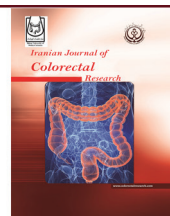


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Mitochondria-Targeted Radiosensitization in Colorectal Cancer: A Review

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Abstract

Colorectal cancers (CRC) are the third most common malignancy worldwide. Resistance to conventional treatments, along with their associated side effects, is a major cause of the high mortality rate in these cancers. Recent evidence demonstrates that mitochondrial dysfunction plays an important role in tumor progression, cancer stem cell (CSC) maintenance, and the development of treatment resistance. Targeting mitochondria through genetic methods, pharmacological treatments, or manipulation of mitochondrial dynamics appears to enhance the radiosensitivity of CRC. In this regard, mitochondrial metabolism, reactive oxygen species (ROS) production, and apoptotic pathways are key determinants of radiation response. Pharmacological inhibition of mitochondrial complexes, particularly complexes I and III, can increase oxidative stress and enhance cell death following irradiation. Additionally, targeting mitochondrial dynamics by inducing excessive fission or inhibiting fusion has shown synergistic effects with radiation therapy. Several novel agents, such as metformin, honokiol, and certain small-molecule inhibitors, are currently under investigation for their radiosensitizing potential in CRC models. However, challenges including tumor heterogeneity, optimal timing of administration, and potential toxicity to normal tissues remain unresolved. This review provides an overview of the current state of mitochondrial-targeted radiosensitization in CRC, with a particular focus on pharmacological inhibition of mitochondria. The emerging paradigm of mitochondria-based radiosensitization offers a promising strategy to overcome radioresistance in CRC patients; however, further investigations are required to achieve this goal.

Keywords: Colorectal Neoplasms; Radiation Tolerance; Mitochondria; Radiation-Sensitizing Agents; Neoplastic Stem Cells; Oxidative Stress

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Introduction

Colorectal cancers (CRC) are the third most frequently diagnosed cancer and the second leading cause of cancer-related mortality worldwide (1, 2). In the United States, more than 150,000 new cases of CRC are diagnosed annually, with over 50,000 deaths attributed to this disease each

year (3, 4). Despite significant advances in early detection and therapeutic interventions, the overall prognosis for patients with advanced-stage disease remains discouraging. Surgery, chemotherapy, and radiotherapy remain the mainstays of CRC treatment; however, their clinical efficacy is often compromised by metastasis, recurrence, and therapeutic resistance (5-7). This underscores an urgent and unmet medical

need for the development of new strategies to improve the effectiveness of current treatments. Radiotherapy is utilized in approximately 50% of all cancer cases, with the primary goal of maximizing tumor cell destruction while minimizing exposure to adjacent healthy tissues (8). The underlying mechanism of radiation therapy involves inducing double-strand DNA breaks, leading to cell death. However, a tumor's response largely depends on its intrinsic biology and the surrounding microenvironment. Variations in treatment response rates reflect the biological heterogeneity of colon and rectal cancers, as well as the presence of intrinsic or acquired resistance mechanisms that limit the cytotoxicity of radiation therapy. The high prevalence of radioresistance observed in approximately 50% of colon and rectal cancers (9) highlights the need for effective radiosensitizing therapies. Among the various factors contributing to radioresistance, mitochondrial dysfunction and metabolic reprogramming are recognized as two of the most critical determinants (10-12). Mitochondria are traditionally described as the cell's "energy factories," but they also perform essential functions such as regulating apoptosis, maintaining calcium homeostasis, regulating components of the innate immune system, and facilitating intercellular communication through metabolic signaling. Evidence from studies on mitochondrial fission indicates that cells with increased mitochondrial fission undergo metabolic reprogramming, which contributes to cancer cell proliferation, metastasis, and chemoresistance (13-16). CSC represent a subpopulation characterized by enhanced oxidative phosphorylation (OXPHOS) activity, rendering them resistant to therapies and responsible for tumor recurrence (17, 18). This review highlights recent advances in targeting mitochondria to enhance radiotherapy efficacy in CRC treatment. We also analyze strategies aimed at disrupting mitochondrial metabolism in CSC, as well as pharmaceutical approaches targeting mitochondrial function. By integrating these preclinical and translational studies into a coherent framework, we aim to bridge biological insights with practical applications. Furthermore, radiotherapy can induce gastrointestinal toxicity, such as mucositis, which limits treatment tolerance. Interestingly, natural products with mitochondrial modulatory properties have demonstrated protective effects against chemotherapy-induced intestinal mucositis (7), suggesting that similar mitochondrial-targeted approaches might mitigate radiation-induced gastrointestinal damage while enhancing tumor radiosensitivity.

