Molecular Mechanisms of Chemoradiotherapy Resistance in Esophageal Cancer and Clinical Response Strategies: From the Tumor Microenvironment to Precision Medicine

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Abstract. Esophageal squamous cell carcinoma (ESCC) is the sixth leading cause of cancer-related deaths globally, with more than half of cases occurring in China. Although chemoradiotherapy (CRT) is a major treatment modality for ESCC, its efficacy is often limited by tumor resistance. The 5-year survival rate of esophageal cancer patients is less than 30%, and the prognosis is poor. The mechanisms of induced resistance in cancer mainly include multi-dimensional factors such as the regulation of the tumor microenvironment (TME), the metabolic reprogramming of cancer-associated fibroblasts (CAFs), and the imbalanced proliferation of cancer stem cells. New strategies are urgently needed to break through this bottleneck. The study primarily focuses on reviewing the regulation of the tumor microenvironment, abnormal drug metabolism and transport, epigenetic modifications, and signaling pathways, aiming to reveal the mechanisms of CRT resistance, summarize strategies to overcome CRT resistance, and explore new treatment strategies such as targeted therapy and immunotherapy combination. This review emphasize the importance of multidisciplinary collaboration and individualized treatment to improve the cure rate and survival of ESCC patients.

Keywords: Esophageal cancer, Chemoradiotherapy resistance, Tumor microenvironment, Precision therapy, Metabolic intervention.

1. Introduction

Esophageal carcinoma, ranking as the seventh most prevalent malignant tumor globally, exhibits over 470, 000 annual new cases [1]. In China, it constitutes the seventh most common malignancy with approximately 188, 000 mortality cases in 2022, demonstrating an ascending epidemiological trend [2]. Histopathological classification primarily distinguishes adenocarcinoma from squamous cell carcinoma, with the latter predominating in Asian and Eastern European populations. While surgical resection combined with chemoradiotherapy (CRT) remains the standard therapeutic approach for non-metastatic esophageal squamous cell carcinoma, most patients present with locally advanced stage at initial diagnosis, thereby missing the optimal window for surgical intervention. For unresectable cases, CRT serves as the cornerstone treatment for intermediate to advanced stages, yet suboptimal 5-year survival rates persist due to heterogeneous therapeutic resistance. Current research delineates a multidimensional resistance network encompassing tumor microenvironment (TME) modulation, cancer-associated fibroblast metabolic reprogramming, and aberrant cancer stem cell proliferation mechanisms.

Cytokines and matrix components in the tumor microenvironment can affect the chemoradiotherapy of tumor cells. The tumor microenvironment contains various non-malignant cells, such as immune cells, fibroblasts, and endothelial cells. These cells interact with tumor cells by secreting cytokines, chemokines, and growth factors, thus influencing tumor growth and metastasis [3]. The CRT resistance of esophageal cancer is closely related to multiple factors in the tumor microenvironment, including immunosuppression, hypoxia, metabolic reprogramming, cancer associated fibroblasts, and extracellular matrix remodeling [4]. Through precision treatment methods such as molecular targeted therapy, immunotherapy, epigenetic therapy, and combined individualized therapy, targeting key components in the tumor microenvironment and treating according to the molecular characteristics of esophageal cancer can overcome CRT resistance and provide new treatment strategies for esophageal cancer patients.

However, presently there is a lack of comprehensive review that summarizes the mechanisms of chemoradiotherapy resistance in esophageal cancer and how to achieve precise treatment to improve prognosis. Therefore, the objects of this paper are: 1) outlining the mechanism of chemotherapy resistance; 2) summarizing strategies to overcome resistance to chemoradiotherapy. Studying the molecular mechanisms of CRT resistance in esophageal cancer, proposing hypotheses regarding the regulation of the tumor microenvironment, drug metabolism regulation, abnormal transport, epigenetics, and signaling pathways, and combining strategies such as targeted therapy, immunotherapy, and combination therapy can help better understand the mechanisms of CRT resistance in esophageal cancer. This can suggest new treatment targets for novel intervention strategies in esophageal squamous cell carcinoma and improve the prognosis of CRT resistant patients.

2. Chemotherapy resistance mechanism

2.1. The regulatory role of TME

ESCC tumors exhibit CAF-rich TMEs, where a unique antigen-presenting CAF subset (apCAF) identified via scRNA-seq disrupts heparan sulfate metabolism to drive immune evasion by modulating glycosaminoglycan biosynthesis in T/B cells and macrophages [5]. Activated stromal components differentiate into CAFs, fueling NOX5+ tumor malignancy [6]. These findings underscore CAFs as metabolic orchestrators of immunosuppressive TMEs, highlighting their therapeutic targeting to restore anti-tumor immunity.

