Advances in the Application of Living Cells in Tumor Radiosensitization

Graphical abstract

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In brief

This review systematically summarizes the latest research progress in utilizing living cells (eukaryotic and prokaryotic) for tumor radiosensitization. Dual roles as targeted carriers for radiosensitizer delivery and dynamic modulators of the tumor microenvironment (TME) are highlighted. Key mechanisms include the following: (1) stem cell-mediated STAT3/DNA repair inhibition; (2) immune cell-driven immunogenic cell death (ICD) synergy; (3) bacterial enzymatic hypoxia alleviation; and (4) cyanobacterial photosynthetic oxygen generation. The integration of these approaches overcomes conventional radiotherapy limitations by synergistically amplifying radiation-induced damage, while suppressing resistance pathways. We further discuss translational challenges in biosafety, manufacturing scalability, and clinical trial design, providing a roadmap for future development.

Highlights

- Dual-function living cells: Eukaryotic (stem/immune/blood cells) and prokaryotic (bacteria/cyanobacteria) systems serve as tumor-targeting carriers and dynamic TME modulators, enabling spatiotemporally preciseradiosensitization.
- Mechanism diversity: Stem cells inhibit DNA repair via STAT3 downregulation; bacteria reverse hypoxia through catalase/nattokinase expression; NK cells induce ferroptosis via IFN-γ; cyanobacteria generate O^2 via photosynthesis.
- Clinical synergy: CAR-T/radiotherapy combinations demonstrate sustained responses in lymphoma/liver metastasis patients (phase I/II trials), while engineered *Salmonella* enhances tumor targeting in melanoma.

Advances in the Application of Living Cells in Tumor Radiosensitization

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Abstract

Radiation therapy (RT) has a critical role in cancer treatment, yet the efficacy is often limited by tumor resistance mechanisms, such as cellular DNA repair activation, heterogeneous cell cycle, hypoxia, and an immunosuppressive microenvironment. Conventional radiosensitization strategies face significant challenges, which are caused by insufficient efficiency, a short treatment window, and off-target toxicities. In contrast, living cells offer a novel strategy to overcome these limitations by leveraging innate characteristics, including tumor chemotaxis and radiosensitization factor secretion. Living cells have recently been applied in radiotherapy to amplify tumor cell killing effects and avoid healthy tissue damage. This review systematically summarizes recent advances in living cell-based radiosensitization strategies, emphasizing the dual roles as tumor targeting carriers and dynamic microenvironment modulators. The radiosensitization mechanisms underlying diverse cell types are analyzed. For example, stem cells enhance radiotherapy via STAT3-mediated DNA repair inhibition, while immune cells and bacteria use immunogenic cell death synergy to induce immune activation. Finally, the challenges and prospects of living cells in achieving radiosensitization are highlighted.

Keywords

Living cells, radiosensitization, tumor microenvironment, tumor radiotherapy, tumor targeting delivery.

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Introduction

Radiation therapy (RT) is an important tumor treatment modality. RT directly damages DNA to kill tumor cells and simultaneously induces cells to produce reactive oxygen species (ROS), thereby inducing cell death [1]. Nevertheless, clinical efficacy is significantly constrained by multiple resistance mechanisms arising from tumor cell intrinsic adaptations and extrinsic microenvironment barriers [2]. Hypoxia is a hallmark of solid tumors that diminishes oxygen-dependent free radical formation and subsequent DNA damage during irradiation [3]. DNA repair pathways, including homologous recombination (HR) and non-homologous end joining (NHEJ), rapidly restore gene integrity following radiation-induced double-strand breaks (DSBs) [4]. Concurrently, the immunosuppressive tumor microenvironment (TME) causes immune evasion by Treg infiltration and immune checkpoint ligand upregulation after irradiation. Moreover, heterogeneous cell cycle distribution across tumor cells introduces additional therapeutic challenges because different radiosensitivities among tumor cells mediate tumor recurrence [5].

Current research has developed physical and chemical radiosensitization strategies to address these challenges in radiotherapy [6]. Conventional strategies enhance ROS generation and DNA damage by regulating intracellular signaling pathways or remodeling the TME [7]. However, these strategies face limitations in clinical practice, including insufficient efficacy, transient effects, and off-target toxicity [8]. Biological radiosensitization strategies utilizing living cells (e.g., stem cells, immune cells, and bacteria) have emerged as novel solutions [9–11]. For example, living cells deliver radiosensitizers into tumor tissues through chemotactic movement and microenvironment-responsive payload release [12]. Living cell-based radiosensitization demonstrates superior efficacy and safety compared to physical/chemical approaches and relies on localized cytokine storm instead of conventional systemic toxicities and enhanced specificity through tumor targeting. In contrast, living cells utilize intrinsic properties to dynamically regulate the TME and achieve precision modulation radioresistance challenges [13]. Living cells overcome the limitations of conventional strategies and achieve effective radiosensitization by

leveraging inherent tumor chemotaxis and functional activity [14].

RT resistance is not driven by isolated factors. Indeed, the interconnected resistance pathways collectively undermine radiotherapy outcomes [15]. Resistance pathways form a self-reinforcing network through HIF-1α/NF-κB-mediated crosstalk, through which hypoxia stabilizes HIF-1α to upregulate DNA repair enzymes and immunosuppressive ligands. Radiation-induced DNA damage activates NF-κB to amplify PD-L1 expression and Treg infiltration and the resultant immunosuppression maintains hypoxia by impairing vascular normalization. However, conventional strategies often fail to achieve effective tumor suppression by neglecting crosstalk between resistance pathways [16]. Recent advances in understanding radiosensitization mechanisms and living cell biological capabilities have propelled the development of multifunctional living cells [17]. Living cells integrate capabilities, such as hypoxia alleviation, DNA repair inhibition, and immune activation, shifting from single-function interventions to synergistic multi-target modulation [18, 19]. In this review recent advances in the application of living cells in tumor radiosensitization are summarized and various radiosensitization strategies of different living cell types are analyzed. Finally, challenges and future directions for living cell-based radiosensitization are discussed (**Figure 1**).

This review used a systematic search strategy in PubMed, Web of Science, and Scopus (January 2015–June 2025). Keywords included 'living cells,' 'radiosensitization,' 'bacteria radiotherapy,' 'stem cell radiotherapy,' 'immune cell radiotherapy,' and 'tumor microenvironment.' The inclusion criteria were as follows: (i) original studies reporting living cell-based radiosensitization; (ii) mechanistic investigations of radioresistance modulation; and (iii) clinical trials (any phase). The exclusion criteria were as follows: (i) non-English publications; (ii) non-cancer applications; and (iii) reviews without primary data. Of the 537 studies retrieved, 35 met the eligibility criteria.

Potential role of living cells in tumor radiosensitization

Increasing the amount of radiation-induced damage

Amplifying radiation-induced damage represents a radiosensitization strategy to overcome tumor heterogeneity, transcend dose limitations, and improve the clinical prognosis. Radiosensitizers are compounds or materials designed to increase tumor vulnerability to irradiation through dual mechanisms [amplifying initial radiation damage (e.g., ROS/DNA radicals) or suppressing DNA repair pathways] [20]. In recent years radiosensitizers have been extensively investigated in preclinical research, predominantly through mechanisms involving direct DNA damage increasing or indirect ROS amplification to enhance therapeutic efficacy [21].

Despite promising preclinical outcomes, the clinical translation of radiosensitizers is constrained by ruleless biodistribution and systemic toxicity [22]. Moreover, radiotherapy activates the immune system by inducing the release of cellular damage-associated molecular patterns (DAMPs) and tumor-associated antigens from cancer cells [12]. However, the immune activation impact of radiotherapy is frequently diminished by various mechanisms, including regulatory T cell (Treg) infiltration and programmed death-ligand 1 (PD-L1) upregulation [23]. Traditional immune activation strategies (e.g., immune checkpoint inhibitor therapy and systemic cytokine administration) are limited by system toxicity and incomplete immunosuppression recovery [19].