The relevant studies were identified through a comprehensive search of the PubMed, Scopus, and Google Scholar using keywords related to mitochondrial dysfunction and radiosensitization in CRC. The search was limited to English-language articles published between 2015 and 2025.

Mitochondrial Dysfunction and Radioresistance in CRC

Mitochondrial Biology and Function in Cancer

Although mitochondria are traditionally known as the "energy-producing" compartments of eukaryotic cells, they perform numerous functions beyond ATP production. They exhibit dynamic processes such as fusion, fission, and degradation, which are essential not only for efficient ATP synthesis but also for various cellular activities, including cell differentiation, apoptosis, regulation of calcium concentration, innate immunity, and the metabolism of fatty acids and amino acids. Mitochondrial fusion and fission dynamics play a key role in signal transduction and metabolism in CRC cells. Studies have shown that excessive mitochondrial fission leads to metabolic reprogramming in CRC cells, thereby promoting cancer cell growth, migration, and resistance to chemotherapy (19). These findings suggest that multiple factors contribute to the development of radioresistance in cancer cells, with mitochondrial dysfunction being a significant contributor. Ionizing radiation (IR) induces DNA damage, primarily causing double-strand breaks (DSBs) that activate the DNA damage response (DDR). The DDR comprises signaling pathways designed to detect damage, facilitate repair, and inhibit cell cycle progression to ensure genomic integrity. Since mitochondrial dysfunction contributes to genomic instability, understanding the interplay between mitochondria and the DDR is crucial (20). Under certain pathological or stress conditions, mitochondrial DNA (mtDNA) can be released into the cytoplasm, where it functions as a damage-associated molecular pattern (DAMP). The cytosolic DNA-sensing cGAS-STING pathway mediates the link between radiotherapy-induced genomic instability and tumor immunity (21). Notably, mtDNA leakage into the cytoplasm due to mitochondrial dysfunction activates the cGAS-STING axis. Recent studies have demonstrated that irradiation-induced mitochondrial outer membrane permeabilization (iMOMP) triggered by X-ray exposure, is critical for elevating levels of phosphorylated eukaryotic initiation factor 2 α (p-eIF2 α) and activating transcription factor 4 (ATF4), which contribute to radioresistance in CRC cells (20).

p32 as a Novel Regulator of Mitochondrial Function and Radiosensitivity

p32, also known as CIQBP, is a multifunctional, multicompartmental homotrimeric protein that is overexpressed in various cancer types, including colon cancer. Primarily localized in the mitochondria, p32 regulates mitochondrial protein translation and plays a crucial role in maintaining mitochondrial OXPHOS. Studies have demonstrated

