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Nanomaterials-Loaded circRNAs Influence Oral Squamous Cell Carcinoma by Regulating Ferroptosis: Mechanisms, Therapeutic Potential, and Future Perspectives

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Abstract: *Oral Squamous Cell Carcinoma (OSCC) is a highly invasive malignant tumor with poor prognosis, and its treatment faces severe challenges due to the widespread presence of chemoresistance. Ferroptosis, a unique iron-dependent regulated cell death mode, has emerged as a highly promising target to bypass traditional apoptotic pathways and overcome therapeutic resistance in OSCC. Circular RNAs (circRNAs), a class of non-coding RNAs with covalent closed-loop structures and high stability, exhibit significant dysregulation in OSCC and deeply participate in tumor progression as key regulatory nodes. This review systematically elaborates on the core molecular mechanisms by which circRNAs regulate ferroptosis in OSCC and explores their potential as diagnostic biomarkers and therapeutic targets. Studies have shown that specific oncogenic circRNAs (such as circFNDC3B and circ_0000140) can upregulate the expression of SLC7A11, a key subunit of System Xc^-, by acting as microRNA (miRNA) sponges, thereby inhibiting ferroptosis and ultimately promoting the malignant progression of OSCC and resistance to chemotherapeutic drugs such as cisplatin. Therefore, targeting this "circRNA-miRNA-SLC7A11" regulatory axis provides an innovative therapeutic strategy to reverse OSCC resistance. However, the clinical translation of circRNAs is limited by their in vivo delivery efficiency and targeting ability. To this end, nanomaterial-based delivery systems, such as lipid nanoparticles (LNPs) and polymeric nanoparticles, with advantages of enhanced stability, targeted delivery, and reduced immunogenicity, offer an ideal solution for the precise and efficient delivery of therapeutic circRNAs. Through engineering design, nanocarriers can even synergize with circRNA payloads to co-induce ferroptosis, thereby maximizing therapeutic effects. Despite the challenges in specificity, potential toxicity, and large-scale production in this field, nanomaterial-mediated circRNA ferroptosis-inducing therapy represents a transformative multimodal synergistic therapeutic paradigm with the potential to overcome the bottlenecks in OSCC treatment.*

Keywords: *Oral Squamous Cell Carcinoma (OSCC), Ferroptosis. Circular RNAs (circRNAs), Nanomaterial Delivery Systems, Chemoresistance, Therapeutic Targets, Diagnostic Biomarkers, System Xc^-/SLC7A11, Regulatory Axis, Multimodal Therapy*

1. Introduction: Oral Squamous Cell Carcinoma and the Rise of Ferroptosis

1.1 Oral Squamous Cell Carcinoma (OSCC): Current Treatment Landscape and Challenges

Oral Squamous Cell Carcinoma (OSCC) constitutes a severe global public health challenge, accounting for approximately 2% of all cancer cases and up to 90% of oral malignant tumors [1]. It is clinically characterized by high invasiveness, rapid disease progression, extensive local infiltration, and generally poor prognosis [1]. Currently, the standard treatment regimen for OSCC is multimodal combination therapy, typically integrating surgical resection, radiotherapy, and chemotherapy, with cisplatin-based chemotherapy often used as first-line treatment [1].

However, despite certain progress in traditional treatment modalities over recent decades, the five-year overall survival rate of OSCC patients remains stagnant at 50-60%, failing to achieve a breakthrough [2]. Chemoresistance, particularly to cisplatin, is the core obstacle hindering successful treatment. This resistance not only severely limits the clinical efficacy of chemotherapy but also serves as a key driver of tumor recurrence and distant metastasis after conventional treatment [1].

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Faced with the severe challenges of high mortality, strong invasiveness, and persistent resistance in OSCC under standardized treatment, the development of novel therapeutic strategies has become an urgent priority. The long-term stagnation of the five-year survival rate further highlights the limitations of existing treatment paradigms. This clinical dilemma provides a solid theoretical basis for exploring innovative therapeutic pathways. Therefore, emerging strategies such as regulating ferroptosis and applying advanced delivery systems like nanomaterials are being regarded as frontier directions with the potential to break through the bottlenecks in OSCC treatment and achieve transformative effects.

1.2 Ferroptosis: A Unique Regulated Cell Death and Its Application Prospects in Cancer Treatment

Ferroptosis is defined as a unique, non-apoptotic form of regulated cell death (RCD), whose molecular mechanisms differ significantly from classical cell death modes such as apoptosis, autophagy, and necrosis [1]. Its core biochemical feature lies in iron-dependent accumulation of reactive oxygen species (ROS), which triggers destructive lipid peroxidation, ultimately impairing mitochondrial function and initiating cell death [1].

Morphologically, cells undergoing ferroptosis exhibit characteristic changes, including mitochondrial shrinkage, reduction or disappearance of mitochondrial cristae, and increased mitochondrial membrane density [1]. A variety of small-molecule compounds can effectively induce ferroptosis, among which Erastin and RSL3 are representative inducers that function by targeting key regulatory pathways.

The inherent pathophysiological feature of OSCC is a significant imbalance between oxidative stress and antioxidant defense systems, creating an ideal biochemical environment for the triggering of ferroptosis [5]. Crucially, mesenchymal or dedifferentiated cancer cells that are typically resistant to traditional chemotherapy and apoptosis inducers show high sensitivity to ferroptosis [10], revealing the selective dependence of invasive cancer cell subsets on this pathway.

Thus, ferroptosis is not merely an alternative cell death mechanism but rather profoundly reveals an inherent metabolic vulnerability shared by various invasive, drug-resistant cancers including OSCC. The specific dependence of cancer cells on iron (or "iron addiction") [5] has thus opened a unique therapeutic window, offering a highly promising new strategy for targeting tumors refractory to traditional apoptosis-inducing therapies.

