Role of disulfide death in cancer (Review)

XUE LI and DANXIA ZHU

Oncology Department, The Third Affiliated Hospital of Soochow University, Changzhou, Jiangsu 213000, P.R. China

Received July 24, 2024; Accepted October 24, 2024

DOI: 10.3892/ol.2024.14801

Abstract. The research field of regulated cell death is growing extensively. Following the recognition of ferroptosis, other unique and distinct forms of regulated cell death, including cuproptosis and disulfide death, have been identified. Disulfide death occurs due to the abnormal accumulation of disulfides within cells in environments lacking glucose, leading to contraction of the actin cytoskeleton, which ultimately triggers various signaling pathways and cell death. The induction of disulfide death in the treatment of cancer may exhibit significant therapeutic potential. Therefore, in the present review, a comprehensive and critical analysis of the current understanding of the molecular mechanisms and regulatory networks of disulfide death is presented. In addition, the potential physiological functions of disulfide death in tumor suppression and immune surveillance as well as its pathological roles and therapeutic potential are described. The core focus areas for future research into this form of cell death are also explored. Given the current lack of extensive clinical findings and well-defined key concepts, these may be regarded as pivotal points of interest in future studies.

Contents

1. Introduction

Cells represent the fundamental units and building blocks of life, serving a pivotal role in various aspects of existence through their proliferation, differentiation, functional characteristics and eventual death. Cell death was initially perceived to be passive and unregulated. However, by the 1970s, apoptosis was discovered to be is a form of programmed cell death, executed through developmentally programmed pathways (1). The broader classification of regulated cell death refers to death programs that are molecularly regulated but not always associated with developmental programming (2). One such example includes ferroptosis, a term that was first introduced in 2012 (3), and which has had a profound impact on research into metabolic reprogramming in cancer. Ferroptosis is driven by the iron-dependent peroxidation of phospholipids and is influenced by a variety of cellular metabolic events, including redox balance, iron handling, mitochondrial activity and the metabolism of amino acids, lipids and sugars, as well as a number of disease-related signaling pathways (3).

Copper-induced death, also known as cuproptosis, is another type of regulated cell death, which results from toxic stress inflicted on proteins associated with the tricarboxylic acid (TCA) cycle within the mitochondria due to lipid acylation (4). By contrast, disulfide-induced cell death, also known as disulfide death or disulfidptosis, arises from the accumulation of abnormal disulfide bonds in cells expressing high levels of solute carrier family 7 member 11 (SLC7A11) when starved of glucose. This leads to the formation of disulfide bonds between actin cytoskeletal proteins, which disrupts the F-actin network. The F-actin network comprises actin filaments that interact with myosin to generate movement within the cell and thereby contribute to processes such as cell migration and deformation. Disruption of this network leads to structural damage and ultimately triggers cell death (5). However, gaps remain in our understanding of the field of disulfide death. Research in this field has evolved through the exploration of trace elements, amino acid metabolism, redox reactions and cell death, and has generated a large volume of published research (5). Therefore, it is imperative to critically examine and consolidate recent research progress. In the present review, the causes, regulatory mechanisms and potential physiological roles of disulfide death, as well as associated therapeutic approaches and their effects on tumors are explored. Additionally, new theoretical challenges and issues facing this field are discussed, and recommendations are offered to guide future research into disulfide death.

2. Mechanism of disulfide death

Sulfur is not only an essential element for living organisms but is also one of the most abundant resources on Earth. A

Correspondence to: Dr Danxia Zhu, Oncology Department, The Third Affiliated Hospital of Soochow University, 99 Juqian Street, Tianning, Changzhou, Jiangsu 213000, P.R. China
E-mail: zhudanxia66@163.com

