

Progress on Molecular Mechanism of Disulfide Death in Gastric Cancer and its Clinical Targeted Treatment Strategy

Yujie Liu *

Department of HaiDe college, Ocean University of China, Qingdao, 266100, China

* Corresponding Author Email: 23220001037@stu.ouc.edu.cn

Abstract. Disulfide death is a newly discovered regulatory cell death mode in 2023, which is driven by the high expression of SLC7A11 and glucose starvation, and is characterized by the collapse of actin skeleton. It shows great potential in the targeted treatment of gastric cancer. This paper systematically reviewed the molecular mechanism of disulfide death, summarized the research progress of disulfide death related genes (DRGs) in the prognosis evaluation, molecular typing and immune microenvironment regulation of gastric cancer, and discussed the targeted treatment strategy based on Glucose Transporter 1 (GLUT) inhibitor, SLC7A11 precise regulation and nano drug delivery system. The results showed that the DRGs related prognostic model can effectively predict the survival of gastric cancer patients, and its low-risk group often presents an "immune fever" phenotype, while the GLUT inhibitor bay-876 has been confirmed in preclinical models to induce disulfide death and inhibit tumor growth. However, the field still faces challenges such as the lack of specific detection markers, functional studies mostly stay in correlation inference and lack of causal mechanism verification. The further research need to analyze the real role of disulfide death in the tumor microenvironment with the help of single-cell and space omics technology, and accelerate the clinical transformation process by carrying out clinical trials with SLC7A11 expression level as a hierarchical marker.

Keywords: Disulfide death; Gastric cancer; GLUT inhibitors; Prognostic model; Immune microenvironment.

1. Introduction

Gastric cancer is the fifth most common malignant tumor and the fourth leading cause of cancer-related death worldwide. According to GLOBOCAN 2020 statistics, there are about 1.089 million new cases and 769 million deaths worldwide every year, of which East Asia bears the major disease burden [1]. Although surgery, chemotherapy, targeted and immunotherapy have improved the prognosis of patients to some extent, most patients have reached advanced stage at the time of diagnosis, and the high heterogeneity of tumors and complex drug resistance mechanisms lead to a 5-year survival rate of less than 20% [2]. Therefore, exploring new ways of tumor cell death and translating it into therapeutic strategies is the bottleneck of precision medicine for gastric cancer. Regulatory cell death (RCD) is the core mechanism to maintain tissue homeostasis, and its dysfunction is closely related to tumor development. Following the classic apoptosis, the successive discovery of non apoptotic RCD such as iron death, pyroptosis and copper death has opened up a new path for cancer treatment [3].

However, cancer cells often escape apoptosis in many ways. Although other RCD pathways have therapeutic potential, they also have limitations. In 2023, Liu et al. First defined a brand-new RCD - disulfide death [4]. This study confirmed that in tumor cells with high expression of SLC7A11, glucose deficiency would trigger NADPH depletion and abnormal intracellular disulfide accumulation, resulting in intermolecular disulfide crosslinking of actin skeleton proteins, skeleton contraction and rapid cell death. This finding revealed that SLC7A11 resists iron death when nutrition is sufficient and promotes disulfide death when glucose is deficient [5]. Since then, disulfide death has rapidly become a frontier hotspot in tumor research. A number of bioinformatics studies on gastric cancer have found that the differential expression of DRGs and disulfide death related long noncoding RNAs (DRLs) is closely related to patient prognosis, tumor microenvironment (TME) and drug

sensitivity [6-8]. At the same time, targeted drugs such as glucose transporter 1 (GLUT) inhibitors have shown antitumor activity of inducing disulfide death in preclinical models [4].

This article aims to systematically sort out the molecular mechanism of disulfide death, review its research status in gastric cancer, and further explore the targeted treatment strategies and clinical transformation prospects based on this mechanism.

2. The Core Molecular Mechanism of Disulfide Death

2.1. SLC7A11 and Redox Imbalance

SLC7A11 (XCT), as the light chain subunit of the cystine / GLUTamate antiporter system XC⁻, mediates extracellular cystine intake and intracellular GLUTamate excretion in a 1:1 ratio [5]. The ingested cystine is rapidly reduced to cysteine, which is the rate limiting precursor for the synthesis of GLUTathione (GSH), the most abundant antioxidant in cells. GSH provides reducing equivalents for GLUTathione peroxidase 4 (GPx4), converting toxic lipid peroxides into non-toxic lipid alcohols, thereby inhibiting iron death [5]. Therefore, SLC7A11 has traditionally been regarded as a key gene to protect tumor cells. In most tumors, SLC7A11 is highly expressed to meet the needs of cancer cells to combat oxidative stress under high-speed proliferation and high metabolic activity. However, in the absence of glucose, the function of pentose phosphate pathway (PPP) is limited, and cytoplasmic NADPH production is severely insufficient. At this time, a large amount of cystine intake caused by high expression of SLC7A11 cannot be effectively reduced, but exacerbates NADPH depletion, resulting in abnormal accumulation of cystine and other disulfides in the cell, forming "disulfide stress" [4].