that p32 is highly expressed in colorectal tumors, with elevated p32 levels significantly correlating with poorer patient survival rates. In p32-knockout CRC cells, researchers found reduced cell viability, mitochondrial damage characterized by abnormal morphology, and diminished mitochondrial cristae formation. Additionally, mtDNA leakage and increased sensitivity to radiation were noted. Mechanistically, p32 depletion induces mitochondrial fragmentation and mtDNA leakage via the mitochondrial permeability transition pore (mPTP). These effects can be mitigated by Mdivi-1, a mitochondrial fission inhibitor, or cyclosporin A (CsA). The cytoplasmic DNA sensing pathway involving cGAS-STING-TANK-binding kinase 1 (TBK1) is activated upon p32 depletion; this activation is reversed in a p32/TBK1 double-knockout model. Activation of this pathway affects the DDR and increases radiosensitivity in colon cancer cells (19). Pharmacological inhibition of p32/C1QBP using the small molecule M36 significantly reduces the viability, clonogenic ability, and proliferation rate of colon cancer cell lines in a dose-dependent manner. Treatment with M36 significantly impacts mitochondrial integrity and dynamics, underscoring the critical role of p32/C1QBP in maintaining mitochondrial homeostasis. Collectively, these findings suggest that targeting mitochondrial dysfunction can enhance the efficacy of radiotherapy, and combining radiotherapy with mitochondrial-targeted therapies may improve clinical outcomes for CRC patients (19, 21).

Pharmacological Targeting of Mitochondria for Radiosensitization

Tigecycline as a Mitochondrial Inhibitor

Tigecycline is a broad-spectrum glycylcycline antibiotic approved by the U.S. Food and Drug Administration (FDA). It exhibits strong mitochondrial inhibitory effects by interfering with the binding of the translation machinery to the mitochondrial 30S ribosomal subunit, thereby abolishing the translation of mitochondrially encoded proteins essential for electron transfer chain function (9). Tigecycline has been shown to significantly decrease oxygen consumption rates (OCR) and induce energy stress, triggering apoptosis in leukemia stem cells and non-small cell lung cancer (NSCLC) cells. A dose-response curve was obtained for tigecycline-treated HCT-116 colorectal cells. The concentration that inhibited 50% of cell viability after 48 hours of incubation (48-h IC₅₀, 93 μ M) was used in combination with radiotherapy (4Gy). Treatment with this mitochondrial inhibitor at the IC₅₀ concentration, combined with radiotherapy, sensitized CRC cells to radiation and significantly increased both the number of apoptotic cells and caspase-3 activity. Additionally, the expression of pro-apoptotic genes increased, while anti-apoptotic

gene expression decreased compared to monotherapy treatments (9).

Metformin as a Metabolic Radiosensitizer

In a recent study, metformin was applied to rectal cancer as a novel metabolic modulator and radiosensitizer, demonstrating a significant radiosensitizing effect on both radioresistant and radiosensitive colon cancer cells in vitro. Transcriptomic and functional analyses revealed that metformin altered energy metabolism, mitochondrial function, cell cycle distribution and progression, cell death, and antioxidant levels in colorectal cells. Using an ex vivo model, metformin markedly downregulated both OXPHOS and glycolysis in treatment-naïve rectal cancer tissue without affecting the real-time metabolic profile of non-cancerous rectal tissue. Furthermore, compared to non-cancerous rectal tissue, the protein secretome of rectal cancer tissue responded differently to metformin treatment. Recent findings also indicate that metformin and 2-deoxy-D-glucose act synergistically to overcome radioresistance by suppressing p-eIF2 and ATF4 (20).

Liposomes loaded with metformin and 2-deoxy-D-glucose were developed for fractionated radiotherapy of CRC, demonstrating effective outcomes against both local and metastatic CRC tumors by overcoming radioresistance and reversing T lymphocyte exhaustion.

It can be concluded from the above data that metformin has the potential to be developed as an effective anti-metabolic agent with radiosensitizing effects on rectal cancer (22).