Living cells address these limitations by utilizing innate biological functionalities, including tumor targeting and microenvironment responsiveness. For example, stem cells are designed to actively transport high-Z element nanoparticles to tumor sites through chemotactic movement [24], while macrophages are programmed to release cytotoxic payloads in response to tumor-associated inflammatory signals [25]. Living cells induce tumor damage and avoid systemic toxicity by the targeted delivery of radiosensitizers. Additionally, radiation exerts the most potent cytotoxic effect on cells during the G2/M phase of the cell cycle. Tumor cell cycle heterogeneity drives radiotherapy resistance by reducing the proportion of radiosensitive G2/M-phase cells [26]. Living cells enable constrained regulation of tumor cell cycle dynamics, thereby expanding the therapeutic window for radiation-induced mitotic disruption [27]. Furthermore, *Salmonella* arrest tumor-specific cell cycle with apoptosis induction through caspase pathway activation [28]. Therefore, living cells efficiently overcome radioresistance by increasing the amount of radiation-induced damage.

Decreasing the efficiency of post-radiation DNA repair

Increasing radiation-induced damage corresponds to an increase in radiation dose. As a result, a preferable method for enhancing irradiation efficacy is achieved by targeting DNA repair mechanisms [20]. DNA repair inhibition represents a core radiosensitization strategy that is complementary to damage amplification. Tumor cells efficiently repair radiation-induced DNA double-strand breaks (DSBs) through HR and NHEJ pathways, significantly diminishing radiotherapy efficacy [29]. Conventional DNA repair inhibition strategies, including PARP inhibitors and glutathione (GSH)-depleting agents, suppress DNA repair pathways and damage gene integrity in healthy cells, while increasing risks of secondary malignancies [30]. Living cells overcome these limitations via tumor-targeted precision. For example, engineered neutrophils selectively deliver BRCA1-targeting siRNA to tumors and restrict HR pathway silencing, while bacteria secrete redox-modulating factors to diminish local tumor cell gene integrity [1, 31]. Living cells can easily achieve DNA damage repair inhibition and preserve systemic gene stability compared to systemic inhibitors.

Furthermore, oxygen serves as the fuel to stabilize DNA damage caused by radiation and prevents the DNA self-repair process [32]. However, the efficacy of radiotherapy has been severely limited due to the hypoxia status in most solid tumors [33]. Conventional approaches, including hyperbaric
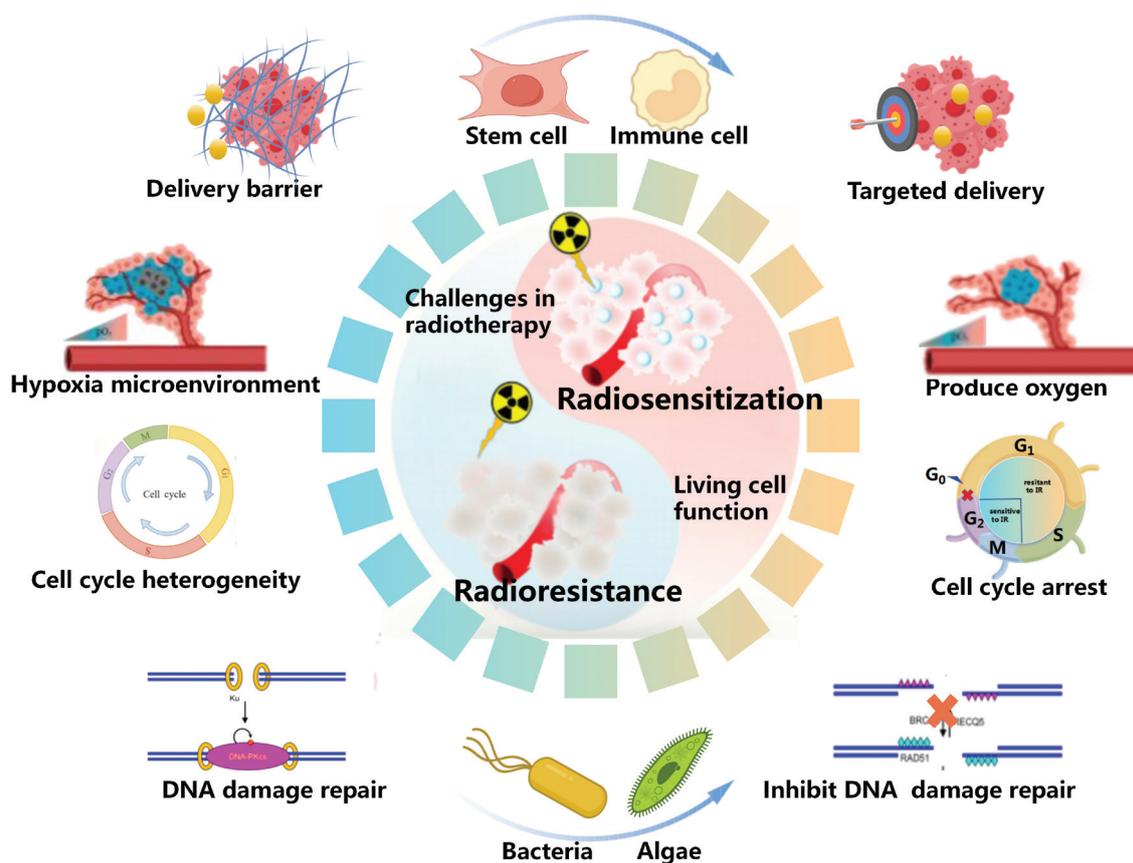
Figure 1 Schematic illustration of living cells in tumor radiosensitization application. This figure illustrates the key factors mediating radioresistance and the mechanisms by which living cell-based platforms synergistically enhance radiotherapy efficacy through targeted delivery, hypoxia modulation, DNA repair inhibition, and cell cycle intervention.

oxygen therapy and vascular normalization strategies, are constrained by insufficient oxygen production and transient therapeutic effects [34]. In contrast, living cells are able to sustain a sufficient tumor oxygen level through consistent oxygen generation [35]. For example, engineered bacteria stably express oxygen-generating enzymes to achieve prolonged oxygen generation compared to small-molecule oxygen carriers [11]. Similarly, photosynthetic cyanobacteria leverage light-triggered oxygen generation to dynamically regulate tumor oxygen levels [36]. In conclusion, living cells mediate stable inhibition of DNA repair, offering a potential solution for enhancing radiotherapy efficacy.

Targeting manipulation of two or more individual pathways

The interdependence of radioresistance pathways (DNA repair enables immunosuppression and hypoxia sustains cell cycle heterogeneity, and vice versa) forms a self-reinforcing network that single-target interventions cannot disrupt. Building on this framework, simultaneous targeting of two or more pathways becomes essential to overcome cross-pathway compensation [37]. Living cells address these challenges through synergistic radioresistance modulation via multiple functional integration compared to conventional approaches. For example, engineered T cells co-deliver PD-1 antibodies and interleukin-12 (IL-12) within tumor lesions,

simultaneously depleting Treg populations and recovering cytotoxic T lymphocyte activity [38].

Furthermore, living cells integrate mechanisms, including immune system activation, metabolic reprogramming, and extracellular matrix remodeling, to achieve coordinated optimization of tumor radiosensitization and systemic biosafety [39]. Unlike traditional combined therapies that are limited by off-target drug interactions and cumulative toxicities, living cells serve as tumor targeting carriers and dynamic microenvironment modulators that disrupt radioresistance networks, while preserving physiologic tissue homeostasis [40].