1.3 Interaction Between Ferroptosis and OSCC Pathogenesis: A Promising Therapeutic Vulnerability

Accumulating evidence indicates that OSCC cells are highly sensitive to ferroptosis inducers. In various OSCC models, ferroptosis inducers have demonstrated strong anti-tumor activity, and this effect is equally significant in cases resistant to conventional radiotherapy and chemotherapy [5].

More importantly, inducing ferroptosis is not only a direct killing method but also has been confirmed as an effective strategy to reverse cisplatin resistance and enhance tumor sensitivity to radiotherapy and chemotherapy [1]. An observation revealed that cisplatin-resistant OSCC cells often exhibit lower basal levels of reactive oxygen species (ROS) and lipid peroxidation, suggesting that their resistant phenotype may be closely related to the suppressed state of the ferroptosis pathway [2].

In addition to direct cytotoxic effects, the potential of ferroptosis as an immunogenic cell death (ICD) has received increasing attention. This property means that inducing ferroptosis can actively reshape the tumor immune microenvironment against OSCC, thereby potentially enhancing the response to immunotherapy [5].

In summary, the value of ferroptosis as a therapeutic target in OSCC is reflected in multiple aspects. It can not only directly eliminate cancer cells with primary or secondary resistance to standard therapies but also, more importantly, break the treatment deadlock and restore the sensitivity of resistant cells to existing therapies. This potential to "convert stubbornness into sensitivity" suggests that targeting ferroptosis is expected to reconstruct OSCC treatment strategies and significantly improve patient prognosis.

However, the interaction between ferroptosis and tumor immunity is more complex than expected, presenting a "double-edged sword" effect. On one hand, ferroptosis can activate anti-tumor immunity by releasing damage-associated molecular patterns (DAMPs) [7]. On the other hand, persistent lipid peroxidation and inflammatory responses may create an immunosuppressive tumor microenvironment and even promote tumor progression under specific conditions [10]. Therefore, in-depth understanding of the precise mechanisms and context dependence regulating the immune effects of ferroptosis is crucial

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for ensuring its safe and effective clinical application. This is particularly important for designing combined treatment regimens (especially in combination with immune checkpoint inhibitors) that can synergistically enhance efficacy while avoiding potential tumor-promoting risks.

2. The Role of Circular RNAs (circRNAs) in OSCC: Biogenesis, Functions, and Dysregulation

2.1 Overview of circRNA Biogenesis and Their Unique Properties

Circular RNAs (circRNAs) are a class of endogenous non-coding RNAs with covalently closed circular structures, lacking free 5' caps or 3' polyadenylated tails [8]. Their biosynthesis mainly originates from a non-canonical splicing event called "back-splicing", where the 5' splice site downstream in the precursor mRNA (pre-mRNA) connects to the 3' splice site upstream [8].

This unique topological structure endows circRNAs with several key properties, the most prominent of which is high resistance to exonuclease degradation, resulting in a much longer half-life compared to their corresponding linear RNAs (such as mRNA) [15]. Additionally, the expression profiles of circRNAs exhibit high tissue and cell type specificity [7], and they are widely and abundantly expressed in mammalian tissues, participating in the regulation of various basic biological processes [16].

This inherent high stability is a core advantage of circRNAs as therapeutic molecules. As confirmed by multiple studies, circRNAs can mediate "more sustained antigen expression" compared to linear mRNA [19]. In the context of therapeutic delivery (especially via nanocarriers), this means that a single administration can achieve more sustained pharmacological effects, thereby reducing administration frequency, improving patient compliance, and directly overcoming the core bottlenecks of poor stability and short duration of action in linear RNA therapies. This provides a new design paradigm for the development of long-acting RNA drugs.

2.2 Multiple Biological Functions of circRNAs

CircRNAs exert complex regulatory functions through various molecular mechanisms, playing key roles in gene transcription, protein translation, cell proliferation, and even tumorigenesis [15].

As miRNA sponges, which is the most classical function of circRNAs, they can competitively bind and sequester specific miRNAs through miRNA response elements (MREs) in their sequences, thereby relieving the inhibitory effect of miRNAs on their target mRNAs and indirectly regulating gene expression [8]. For example, ciRS-7 efficiently "adsorbs" miR-7 through its multiple binding sites, thereby upregulating the expression of miR-7 target genes (mostly oncogenes); circHIPK3 can bind to multiple miRNAs (such as miR-124) simultaneously, exerting extensive regulatory effects [16].

As protein modulators/scaffolds, circRNAs can act as "molecular sponges" to sequester specific proteins or as "scaffolds" to promote the assembly of multi-protein complexes, thereby regulating protein activity, localization, and stability [12]. For instance, the circRNA cia-cGAS has been confirmed to bind and sequester nuclear cGAS, thereby regulating its function [16].

Regarding protein coding, although long regarded as non-coding RNAs, emerging evidence reveals that some circRNAs possess protein-coding potential. Their translation is independent of the traditional 5' cap structure and is initiated through cap-independent mechanisms such as internal ribosome entry sites (IRES) or N^6-methyladenosine (m^6A) modification [15]. This enables circRNAs to translate into functional proteins or polypeptides, adding a new dimension to their biological functions.

The multifunctionality of circRNAs far exceeds their initially recognized role as miRNA sponges, revealing a much more complex regulatory network [12]. This property greatly expands the imagination for their use as therapeutic tools. circRNA-based therapies can be designed to intervene in disease pathways at multiple levels: from post-transcriptional regulation (as miRNA sponges) to protein function modulation (as protein sponges or scaffolds), and even direct expression of therapeutic proteins. This multi-dimensional intervention capability provides a powerful and flexible strategy combination for regulating ferroptosis and other oncogenic pathways in OSCC.

2.3 Dysregulation of circRNAs in OSCC and Their Dual Roles

In OSCC, the expression profiles of numerous circRNAs are significantly dysregulated compared to adjacent normal tissues [11]. These abnormally expressed circRNAs are deeply involved in the

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occurrence and development of OSCC, influencing key tumor cell behaviors such as cell proliferation, apoptosis, and metastasis by regulating gene transcription and post-transcriptional processes [13].