2.2. Disulfide Crosslink Driven Collapse of the Actin Backbone

Under normal physiological conditions, the cytosol presents a reducing environment, and protein cysteine residues exist in the form of thiols (-SH). When disulfide stress occurs, a large number of abnormally accumulated disulfides can redox thiol groups on sensitive proteins, forming unnatural intermolecular disulfide bonds. Liu et al identified the actin skeleton protein as the main target of disulfide crosslinking in SLC7A11 overexpressing cells after glucose starvation through bioorthogonal chemical proteomics, including thin filament protein α/b (flna/b), non muscle myosin heavy chain 9 (MYH9) and ankle protein 1 (TLN1) [4]. The experiment confirmed that these proteins formed high molecular weight complexes under non reducing electrophoresis, and there was a specific intermolecular crosslinking peptide at the c988-c1379 site of MYH9. Morphologically, the cells showed significant features of F-actin contraction and detachment from the plasma membrane. These changes could be reversed by disulfide reducing agents (such as 2-mercaptoethanol) but not inhibited by reactive oxygen species (ROS) scavengers [4]. This indicates that disulfide death is a kind of ROS independent skeletal toxicity event directly driven by disulfide bonds.

2.3. Regulatory Role of rac1-wrc-arp2/3 Pathway

Genome wide crispr/cas9 screening revealed the critical regulatory role of Rac1 wave regulatory complex (WRC) -arp2/3 signaling axis on disulfide death. This pathway is activated by the small GTPase Rac1, which activates the arp2/3 complex through WRC (its core component is nckap1), driving branch actin polymerization and lamellipodia formation [4]. Knockdown of nckap1 or other components of WRC could partially inhibit disulfide death, while expression of persistently activated Rac1 promoted disulfide death. This indicates that the dense actin branching network in lamellipodia generated by rac1-wrc-arp2/3 pathway provides a rich spatial platform for the formation of intermolecular disulfide bonds under disulfide stress [4].

3. Research Status of Disulfide Death in Gastric Cancer

3.1. Expression, Molecular Typing and Prognostic Model of Disulfide Death Regulatory Genes (DrGs)

A number of bioinformatics analyses have consistently shown that DRGs are widely differentially expressed in gastric cancer tissues and are significantly correlated with prognosis [6~8]. Based on consensus clustering, gastric cancer can be divided into 2 to 3 disulfide death subtypes with different survival outcomes and immune characteristics. Generally, subtypes presenting high expression of DRGs and high immune / stromal scores have a poor prognosis and are defined as "immune rejection" cold tumors [6,7]. Based on these differential genes, researchers constructed multiple prognostic risk models to quantify individual disulfide death characteristics (Table 1).

Table 1. Overview of disulfide death related prognostic models for gastric cancer.

Research	Model type	Number of genes	Core genes /lncnas	Key findings
[6]	DRG model	4	PPP1R14A, HEYL, COL10A1, TFF2	COL10A1 knockdown inhibited proliferation and migration and reduced F-actin expression
[7]	DRG model	19	APC11.etc	Apc11 overexpression promotes GC cell proliferation and migration
[8]	DRG model	6	PLS3, GRP, APOD, SGCE, COL8A1, VAMP7	APOD is an independent prognostic factor and potential therapeutic target
[9]	DRIG model	4	GLA, HIF-1 α , VPS35, CDC37	Develop online dynamic nomogram
[10]	DRL model	3	AC107021.2, AC129507.1, FRMD6-AS2	Ac129507.1 $\rightarrow$ flna/tln1 $\rightarrow$ focal adhesion axis; Ac107021.2 $\rightarrow$ myh10 $\rightarrow$ actin axis
[11]	DRL model	4	PINK1-AS, AC107021.2, AL359182.1, AC009486.1	After 201 model screening, al359182.1 is a new target