The mechanisms of multidrug resistance remain incompletely understood, with the tumor microenvironment (TME) being a key obstacle. Cancer-associated fibroblasts (CAFs) remodel the extracellular matrix (ECM) to create physical barriers impeding drug delivery and immune infiltration. Studies demonstrate S100A8 can reprogram CAFs to modulate chemosensitivity in esophageal squamous cell carcinoma (ESCC), with its peripheral blood levels serving as predictive biomarkers for chemotherapy response [7]. Direct CAF elimination may promote tumor invasion, and current CAF-targeting clinical trials show limited progress. Developing CAF reprogramming strategies to maintain stromal homeostasis shows promise for achieving safe therapeutic enhancement [8].

The esophageal cancer microenvironment harbors immunosuppressive cells that suppress antitumor immunity via immunosuppressive cytokines (IL-10, TGF-β) and checkpoint molecules (PD-L1). M2-like TAMs drive chemoresistance through dual mechanisms: secreting IL-10/TGF-β to inhibit immune effector functions while promoting tumor cell survival/proliferation, and releasing growth factors (EGF, VEGF) to sustain drug-resistant niches [9]. Research indicates that TREM2+ TAMs infiltration in esophageal squamous cell carcinoma (ESCC) correlates with poor prognosis and may serve as a biomarker for outcome prediction and immunotherapy modulation in this patient cohort.

TAMs facilitate tumor cell proliferation, migration, angiogenesis, and immune evasion. The cytokines they secrete can promote the survival and proliferation of tumor cells, thus enhancing their tolerance to chemotherapy. TAMs communicate with immune cells and other immune components infiltrating the tumor microenvironment (TIME). By releasing numerous cytokines, growth factors, chemokines, and exosomes, this process contributes to the establishment of an immune-evasive tumor niche in esophageal carcinoma, where malignant cells circumvent host defense mechanisms through microenvironmental reprogramming [10]. Both cellular elements (e.g., stromal cells, immune cells) and acellular factors (e.g., extracellular matrix, cytokines) within the esophageal neoplastic ecosystem engage in dynamic cross-talk through multiple signaling pathways. These intricately coordinated biological networks create a permissive milieu for tumor progression and therapeutic resistance. Deciphering the molecular dialogue between malignant epithelium and its surrounding tumor ecosystem represents a critical foundation for developing next-generation targeted therapies and immunomodulatory interventions.

2.2. Abnormalities in drug metabolism and transport

Multidrug resistance compromises therapeutic efficacy in esophageal cancer, being a major contributor to chemotherapy failure. ABC transporter upregulation mediates drug efflux, reducing intracellular chemotherapeutic accumulation [11]. Esophageal cancer cells develop resistance to multiple chemotherapeutic drugs, and these drugs cannot effectively kill cancer cells. Therefore, developing effective ABCB1 inhibitors is a key strategy to overcome CRT resistance in esophageal cancer. Neoadjuvant chemotherapy (NAC) can enhance the anti-tumor immune response by altering the composition of immune cells in the tumor microenvironment. NAC can induce the proliferation of CD4+ and CD8+ T lymphocytes in the tumor microenvironment and maintain the expression of HLA class I molecules [12], thereby enhancing the ability of the immune system to recognize and attack tumors and helping to improve the treatment response rate of patients.

The types and functions of immune cells play a crucial role in the tumor microenvironment of esophageal squamous cell carcinoma. The composition and activity of immune cells directly affect the progression of esophageal cancer and the prognosis of patients. Hypoxia often exists within esophageal cancer, and this hypoxic state can lead to tumor cells being insensitive to chemotherapy. Hypoxia can inhibit the progression of the cell cycle and cause cells to enter a dormant state, thereby increasing chemoresistance [4]. Enhancing antioxidant capacity can protect normal cells from drug induced oxidative damage, reduce side effects, improve treatment efficacy, and is of great significance in the treatment of esophageal cancer.

Hypoxia induced HIF1α upregulates the expression of g RB binding protein 7 (RBBP7). By increasing the expression of cyclin dependent kinase 4 (CDK4), it promotes the viability, proliferation, and stemness of esophageal cancer cells. Luciferase reporter gene experiments have confirmed that HIF1α regulates the expression of RBBP7 through transcription [13]. Hypoxia induces high expression of RBBP7 (at least partially mediated by HIF1α), which upregulates the expression of downstream CDK4, thus promoting the tumor progression of esophageal cancer cells. HIF-1α drives tumor aerobic glycolysis, and its therapeutic targeting offers a promising strategy for suppressing glycolysis in cancer treatment. Artemisinin targets the HIF - 1α target and reduces the level of glycolysis by downregulating the protein level of HIF - 1α, thereby inhibiting the development of esophageal cancer [14].

