The Role of Ferroptosis in Lung Cancer and Its Immunotherapeutic Targeting Strategy

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Abstract. Ferroptosis, an iron-dependent mode of cell death, exhibits unique potential in lung cancer therapy through the mechanisms of lipid peroxidation accumulation and glutathione peroxidase 4 (GPX4) inactivation. Lung cancer cells are highly sensitive to ferroptosis due to metabolic abnormalities and elevated levels of reactive oxygen species (ROS), in which the targeted inhibition of GPX4 and the regulation of the Nrf2 signaling pathway become key molecular mechanisms. Ferroptosis not only directly induces tumor cell death, but also significantly enhances the immunotherapeutic effect by releasing tumor antigens and remodeling the immunosuppressive microenvironment. However, the non-specific toxicity of ferroptosis inducers, drug resistance due to tumor heterogeneity, and the efficiency of targeted delivery still need to be addressed. In this paper, we will systematically explore the synergistic mechanism of ferroptosis and immunotherapy, and propose that the development of microenvironment-responsive drug delivery systems and combined therapeutic strategies is the direction of future breakthroughs. It provides a new idea for ferroptosis-targeted therapy to overcome immunotherapy resistance in lung cancer, but its clinical translation needs to be continuously explored in the in-depth analysis of the mechanism and technological innovation.

Keywords: Ferroptosis, lung cancer, GPX4, reactive oxygen species, Nrf2 signaling pathway.

1. Introduction

Lung cancer is one of the leading causes of cancer-related deaths in the world. In recent years, traditional therapies such as chemotherapy, radiotherapy, and immunotherapy (e.g., PD-1/PD-L1 inhibitors, etc.) have made remarkable progress in lung cancer treatment. However, due to the tumor immune micro-environment, which consists of tumor cells, immune cells, stromal cells, and a variety of cytokines and signaling molecules, complexity and specificity, playing a key role in tumorigenesis, development, metastasis, and therapeutic resistance, resulting in lung cancer resistance to traditional therapies to traditional therapies continues to rise, the prevalence rate is still high. It has been found that the immunosuppressive state in the tumor immune microenvironment is an important factor limiting the efficacy of immunotherapy, and the regulation of tumor cell death modes, particularly ferroptosis, may become a new strategy to remodel the immune microenvironment and enhance the efficacy of immunotherapy.

Ferroptosis constitutes an iron-mediated regulatory cell death mechanism driven by lipid peroxide accumulation and glutathione peroxidase 4 (GPX4) dysfunction. This process demonstrates dual oncotherapeutic effects through direct cytotoxic efficacy against malignant cells and immunomodulatory capacity via immunogenic molecule release, which reprograms tumor immune microenvironments and potentiates antitumor immunity. Emerging studies reveal dynamic interplay between ferroptotic processes and tumor-associated immune components, particularly macrophage polarization states, T lymphocyte activation patterns, and immune checkpoint regulators including PD-L1. These mechanistic insights establish ferroptosis modulation as both a standalone therapeutic strategy for pulmonary malignancies and a synergistic enhancer of combinatorial immunotherapeutic regimens.

The aim of this paper is to summarize the mechanism of ferroptosis in lung cancer and the significance of targeting ferroptosis for lung cancer immunotherapy. By summarizing the research progress on the interaction between ferroptosis and tumor immune microenvironment in recent years, the potential application of ferroptosis in lung cancer immunotherapy will be deeply explored, and a

review will be made on the molecular mechanism of ferroptosis and its role in lung cancer; the regulation of ferroptosis on tumor immune microenvironment; and the synergistic effect of targeted ferroptosis and immunotherapy.

2. Molecular mechanisms of ferroptosis

Ferroptosis, an iron-dependent regulated cell death pathway recently identified, is pathologically characterized by excessive iron deposition and uncontrolled lipid peroxidation during cellular demise. This distinctive cell death modality is initiated through ferroptosis-inducing agents that disrupt glutathione peroxidase (GPX) activity via multiple molecular routes, ultimately compromising cellular redox homeostasis and precipitating lethal accumulation of lipid-reactive oxygen species (ROS). Contemporary research has delineated ferroptosis as a critical contributor to diverse pathological conditions spanning oncological progression, neurological degeneration, ischemic tissue damage, and hematological dysfunction. Importantly, ferroptotic stress within tumor microenvironments induces immunosuppressive reprogramming through inflammation-mediated mechanisms, thereby facilitating malignant proliferation and therapeutic resistance [1-2].

The ferroptotic process is molecularly defined by lipid peroxidation events involving both enzymatic (e.g., lipoxygenase-mediated) and non-enzymatic (Fenton reaction-driven) oxidation mechanisms. Central to this process is the peroxidation of polyunsaturated fatty acids (PUFAs), whose metabolic incorporation into membrane phospholipids via ACSL4-mediated esterification critically determines cellular vulnerability to ferroptosis. Iron metabolism exerts dual regulatory roles through Fenton reaction-driven ROS generation and thiol antioxidant system disruption. The pathophysiological manifestation of ferroptosis arises from the systemic imbalance between iron-mediated oxidative stress and thiol-based redox buffering capacity, with Fenton-derived ROS serving as the principal executor of iron-overload associated cytotoxicity [3]. Substantial clinical evidence correlates ferroptosis dysregulation with multiple ROS-associated pathologies including malignant transformation, neurodegenerative disorders, and chronic inflammatory diseases.