These dysregulated circRNAs can play dual roles as oncogenic molecules or tumor suppressors based on their downstream effects. For example, oncogenic circHIPK3 upregulates the expression of NUPR1 by adsorbing miR-637, thereby promoting OSCC progression [8]. Given their high stability, abundance, and tissue-specific expression, circRNAs are emerging as highly promising diagnostic and prognostic biomarkers as well as novel therapeutic targets for OSCC [7].

The highly tissue- and disease-specific dysregulation of circRNAs in OSCC makes them ideal mediators for precision medicine. On one hand, they can serve as highly sensitive and specific biomarkers for early disease diagnosis and prognostic risk stratification [11, 14]. On the other hand, their abnormal expression in tumor tissues themselves constitutes clear therapeutic targets, providing possibilities for the development of targeted therapies that minimize off-target effects, thereby precisely attacking tumor cells.

3. Complex Regulatory Network: circRNAs Regulating Ferroptosis in OSCC

3.1 Core Molecular Mechanisms of Ferroptosis Regulation (Iron Metabolism, Lipid Peroxidation, System Xc^-/GSH/GPX4 Axis)

The fundamental driving force of ferroptosis is the iron-dependent accumulation of reactive oxygen species (ROS) and subsequent lipid peroxidation [1]. Key regulatory pathways and components are as follows.

Iron metabolism serves as the initiating trigger for ferroptosis, as iron availability directly fuels oxidative reactions. Cells primarily uptake iron through the interaction between transferrin (Tf) and its receptor (TFRC): Tf binds to iron ions in the blood to form a Tf-Fe^{3+} complex, which then binds to TFRC on the cell membrane and enters the cell via endocytosis. Within endosomes, Fe^{3+} is reduced to Fe^{2+} and released into the cytoplasm for cellular utilization, ensuring efficient and controlled iron acquisition. Intracellular iron is mainly stored in ferritin, a complex composed of heavy chains (FTH1) and light chains (FTL), which safely sequesters iron to prevent its involvement in harmful redox reactions. When cellular iron demand increases, ferritin undergoes autophagic degradation (ferritinophagy) to release stored iron, thereby elevating intracellular free iron levels. Disruption of cellular iron homeostasis leads to iron overload: excess Fe^{2+} reacts with hydrogen peroxide (H_2O_2) via the Fenton reaction to generate highly reactive hydroxyl radicals (·OH), which oxidize lipids, proteins, and DNA, resulting in cell damage and death [6]. Conversely, CDGSH iron sulfur domain 2 (CISD2) mitigates ferroptosis by reducing free iron concentrations [6].

The System Xc^-/GSH/GPX4 antioxidant pathway acts as the cornerstone of ferroptosis regulation. System Xc^-, a cystine/glutamate antiporter, mediates the exchange of intracellular glutamate with extracellular cystine. Cystine is then reduced to cysteine, a key precursor for glutathione (GSH) synthesis. GSH serves as an essential substrate for glutathione peroxidase 4 (GPX4), a lipid repair enzyme that converts cytotoxic lipid hydroperoxides (PLOOHs) into less toxic lipid alcohols (PLOHs). Inhibition of System Xc^- reduces cystine uptake, impairing GSH synthesis; direct inhibition of GPX4 activity further diminishes lipid peroxide clearance. These changes collectively reduce intracellular GSH levels and GPX4 function, preventing effective clearance of intracellular lipid peroxides. The accumulation of these highly reactive species disrupts cell membrane structures and ultimately triggers ferroptosis [1].

Lipid metabolism provides critical substrates for ferroptotic lipid peroxidation, with polyunsaturated fatty acids (PUFAs) acting as key players. Acyl-CoA synthetase long-chain family member 4 (ACSL4) catalyzes the binding of free PUFAs to coenzyme A (CoA) to generate PUFA-CoAs, which are then esterified into membrane phospholipids by lysophosphatidylcholine acyltransferase 3 (LPCAT3). These phospholipids are subsequently oxidized by lipoxygenases (ALOXs) or cytochrome P450 oxidoreductase (POR) to form harmful lipid peroxidation products, initiating the ferroptotic cascade [6].

p53, a major tumor suppressor, induces ferroptosis by downregulating SLC7A11 expression and inhibiting cystine uptake. SLC7A11, a key subunit of System Xc^-, mediates the transport of extracellular cystine into cells while exporting intracellular glutamate. As a precursor for GSH synthesis, cystine availability directly impacts cellular antioxidant capacity. p53 binds to the promoter region of the SLC7A11 gene, transcriptionally repressing its expression to reduce cystine uptake and diminish GSH synthesis, thereby promoting ferroptosis [5].

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Nrf2 is a key transcription factor regulating intracellular redox balance and protecting cells from oxidative stress. Under normal conditions, Nrf2 binds to Keap1 (Kelch-like ECH-associated protein 1) in the cytoplasm and undergoes degradation via the ubiquitin-proteasome system. Under oxidative stress, Keap1 undergoes conformational changes, leading to Nrf2 dissociation, nuclear translocation, and binding to antioxidant response elements (AREs) to initiate transcription of antioxidant genes. p62 (SQSTM1) stabilizes Nrf2 by competitively binding to Keap1 via its KEAP1 interaction region (KIR), promoting Nrf2 nuclear translocation. Activated Nrf2 upregulates genes related to iron and ROS metabolism, including NQO1, HO1, and FTH1. By enhancing the expression of iron storage proteins like FTH1, Nrf2 reduces intracellular free iron concentrations, decreasing ROS production via iron-catalyzed Fenton reactions and inhibiting ferroptosis [5].