Key words: disulfide death, tumors, SLC7A11, glucose starvation

number of sulfur compounds participate in the formation of inorganic sulfate salts, and sulfur is also incorporated into eukaryotes, e.g., via the amino acids methionine, cysteine and cysteine (6). Methionine is considered a key amino acid, as it plays a central role in polyamine synthesis by serving as a methyl donor, and is involved in the production of glutathione (GSH) (7). Methionine is a precursor for cysteine in the synthesis of GSH; the latter primarily exists in the body in its reduced thiol form and an oxidized disulfide form (8). The liver is the primary source of GSH, where it plays a crucial role in antioxidative protection, detoxification, cysteine storage and the regulation of immune function (9). GSH deficiency or changes in the GSH/GSSG ratio increase the vulnerability of cells to oxidative stress, inflammation and tumor progression. By contrast, elevated GSH levels increase antioxidant capacity and resistance to oxidative stress, a phenomenon evident in various tumors (10). Exogenous GSH has been shown to inhibit inflammatory responses via the modulation of reactive oxygen species (ROS), whereas endogenous GSH has been shown to serve a role in the precise regulation of the innate immune response to infection, thereby modulating inflammation (10). Thus, GSH has a dual role in the inflammatory response; it acts both as an antioxidant by scavenging ROS during oxidative stress and as a signaling molecule that regulates protein function through thiol-disulfide bond exchange reactions, such as protein glutathionylation. Numerous examples of this regulatory role in oncogenes including p53, hypoxia-inducible factor-1 and, c-jun are included in a database developed by Chen *et al* (11) and are also discussed in a previous review (12). GSH-deficient regulatory T cells (Tregs) exhibit increased serine uptake and *de novo* synthesis, which enhances the one-carbon metabolic pathway. GSH not only controls the redox state of Tregs, but also serves as a negative feedback regulator to limit serine input/synthesis. The inhibition of serine uptake restores the suppressive function of GSH-deficient Tregs. According to relevant experiments, using mice that specifically ablate the catalytic subunit of Treg glutamate cysteine ligase (Gclc), the researchers found that removing GSH from Treg alters serine introduction and synthesis, and that the integrity of this feedback loop is critical to Treg's ability to inhibit it (13). Thus, GSH not only controls the redox state of Tregs, but also serves as a negative feedback regulator to limit serine input/synthesis (13).

SLC7A11 is a cystine/glutamate antiporter, also known as xCT, that plays a key role in numerous cancer types (14-16), such as colorectal cancer (17), gastric cancer (18), breast cancer (19) and non-small cell lung cancer (20). SLC7A11 facilitates the cellular import of cystine and export of glutamate. Once inside the cell, cystine is converted to cysteine with the consumption of nicotinamide adenine dinucleotide phosphate (NADPH) generated via the pentose phosphate pathway (PPP). Thus, SLC7A11 facilitates the biosynthesis of GSH from cysteine and thereby promotes the antioxidative defense (21). The cystine/glutamate antiporter system X_c^- is primarily a dimeric structure comprising SLC7A11 as a light chain subunit and SLC3A2 as a heavy chain subunit. The former regulates the biological activity of X_c^- while the latter anchors the SLC7A11 protein to the cell membrane (22) (Fig. 1).

The inward and outward transport of GSH, including its disulfide-bonded form, proceeds via the X_c^- system (23). Under normal physiological conditions, the reducing cellular environment promotes the formation of disulfide bonds in cytoplasmic proteins. Disulfide bond activation has been suggested to depend on three key features: i) High expression of SLC7A11, since high levels of extracellular cystine uptake and intracellular cysteine accumulation contribute to the occurrence of disulfide bond stress in cellular metabolic processes. Furthermore, the high expression of SLC7A11 stimulates tumor growth but also inhibits tumor metastasis (21,22,24-27). ii) Glucose is critical to metabolic processes, and its metabolism through the PPP generates NADPH in its reduced form (28). The deprivation of glucose and administration of anti-glycolytic drugs can cause tumor cells to die. This death may be due to necrosis, mitochondrial- or caspase-8-mediated apoptosis, or the formation of abnormal disulfide bonds between actin cytoskeletal proteins (29). iii) The excessive accumulation of disulfides promotes the formation of disulfide bonds between actin cytoskeletal proteins. This results in the contraction of actin and its detachment from the plasma membrane, ultimately leading to cell contraction and death (30) (Fig. 1). When the expression of SLC7A11 is low and combined with a state of glucose deprivation or the interruption of glucose intake, intracellular glucose levels decrease. This inhibits the production of glucose 6-phosphate via the inhibition of hexokinase, and also suppresses the generation of NADPH and pyruvate through the PPP and glycolysis (28). As a result, pyruvate levels are effectively reduced via the TCA cycle and mitochondrial oxidative phosphorylation. These physiological processes trigger oxidative stress and deplete ATP levels, which in turn increases the expression levels of Bax and Bak. Cytochrome *c* is then released from the mitochondria, which activates caspase-3 and further promotes membrane blebbing and cell apoptosis mediated by poly (ADP-ribose) polymerase (31). By contrast, the high expression of SLC7A11 combined with glucose starvation or reduced intake leads to a marked intake of cystine, decreased cysteine levels, reduced consumption of NADPH, and the accumulation of intracellular disulfides, ultimately triggering a disulfide bond stress response. This stress activates the Rac-WAVE regulatory complex (WRC)-actin related protein 2/3 (Arp2/3) signaling pathway, thereby producing abnormal disulfide bonds and sulfidation in the actin cytoskeleton of muscle cells (32).