Advances in eukaryotic cells for tumor radiosensitization

Stem cells

Stem cells represent a unique cellular population characterized by self-renewal capacity and differentiation potential [41]. The distinctive biological properties of stem cells exploit chemotaxis, immunomodulation, and microenvironment sensing to overcome radioresistance. [42]. Stem cells actively migrate toward tumor sites via chemokines (e.g., SDF-1 and CXCR4). This targeting capability offers stem

cells dual advantages for enhancing localized radiation cytotoxicity, while reducing systemic toxicity [43]. Stem cells are simply divided into three different varieties (adult stem cells, embryonic stem cells, and induced pluripotent stem cells [iPSCs]). Embryonic stem cells have a high probability of immune rejection and ethical dilemmas and iPSCs have genetic instability. Therefore, embryonic stem cells have not been widely used in current research [44].

Mesenchymal stem cells (MSCs) are the most widely utilized stem cell type. MSCs can be engineered to deliver radiosensitizers through surface modifications, internalization strategies, or gene transfection approaches [45]. Yun et al. reported that engineered MSCs selectively accumulate in tumor tissues in colon cancer models, significantly improving therapeutic efficacy by increasing radiation energy deposition [46]. Notably, stem cell intrinsic protective mechanisms (e.g., antioxidant stress resistance) preserve migratory activity and cellular viability. MSCs loaded with high atomic number (high-Z) nanoparticles achieved a 20-fold increase in tumor-specific drug concentration in non-small cell lung cancer (NSCLC) models, markedly suppressing orthotopic tumor growth [47]. Furthermore, MSCs serve as gene delivery vectors for tumor radiosensitization. Wang et al. demonstrated that an MSC-expressed sodium iodide symporter efficiently improves radiotherapy outcomes [48]. MSCs exhibit limited targeting efficiency for brain tumors restricted by the blood-brain barrier, whereas neural stem cells (NSCs) leverage intrinsic glioma chemotaxis to pass through delivery barriers, enabling extensive intratumor distribution of radiosensitizers in glioblastomas [49].

In addition to radiosensitizer delivery, stem cells exhibit a remarkable potential in modulating tumor biology [50]. Studies have shown that low-dose radiation activates MSCs to secrete antitumor cytokines, inhibiting proliferation and inducing cytotoxic synergy. Combining non-irradiated MSCs with radiation *in vivo* amplifies therapeutic effects through enhanced bystander effects on both primary and distant lesions, which is attributed to increased tumor cell loss and reduced proliferation [51]. Mechanistically, MSCs impair tumor DNA repair by suppressing STAT3 activation. STAT3 is a key regulator of the damage response, while amplifying radiation-induced cytotoxicity in preclinical models. In addition, MSCs reduce ALDH+ cancer stem cell populations, modulate stemness markers, and inhibit tumor metastasis [52]. Complementary research involving verified STAT3 downregulation as a therapeutic mechanism identified IFN-γ-induced transmembrane protein 1 (IFITM1) activation to be critical for enhancing radiotherapy suppression of hepatocellular carcinoma invasion [53] but is limited by inherent tumorigenic risks and prohibitive manufacturing costs. Future directions require synergistic optimization through gene editing technologies to enhance cellular safety profiles and advanced material engineering approaches to improve drug-loading efficiency. These innovative strategies will collectively pave the way for the clinical realization of precision stem cell-based radiosensitization therapies. Furthermore, MSC-based strategies carry tumorigenicity risks. MSCs can paradoxically promote tumor growth via STAT3-mediated secretion of VEGF/IL-6 [52, 54]. Mitigation strategies include the following: (i) genetic insertion of suicide genes (HSV-TK); (ii) pre-treatment irradiation to halt proliferation; and (iii) stringent *in vivo* tumorigenicity screening (e.g., oncogene expression profiling). These approaches preserve radiosensitization function, while minimizing oncogenic potential (**Figure 2**).
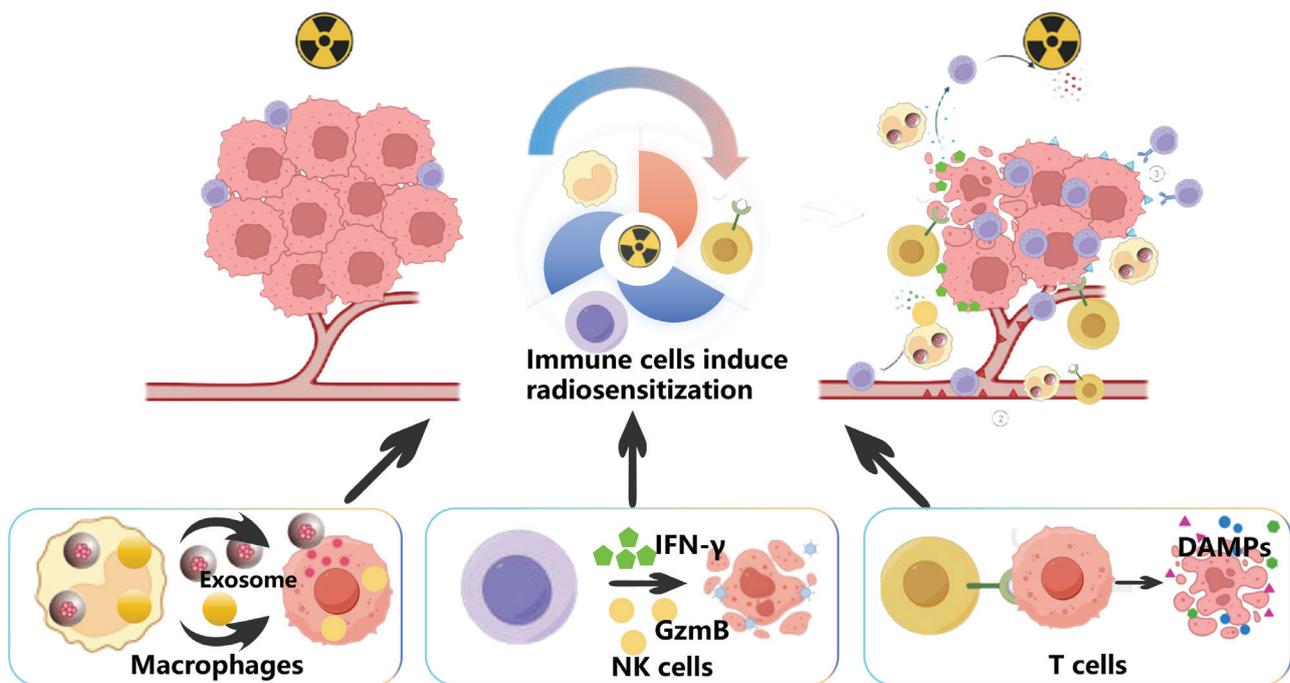
Immune cells

Immune cells, comprising innate and adaptive immunity components, are specialized cellular entities endowed with pathogen recognition, antigen presentation, and cytotoxic effector functions [55]. The unique radiosensitization properties of immune cells come from the following three main attributes: (i) intrinsic tumor tropism via chemokine receptor signaling (e.g., the CCR5/CXCR3 axis); (ii) dynamic crosstalk with irradiated tumor cells; and (iii) capacity to convert a "cold" immunosuppressive TME into "hot" immune responsive states [56]. These characteristics of immune cells give facilitate dual functions for targeted radiosensitizer delivery and systemic immune activation [57]. The latest research showed the inherent immunotherapy function of various immune cells on activation of immunosuppressive microenvironment after radiotherapy. Each cell type also has its own unique characteristics adapted to the radiosensitization mechanism [55] (**Figure 3**).