Norcantharidin and the Modulation of Mitochondrial Dynamics

Research has demonstrated that Norcantharidin (NCTD) sensitizes CRC cells to IR by disrupting mitochondrial morphology and function. In the control group, patients' mitochondria predominantly exhibited a rod-like shape; however, in the combination treatment group, mitochondrial fragmentation increased, resulting in a more punctate mitochondrial appearance compared to those treated with IR alone. Combination therapy led to a decrease in mitochondrial membrane potential, a key indicator of mitochondrial dysfunction. The combination of IR and NCTD activated dynamin-related protein 1 (DRP1), a critical regulator of mitochondrial fission. Phosphorylation of DRP1 at serine-616 leads to its activation and promotes further mitochondrial fission. In CRC cells treated with IR and NCTD, expression of mitochondrial fusion proteins (Mfn1, Mfn2), and Optic Atrophy 1 (OPA1) decreased, indicating that the combination disrupts the balance between mitochondrial fission and fusion (23). Additionally, NCTD increased CRC cell apoptosis by upregulating intracellular and mitochondrial ROS levels. Incubation with the

ROS scavenger (N-acetyl cysteine, NAC) reversed this effect, confirming the involvement of ROS in the anticancer activity of NCTD. In vivo mouse studies demonstrated a reduced number and size of tumors in animals treated with both NCTD and IR compared to those receiving individual treatments, with no evidence of toxicity (23, 24).

Mitochondria-Modulating Liposomes for Reversing Radioresistance

Nanotechnology has recently enabled the development of mitochondria-targeting liposomes that can convert CRC cells from radioresistant to radiosensitive. Analyses of clinical CRC samples reveal that the phosphorylation pattern of the translation initiation factor eIF2 α (p-eIF2 α) and the ATF4 differ upon initial exposure to X-ray irradiation. These two factors become elevated and maintain a state of radioresistance when the same cells undergo subsequent radiotherapy. In radioresistant CT26 cells, this mechanism is attributed to incomplete permeability of the mitochondrial outer membrane caused by X-ray irradiation, which leads to increased levels of both p-eIF2 α and ATF4, thereby maintaining radioresistance. Treatment with metformin and 2-deoxy-D-glucose synergistically reverses radioresistance in CT26 cells by inhibiting both p-eIF2 α and ATF4.

The development of mitochondrial-modulating liposomes containing both metformin and 2-deoxy-D-glucose (M/D-lipo) aims to enhance the efficacy of fractionated radiotherapy for CRC by modulating both glycolysis and oxidative metabolism in CRC cells. Treatment with M/D-lipo was shown to inhibit the extracellular acidification rate (ECAR) and OCR in radioresistant CT26 cells, thereby suppressing both mitochondrial function and glycolysis. In vivo studies demonstrated that M/D-

lipo treatment resulted in almost complete tumor ablation, an abscopal effect, and 100% survival in treated subjects following four fractions (4 x 10 Gy) of X-irradiation. The combination of M/D-lipo with RT induced immunogenic cell death, increased infiltration of CD8⁺ T cells, and decreased the number of FOXP3⁺ regulatory T cells (Tregs). The anti-tumor efficacy of M/D-lipo combined with radiotherapy was significantly reduced after CD8⁺ T cell depletion, confirming the importance of enhanced CD8⁺ T cell-mediated anti-tumor immunity in achieving the therapeutic effect. Thus, our data support a mechanism whereby modulating oxidative metabolism with liposomal constituents offers a novel therapeutic strategy to overcome radioresistance in CRC (20). A summary of key pharmacological strategies targeting mitochondria for radiosensitization in CRC, including their mechanisms of action, molecular targets, and key findings, is presented in Table 1.

Mitochondrial Targeting of CSC to Overcome Radioresistance

CSC and Mitochondrial Dependence

CSC are a subpopulation within tumors characterized by preferentially high levels of OXPHOS. This metabolic feature contributes to CSC ability to develop resistance and to recur after treatment (9). CSC exhibit a distinct mitochondrial morphology, characterized by perinuclear localization and an abundance of small globular and linear tubular structures, in contrast to the larger, branched mitochondria found in non-CSC. These CSC are addicted to OXPHOS and display a higher mitochondrial membrane potential compared to their non-CSC counterparts. Inhibitors of the respiratory chain complexes have been shown to