For example, the four gene model (including ppp1r14a, Heyl, COL10A1, TFF2) established by Liu et al using lasso regression can effectively predict the survival of patients, and the silencing of COL10A1 can inhibit the proliferation of gastric cancer cells and reduce the expression of F-actin [6]. In addition, a variety of DRGs models containing core genes such as plaps3, APOD, GLA, HIF-1 α [7,9], as well as DRLs models containing lncRNAs such as ac107021.2, PINK1 as [10,11], have shown good prognostic prediction ability in different cohorts. The core genes of these models are often associated with immune cell infiltration, tumor mutation burden (TMB) and microsatellite instability (MSI), suggesting that the disulfide death signature can not only be used for prognostic evaluation, but also may predict the response to immunotherapy.

3.2. Functional Exploration of DRGs in the Biological Behavior of Gastric Cancer

Compared with a large number of studies on prognostic models, the functional validation of specific DRGs is still in its infancy, but some important findings have been obtained. In addition to the aforementioned COL10A1, Zhang et al confirmed that apc11 in the 19 gene model is highly expressed in gastric cancer, and its knockdown can significantly inhibit cell proliferation and migration [7]. Li et al., through tissue microarray verification, found that GLA, HIF-1 α , vps35 and cdc37 in their model were significantly upregulated in gastric cancer tissues, and were positively correlated with higher Tumor-Node-Metastasis (TNM) classification and SLC7A11 expression [9]. The knockdown of guanidinoacetate N-methyltransferase gene (GAMT) gene newly identified by Wu et al. Can not only inhibit the proliferation and migration of human gastric adenocarcinoma cell line (AGS) cells, but also significantly enhance the sensitivity of gastric cancer cells to 5-fluorouracil, oxaliplatin and other chemotherapeutic drugs [12]. These studies collectively suggest that disulfide

death related genes not only participate in the maintenance of the malignant phenotype of gastric cancer but also may become potential targets to overcome chemoresistance.

4. Therapeutic Strategies for Gastric Cancer Targeting Disulfide Death

4.1. GLUT1 Inhibitors

Limiting glucose uptake by GLUT inhibitors to block ppp-nadph production is currently the most direct strategy to induce disulfide death. The highly selective GLUT1 inhibitor bay-876 and GLUT1/3 inhibitor kl-11743 can significantly inhibit tumor growth in xenograft tumors with high expression of SLC7A11 and patient derived xenograft tumor (PDX) models, and cause increased intratumoral actin backbone disulfide crosslinks, but are ineffective in SLC7A11 low expression tumors, confirming the targeting and effectiveness of this strategy [4]. At the same time, natural products such as epigallocatechin gallate (EGCG) and genistein also have the activity of inhibiting GLUT, which provides the possibility of developing low toxicity combination therapy [13]. In addition, KL-11743, as an orally available pan class I GLUT inhibitor, can simultaneously block GLUT1-4, showing a broader spectrum of glucose metabolism inhibition effects than BAY-876 in preclinical models [14]. Therefore, GLUT inhibitors are especially suitable for gastric cancer with high expression of SLC7A11.

4.2. Precise Regulation of SLC7A11

In terms of SLC7A11 overexpression sensitization, Nrf2 agonists can upregulate SLC7A11 transcription by promoting Nrf2 nuclear translocation and are binding. The reported Nrf2 agonists include dimethyl fumarate (DMF), sulforaphane, tetrathiomolybdate (TTM) and EGCG [14]. Among them, sulforaphane can lead to the release of Nrf2 by modifying the cysteine residues of Keap1, which has been confirmed by multiple clinical trials to have chemopreventive potential. TTM is a copper chelator, but at the same time it can activate Nrf2 and upregulate the expression of its target genes (including SLC7A11, HMOX1, GCLM) through an autophagy dependent mechanism [15]. In terms of SLC7A11 inhibition, sulfasalazine, a marketed drug, can act as a competitive inhibitor of SLC7A11, blocking cystine uptake and depleting GSH, inducing iron death [3]. Sorafenib, a multi-target kinase inhibitor, can also inhibit system XC⁻ function. In addition, hg106 is a highly selective SLC7A11 inhibitor identified in recent years, which selectively induced apoptosis but not iron death by inhibiting cystine uptake and GSH synthesis in KRAS mutant lung cancer cells, revealing the complexity of SLC7A11 inhibition inducing different death modes [16]. It should be pointed out that SLC7A11 inhibition reduces the substrate source of disulfide death while blocking cystine intake, so it negatively regulates disulfide death. In iron death resistant gastric cancer, increasing the expression of SLC7A11 and combined with GLUT inhibition may be a better treatment option.