Among different types of immune cells, macrophages are the most widely used carrier type. Macrophages can efficiently load nanoparticles based on phagocytosis effects without affecting normal function. Li et al. designed a radiosensitizer delivery strategy, known as the "Trojan horse," and successfully delivered gold nanorods to tumor areas [58]. With further study on the secretion characteristics of macrophages, Fu et al. reported that macrophages promote drug release through exosome-mediated cellular communication, thus significantly increasing the local drug concentration of tumors. Based on this feature Fu et al. realized the precise controlled release and local accumulation of doxorubicin (DOX), a classical radiosensitized agent, at the tumor site [59]. Macrophages deliver antigen and have a critical role in RT remote effects. Macrophages easily mediate radioresensitizer secretion and orchestrate antitumor immune responses within the tumor microenvironment, thereby contributing to effective tumor regression.

Natural killer (NK) cells with rapid killing, immunomodulatory, and antigen-independent characteristics enhance tumor radiotherapy sensitivity through multiple mechanisms involving synergistic killing and metabolic regulation, especially through the secretion of cytokines and cytotoxic molecules [60]. A key mechanism underlying tumor radiotherapy sensitivity involves IFN-γ-driven ferroptosis, an iron-dependent form of regulated cell death, which has emerged as a critical pathway to overcome radioresistance in solid tumors. NK cell-derived IFN-γ triggers lipid peroxidation and disrupts redox homeostasis in tumor cells n prostate cancer-bearing mice, which promotes ferroptosis and amplifies radiation-induced damage. In addition to cytokine-mediated effects, NK cells directly execute tumor cell killing through the release of granzymes (notably granzyme B [GzmB]), which induces DNA fragmentation and apoptosis

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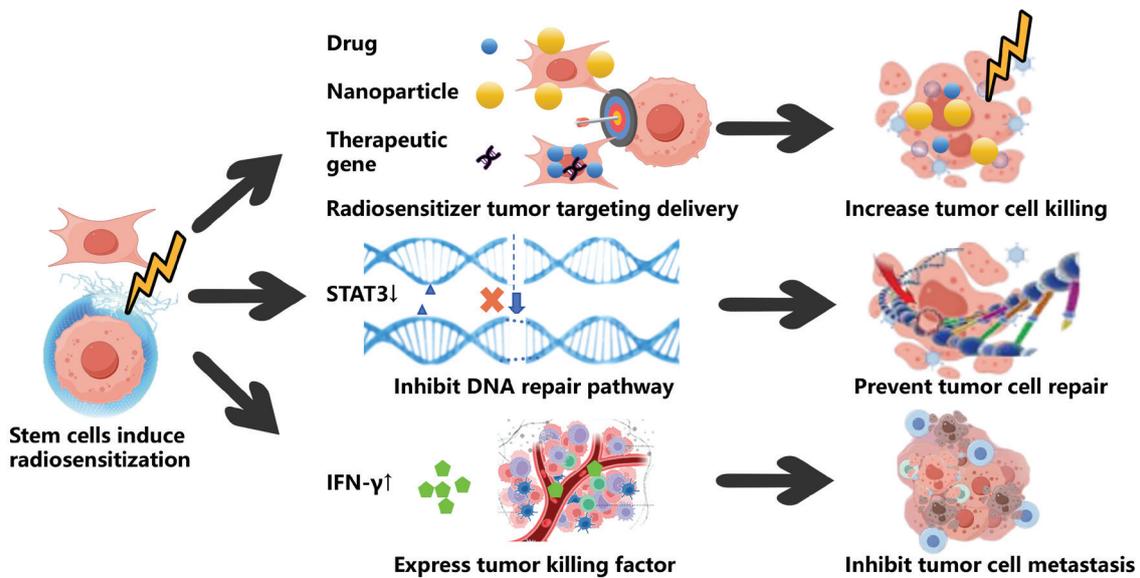
Figure 2 Application of stem cells for tumor radiosensitization. This figure exhibits the progress in the application of stem cells in radiotherapy sensitization, which can inhibit tumor growth, recurrence, and apoptosis in terms of targeted delivery of a radiotherapy sensitizer, inhibition of DNA repair, and expression of functional factors.

Figure 3 Application of immune cells for tumor radiosensitization. This figure introduces the unique biological characteristics of three different immune cells (macrophages, NK cells, and T cells), and the different mechanisms in the application of radiotherapy sensitization.

[61]. Up-regulated tumor cell-intrinsic GzmB expression has been shown to significantly enhance radiosensitivity independent of immune cell activity, highlighting the dual role of GzmB in direct cytotoxicity and metabolic regulation. In conclusion, these findings illustrate the intricate interplay between NK cell-secreted factors and tumor cell responses. Indeed, IFN-γ-mediated ferroptosis and GzmB-driven DNA damage are promising targets for improving tumor radiotherapy efficacy [62]. Chimeric antigen receptor natural killer (CAR-NK) cells are genetically engineered

immune cells that combine the inherent cytotoxicity of NK cells with the antigen-targeting capability of CAR technology. CAR-NK cells enhance antitumor efficacy in radiosensitization through multi-mechanism synergy [63]. For example, CAR-mediated recognition of tumor-specific antigens enables precise elimination of radiation-surviving cells. In addition, CAR-NK cells deplete immunosuppressive cells (e.g., Tregs and tumor-associated macrophages [TAMs]) to enhance CD8+ T-cell infiltration. Xia et al. confirmed in an *in situ* pancreatic tumor model that Robo1-CAR-NK cells

combined with radiotherapy synergistically reduce the tumor load and prolong survival, highlighting the clinical transformation potential [64].

The combination of chimeric antigen receptor T (CAR-T) cell therapy with radiotherapy has emerged as an innovative strategy to enhance tumor radiosensitivity by promoting immunogenic cell death (ICD) [65]. Radiation facilitates ICD through the release of DAMPs [66]. These molecules synergistically activate dendritic cells and initiate tumor-specific T-cell responses. CAR-T cells further amplify this mechanism by enhancing antigen presentation and establishing a pro-inflammatory TME [67]. Preclinical studies have demonstrated that CAR-T cells effectively target radiosensitive parental tumor cell lines. CD98hc-targeted CAR-T cells combined with localized radiotherapy enhanced calreticulin (CRT) exposure and promoted CD8+ T-cell infiltration in head and neck squamous cell carcinoma (HNSCC)-bearing mice, leading to improved tumor control effect [68]. Notably, redirected UniCAR-T cells exhibited significant growth inhibition of radioresistant cancer cells even in immunodeficient mice models [69]. These collective findings substantiate the potential of CAR-T cells to overcome radioresistance. Currently, the clinical translation of CAR-T and radiotherapy combined therapy is progressing rapidly. Six patients with hepatic metastases received CAR-T and RT combined therapy in a phase 1b trial. The outcomes have shown that intra-arterial delivery of cytokine-armored CAR-T cells synergizes with radiation-induced ICD, generating sustained antitumor responses [70]. Moreover, the tumor marker levels were decreased in the test patients and prolonged the survival time. A phase II clinical trial testing the combined therapy efficacy was subsequently conducted in non-Hodgkin lymphoma patients [71]. Six patients showed a higher overall response rate after treatment and one patient achieved complete remission. Nevertheless, there are some challenges associated with combined therapy. A CAR-T cell-based radiosensitization strategy requires a suitable radiation dose to balance the ICD induction effect with CAR-T cell viability. In addition, the manufacturing cost of CAR-T cells is expensive and it is difficult to promote the application of CAR-T cells.