Table 1: Summary of Mitochondrial-Targeted Pharmacological Strategies for Radiosensitization in CRCs

Therapeutic Strategy	Mechanism of Action	Molecular Targets	Key Findings in CRCs	Study Stage	Ref
Tigecycline	Inhibition of mitochondrial translation via binding to 30S ribosomal subunit	Inhibition of OXPHOS, reduced mitochondrial-encoded protein production	Decreased CD44 expression, increased apoptosis, increased caspase-3 activity, upregulation of pro-apoptotic genes (Bax, Bad), downregulation of anti-apoptotic genes (Bcl-2, Bcl-xl)	in vitro	(9)
Metformin	Inhibition of mitochondrial complex I	Reduced OXPHOS and glycolysis, modulation of energy metabolism	Radiosensitization of resistant and sensitive cells, reduced p-eIF2 α and ATF4 phosphorylation, reduced self-renewal ability of CSC	in vitro / ex vivo	(22)
NCTD	Disruption of mitochondrial morphology and function	DRP1 activation, Ser616 phosphorylation, reduced Mfn1/Mfn2/OPA1, increased ROS	Increased mitochondrial fragmentation, reduced mitochondrial membrane potential, increased apoptosis, reduced tumor size and number in mouse model	in vitro / in vivo	(23)
M/D-lipo	Dual inhibition of glycolysis and OXPHOS via nanocarrier liposomes	Reduced ECAR and OCR, inhibition of p-eIF2 α and ATF4	Induction of immunogenic cell death, increased CD8 ⁺ T cell infiltration, reduced Treg cells, abscopal effect, 100% survival in mouse model	in vitro / in vivo	(20)

suppress sphere formation, indicating that CSC rely heavily on mitochondrial metabolism for growth and survival. This dependence on OXPHOS metabolism has also been observed in 5-fluorouracil (5-FU)-resistant CRC cells, which express increased levels of CD133 and form more spheres, suggesting that CSC similarly depend on mitochondrial metabolism for survival and maintenance. OXPHOS-dependent CD133+/CD44+/Lgr5+ CRC cells exhibit high mitochondrial membrane potentials and are highly reliant on OXPHOS (25). The combination of respiratory chain complex inhibitors with chemotherapy has demonstrated significant effects in reducing sphere size and promoting cell death in these cells (9, 26). This OXPHOS dependence of CSC presents an opportunity to develop therapies targeting OXPHOS to eliminate CSC and overcome resistance to conventional cancer treatments. Furthermore, combining OXPHOS inhibitors with immunotherapies may enhance the immune response against cancer and reduce the likelihood of drug resistance.

Apoptosis and Mitophagy in CSC

Anti-apoptotic proteins including c-FLIP, members of the Bcl-2 family, and IAPs—play a crucial role in the survival of CSC by being dysregulated within apoptosis pathways. Compared to treated groups, CD133+ colorectal cancer stem cells (CCSCs) exhibit lower levels of Bax and Bak oligomerization and higher levels of Bcl-2 proteins. CCSCs also display decreased mitochondrial priming and an accumulation of anti-apoptotic proteins, contributing to chemoresistance. Bcl-xl inhibitors (e.g., A-1155463 and WEHI-539) have shown potential to sensitize CSC to chemotherapy, indicating promise for radiosensitization (27). Mitophagy, the selective autophagic degradation of mitochondria, is significantly increased in CCSCs compared to non-CCSCs. Among CD133+ and CD44+ CCSCs, expression of the mitophagy-related protein BCL2/

adenovirus E1B 19 kDa protein-interacting protein 3-like (BNIP3L) is markedly higher; knockdown of BNIP3L via siRNA sensitizes CCSCs to doxorubicin (28). Furthermore, RAS-associated proteins RAB5 and RAB7 are essential for maintaining the CD44v9+/CD133+ CCSCs population, and their depletion reduces the proportion of CCSCs within tumors. Therefore, targeting mitochondrial quality-control mechanisms in CSC provides a promising strategy to overcome therapy resistance. Combining mitochondria-directed therapies with radiotherapy may effectively eradicate the CSC population responsible for tumor recurrence (29). The role of mitochondria in CSC and the mechanisms contributing to radioresistance are summarized in Table 2.