Autophagy plays a key role in ferroptosis execution through multiple mechanisms, including ferritin degradation (ferritinophagy) and lipid droplet degradation (lipophagy). Ferritinophagy, a selective autophagic process, involves autophagosomes encapsulating ferritin and transporting it to lysosomes for degradation, releasing stored iron ions. This increases intracellular free iron levels, which generate large amounts of ROS via the Fenton reaction, promoting lipid peroxidation and ferroptosis. Lipophagy involves autophagosomal encapsulation and lysosomal degradation of lipid droplets, releasing free fatty acids. These fatty acids undergo β-oxidation to generate acetyl-CoA, promoting mitochondrial respiration and ROS production; they also serve as substrates for lipid peroxidation, directly participating in the ferroptotic chain reaction [3].

FTO (fat mass and obesity-associated gene) sensitizes OSCC cells to ferroptosis through its role in RNA methylation. m^6A is the most common internal RNA modification, regulating mRNA stability, splicing, translation, and localization. FTO removes m^6A modifications from target mRNAs, affecting their expression. In OSCC cells, FTO specifically demethylates ACSL3 and GPX4 mRNA, reducing their stability, shortening their half-life, and decreasing their expression. Reduced ACSL3 and GPX4 protein levels impair cellular resistance to ferroptosis [20].

HMOX1 (heme oxygenase 1) upregulation triggers ferroptosis by promoting intracellular Fe^{2+} accumulation via direct Fe^{2+} release and induction of ferritinophagy, which enhances Fenton reactions and lipid peroxidation. This process is regulated by the Nrf2-SLC7A11-HMOX1 and HIF1α-HMOX1 axes [4].

Table 1: Key Regulators of Ferroptosis and Their Roles in OSCC

Regulator Name	Role in Ferroptosis	Mechanism/Pathway	Specific Role in OSCC (if mentioned)	Related Literature ID
GPX4	Inhibitor	Converts lipid peroxides to alcohols	Impaired in OSCC; sensitive to high FTO expression in OSCC cells	10.3389/fphar.2024.1402514
SLC7A11	Inhibitor	Cystine uptake, component of System Xc^-	Impaired in OSCC; upregulation by circ_0000140 promotes resistance; regulated by circFNDC3B via miR-520d-5p	10.3389/fphar.2024.1402514
ACSL4	Driver	PUFA esterification, key enzyme for lipid peroxidation	Inhibition confers resistance to ferroptosis	10.3390/ijms242015127
TP53	Driver	Tumor suppressor, downregulates SLC7A11	Risk score associated with TP53 mutations	10.3389/froh.2024.1461022
HMOX1	Driver	Promotes Fe^{2+} accumulation	Synergizes with cisplatin to overcome resistance	10.1016/j.phymed.2023.154701
CISD2	Inhibitor	Reduces free iron concentration	Gene in ferroptosis-related prognostic model	10.3390/ijms242015127

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FTO	Driver	Demethylates ACSL3 and GPX4 mRNA	High expression sensitizes OSCC cells to ferroptosis	10.3390/ijms242216339
Nrf2	Inhibitor	Redox homeostasis, upregulates iron/ROS metabolism genes	Chronic activation supports cancer cell proliferation and resistance	10.3389/fphar.2024.1402514
FTH1/FTL	Inhibitor	Iron storage proteins	Ferritinophagy leads to iron accumulation	10.3389/froh.2024.1461022
LPCAT3	Driver	Lipid metabolism, forms membrane phospholipids	Inhibition confers resistance to ferroptosis	10.3390/ijms242015127
ALOXs	Driver	Oxidizes PL-PUFAs to form lipid hydroperoxides	Involved in lipid metabolism	10.3390/ijms242015127
System Xc^-	Inhibitor	Cystine/glutamate antiporter	Impaired in OSCC; inhibition induces ferroptosis	10.3892/ijmm.2023.5248

Multiple studies describe a complex network of pathways (iron metabolism, System Xc^-/GSH/GPX4, lipid metabolism, p53, Nrf2, autophagy) converging on the core mechanism of ROS and lipid peroxide accumulation [5]. For example, autophagy-mediated ferritinophagy directly affects iron availability, promoting the Fenton reaction [5]; p53-mediated regulation of SLC7A11 directly impacts the GSH/GPX4 axis [6]. This interconnected network indicates that effective ferroptosis targeting may require multi-pronged strategies to prevent compensatory mechanisms. A comprehensive understanding of these interactions is crucial for designing robust interventions that avoid off-target effects or pro-survival pathway activation.Table 1 demonstrates the key regulators of ferroptosis and their roles in OSCC.

3.2 Identified Specific circRNA-Ferroptosis Axes in OSCC

Emerging studies reveal that circRNAs are not passive molecules within cells but function as key regulators, deeply involved in modulating ferroptosis and thereby profoundly influencing OSCC progression [8].

The circFNDC3B/miR-520d-5p/SLC7A11 axis: circFNDC3B has been identified as a critical oncogenic circRNA in OSCC. Its core mechanism involves acting as a molecular sponge for miR-520d-5p, where competitive binding relieves miR-520d-5p-mediated inhibition of the downstream target gene SLC7A11, leading to increased SLC7A11 expression. Elevated SLC7A11 maintains cellular antioxidant capacity, thereby suppressing ferroptosis. Functional experiments demonstrate that knockdown of circFNDC3B results in downregulated expression of GPX4 and SLC7A11, accompanied by increased ROS and iron ion levels, ultimately inducing ferroptosis in OSCC cells. Importantly, overexpression of SLC7A11 can reverse the ferroptosis-promoting effect caused by circFNDC3B knockdown, directly validating the existence of the circFNDC3B-miR-520d-5p-SLC7A11 regulatory axis [8].

The circ_0000140/miR-527/SLC7A11 axis: circ_0000140 is significantly upregulated in cisplatin-resistant OSCC tissues and cells, and its high expression promotes chemoresistance by inhibiting ferroptosis. This effect is also mediated through a ceRNA mechanism: circ_0000140 acts as a sponge for miR-527, alleviating miR-527-dependent repression of SLC7A11. Consequently, knockdown of circ_0000140 effectively enhances ferroptosis and restores OSCC cell sensitivity to cisplatin [2]. Subcellular localization analysis indicates that circ_0000140 is primarily distributed in the cytoplasm [13].

