in Treating Participants with Malignant Mesothelioma or Non-Small Cell Lung Cancer with Pleural Disease Undergoing Surgery	Roswell Park Cancer Institute (New York)	Active, not recruiting	Phase I
	NCT05522036	2022-01	Clinical Evaluation of a Short Illumination Duration (35 Minutes) When Performing PDT of AK Using the Dermaris ® (Dermaris-35)	Centre Dermatologique du Roy	Completed	Not Applicable
	NCT05551299	2023-02	Treatment of Non-resectable Bile Duct Cancer with Radiofrequency Ablation or Photodynamic Therapy (CARP)	University of Leipzig (Aachen, Germany)	Recruiting	Phase IV
	NCT06044142	2023-03	Curcumin VS Photo-bio-modulation Therapy of Oral Mucositis in Pediatric Patients Undergoing Anti-Cancer Non-invasive Treatment	Riyadh Elm University	Completed	Phase I
	NCT05363826	2023-04	Intracavitary Photodynamic Therapy as an Adjuvant to Resection of Glioblastoma or Gliosarcoma Using IV Photobac®	Photolitec LLC (United States, New York)	Recruiting	Phase I
	NCT05937529	2023-09	Impact of Madecassoside and 5% Panthenol Cream in Post Photodynamic Therapy for Actinic Keratosis	Merete Haedersdal	Completed	Not Applicable
	NCT05374915	2024-02	Efficacy and Safety Study of REM-001 Photodynamic Therapy for Treatment of Cutaneous Metastatic Breast Cancer (CMBC)	Kintara Therapeutics, Inc. (New York)	Recruiting	Phase II
	NCT06577311	2024-08	Evaluating the Use of Photodynamic Therapy to Treat Facial Cutaneous Squamous Cell Carcinoma in Situ (SCCis)	The Center for Clinical and Cosmetic Research	Recruiting	Phase II
Radiotherapy	NCT06747026	2015-01	Real-World Immuno-Radiotherapy for Advanced NSCLC (OCEANUS)	Fengming Kong	Completed	Observational
	NCT03186898	2018-01	Radiation Therapy with Protons or Photons in Treating Patients with Liver Cancer	NRG Oncology (Georgia, United States)	Recruiting	Phase III
	NCT04473937	2021-01	Radiation Post-CAR T in Refractory Lymphoma	Massachusetts General Hospital (United States)	Terminated	Not Applicable
	NCT06764420	2023-05	Effect of Arginine and Glutamine on Radiation-induced Oral Mucositis: a Triple Blinded Randomized Controlled Clinical Trial	Ain Shams University	Completed	Not Applicable
	NCT06201078	2023-07	Stereotactic Re-irradiation of Local Recurrences of Prostate Cancer After Radiotherapy (PROSTARE)	Maria Sklodowska-Curie National Research Institute of Oncology (Gliwice, Poland)	Recruiting	Phase II
	NCT06335693	2024-03	Adjuvant Hypofractionated Radiotherapy for Prostate Cancer	Changhai Hospital (Shanghai, China)	Recruiting	Not Applicable

thermal ablation. However, there are still several challenges in cancer treatment, such as concerns regarding the safety of biological materials, toxicity, and the limited therapeutic efficacy of radiation therapy. In the future, further exploration of therapeutic strategies for cancer is needed. Notably, we have summarized and listed the clinical trials involving PTT, PDT, and radiotherapy in Table 3. For photothermal therapy, we have highlighted two key clinical trials, one of which has reached Phase III. Thus, the safety and efficacy of PTT still require more clinical trials for confirmation. For photodynamic therapy, we listed six clinical trials. Two of them have reached Phase II and one of them has reached Phase IV. Additionally, four trials are in the recruiting phase, while the others have yet to recruit. Since there are many clinical trials on the application of radiotherapy in tumors, we only briefly enumerating five clinical trials. The study status of three clinical trials was not applicable; one clinical trial has been reached in phase II and the other has reached in Phase III.

Myc plays a vital role in almost every aspect of tumorigenesis, regulating proliferation, apoptosis, differentiation, and metabolism. Thus, Myc inhibition would be an effective approach to treat many types of cancer. However, direct targeting of Myc has been challenging owing to its "undruggable" protein structure. Current strategies mainly involve indirect targeting of Myc by inhibiting its regulation and stability.[124] We hope that this review will provide an insight into the role of synergistic therapy of Myc inhibitors with photothermal therapy, photodynamic therapy and radiotherapy respectively in cancer treatment and their potential clinical application. Myc inhibitors combined with photothermal, radiotherapy and photodynamic therapy can strengthen immune response and help to reverse the immune-suppressive environment in tumors. Moreover, the combined application of these therapies can reduce the adverse effects associated with cancer drug treatment. In addition, gene therapy is capable of modifying or manipulating gene expression and altering the biological characteristics of cells, thus demonstrating remarkable advantages in the treatment of cancer.[125] Short interfering RNA (siRNA) is able to inhibit the expression of c-Myc, suppress the proliferation of colorectal cancer Volo cells, and restrain the aggressiveness of these cells.[126] The animal experiment demonstrated that the combination of a Myc inhibitor and lipid-mediated CD47 siRNA was capable of decelerating tumor growth rate, diminishing tumor volume, and remarkably prolonging the survival period of mice. Significant anti-tumor efficacy was observed in the combined treatment group in comparison to the single-drug treatment group, suggesting a promising therapeutic approach for combating tumors.[127] Gene therapy in combination with Myc inhibitors can exert a bidirectional targeting function, demonstrating great potential. In summary, combining photothermal therapy, radiotherapy, and photodynamic therapy with Myc inhibitors offers a more precise and safer method for treating tumors, with broad potential for clinical application. In conclusion, our detailed description of Myc overexpression in various cancers implies that inhibiting Myc gene expression could potentially inhibit tumor development. On account of the Myc gene's complex structure, Myc activity is hard to suppress. As a result, indirect inhibitors have emerged, such as Bromodomain and terminal (BET) domain inhibitors, antisense oligonucleotides (ASOs), and small molecules like KJ-Pyr-9. When Myc inhibitors are combined with photothermal, photodynamic and radiation therapies, the tumor therapy could be more precise and safer and holds clinical potential.

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Disclosure

The authors declare that they have no conflicts of interest to report regarding the present study.

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