2.3. Epigenetics and abnormal signaling pathways

DNA methylation is one of the earliest discovered and most intensively studied epigenetic regulatory mechanisms. In eukaryotes, DNA methylation mainly occurs at the 5th carbon atom of cytosine in CpG dinucleotides, forming 5 - methylcytosine (5 - mC). DNA methylation inhibitors interfere with the function of DNA methyltransferases (DNMTs), preventing them from adding methyl groups to the cytosine residues of DNA [15]. This can reverse abnormal hypermethylation states, especially the hypermethylation in the promoter regions of tumor suppressor genes, thus restoring the expression of these genes.

During anti-cancer treatment, the hypermethylation of radiation resistance associated protein kinases (DAPK), CHFR, and FGF5 is related to the weakened response to CRT in ESCC. DNMTs play an important role in this process. The hypermethylation of the promoter region of the p53 gene, which leads to the silencing of this tumor suppressor gene, is one of the common epigenetic changes in esophageal cancer. This methylation causes the silencing of the p53 gene, resulting in the loss of its ability to regulate the cell cycle and apoptosis and promoting tumorigenesis [16]. In esophageal cancer, low levels of SOX17 protein expression can serve as a biomarker for predicting poor responses of ESCC patients to CCRT. Overexpression of SOX17 sensitizes ESCC cell lines to cisplatin, radiotherapy, and CRT treatment. SOX17 inhibits the expression of DNA repair and damage response genes through transcriptional regulation. Re activating the expression of SOX17 can enhance the sensitivity of ESCC cells to CCRT, providing a new strategy for overcoming drug resistance [17] (Table 1).

Table 1. Mechanisms of Chemotherapy Resistance in Esophageal Cancer

Research type	Sample type	Chemotherapeutic drugs	Key molecules or pathways	Mechanism	Type of Resistance	References
In vitro study	Samples from ESCC patients	None	Heparan sulfate/heparin metabolic pathway	Metabolic reprogramming of fibroblasts in the TME	Secondary resistance	[5]
In vitro study	TREM2+ TAM in patients with ESCC	None	TREM2 receptor	Immunosuppressive TME and immunotherapy regulation	Primary resistance	[9]
In vitro study	Human esophageal cancer cell lines KYSE - 150, KYSE - 170	None	Aerobic glycolysis, HIF-1α	Inhibit glycolysis	Primary resistance	[14]
In vitro study	EC-18, KYSE 30 and HEK 293 cell lines	None	CAF, exosome, miR-3656, ACAP2, ACAP2/PI3K-AKT signaling pathway	Abnormal signal pathway	Secondary resistance	[20]
Animal study	Mouse	5-FU/CDDP	RhoA-ROCK-MLC 2-MRTF-A pathway	Block the S100A8-CD147 pathway	Secondary resistance	[7]
Clinical study	Esophageal cancer patients with no history of immunotherapy, targeted therapy, or radiotherapy	Carboplatin/Nedaplatin, Albumin-bound Paclitaxel	PD-L1	Immune environment resistance	Secondary resistance	[12]
Clinical study	Seventy CCRT-treated esophageal squamous cell carcinoma patients	Cisplatin	SOX17	DNArepair	Secondary resistance	[17]

The activation of multiple signaling pathways, such as the Nuclear factor kappa B (NF-κB) pathway and the PI3K/Akt pathway, is also associated with chemoresistance. These pathways directly affect the response of esophageal cancer cells to chemotherapy by regulating processes such as cell survival, proliferation, and apoptosis. NF-κB is a transcription factor involved in regulating immune responses and cell survival. In esophageal squamous cell carcinoma, abnormal activation of NF-κB may promote the survival and proliferation of tumor cells and play an important role in the tumor microenvironment [18]. The cooperation between different receptors that can activate canonical and non-canonical NF-κB contributes to the functional diversity of this signaling pathway. We can find ways to enhance immune protection and vaccination, as well as improve treatment regimens when the NF-κB signal is out of control. The research results emphasize the high expression of key components of the PI3K/AKT/mTOR pathway in human cell lines and carcinogen-induced animal models of esophageal cancer [19]. The PI3K/AKT/mTOR signaling pathway is related to the occurrence of esophageal squamous cell carcinoma. MK 2206 and BEZ 235, which block the PI3K/AKT/mTOR signaling pathway, can inhibit cell proliferation, induce apoptosis, and cause cell cycle arrest by inhibiting AKT phosphorylation, thus achieving the result of suppressing the growth of esophageal tumor cells.