Blood cells

Blood cells are widely utilized in drug delivery due to abundant availability, inherent biocompatibility, and changeability [72–75]. Among the blood cells, red blood cells (RBCs) possess unique biological advantages as the most abundant blood cells in humans. RBCs have a long circulation time because of CD47-mediated evasion of the mononuclear phagocyte system. In addition, the biconcave morphology provides exceptional gas exchange capacity through optimized surface-to-volume characteristics [76]. These intrinsic properties position RBCs as natural oxygen carriers with therapeutic potential. Hypoxia in solid tumors, which is driven by abnormal vasculature and excessive hypoxia-inducible factor secretion, significantly diminishes oxygen-dependent radiation damage [77]. RBCs have been engineered into oxygen-delivery platforms to reprogram the hypoxia

TME by capitalizing on the hemoglobin-rich composition. RBC-based systems triple tumor oxygenation levels in glioblastoma models by directly enhancing radiation-induced DNA damage, while suppressing HIF-1α-mediated resistance pathways [78]. Zhou et al. further designed a two-stage oxygen delivery system combining perfluorocarbon nanoparticles with RBCs. This innovative design enhanced tumor penetration and achieved targeted oxygen release in hypoxic regions through precise physical activation [79]. With advances in technology, RBCs are transformed from passive carriers to active oxygen modulators.

In addition to RBC-mediated strategies, platelets have unique roles in radiosensitization. Platelets are anucleate cytoplasmic fragments derived from megakaryocytes that circulate for 8–10 days, providing circulatory stability for radiosensitizer delivery. Platelets naturally accumulate at irradiated tumor sites due to vascular injury with engineered platelets observed within tumors 24 h post-injection. Recent studies highlight platelets against radioresistance through distinctive biological properties. Xia et al. designed platelet-based hybrids combining hemoglobin and gold nanoparticles (AuNPs) to simultaneously address hypoxia and DNA repair [80]. Platelets leverage the wound accumulation property to deposit oxygen-releasing hemoglobin in tumor cores and secrete miR-223, which silence a key homologous recombination protein (Rad51) to inhibit DNA damage repair [81]. This strategy suppressed tumors and distant lung metastases in breast cancer models, demonstrating the ability of platelets to simultaneously target microenvironmental and molecular resistance. Blood cells offer advantages in biocompatibility and circulatory stability, yet a short functional lifespan and passive targeting dependency remain as barriers to clinical translation. Future efforts require optimized design through targeted signal peptide modification to address these barriers (**Table 1**).

Advances in prokaryotic cells for tumor radiosensitization

Gram-negative bacteria

Gram-negative bacteria exhibit unique advantages in tumor radiosensitization due to inherent biological properties [11]. Rich lipopolysaccharides (LPSs) in the outer membrane composition enable immune activation through TLR4 signaling, while surface flagella facilitate autonomous motility and stromal penetration for tumor specific colonization [82]. Gram-negative bacteria, like *Escherichia coli* and *Salmonella*, demonstrate exceptional toward radioresistant hypoxic regions. Genetic engineering further extend the radiosensitization function. For example, engineered LPS modification reduces systemic toxicity, while preserving immunogenicity. Inducible promoters enable tumor-localized expression of radiosensitizing enzymes or conversion of prodrugs [83]. Notably, the periplasmic space of Gram-negative bacteria serves as a natural compartment for nanomaterial encapsulation.

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Table 1 Application of Eukaryotic Cells in Tumor Radiosensitization

Type of Living Cells	Radiosensitization Strategy	Function	Study Type	Tumor Type	Ref.
MSC	Targeted deliver of radiosensitizers (Au/Bi$_2$Se3 NPs)	Amplification of radiation energy deposition (ROS ↑, damaged DNA ↑)	Preclinical in mice	Colon/lung tumor (HT-29/A549 cells)	[46, 47]
	Targeted delivery of radiosensitive genes	Delivery of the sodium iodide symporter gene (ROS ↑,)	Preclinical in mice	Hypopharyngeal carcinoma	[48]
	Improvement in the immunosuppressive environment	Secrete anti-tumor cytokines (TNF-α ↑, IFN-γ ↑)	Preclinical at the cellular level	Melanoma (A375 and G361 cells)	[51]
	Inhibit DNA damage repair	Downregulated expression of signal transducers (IFITM1 ↓, STAT3 ↓)	Preclinical in mice and at the cellular level	Breast/liver tumor (MDA-MB-231/Huh7 cells)	[52, 53]
NSC	Targeted delivery of radiosensitizers	Accumulate radiation energy absorption (ROS ↑, Tumor volume ↓)	Preclinical in mice	Glioblastoma (U87-MG cells)	[49]
Macrophage	Targeted delivery of radiosensitizers	Increase tumor apoptosis (ROS ↑, damaged DNA ↑)	Preclinical in mice	Breast/liver tumor (MDA-MB-231/ HepG2 cells)	[58, 59]
NK cell	Improvement in the immunosuppressive environment	Secrete anti-tumor cytokines (IFN-γ ↑)	Preclinical in mice	Prostate tumor (PC3 cells)	[61]
	Arrest the tumor cell cycle	Secrete cell metabolism regulation protein (granzyme B ↑)	Preclinical in mice	Lung tumor (A549 cells)	[62]
	Improvement in the immunosuppressive environment	Deplete immunosuppressive cells (IL-10 ↓, TGF-β ↓)	Preclinical in mice	Pancreatic tumor	[64]
T cell	Improvement in the immunosuppressive environment	Mediate tumor cell lysis (tumor-associated antigens ↑)	Preclinical in mice and at the cellular level	HNSCC	[68, 69]
	Improvement in the immunosuppressive environment	Mediate tumor cell lysis (tumor-associated antigens ↑)	Clinical trials in humans (NCT03196830)	Lymphoma	[71]
	Improvement in the immunosuppressive environment	Mediate tumor cell lysis (tumor-associated antigens ↑)	Clinical trials in humans (NCT02416466)	Liver tumor	[70]
RBC	Targeted delivery of radiosensitizers	Increase tumor apoptosis (ROS ↑, damaged DNA ↑)	Preclinical in mice and at the cellular level	Colon/breast tumor (HT-29/MDA-MB-231 cells)	[72, 75]
	Overcome tumor hypoxia limitation	Release oxygen in tumors and precise antiangiogenesis (oxygen level ↑)	Preclinical in mice	Melanoma/colon tumor (A375/CT26 cells)	[78, 79]
PLT	Overcome tumor hypoxia limitation and inhibit DNA damage repair	Achieving dual modulation (oxygen level ↑, damaged DNA ↑)	Preclinical in mice	Cervical tumor (ID8 cells)	[80]
	Inhibit DNA damage repair	Secrete DNA damage repair inhibition cytokine (miR-223 ↑)	Preclinical at the cellular level	Breast tumor (MDA-MB-231 cells)	[81]

Recent advances integrate bacterial vectors with high-Z element nanosystems [84]. In a representative study Duo et al. used *Salmonella* to transport AuNPs through tumor the ECM via flagellum-driven chemotaxis. *Salmonella* achieved higher intratumoral AuNP retention compared to passive diffusion [85].

Engineered Gram-negative bacteria have been widely used in radiosensitization. Catalase (CAT)-mediated decomposition of intratumoral hydrogen peroxide into oxygen represents a promising strategy to ameliorate hypoxia and potentiate radiotherapy efficacy. However, conventional CAT delivery systems are hindered by inefficient tumor targeting and poor spatiotemporal controllability. To address these limitations, engineered bacteria have emerged as precision platforms for hypoxia modulation. Huang et al. pioneered engineered *E. coli* Nissle 1917 (ECN) with tumor-localized CAT expression, achieving sustained hypoxia alleviation through enzymatic oxygen generation [86]. Building on this finding,

Liu et al. developed ultrasound-responsive bacteria (UEB) featuring stimulus-dependent CAT activation, which minimized oxidative stress in healthy tissues by restricting oxygen production to sonicated tumor regions [87]. Lei et al. further enhanced therapeutic synergy by integrating UEB with AuNPs, coupling enzymatic oxygenation with radiation dose amplification through high-Z element-mediated energy deposition [88]. In addition to enzymatic oxygenation, bacterial systems concurrently address hypoxia-exacerbating microenvironmental barriers. Zhang et al. engineered *Salmonella* to secrete nattokinase, which degraded the fibronectin-rich ECM and suppressed CAF activity, thereby reducing tumor stiffness and improving oxygen perfusion [89].