The cellular defense against ferroptosis primarily relies on the glutathione (GSH)-glutathione peroxidase 4 (GPX4) axis. GSH biosynthesis, a tripeptide (γ-glutamyl-cysteinyl-glycine) synthesis process regulated by the rate-limiting glutamate-cysteine ligase (GCL) complex (comprising catalytic GCLC and regulatory GCLM subunits), is critically dependent on cystine uptake through the xCT transporter (SLC7A11/SLC3A2 heterodimer). Given the intracellular scarcity of free cysteine, the xCT-mediated cystine-glutamate antiport system becomes essential for maintaining GSH synthesis, with intracellular cystine reduction to cysteine constituting the rate-determining step in this metabolic pathway [4].

Multiple signaling networks converge to regulate ferroptosis sensitivity, including the Nrf2 antioxidant response pathway, p53 tumor suppressor axis, and HSPB1-mediated stress adaptation mechanisms. The Nrf2-Keap1 signaling module acts as a master regulator of oxidative stress responses through transcriptional activation of cytoprotective genes involved in iron metabolism regulation, GSH biosynthesis, and ROS detoxification [5]. Experimental validation comes from Cai et al., who demonstrated trabectedin's capacity to induce ferroptosis in non-small cell lung cancer (NSCLC) cells via coordinated modulation of two distinct pathways: the HIF-1α/IRP1/TFR1 iron acquisition axis and the Keap1/Nrf2/GPX4 antioxidant defense axis. This dual-targeting strategy establishes a mechanistic framework for exploiting ferroptosis induction in NSCLC therapy [6].

3. The role of ferroptosis in lung cancer

Ferroptosis has now been found in various types of lung injury or disease, such as PM2.5-induced lung injury, lung epithelial injury and acute lung injury. It has been found that ferroptosis plays a crucial role in the development, metastasis, and treatment of lung cancer [7].

3.1. Direct killing of lung cancer cells by ferroptosis

Specific ferroptosis inducers trigger lung cancer cell death via GPX4 or system Xc- inhibition. As reported by Cong Zhou et al. [8], the steroidal saponin Timosaponin AIII (Tim-AIII) exhibits potent antitumor effects in multiple malignancies, with pronounced activity in breast and liver cancers. In NSCLC, Tim-AIII binds HSP90 to form a molecular complex that induces GPX4 ubiquitination and degradation, thereby activating ferroptosis. Mechanistically, Tim-AIII promotes HSP90-mediated GPX4 ubiquitination, which drives ferroptotic cell death. Experimental data confirm that this process results in cell cycle arrest, suppressed proliferation, and reduced migratory capacity in NSCLC cells.

3.2. Ferroptosis and lung cancer metastasis

Ferroptosis modulates pulmonary carcinoma cell infiltration and dissemination through its regulatory influence on epithelial-mesenchymal transition (EMT) dynamics. EMT, a biological process critically implicated in oncogenesis, has been recognized as a principal driver of neoplastic dissemination and post-therapeutic recurrence. Current therapeutic investigations have revealed multiple molecular targets within EMT-associated signaling cascades that may inhibit pulmonary adenocarcinoma metastasis. Experimental evidence demonstrates that ferroptosis activation potentiates EMT suppression through bidirectional regulatory mechanisms, wherein their mutual interactions collectively govern malignant infiltration, metastatic progression, and tumor-associated inflammatory cascades. This pathophysiological crosstalk suggests that pharmacological modulation of ferroptosis-EMT axis mechanisms could yield novel therapeutic interventions.

In seminal research conducted by Zhang et al. [9], the natural compound crospovidic acid (CA) exhibited potent anti-metastatic effects through YAP-mediated ferroptosis induction coupled with EMT pathway inhibition. As a phytochemical with documented antineoplastic properties, CA demonstrated particular efficacy in pulmonary adenocarcinoma models, primarily through apoptosis induction and metastatic pathway disruption. Mechanistic analyses revealed CA's dual action: facilitating ferroptotic cell death via glutathione metabolism regulation through YAP/GSS signaling axis, while concurrently suppressing EMT-mediated metastatic transformation. This synergistic mechanism underscores CA's therapeutic potential as a ferroptosis-activating agent for metastatic pulmonary carcinoma management, providing experimental validation for targeting ferroptosis-EMT interactions in anticancer strategies.