4.3. Nano Drug Delivery System and Combination Therapy Strategy

Nano drug delivery system is a kind of drug carrier with a size of 1-1000 nm. It can achieve tumor selective enrichment by enhancing the permeation and retention (EPR) effect or actively targeting ligands, and has the advantages of multi drug co loading, controlled release and improving drug solubility and stability. It is an important tool to promote the clinical transformation of disulfide death strategy. At present, its application in the field of disulfide death mainly focuses on the following directions:

4.3.1. GLUT inhibitor nanocarriers

Wang et al developed a degradable nanoparticle, CO loaded bay-876 with cystine containing polymer, and successfully induced disulfide death in a bladder cancer model combined with sonodynamic therapy [17]. This nanosystem not only blocks glucose uptake by releasing bay-876 to inhibit GLUT1 but also releases a large amount of cystine through polymer degradation to aggravate intracellular disulfide stress. At the same time, ROS generated by sonodynamic effect further depletes

GSH and NADPH, forming a triple hit, and enhancing the efficacy of anti-PD-1 immunotherapy. This design provides an important reference for the nano immune combination therapy of gastric cancer.

4.3.2. Glucose starvation simulation nanosystem

Yu et al recently reported a single atom nanoenzyme, which can simultaneously simulate the activities of glucose oxidase (GOx) and GLUTathione peroxidase (GPX): the former catalyzes the oxidation of local glucose to gluconic acid and H_2O_2 in tumor, cutting off the PPP source of NADPH; The latter depletes GSH and weakens the disulfide reduction ability of cells [18]. The nanozyme can effectively induce disulfide death of SLC7A11 overexpressing tumor cells in vivo and promote immunogenic cell death (ICD) and CD8⁺ T cell infiltration. Designed by Guo et al GOx-IA@HMON@IO smart nanomedicine realized the triple synergistic effect of disulfide death, iron death and immunosuppression reversal under the guidance of MRI - glucose consumption by GOx induced disulfide death, iron ion and IA induced iron death, while the relief of tumor hypoxia further enhanced the function of cytotoxic T lymphocytes (CTLs) - achieved complete tumor regression in the triple negative breast cancer model, and showed good biosafety [19].

4.3.3. Disulfide responsive nanomedicines

Based on the characteristics of high GSH in TME, cross-linked polymers containing disulfide bonds (such as PEG-SS-PLGA) were designed, which can be specifically degraded in tumor tissues to release the load and further enhance the disulfide death effect. Zhen et al further reported a nanoscale metal organic framework (nmof) loaded with digitonin, which achieved multimodal killing of tumor cells using mitochondria targeted radiotherapy radiation dynamic therapy combined with disulfide death induction [20].

4.3.4. Combined with immunotherapy

Several studies on gastric cancer have revealed that the low-risk score group of disulfide death (that is, the group that may be more sensitive to disulfide death induction) is often enriched with CD8⁺ T cells, follicular helper T cells and plasma cells, presenting an "immune fever" phenotype, and has a higher response potential to anti-pd-1/ctla-4 treatment [6,12]. This suggests that GLUT inhibitors or SLC7A11 regulation may transform "cold" tumors into "hot" tumors by inducing ICD

5. Conclusion

As a new redox and metabolism driven RCD, the core mechanism of disulfide death lies in the high expression of SLC7A11 combined with NADPH depletion, disulfide accumulation and actin skeleton collapse triggered by glucose starvation, which provides a new target for targeting the metabolic vulnerability of tumors. In the field of gastric cancer, the molecular typing and prognostic model based on DRGs initially showed its potential for clinical application and revealed its close relationship with the immune microenvironment. New therapeutic strategies such as GLUT inhibitors, SLC7A11 precise regulation and nano drug delivery system have shown attractive prospects in preclinical research. However, the research in this field still faces multiple challenges. The primary problem is the urgent need to identify specific molecular markers, such as specific disulfide crosslinked skeletal proteins, in order to build its clinical accurate evaluation system. Secondly, most of the existing studies are based on expression correlation analysis. In the future, it is necessary to clarify the specific signaling pathways of key DRGs regulating disulfide death through CRISPR screening, conditional gene regulation and in vivo metabolic imaging and other causal studies. In addition, it is necessary to systematically analyze the heterogeneity of disulfide death in different cell types and its remodeling effect on the TME by using technologies such as patient derived organoids (PDO) and single cell / space omics. Finally, developing a highly selective targeted drug delivery system, designing the optimal combination therapy, and conducting clinical trials in gastric cancer patients stratified by molecular markers (such as SLC7A11 expression level) are the key steps to push this new mechanism from concept to clinical application.