Engineered bacteria efficiently regulate tumor cell cycles into radiosensitive phases. Wang et al. developed a prodrug system using bacteria to deliver 5-fluorouracil (5-FU) in response to tumor-specific high GSH signals. The system is able to control the release of 5-FU, shifting tumor cells from the radioresistant S-phase to radiosensitive G2/M-phase [90]. To further expand functionality, Pan et al. engineered bacteria to co-deliver high-Z materials nanoparticles and express cytolytic toxin A, simultaneously enhancing radiation energy deposition and inducing tumor cell cycle arrest [91]. Moreover, Gram-negative bacteria can also self-arrest the cell cycle by the regulated factor and enhance the radiosensitization effect. Cytolethal distending toxin (CDT) is one of the most widely studied bacterial toxins produced by Gram-negative bacteria. CDT has been reported to arrest the cell cycle in the most radiosensitive phase, thus continuously enhancing ionizing radiation (IR)-induced DSBs [92].

Gram-positive bacteria

In contrast to Gram-negative bacteria, Gram-positive species exhibit less efficient secretion systems and lower yields of heterologous protein expression. The capacity of Gram-positive bacteria to enhance radiotherapy efficacy primarily relies on non-engineered mechanisms, such as pattern recognition receptor-mediated immune activation and hypoxia-targeted selective spore germination [54]. Gram-positive bacteria exhibit a high frequency of the immunostimulatory CpG gene sequence with potent activation of human Toll-like receptor 9 (TLR9). CpG gene sequences in Gram-positive bacteria specifically activate plasmacytoid dendritic cells and TLR9-expressing B cells, enhancing co-stimulatory molecule expression with favorable safety profiles [93]. Mason et al. established this approach and demonstrated that CpG synergize with radiotherapy in fibrosarcoma models increasing tumor antigen release, dendritic cell activation,
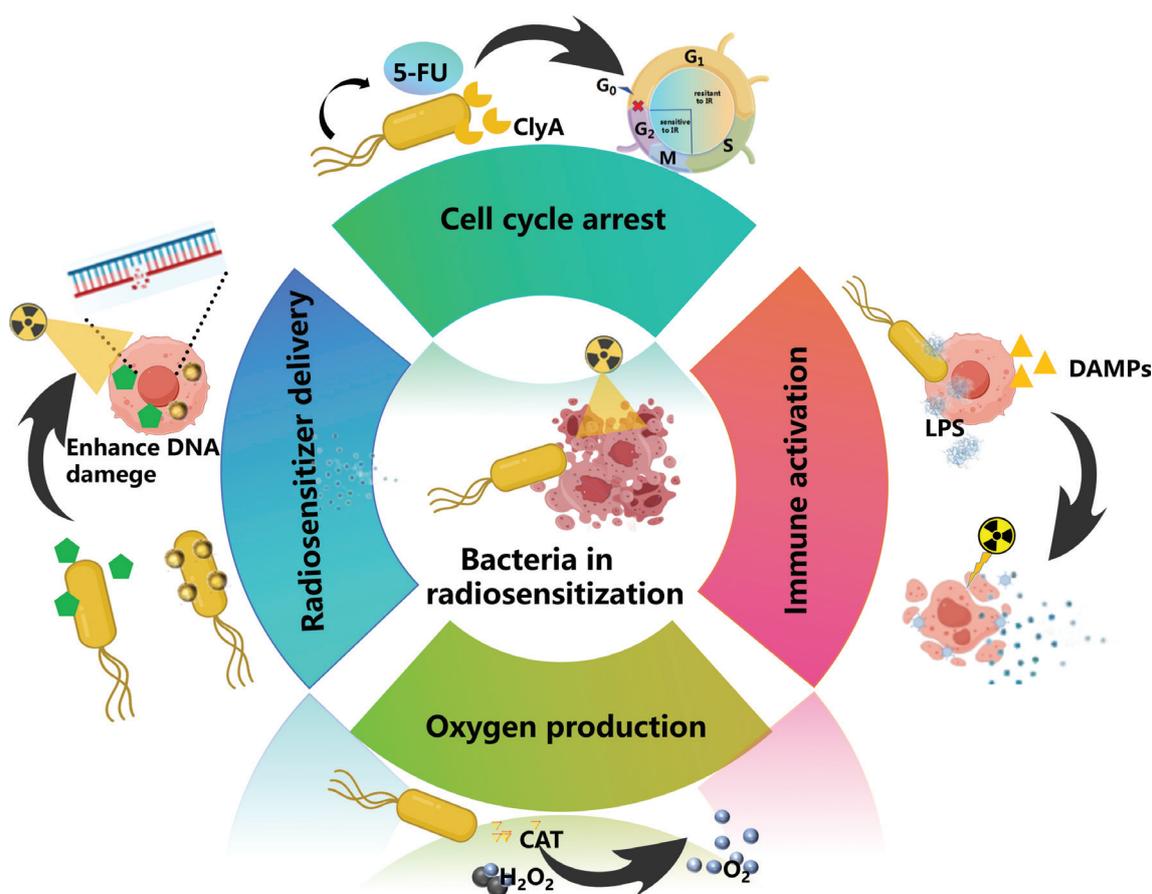
Figure 4 Application of bacteria for tumor radiosensitization. This figure introduces the strategies and specific application examples of engineered bacteria in radiotherapy sensitization, such as delivery of a radiotherapy sensitizer, improvement in the anaerobic environment, regulation of the cell cycle, and activation of the immune response.

and cytotoxic T-cell infiltration, while inducing necrotic cell death and inflammatory remodeling [94]. Subsequent studies revealed that CpG not only amplify radiation-induced abscopal effects in immunologically "cold" tumors but also establish systemic antitumor memory. However, the mechanistic interplay between CpG and radiation remains underexplored, warranting deeper investigation into radiation-immune crosstalk [95].

Obligate anaerobic bacteria (e.g., *Bifidobacterium* and *Clostridium novyi*-NT) exhibit unique tumor-targeting capabilities by exploiting hypoxic regions within the TME by complementing conventional immune activation strategies. Gram-positive bacteria selectively grow and release spores in hypoxic regions, where the proliferative activity physically disrupts the structural integrity of tumor cores, degrades fibrotic stroma, and restores vascular perfusion to alleviate hypoxia [96, 97]. Wang et al. demonstrated that *Bifidobacterium* significantly augments the abscopal effect of radiotherapy in immunologically "cold" tumors. Wang et al. revealed that *Bifidobacterium*-mediated vascular normalization increased tumor oxygenation using a murine model of triple-negative breast cancer. Concurrently, bacterial colonization triggeres localized ICD, releasing tumor-associated antigens that synergize with radiation to boost CD8+ T-cell infiltration. These findings highlight the transformative role of obligate anaerobes as dual functional agents capable of simultaneously modulating TME biophysics and immunogenicity, offering a novel strategy in radiosensitization [98]. Various bacteria demonstrate potential in hypoxia modulation and localized toxin delivery. However, spore dissemination and potential germination in healthy organs are concerning. Preclinical toxicity studies in immunocompetent mice revealed that intravenously administered *C. novyi*-NT spores primarily germinate in hypoxic tumor regions with minimal off-target effects. Furthermore, genetic insertion of auxotrophic markers enables pharmacologic control of bacterial proliferation. Future efforts require optimized design through synthetic gene circuits and immune-evasion coatings to solve these problems (**Figure 4**).