Both circFNDC3B [8] and circ_0000140 [2] are consistently reported to be upregulated in OSCC and actively suppress ferroptosis; conversely, their inhibition induces ferroptosis. This recurring pattern establishes a direct link between these oncogenic circRNAs and ferroptosis suppression, which in turn drives tumor progression and drug resistance. This strong correlation highlights these anti-ferroptotic oncogenic circRNAs as ideal candidates for targeted therapeutic intervention. Specific inhibition of these circRNAs may resensitize OSCC cells to ferroptosis, promoting cell death and potentially overcoming existing resistance mechanisms, thereby providing clear molecular targets for developing novel

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anticancer therapies.

A notable commonality between circFNDC3B (via miR-520d-5p) and circ_0000140 (via miR-527) is their shared mechanism of regulating ferroptosis through modulation of SLC7A11 expression [2]. As a key component of System Xc^-, SLC7A11 is central to the GPX4 antioxidant pathway and serves as the primary defense mechanism against ferroptosis [1]. This convergence on SLC7A11 strongly suggests it acts as a critical regulatory hub in circRNA-mediated ferroptosis modulation in OSCC. This finding holds significant therapeutic value: strategies specifically targeting the SLC7A11 axis—whether through delivery of circRNAs that directly downregulate SLC7A11 or inhibition of oncogenic circRNAs that promote its expression—may be particularly effective in inducing ferroptosis and overcoming resistance in OSCC.

3.3 Targeting circRNA-Ferroptosis Axes: A New Strategy to Overcome OSCC Resistance

Cisplatin resistance is the core clinical bottleneck leading to chemotherapy failure and poor prognosis in OSCC [1]. Accumulating evidence indicates that this resistant phenotype is closely related to the inhibition of intracellular ferroptosis. Compared to sensitive cells, cisplatin-resistant OSCC cells typically exhibit lower basal levels of ROS and lipid peroxidation [2]. Based on this, actively inducing ferroptosis has been confirmed as a highly promising strategy to overcome or reverse cisplatin resistance in OSCC [1].

Specific circRNAs, such as circ_0000140, are key molecular switches linking resistance and ferroptosis inhibition. In resistant OSCC cells, circ_0000140 upregulates SLC7A11 expression through its "sponge" effect (adsorbing miR-527), thereby strengthening the GSH/GPX4 antioxidant defense line, inhibiting ferroptosis, and ultimately leading to cisplatin resistance. Therefore, targeting and knocking down circ_0000140 can precisely disrupt this defense mechanism, effectively induce ferroptosis, and successfully restore cellular sensitivity to cisplatin [2]. This provides direct experimental evidence for reversing resistance by regulating specific circRNAs.

In summary, cisplatin resistance in OSCC is not an isolated phenomenon but a specific cellular state driven by the key regulatory axis of "circRNA-ferroptosis". This finding connects the abstract "resistance" with specific molecular events (i.e., upregulation of oncogenic circRNAs → inhibition of ferroptosis pathways), establishing a clear causal chain. This not only provides a new perspective for understanding resistance mechanisms but also, more importantly, opens up new therapeutic pathways. By targeting this axis, such as specifically inhibiting anti-ferroptotic oncogenic circRNAs (such as circ_0000140) or delivering artificially designed ferroptosis-promoting circRNAs, it is expected to reactivate ineffective chemotherapy regimens and convert drug-resistant OSCC cells into treatment-sensitive cells. This represents an innovative strategy to fundamentally overcome chemotherapy resistance, which is expected to significantly improve the treatment outcomes of OSCC patients.Table 2 shows the relationship between circRNAs and ferroptosis in OSCC.

Table 2: Identified circRNAs Regulating Ferroptosis in OSCC

circRNA Name	Expression in OSCC	Role in OSCC	Mechanism of Ferroptosis Regulation	Impact on Ferroptosis	Consequences in OSCC	Related Literature ID
circFNDC3B	Upregulated	Oncogene	Acts as a sponge for miR-520d-5p, regulates SLC7A11 expression, inhibits GPX4	Weakens ferroptosis	Promotes malignant progression, reduces sensitivity to ferroptosis inducers	10.3389/fcell.2023.1160381
circ_0000140	Upregulated	Promotes chemoresistance	Acts as a sponge for miR-527, regulates SLC7A11 axis	Inhibits ferroptosis	Increases cisplatin resistance	10.3389/fphar.2024.1402514

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4. Nanomaterial-Mediated circRNA Delivery: A Novel Therapeutic Strategy for OSCC

4.1 Core Advantages of Nanomaterials for Nucleic Acid Delivery

Nanomaterial-based delivery systems have emerged as highly promising approaches in cancer treatment, particularly due to their ability to precisely deliver therapeutic agents to targeted pathological sites [23]. These systems possess unique capabilities to trigger specific regulated cell death (RCD) mechanisms, such as ferroptosis, with enhanced selectivity, especially in drug-resistant cancer cells [23]. The main advantages of nanomaterials for delivering nucleic acids (including circRNAs) are multifaceted:

Enhanced stability: Nanoparticles (such as lipid nanoparticles, LNPs) form a protective barrier by encapsulating circRNAs, effectively preventing direct contact between nucleases and circRNAs, thereby significantly reducing the risk of degradation. For example, LNPs are composed of ionizable lipids, cholesterol, phospholipids, and polyethylene glycol (PEG) lipids. This structure not only enhances the stability of the particles but also protects the encapsulated circRNAs. Meanwhile, due to the protection of nanoparticles, the stability of circRNAs in vivo is significantly improved, thereby extending their functional half-life. This means that circRNAs can continuously exert their biological effects for a longer period, such as sustained expression of therapeutic proteins or regulation of gene expression [15].