References

- [1] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*, 2021; 71: 209-249.
- [2] Ajani JA, D'Amico TA, Bentrem DJ, et al. Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*, 2022; 20: 167-192.
- [3] Stockwell BR. Ferroptosis turns 10: Emerging Mechanisms, Physiological Functions, and Therapeutic Applications. *Cell*, 2022; 185: 2401-2421.
- [4] Liu X, Nie L, Zhang Y, et al. Actin cytoskeleton vulnerability to disulfide stress mediates disulfidptosis. *Nat Cell Biol*, 2023; 25: 404-414.
- [5] Koppula P, Zhuang L, Gan B. Cystine transporter SLC7A11/xCT in cancer: ferroptosis, nutrient dependency, and cancer therapy. *Protein Cell*, 2021; 12: 599-620.
- [6] Liu Z, Sun L, Zhu W, et al. Disulfidptosis signature predicts immune microenvironment and prognosis of gastric cancer. *Biol Direct*, 2024; 19: 65.
- [7] Zhang T, Chen Y, Xiang Z. Machine learning-based integration develops a disulfidptosis-related lncRNA signature for improving outcomes in gastric cancer. *Artif Cells Nanomed Biotechnol*, 2025; 53: 1-13.
- [8] Li Q, Yin LK. Comprehensive analysis of disulfidptosis related genes and prognosis of gastric cancer. *World J Clin Oncol*, 2023; 14: 373-399.
- [9] Zhang P, Chen Z, Lin X, et al. Unravelling diagnostic clusters and immune landscapes of disulfidptosis patterns in gastric cancer through bioinformatic assay. *Aging*, 2023; 15: 15434-15450.
- [10] Tang J, Yang J, Yin LK. Prognostic value of disulfidptosis-associated genes in gastric cancer: a comprehensive analysis. *Front Oncol*, 2025; 15: 1512394.
- [11] Yu J, Yin L, Li M, et al. Disulfidptosis-related lncRNA signatures in gastric cancer: regulation of MYH10-driven cytoskeletal remodeling and therapeutic implications. *Discov Oncol*, 2025; 16: 1385.
- [12] Wu W, Tao G, Chen Z, et al. Identification of disulfidptosis-related subtypes in gastric cancer and GAMT is a key gene during disulfidptosis. *Sci Rep*, 2025; 15: 111.
- [13] Li X, Xu J, Yan L, et al. Targeting Disulfidptosis with Potentially Bioactive Natural Products in Metabolic Cancer Therapy. *Metabolites*, 2024; 14: 604.
- [14] Gu Q, An Y, Xu M, et al. Disulfidptosis, A Novel Cell Death Pathway: Molecular Landscape and Therapeutic Implications. *Aging Dis*, 2025; 16(2): 917-945.
- [15] Zhang M, Qiu H, Mao L, et al. Ammonium tetrathiomolybdate triggers autophagy-dependent NRF2 activation in vascular endothelial cells. *Cell Death Dis*, 2022; 13(8): 733.
- [16] Hu K, Li K, Lv J, et al. Suppression of the SLC7A11/glutathione axis causes synthetic lethality in KRAS-mutant lung adenocarcinoma. *J Clin Invest*, 2020; 130(4): 1752-1766.
- [17] Wang K, Li L, Liang G, et al. Sonodynamic activated nanoparticles with Glut1 inhibitor and cystine-containing polymer stimulate disulfidptosis for improved immunotherapy in bladder cancer. *Biomaterials*, 2025; 319: 123178.
- [18] Yu W, Jin D, Zhang Y, et al. Provoking tumor disulfidptosis by single-atom nanozyme via regulating cellular energy supply and reducing power. *Nat Commun*, 2025; 16(1): 4877.
- [19] Guo S, Li Z, Zhou R, et al. MRI-guided tumor therapy based on synergy of ferroptosis, immunosuppression reversal and disulfidptosis. *Small*, 2024; 20(30): e2309842.
- [20] Zhen W, Fan Y, Germanas T, et al. Digitonin-loaded nanoscale metal-organic framework for mitochondria-targeted radiotherapy-radiodynamic therapy and disulfidptosis. *Adv Mater*, 2024; 36(10): e2405494.