Conclusion

Mitochondrial dysfunction and metabolic reprogramming have emerged as critical factors contributing to radioresistance in CRC, positioning mitochondria as a promising therapeutic target for radiosensitization. Recent studies have identified multiple strategies aimed at the mitochondria in CRC. Notably, the p32/C1QBP mitochondrial protein translation regulator shows potential as a target for enhancing radiosensitivity through the activation of the cGAS-STING-TBK1 signaling pathway and inducing mitochondrial dysfunction. Pharmacological approaches using FDA-approved medications such as tigecycline and metformin have shown promise in preclinical settings. Tigecycline sensitizes CRC cells to radiation therapy by inhibiting mitochondrial translation, promoting apoptosis, and reducing markers associated with CSC. Metformin sensitizes both radiosensitive and radioresistant CRC cells to radiation by modulating energy metabolism and mitochondrial function. Additionally, recently identified novel compounds, such as NCTD, sensitize CRC cells to IR via impairing mitochondrial

Table 2: Role of Mitochondria in CSC and Mechanisms of Radioresistance

Feature/Mechanism	Description	Therapeutic Implication	Potential Therapeutic Target	Ref
OXPHOS Dependency	CSC exhibit high levels of OXPHOS and elevated mitochondrial membrane potential	CSC are sensitive to respiratory chain complex inhibitors	OXPHOS inhibition for CSC elimination	(25, 26)
Distinct Mitochondrial Morphology	Perinuclear localization, small globules, linear tubules with fewer branches	Identification of CSC based on morphological features	Targeting mitochondrial dynamics	(9)
Enhanced Mitophagy	Increased BNIP3L expression in CD133+ and CD44+ CCSCs	Sensitization to doxorubicin following BNIP3L knockdown	Mitophagy inhibition with siRNA	(28)
RAS-Associated Proteins (RAB5/RAB7)	Maintenance of CD44v9+/CD133+ CCSCs population	RAB5/RAB7 depletion reduces CCSCs percentage	Targeting endolysosomal pathway	(29)
Apoptosis Dysregulation	Increased anti-apoptotic proteins (Bcl-2, c-FLIP, IAPs), decreased Bax/Bak oligomerization	Induction of chemoresistance	Bcl-xl inhibitors (A-1155463, WEHI-539)	(6)

morphology and function.

Novel nanotechnology-driven formulations of liposomes containing metformin and 2-deoxy-D-glucose represent a promising approach for developing mitochondria-modulating agents that can induce radiosensitization and enhance the antitumor immune response in CRC treatment. Similarly, targeting the mitochondria-dependence of CSC by inhibiting OXPHOS, or modulating apoptosis and mitophagy pathways could lead to the eradication of CSC responsible for tumor recurrence. Although several promising findings have emerged, significant challenges remain in translating these technologies to clinical application. Personalized approaches will be essential to address the heterogeneity of CRC and the complex nature of mitochondrial biology. It is also critical to evaluate the potential off-target effects of mitochondrial inhibitors on normal tissues. Future research should focus on developing more selective mitochondrial-targeting agents, identifying predictive biomarkers for patient stratification, and examining combination strategies that incorporate immunotherapy to harness the immune system against radioresistant tumors. Achieving these objectives presents a significant opportunity for

advancing radiosensitization through mitochondrial targeting in CRC; however, substantial further research is required to successfully implement these advances in clinical practice.

Author contribution

KH.d have Substantial contributions to the conception or design of the work AND drafting the work or reviewing it critically for important intellectual content AND final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

There is no conflict of interest

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