Improved delivery efficiency: Nanoparticles optimize delivery efficiency through their unique physicochemical properties (such as particle size, surface charge, and hydrophilic/hydrophobic balance). These properties enable nanoparticles to more easily cross cell membranes, efficiently delivering circRNAs to target cells and ensuring that therapeutic payloads effectively reach their intracellular targets [17].

Targeted delivery: Nanoparticles can be finely designed to incorporate specific cell surface ligands or surface modifications (such as polyethylene glycol (PEG) chains) to achieve highly selective targeting and preferential uptake by cancer cells. This targeting approach minimizes off-target effects and reduces systemic toxicity, a key consideration in clinical translation [23].

Reduced immunogenicity: Unmodified exogenous circRNAs can bypass intracellular RNA sensors such as RIG-I, thereby avoiding the activation of antiviral defense responses. This property enables circRNAs to be delivered to cells without triggering a strong innate immune response. circRNAs can also evade recognition by Toll-like receptors (TLRs), particularly TLR3, TLR7, and TLR8. These receptors typically respond to linear ssRNA and dsRNA structures as well as RNA degradation products, but the circular structure of circRNAs may render them resistant to these receptors. The purity of circRNA formulations is crucial for maintaining this low immunogenicity, as even trace amounts of linear RNA contaminants may trigger a strong cellular immune response [18].

Although circRNAs themselves exhibit excellent stability [15], their effective and safe delivery to specific tumor sites in vivo remains a significant challenge. Research data consistently highlight the advantages of nanomaterials in "precision delivery", "enhanced cellular uptake", "colloidal stability", and "tumor targeting ability" [23]. Furthermore, the low immunogenicity of nanoformulated circRNAs [18] directly addresses a major safety concern in clinical applications. This indicates a strong synergistic relationship between nanomaterials and circRNAs: nanomaterials effectively solve key delivery and biodistribution challenges associated with therapeutic circRNAs, while circRNAs, in turn, provide excellent payload characteristics (inherent stability, diverse regulatory functions, and potentially lower immunogenicity than other RNA types). This combined approach is indispensable for translating the enormous therapeutic potential of circRNAs into viable and effective treatments for OSCC, enabling targeted and sustained regulation of ferroptosis.

4.2 Cutting-Edge Nanoplatforms for circRNA Delivery

Currently, various nanoplatforms are being actively developed for the therapeutic delivery of circRNAs, each demonstrating unique application potential.

Lipid nanoparticles (LNPs), as an FDA-approved mRNA vaccine delivery technology, show great potential in circRNA delivery. Through key components such as ionizable lipids, they can not only efficiently encapsulate circRNAs, protect them from degradation, but also promote endosomal escape to release payloads into the cytoplasm. The development of novel ionizable lipids has been confirmed to significantly enhance the intensity and duration of in vivo protein expression [17].

Polymeric nanoparticles, represented by PLGA, are favored due to their excellent biocompatibility,

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biodegradability, and low toxicity. Surface modifications (such as PEGylation) can extend their in vivo circulation time and provide possibilities for conjugating targeting ligands, achieving precise targeting of tumors. For example, studies have used PLGA to deliver si-circRNA and successfully inhibited the proliferation of hepatocellular carcinoma cells [25].

Self-assembled nanoparticles are an innovative carrier-free delivery strategy, where therapeutic molecules spontaneously form nanostructures through self-interaction. For instance, co-assembling ferroptosis inducers (sorafenib), photosensitizers, and iron ions can form multifunctional nanoparticles, which have shown significant efficacy in synergistic photodynamic and ferroptosis therapy for oral cancer [24].

Exosomes, as natural extracellular vesicles, possess unparalleled biocompatibility and low immunogenicity, and are regarded as ideal "endogenous" nanocarriers. Studies have shown that macrophage-derived exosomes can deliver circRNAs to regulate ferroptosis in other cancer cells, revealing their great potential in natural or engineered delivery [22].

Table 3: Nanomaterial Platforms for circRNA Delivery in Cancer Therapy

Nanomaterial Type	Main Characteristics/Advantages	Specific Examples/Components	Application/Relevance in circRNA Delivery in Cancer	Related Literature ID
Lipid Nanoparticles (LNPs)	High protein expression, lyophilization potential, extended half-life	Novel ionizable lipids (CP-LC-0867, CP-LC-0729)	Sustained luciferase activity in vivo, extended storage and transportation	10.3390/ijms26115138
Polymeric Nanoparticles	Biocompatibility, biodegradability, low toxicity, highly selective targeting	PLGA, PEG chains, si-circROBO1 nanoparticles	Inhibits HCC cell proliferation, enhances tumor targeting	10.2147/IJN.S399318
Self-Assembled Nanoparticles	Carrier-free, multifunctional, synergistic therapy	Sorafenib-Ce6-Fe^{3+} self-assembled nanoparticles	Enhances photodynamic therapy for oral cancer through ferroptosis	10.1016/j.jconrel.2023.12.056
Exosomes	Natural delivery system, intercellular transfer	M2 macrophage-derived exosomes, circ_0088494	Transfers circRNA to immune cells, regulates immunity, inhibits ferroptosis in other cancers	10.3390/ijms241814194

The diversity of the above platforms fully indicates that there is no "one-size-fits-all" optimal solution for circRNA delivery in OSCC. Instead, the selection of an ideal nanocarrier will be a highly customized process, requiring comprehensive consideration of the characteristics of circRNA payloads, differences in the OSCC tumor microenvironment, and desired therapeutic goals (such as direct killing, sensitization, or immune regulation). The future direction must be "tailor-made" nanodrug design: precisely matching and optimizing nanocarriers according to specific OSCC subtypes and circRNA functions to maximize therapeutic efficacy and minimize toxic side effects, ultimately moving towards a true era of personalized nanomedicine.Table 3 lists the nanoplatform for circRNA delivery in cancer therapy.