A study in ESCC comparing CAF-derived exosomal miRNAs to normal fibroblasts (NFs) identified upregulated hsa-miR-3656 in CAF exosomes. This miR-3656/ACAP2 axis promotes ESCC proliferation, migration, and invasion through PI3K-AKT and Wnt/β-catenin pathway activation, with growth-promoting effects demonstrated in vitro and in xenograft models, providing a therapeutic target [20] (Table 1).

3. Strategies to overcome resistance to radiotherapy and chemotherapy

3.1. Targeting TME

Based on the above mechanisms, the following strategies have demonstrated potential for clinical translation by targeting key molecules or pathways, thus exploring novel treatment strategies. CAFs in the TME are key factors in tumor progression, which could remodel the ECM, forming a physical barrier that hinders drug delivery and immune cell infiltration. Researchers established a patient-derived xenograft (PDX) model using tumor tissues from ESCC patients for in vitro and in vivo

experiments [7]. By knocking down or overexpressing S100A8, they studied its effects on the polarization of CAFs and chemoresistance. Cancer-secreted S100A8 binds CD147 on CAFs, activating the RhoA-ROCK-MLC2-MRTF-A pathway to polarize CAFs into myofibroblastic subtypes (myCAFs), thereby promoting chemoresistance. Blocking S100A8-CD147 suppresses CAF activation and collagen deposition, enhancing chemotherapy efficacy. Clinically, elevated peripheral S100A8 levels correlate with chemotherapy resistance, supporting its role as a predictive biomarker [21]. In ESCC, NRF2 mutations drive chemo/radioresistance, making NRF2 inhibition a therapeutic priority. Pyrrolidine dithiocarbamate (PYR) is validated as a potential NRF2 inhibitor, offering a novel strategy for NRF2-high ESCC [22].

The study elucidated the mechanism by which the CCL2-CCR2 axis facilitates immune evasion in esophageal squamous cell carcinoma (ESCC) through recruitment of tumor-associated macrophages (TAMs) and synergistic interaction with the PD-1 signaling pathway [23]. Key findings demonstrated that genetic ablation of CCR2 substantially decreased both tumor incidence rates and TAM infiltration. Pharmacological blockade of the CCL2-CCR2 axis effectively suppressed the secretion of TAM-derived pro-inflammatory cytokines. This investigation highlights the pivotal role of CCL2-CCR2 signaling in esophageal carcinogenesis, offering novel insights into the mechanisms underlying TAM-mediated immune evasion in ESCC while highlighting the therapeutic potential of TAM-targeted preventive strategies and immunomodulatory interventions for ESCC management.

3.2. Combination therapy

The success of targeted therapy (TT) usually depends on the sensitivity of tumor cells to the inhibition of the target. Tumor cells may develop drug resistance through various mechanisms. Therefore, relying solely on the inhibition of a single target usually does not produce long-term and sustained therapeutic effects. This makes combination therapy crucial. When used in combination with radiotherapy, targeted therapy has the potential to improve the treatment effect while possibly reducing the radiation dose. A total of 334 patients received 683 radiotherapy sessions, and 51 different targeted therapeutic substances were administered simultaneously during the radiotherapy process [24]. External beam irradiation was used for different anatomical sites. Studies have shown that the combined administration of RT and TT is generally well tolerated, and no severe acute toxicity was observed.

Therapeutic synergy between CRT and immunomodulatory agents shows enhanced clinical benefits over conventional chemoradiation protocols in managing non-operable locally advanced esophageal carcinoma. Emerging evidence confirms the clinical validity of immune checkpoint modulation across various solid tumors, with particular therapeutic relevance observed in esophageal malignancies [25]. RSK4 is highly expressed in ESCC and is associated with radioresistance and low survival rates in ESCC patients. Researchers tested the therapeutic effect of BI-D1870 in nude mice and PDX models. The results showed that BI-D1870, when used alone or in combination with radiotherapy, can significantly inhibit the growth of ESCC tumors. Among them, the combination therapy (BI-D1870 + radiotherapy) is more effective than the single treatment in reducing tumor volume and weight and increasing apoptosis. RSK4 was found to be a direct downstream transcriptional target of ΔNp63α, which activates the β-catenin signaling pathway by directly phosphorylating GSK-1. Inhibiting RSK4 effectively reduces the characteristics of cancer stem cells (CSCs) and improves radiosensitivity. This indicates that RSK4 is a promising therapeutic target for the treatment of ESCC [26] (Table 2). Pharmacological targeting of RSK4 signaling pathways in conjunction with PD-1 axis blockade has shown promising survival outcomes for chemotherapy-refractory esophageal patients. Current investigations systematically evaluate three therapeutic dimensions: 1) synergistic pairing of immunomodulators with cytotoxic drugs, 2) radiotherapy sequencing parameters and dosage optimization, and 3) temporal coordination of multimodal interventions - all aimed at establishing evidence-based protocols for precision oncology in non-resectable locally advanced esophageal carcinoma management. Tailoring the treatment plan for different patients will make the treatment plan more personalized.