4. Interaction between ferroptosis and tumor immune microenvironment

The tumor microenvironment (TME) establishes essential biological conditions supporting cancer initiation, invasion, and metastatic dissemination. Emerging evidence characterizes TME's immunosuppressive features, including hypoxia, acidic pH, elevated interstitial pressure, abnormal vascular permeability, and chronic inflammation. These pathological components collectively promote immune escape mechanisms and diminish therapeutic responses to immunotherapies, highlighting TME's significance as a therapeutic target in precision oncology. Consequently, TME modulation has become a strategic approach to amplify anti-improve immunity by reversing immunosuppressive mechanisms [10].

Centrosome and spindle pole-associated protein 1 (CSPP1) functions as a centrosomal-microtubule interface protein coordinating cell cycle-dependent cytoskeletal dynamics and ciliogenesis. This biomolecule maintains ubiquitous expression across tissue systems through multilayered regulation involving genetic polymorphisms, epigenetic modifications (particularly DNA methylation), and post-transcriptional miRNA-mediated control. Emerging evidence implicates CSPP1 dysregulation in diverse malignancies, with mechanistic connections to ferroptosis modulation and TME reprogramming. Its oncogenic involvement manifests through multifaceted regulatory capacities in TME progression, stromal remodeling, and immunomodulatory pathways, positioning CSPP1 as a multifunctional regulator in cancer pathobiology.CSPP1 is a potential diagnostic and prognostic biomarker associated with ferroptosis and TME, and can be used as a new

type of cancer biomarker to influence tumor progression through multidimensional regulatory mechanisms, with a central role in inhibiting ferroptosis The interaction between ferroptosis and TME forms a dynamic network, thus CSPP1 may be an important target for combination therapy by regulating key nodes (e.g. GPX4, PD-L1). Future studies need to validate the specific mechanism of CSPP1 in the iron-death-TME axis in combination with experiments and explore its clinical translational potential [11].

5. Conclusion

Ferroptosis inducers show great potential in tumor therapy, but issues related to selectivity and toxicity remain major challenges in current research. First, ferroptosis inducers may cause nonspecific toxicity to normal cells, especially damage to tissues with active iron metabolism, such as liver and kidney, which limits their clinical application. Second, the heterogeneity of the ferroptosis regulatory pathway in tumor cells may lead to differences in the sensitivity of the inducers, and some cells may be resistant to them due to escape from ferroptosis. In addition, the metabolic stability, biodistribution and target delivery efficiency of ferroptosis inducers in vivo also directly affect their selectivity and therapeutic efficacy. Future studies are needed to improve the targeting and reduce the toxicity of ferroptosis inducers through the development of tumor microenvironment-responsive drug delivery systems, the design of highly selective small molecule compounds, and the exploration of combinatorial therapeutic strategies, such as combination with immunotherapy, to promote their safe application in the clinic.

The interaction between ferroptosis and tumor immunity opens up new research directions for cancer therapy, but its complexity also poses many future challenges. First, how ferroptosis precisely regulates the tumor microenvironment, such as T cells, macrophages, and NK cells, still needs to be explored in depth to reveal its specific mechanism of action in different immune cell types. Second, the interaction between ferroptosis and other cell death modes such as apoptosis and necroptosis in tumor immunity is unclear, and further studies are needed to clarify their synergistic or antagonistic effects. In addition, how tumor cells resist the attack of the immune system by escaping ferroptosis and how to reverse this escape by targeted intervention are also the focus of future studies. Finally, the issues of drug resistance, toxicity and bioavailability that ferroptosis inducers may face in clinical applications also need to be addressed by developing more precise delivery systems and combination therapy strategies. In conclusion, the research on the interaction between ferroptosis and tumor immunity is still in its infancy, and future breakthroughs in mechanism analysis, clinical translation and technological innovation are needed to promote its practical application in cancer therapy.

Ferroptosis, as a novel iron-dependent cell death mode, has attracted extensive attention in the field of tumor research in recent years and is expected to open up a completely new direction for cancer therapy. Its unique metabolic regulation mechanism and close association with the tumor microenvironment provide a multi-level research perspective and application potential for future tumor therapy. The interaction between ferroptosis and tumor immunity is one of the core directions for future research, and the activation of anti-tumor immune responses or the reversal of the immune-suppressed TME through the regulation of ferroptosis may provide a new combined strategy for immunotherapy. The development of specific targeted drugs against key regulatory pathways of ferroptosis (e.g., GPX4, System Xc-, etc.) will further improve the precision and effectiveness of treatment. The role of ferroptosis in tumor drug resistance is also of great interest, and future studies may reveal its potential to reverse resistance to conventional treatments (e.g., chemotherapy, targeted therapy). Ferroptosis-based biomarker studies and exploration of individualized treatment regimens will help achieve more precise tumor typing and treatment optimization. Selectivity of ferroptosis inducers, toxicity issues, and innovation of delivery systems are also key technical challenges that need to be overcome in future clinical translation. Ferroptosis research is profoundly changing the landscape of tumor therapy, and in the future, it is expected to promote its widespread application in clinical practice through multidisciplinary intersections and technological innovations, bringing new

hope to cancer patients. The combined application of targeted ferroptosis and immunotherapy provides a new direction for lung cancer treatment, but further research is needed to overcome existing challenges and promote clinical translation.

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