Cyanobacteria

Cyanobacteria are the first autotrophs found on earth with photosynthesis capability. Researchers have widely used cyanobacteria to improve the TME and induce radiosentisization based on cyanobacteria features (**Figure 5**). In addition to chemical strategies, generating oxygen *in situ* can be achieved by a natural photosynthetic system [99]. Qiao et al. showed that modifying the algal surface and delivering RBC membrane (RBCM)-algae to the tumor increases tumor oxygenation. RBCM-algae generated O_2 *in situ* and
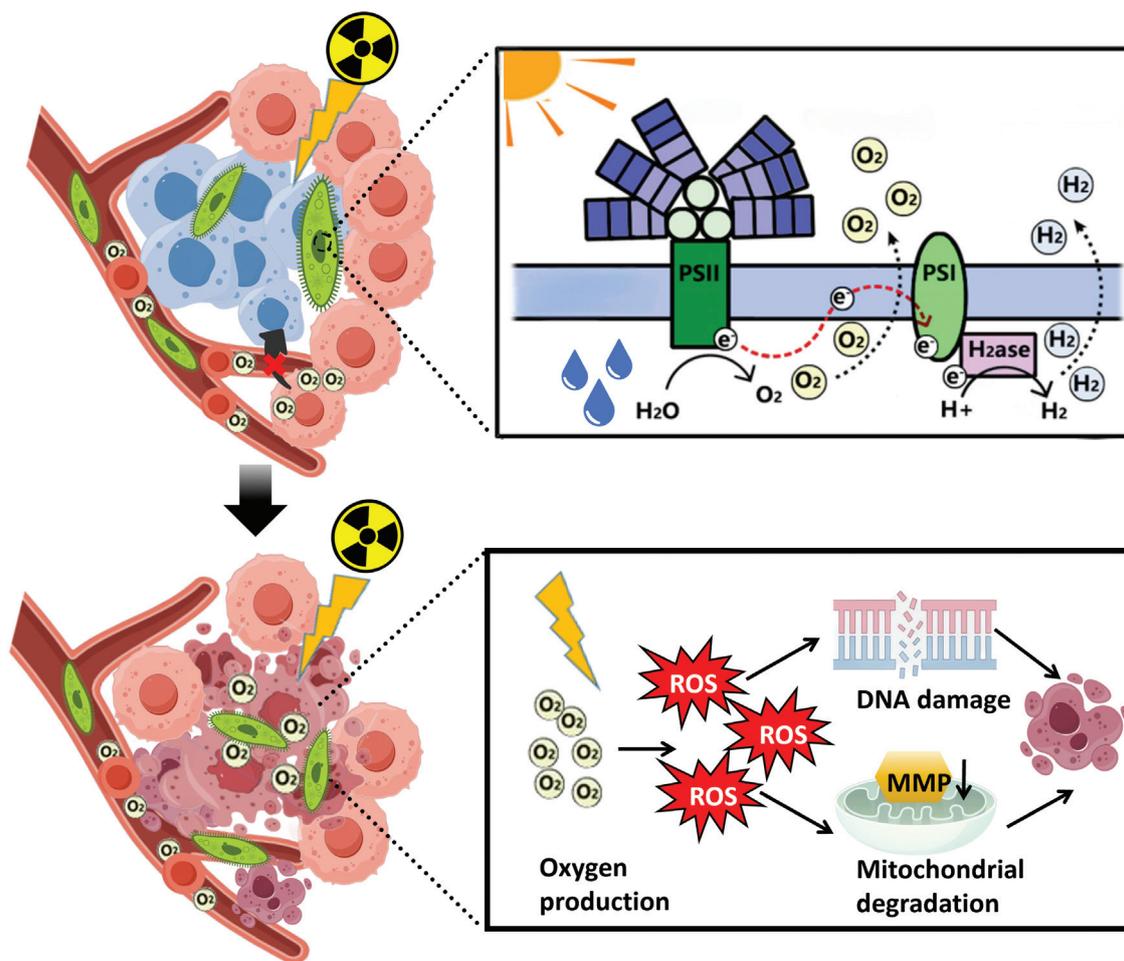
Figure 5 Application of cyanobacteria for tumor radiosensitization. This figure shows the tumor hypoxia microenvironment and the principle and sensitization effect of cyanobacteria oxygen production through photosynthesis.

Table 2 Application of Prokaryotic Cells in Tumor Radiosensitization

Type of Living Cells	Radiosensitization Strategy	Function	Anti-Tumor Efficacy	Tumor Type	Ref.
Escherichia coli	Targeted delivery of radiosensitizers	Delivery of bismuth-based nanomaterials and enhance radiation energy absorption (ROS ↑)	85% ↓	Colon/Breast tumor (CT26/4T1 cells)	[83]
	Targeted delivery of radiosensitizers	Activate prodrug and enhance cytotoxic drug level in tumor (TNF-α ↑, IFN-γ ↑)	75% ↓	Colon tumor (HT29 cells)	[84]
	Overcome tumor hypoxia limitation	Express catalase to decompose hydrogen peroxide (oxygen level ↑)	81% ↓	Breast tumor (MDA-MB-231/4T1 cells)	[86, 87]
	Targeted delivery of radiosensitizers and overcome tumor hypoxia limitation	Express catalase and AuNPs (oxygen level ↑, damged DNA ↑)	92% ↓	Breast tumor (4T1 cells)	[88]
	Regulate tumor cell cycle	Arrest tumor cell cycle in the radiosensitive G2/M phase (damged DNA ↑)	68% ↓	Colon tumor (HT29 cells)	[90, 91]
Salmonella	Targeted delivery of radiosensitizers	Deliver AuNPs into tumor cells (ROS ↑)	77% ↓	Pancreatic tumor (PANC1 cells)	[85]
	Overcome tumor hypoxia limitation	Express nattokinase to degrade ECM (oxygen level ↑)	79% ↓	Colon tumor (CT26 cells)	[89]
	Inhibit DNA damage repair	Sequestering DNA damage repair proteins (damaged DNA ↑)	75% ↓	Breast tumor (MDA-MB-231 cells)	[92]
Clostridium	Improvement in the immunosuppressive environment	Activating immune effect and conferring immune memory (IL-10 ↓, TGF-β ↓)	84% ↓	Fibrosarcoma/Breast tumor (C57/MDA-MB-231 cells)	[94, 95]
	Overcome tumor hypoxia limitation	Release spores and destruct tumor core hypoxia region (oxygen level ↑, TNF-α ↑)	85% ↓	Bladder tumor	[96]
Bifidobacterium	Overcome tumor hypoxia limitation	Release spores and destruct tumor core hypoxia region (oxygen level ↑, TNF-α ↑)	74% ↓	Fibrosarcoma (C57 cells)	[97]
	Improvement in the immunosuppressive environment	Release immune active factors and induce ICD (TNF-α ↑, IFN-γ ↑)	76% ↓	Colon/Breast tumor (CT26/4T1 cells)	[98]
Nostoc	Overcome tumor hypoxia limitation	Alleviate hypoxia by photosynthesis (oxygen level ↑)	69% ↓	Breast tumor/fibrosarcoma (MDA-MB-231/C57 cells)	[100, 101]
Spirulina	Overcome tumor hypoxia limitation and targeted delivery of radiosensitizers	Alleviate hypoxia by photosynthesis and delivery of Bi/Au-based nanomaterials (oxygen level ↑, damaged DNA ↑)	84% ↓	Melanoma/breast tumor (A375/4T1 cells)	[102, 103]

alleviated tumor hypoxia with red light-induced photosynthesis, which further enhanced the radiotherapy effect [100]. Given the potential risks associated with the application of cyanobacteria *in vivo*, Li et al. further reported a biohybrid microalgae system using a biomineralization approach to improve biocompatibility, while keeping the living activities for radiotherapy in breast cancer. The significant suppression of tumor growth and good safety in mice bearing the 4T1 tumor successfully demonstrated the promising anti-tumor effect of the biomineralization algae-mediated radiotherapy [101].