3.3. Metabolic intervention

Table 2. Strategies to Overcome CRT Resistance in Esophageal Cancer

Type of Research	Sample Type	CRT Regimen	Targets/Pathways	Intervention Measures	Experimental Methods	References
In vitro study	Human esophageal carcinoma cells KYSE30, KYSE150, TE3; esophageal epithelial cell line SHEE	None	Induce PANoptosis	DMSO or sulconazole (50 μM)	MTS assay, clonogenic assay	[27]
In vitro study	human esophageal cancer cell KYSE150	None	Glycolysis, metabonomic, HIF-1α, cyclin D1	Baicalein	Flow cytometry assays, quantitative Real-Time PCR	[28]
Animal study	20 cases of xenografts (PDX) derived from patients with esophageal squamous cell carcinoma, and mice	5-FU/CDDP or carrier reagent	S100A8;CD 147-RhoA-ROCK-MLC 2-MRTF-A pathway	S100A8 KO in ESCC cells	RNA-seq	[7]
Animal study	Six-week-old male F344 rats and C57BL/6 mice, Het-1A cells	None	CCL2, CD68	NMBA-trea-ted rats, nitrosamine	Induced by nitrosamine, Gene Set Enrichment Analysis	[23]
Animal study	Nude mice and PDX models	BI-D1870 + radiotherapy	Δ Np63α, RSK4, GSK-3 β	BI-D1870	Knock out a gene	[26]
Clinical study	Patients with histologically confirmed cancer	Radiotherapy and concurrent targeted therapy	Monoclonal antibodies, kinase inhibitors, and signal transduction inhibitors	Combining radiotherapy and concurrent targeted therapy	Combination of radiotherapy and targeted therapy	[24]

Tumor metabolic heterogeneity, driven by cancer evolution and reprogramming, fosters immunosuppression through nutrient competition and TME acidification. In ESCC, a 3-gene metabolic signature (CD38↓, INPP5E↑, POLR3G↓) stratifies high-risk patients with increased Treg infiltration and reduced plasma cells. Experimentally, sulconazole induces multimodal cell death (apoptosis/pyroptosis/necrosis/ferroptosis) via mitochondrial oxidative stress and glycolysis inhibition, enhancing radiosensitivity at low doses [27] (Table 2). Concurrently, baicalein targets HIF-1α to suppress glucose metabolism and modulates the Cyclin D1/CDK4 axis, overcoming radioresistance in ESCC [28] (Table 2).

4. Conclusion and prospects

Due to the resistance of esophageal cancer patients to CRT, the 5-year survival rate of patients after treatment is low, and the prognosis is poor. The CRT resistance of esophageal cancer is extremely complex and heterogeneous. This review, for the first time, integrates the synergistic effects of TME reprogramming, epigenetic mechanisms, stem cell characteristics, and metabolic adaptation to reveal a multi-dimensional drug resistance network. It outlines the clinical challenges of CRT resistance in the treatment of esophageal cancer, summarizes the drug resistance mechanisms discovered in recent years, such as the regulation of the tumor microenvironment, metabolic

reprogramming, cancer stem cells, etc., and explores novel treatment strategies including targeted therapy and immunotherapy combinations. It emphasizes the importance of multidisciplinary collaboration and personalized treatment. The dynamics of circulating tumor DNA, as a prognostic biomarker for locally advanced and metastatic esophageal squamous cell carcinoma, provides more precise personalized treatment for patients.

Firstly, developing novel drugs that can target the bidirectional communication between CAFs and tumor cells is expected to break the protective effect of CAFs on tumor cells, thereby improving the treatment effect. CAFs play a crucial role in the tumor microenvironment of esophageal cancer. CAFs can not only promote the proliferation and migration of esophageal cancer cells but also enhance the invasiveness and drug resistance of tumors through mechanisms such as activating signaling pathways. Furthermore, in-depth exploration of the mechanisms of action and clinical applications of epigenetic drugs will provide novel insights for precision therapy in esophageal cancer. By modulating the epigenetic state of esophageal tumor cells, these agents may reverse chemoresistance, enhance the efficacy of chemotherapeutic agents, and ultimately improve patient survival rates.

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