4.3 Engineering Nano-circRNA Systems: Strategies to Achieve Targeted Ferroptosis Induction in OSCC

The core strategy of this section aims to construct intelligent nano-circRNA delivery systems to achieve precise regulation of the ferroptosis process in OSCC cells. This includes two main design ideas:

First, inhibiting endogenous "oncogenic" circRNAs: By delivering therapeutic nucleic acids (such as siRNA or shRNA) that target and silence endogenous anti-ferroptotic circRNAs (such as circFNDC3B or circ_0000140), directly disrupting the ferroptosis defense mechanism of tumor cells. Preclinical studies have confirmed that silencing circFNDC3B can effectively downregulate GPX4 and SLC7A11, thereby strongly inducing ferroptosis [8].

Second, delivering artificially designed "tumor-suppressive" circRNAs: Constructing and delivering artificial circRNAs with specific functions. These circRNAs can be designed as efficient miRNA sponges (such as adsorbing miR-520d-5p or miR-527), thereby competitively inhibiting the function of endogenous oncogenic circRNAs, indirectly downregulating the expression of key anti-ferroptotic

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proteins such as SLC7A11, and ultimately achieving the goal of inducing ferroptosis [8].

A more cutting-edge design concept is that nanocarriers themselves are no longer merely "passive" transport tools but act as "active" therapeutic components, directly participating in and enhancing the induction of ferroptosis. For example, integrating iron ions (Fe^{3+}) into nanocarriers (such as sorafenib-Ce6 nanoparticles) can directly provide key substrates for the Fenton reaction, generating a strong synergistic killing effect with delivered circRNAs or other drugs (such as photosensitizers) [24].

In summary, the essence of this strategy is to leap from the traditional thinking of "drug delivery" to a new height of "integrated treatment system design". In this paradigm, nanocarriers and circRNA payloads are no longer a simple "carrier-passenger" relationship but are co-engineered into an organic whole. Nanocarriers not only ensure the precise delivery and release of circRNAs but can also be designed as functional components to actively create an environment conducive to ferroptosis by carrying iron ions or other sensitizers; at the same time, circRNAs precisely disrupt the intrinsic defense mechanisms of cells at the molecular level. This multi-dimensional, synergistic integrated design is expected to bring unprecedented therapeutic precision and efficacy to OSCC, providing a highly promising solution to overcome clinical challenges such as drug resistance.

5. Clinical Significance, Challenges, and Future Directions

5.1 circRNAs and Ferroptosis as Prognostic Biomarkers and Therapeutic Targets in OSCC

Both ferroptosis-related genes and circRNAs show great potential as prognostic biomarkers for OSCC [6]. A prognostic model for OSCC based on nine differentially expressed ferroptosis-related genes (CISD2, DDIT4, CA9, ALOX15, ATG5, BECN1, BNIP3, PRDX5, and MAP1LC3A) has shown excellent clinical performance in predicting overall survival [21].

The risk score derived from this ferroptosis-related prognostic model is significantly associated with the immune status of the tumor microenvironment and the TP53 mutation status of OSCC patients, highlighting its ability to capture complex biological factors affecting prognosis [21]. The unique properties of circRNAs, including their excellent stability, high abundance, and highly specific expression patterns, make them highly promising candidates as diagnostic and prognostic biomarkers as well as novel therapeutic targets in various cancers, including OSCC [14].

Research data clearly indicate that both ferroptosis-related genes [5] and circRNAs [11] are dysregulated in OSCC and associated with patient prognosis. The existence of multi-gene prognostic models [21] further confirms this potential. The correlation of the risk score with immune status and TP53 mutations [21] points to deeper integrated biological insights. This predicts the emergence of a comprehensive "ferroptosis-circRNA signature" as an advanced, multi-dimensional biomarker panel for OSCC patients. Such a panel will not only provide more accurate prognostic predictions but also offer insights into the underlying molecular vulnerabilities of individual tumors. This can enable highly personalized treatment strategies, guiding clinicians to identify patients most likely to benefit from ferroptosis-inducing therapies or those at higher risk of developing resistance, thereby optimizing treatment selection and improving patient stratification.

5.2 Synergistic Therapeutic Strategies: Combining Nanomaterial-circRNA Ferroptosis Induction with Traditional Treatments

A significant therapeutic advantage of ferroptosis induction is its proven ability to enhance the sensitivity of tumor cells to traditional treatments such as radiotherapy and chemotherapy. This is particularly evident in overcoming the widespread cisplatin resistance in OSCC [1].

Combination therapies involving ferroptosis regulation have rapidly gained attention due to their synergistic potential [3]. For example, preclinical studies have shown that the combination of melatonin and erastin exerts a synergistic anti-tumor effect on OSCC by simultaneously inducing apoptosis and ferroptosis while inhibiting pro-survival autophagy [9]. Similarly, shikonin has been shown to induce ferroptosis by upregulating HMOX1, synergistically overcoming cisplatin resistance in ovarian cancer (a related squamous cell carcinoma with similar mechanisms) [4].

Nanomaterials provide an ideal platform for facilitating such combination strategies. They can be designed for the co-delivery of ferroptosis inducers with other therapeutic agents, such as sorafenib-Ce6-Fe^{3+} self-assembled nanoparticles, which effectively enhance photodynamic therapy efficacy in oral

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cancer by simultaneously inducing ferroptosis [24].

Research data consistently emphasize that ferroptosis induction can overcome resistance to traditional therapies and enhance their efficacy [1]. The success of specific combination therapies such as melatonin + erastin [9] and shikonin + cisplatin [4] further reinforces the principle of synergy. Crucially, nanomaterials are explicitly identified as ideal platforms for "synergistic delivery" and "synergistic therapy" [24]. This strongly supports the rationale for developing complex nanomaterial-circRNA systems that not only directly induce ferroptosis but also synergistically enhance existing treatment methods. This multi-modal synergistic therapeutic design is expected to significantly improve the treatment outcomes of OSCC, offering more effective therapeutic options for patients.