Cyanobacteria have been strategically integrated into hybrid platforms combining photosynthetic oxygen generation with high-Z element-mediated radiosensitization to further augment radiosensitization efficiency. A representative example is the development of a two-dimensional bismuthene-cyanobacteria system, which synergistically leverages the sustained photosynthetic hypoxia alleviation capability of cyanobacteria and the high-Z radiosensitization properties of bismuth [102]. Expanding this paradigm, Hua et al. engineered a whole-cell inorganic-biohybrid system by conjugating spirulina with gold nanoclusters. This platform operates through a cascade photocatalytic-radiosensitization mechanism, as follows: (i) light-driven oxygen production to reverse tumor hypoxia; (ii) partial conversion of oxygen to cytotoxic superoxide anions via electron transfer at the biohybrid interface; and (iii) oxidation of intracellular GSH to disrupt redox homeostasis [103]. These advances illustrate the evolution of cyanobacteria-based radiosensitization strategies from single-function oxygenators to multi-function therapeutic platforms. However, the depth dependency of light penetration restricts efficacy in solid tumors and scalable manufacturing of biohybrid systems poses engineering challenges. Future efforts should explore up-conversion NP (UCNP)-mediated deep-tissue photoactivation and microfluidic bioreactor technologies to standardize hybrid

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Table 3 Advantages and Disadvantages of Various Living Cells in Radiosensitization

Cell type	Radiosensitization Mechanisms	Advantages	Disadvantages
Stem cells			
MSCs	STAT3-mediated DNA repair inhibition	Precise identification of tumor cells; long cycle duration; immune memory	Surface modification instability; limited efficacy in brain tumors
NSCs	BBB-penetrating radiosensitizer delivery	Natural tendency and selective tumor targeting; ability to penetrate the blood-brain barrier	Short duration of treatment; limited application outside brain tumors
Immune cells			
Macrophages	"Trojan horse" nanoparticle delivery	Chemotaxis; phagocytosis; intercellular communication gradients	Nanoparticle loading may impair functionality
NK cells	IFN-γ-induced ferroptosis + GzmB DNA damage	Intercellular communication gradients; direct DNA fragmentation via granzyme B	Tumor heterogeneity reduces efficacy
T cells	Radiation-enhanced immune activation + DAMP release	Enhance ICD via DAMPs release; amplify CD8+ T-cell infiltration	Risk of cytokine release syndrome; dose optimization challenges
Blood cells			
Red blood cells	Oxygen delivery via hemoglobin	Broad availability; good innate biocompatibility and deformability	Limited drug-loading efficiency; hypoxia modulation requires sustained delivery
Platelets	Hypoxia-responsive miR-223 delivery	Hypoxia-responsive trafficking; deliver oxygen and suppress DNA repair	Short lifespan (8–10 days); complex engineering requirements
Gram-negative bacteria			
Escherichia coli	Redox-modulating factor secretion	Good tumor targeting; low bacterial toxicity; easy to modify and express gene	Potential risk of infection of normal tissues
Salmonella	Flagellum-driven tumor penetration + CDT toxin	Good tumor targeting and penetration; intracellular delivery function	Virulence of bacteria; potential risk in normal tissues infection
Gram-positive bacteria			
Clostridium	Hypoxia-triggered spore germination	Hypoxia tropism; colonization; immune response and destroy tumor hypoxic areas	Difficulty to culture in normal environment; high risk of wound infection
Bifidobacterium	Hypoxia-triggered spore germination	Natural tendency and selective tumor targeting; ability to penetrate the blood-brain barrier	Difficulty to culture in normal environment; genetic modification complexity
Cyanobacteria			
Nostoc	Light-triggered superoxide generation	Light-driven oxygen production to reverse tumor hypoxia; rapid metabolic degradation	Depth dependency of light penetration; engineering challenges in surface modification
Spirulina	Light-triggered superoxide generation	Good tumor targeting; improving hypoxic microenvironment	Biosafety and potential toxicity in humans has not been established

NP-cell assembly. To address depth limitations, UCNPs convert near-infrared light (980 nm) to visible wavelengths (400–650 nm), activating cyanobacteria in orthotopic pancreatic models [102]. Implantable fiber-optic diffusers (e.g., cylindrical diffusers at 630 nm) enable precise light delivery, achieving 5-cm depth coverage in clinical prototypes [104]. Combining UCNPs with magnetically guided biohybrids may further enhance deep-tissue activation (**Table 2**).

Challenges and prospects

Living cell-based radiosensitization strategies, which harness dynamic targeting, microenvironment remodeling, and multifunctional synergy of eukaryotic and prokaryotic cells, represent a novel strategy overcoming conventional radiotherapy limitations. Emerging clinical trials also demonstrate the viability of living cell-radiotherapy combinations, promising preclinical efficacy in achieving localized radiosensitizer delivery and tumor TME reprogramming.

CAR-T cells combined with radiotherapy induced sustained responses in lymphoma/liver metastasis patients by enhancing ICD in phase I/II trials [70, 71]. Intravenous *Salmonella* VNP20009 (NCT00004216) improved tumor targeting in metastatic melanoma [105]. However, the clinical translation faces many challenges. Specifically, current studies predominantly rely on animal models, which fail to fully explore living cell-tumor interactions under physiologic conditions. Humanized organ platforms, including 3D bioprinted tumor models and patient-derived organs, are needed to elucidate the specific radiosensitization mechanism of living cells. Advanced biomanufacturing platforms are critical for standardization. Microfluidic systems achieve > 95% loading efficiency for cell-nanomaterial assemblies [106]. 3D-bioprinted tumor organoids facilitate high-throughput screening of living cell radiosensitization under physiologic hypoxia [107]. Scalable hollow-fiber bioreactors support GMP-compliant expansion of engineered immune cells for clinical use [108]. In contrast, some living cells (e.g., anaerobic bacteria and stem cells) require a rigorous cultivation environment to ensure viability. It is necessary for advanced strategies (e.g.,

quality control system and dynamic feeding technology) to further improve the production process. Moreover, conventional radiosensitizer-loading methods often impair cellular viability or motility. Therefore, new loading techniques, like outer membrane vesicle fusion or CRISPR-based gene transformation, should be explored (**Table 3**).

Biosafety concerns of living cells, including uncontrolled proliferation and immunogenicity, further cause potential toxic risks in clinical application. Genetic "self-exploding" circuits and radiolabeled imaging probes offer real-time monitoring and regulated strategies to ensure living cell radiosensitization efficiency and biosafety. These circuits typically use radiation/hypoxia-activated promoters (RecA/HREs) to drive caspase-9 or cytosine deaminase expression. For example, engineered *E. coli* with X-ray-triggered RecA promoters achieved > 90% bacterial lysis within post-irradiation in murine colon tumors [109]. While validated preclinically, immune clearance and long-term circuit stability require optimization. Progress will not stop here and the living cell-based radiosensitization for enhancing the radiotherapy effect on tumors is still a question warranting further investigation. Clinical translation also faces significant regulatory hurdles. Living cells are classified as advanced therapy medicinal products (ATMPs), which require the following: (i) GMP-compliant manufacturing; (ii) potency assays; and (iii) stability profiling. Autologous therapies incur high costs, necessitating allogeneic 'off-the-shelf' solutions. Key challenges include the following: (i) batch variability in cell functionality (e.g., MSC chemotaxis); (ii) cryopreservation recovery < 60% for bacteria; and (iii) endotoxin control in Gram-negative systems. FDA/EMA guidelines mandate 18-month tumorigenicity/immunogenicity monitoring (e.g.,

anti-CAR antibodies) [110]. As the developments of synthetic biology methods and precision manufacturing technology, living cells are promising to serve as a high-efficacy radiosensitization strategy and widely utilized in clinical cancer treatment.

Data availability statement

The data are available from the corresponding author upon reasonable request.

Author contributions

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Conflict of interest

The authors declare that there are no conflicts of interest.

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