5.3 Challenges and Considerations in Clinical Translation

Despite the promising prospects of nanomaterial-mediated circRNA ferroptosis induction for OSCC treatment, its clinical translation is hindered by multiple challenges. Ensuring high specificity of circRNAs and nanocarriers to avoid off-target effects on healthy cells and tissues remains crucial. Although circRNAs exhibit tissue-specific expression, their precise targeting within complex biological systems requires further optimization, as does the fine regulation of nanoparticle biodistribution and permeability within the tumor microenvironment [23]. Additionally, while nanomaterials and circRNAs are generally regarded as having low immunogenicity [18], the potential systemic toxicity and immune responses associated with long-term or repeated administration demand rigorous evaluation. In-depth research into the degradation products of nanomaterials and their in vivo clearance pathways is also necessary. Large-scale production of therapeutic-grade circRNAs and the maintenance of stability and uniformity in nanoparticle preparation represent key bottlenecks for clinical application; ensuring high-quality, high-purity circRNA formulations is critical, as even trace amounts of linear RNA contaminants may trigger robust immune responses [17]. Despite the ability of nanomaterials to enhance circRNA stability, optimizing in vivo delivery efficiency to ensure sufficient circRNA reaches tumor cells and exerts functional effects in complex biological environments remains a challenge, particularly in overcoming physical barriers within the tumor microenvironment and facilitating endosomal escape post-cellular uptake [24]. Furthermore, ferroptosis operates as a complex regulatory network, with its role varying across cancer types and disease stages [5]; excessive or inappropriate ferroptosis induction may cause normal tissue damage or adverse immune responses [9], underscoring the need for precise control over the extent and timing of induction. Finally, despite significant progress in basic and preclinical research, clinical trial data on nanomaterial-loaded circRNA-mediated ferroptosis regulation in OSCC remain limited [7], and translating laboratory findings into human therapies requires a lengthy and rigorous preclinical and clinical validation process.

5.4 Future Research Directions and Perspectives

To advance nanomaterial-mediated circRNA ferroptosis-inducing therapy toward clinical application, future research should focus on several key areas. First, continuous screening and validation of novel circRNAs—including those with protein-coding potential [15]—that specifically and efficiently regulate ferroptosis in OSCC are essential, alongside in-depth analysis of their precise molecular mechanisms within the ferroptosis network to identify additional therapeutic targets. Second, the design and optimization of advanced nanomaterials are critical, with a focus on developing more intelligent, targeted, safe, and biocompatible nanocarriers. This includes engineering responsive delivery systems tailored to tumor microenvironment characteristics (such as hypoxia, acidic pH, or specific receptors) and designing multifunctional nanosystems capable of synergistic effects, such as co-delivering circRNAs with ferroptosis inducers or chemotherapeutic drugs [24]. Third, more comprehensive in vivo studies using animal models are needed to fully evaluate the efficacy, safety, and pharmacokinetics of nanomaterial-circRNA systems in OSCC treatment, with a priority on establishing preclinical models that accurately simulate the complex tumor microenvironment and resistance mechanisms of OSCC. Fourth, exploring combination therapy strategies is vital, with in-depth research into the synergistic effects of nanomaterial-circRNA ferroptosis induction with existing treatments (e.g., radiotherapy, chemotherapy, immunotherapy); special attention should be paid to how ferroptosis induction can enhance the efficacy of immune checkpoint inhibitors and overcome secondary resistance [3]. Fifth, further validation and development of comprehensive biomarkers based on circRNAs and ferroptosis-related genes are necessary to enable early diagnosis, prognostic evaluation, and prediction of treatment response in OSCC [14], facilitating precision medicine and personalized treatment planning. Finally, with sufficient preclinical data support, clinical trials of nanomaterial-circRNA ferroptosis-inducing therapy should be

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gradually initiated to evaluate its safety and efficacy in humans, requiring close collaboration across multidisciplinary teams and the development of rigorous clinical research protocols.

6. Conclusion

The treatment of oral squamous cell carcinoma (OSCC) faces severe challenges, particularly the widespread presence of drug resistance, which limits the efficacy of traditional therapies[1]. Ferroptosis, as a unique mode of regulated cell death, has emerged as a promising therapeutic target in OSCC due to its sensitivity and potential to overcome resistance[5]. Circular RNAs (circRNAs), with their excellent stability, diverse biological functions, and abnormal expression in OSCC, are recognized as key molecules regulating ferroptosis and hold promise as novel diagnostic biomarkers and therapeutic targets[7]. Specifically, certain oncogenic circRNAs (such as circFNDC3B and circ_0000140) inhibit ferroptosis by regulating key genes like SLC7A11, thereby promoting OSCC progression and chemoresistance[2]. Therefore, targeting these circRNAs or introducing ferroptosis-promoting circRNAs is expected to reactivate the ferroptosis pathway in OSCC cells and reverse resistance.

The emergence of nanomaterials provides a solution for the effective delivery of circRNAs, overcoming challenges in stability and targeting in vivo applications[23]. Various nanoplatforms, including lipid nanoparticles[17], polymeric nanoparticles[25], self-assembled nanoparticles[24], and exosomes[22], can achieve targeted delivery of circRNAs, improve cellular uptake efficiency, and reduce immunogenicity. Through sophisticated design, nanomaterials themselves can even act as ferroptosis inducers, synergizing with circRNA payloads to achieve stronger anti-tumor effects. Although clinical translation faces challenges such as specificity, toxicity, production scale, and in vivo delivery efficiency, nanomaterial-mediated circRNA ferroptosis induction offers an innovative, multi-modal synergistic strategy for OSCC treatment[23]. Future research should focus on discovering more key circRNAs, optimizing nanocarrier design, strengthening in vivo studies, and actively promoting clinical trials, with the ultimate goal of translating this cutting-edge technology into effective therapeutic options to improve the prognosis of OSCC patients.

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