3. Regulation of cellular metabolism and disulfide death

Conditions of glucose starvation. The primary characteristic of the tumor microenvironment is hypoxia, which is closely associated with the rapid progression and metastasis of cancer (33). Hypoxia inhibits the formation of disulfide bonds and impairs protein folding in the endoplasmic reticulum (ER), thereby disrupting ER homeostasis (34). In most types of cancer, hypoxia causes the cellular energy supply to be derived primarily from glycolysis and the PPP. A key factor in triggering disulfide death is the interruption of glucose metabolism during glucose starvation, as this impairs the PPP pathway and thereby reduces the generation of NADPH. However, cancer cells have the ability to exploit the tumor microenvironment to grow rapidly in nutrient-poor conditions (35). Glucose metabolism is inextricably associated with lipid and amino acid metabolism, and the regulation of one aspect may cause

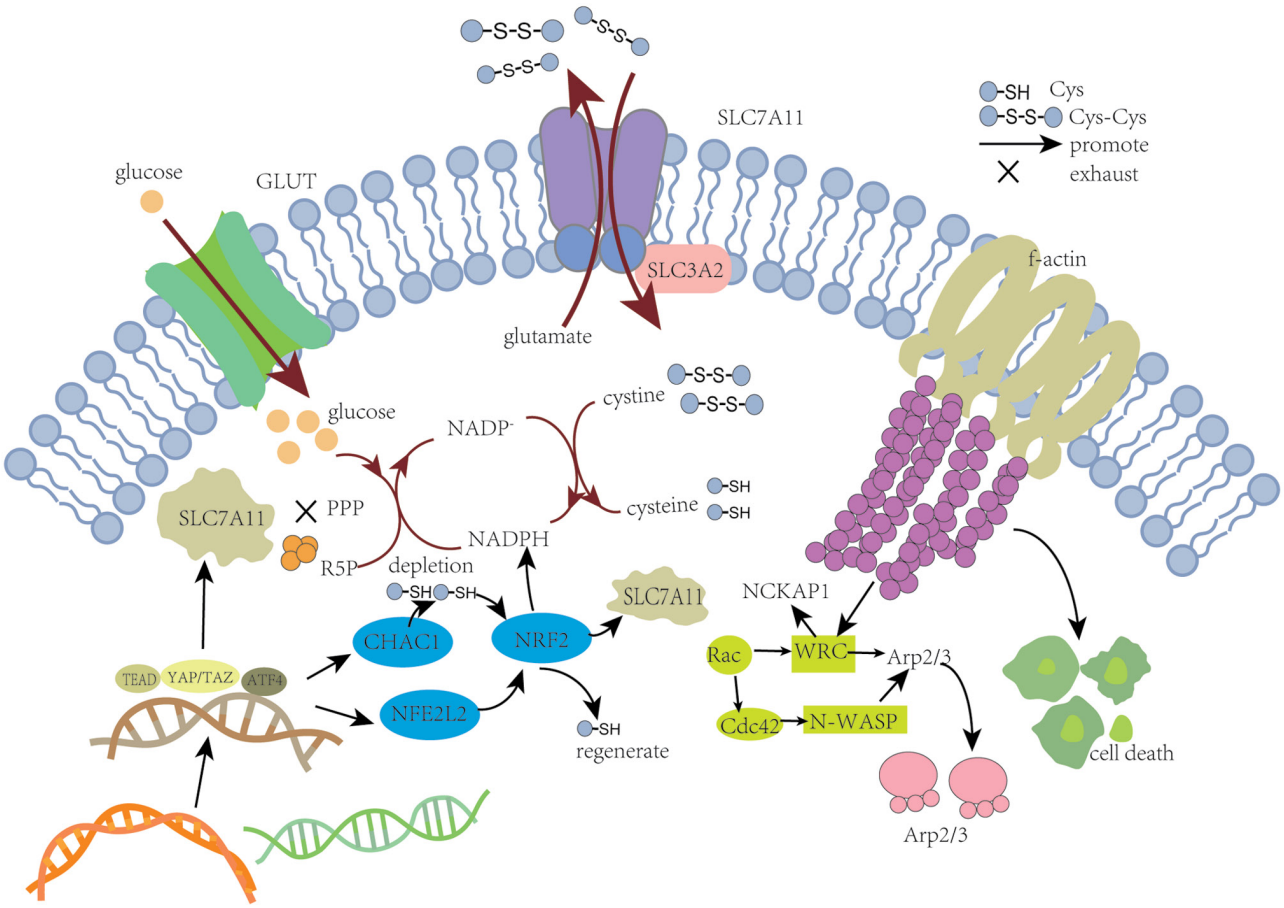

Figure 1. Mechanisms of disulfide death and their regulation. ATF4, activating transcription factor 4; Arp2/3, actin related protein 2/3; Cdc42, cell division control protein 42; CHAC1, ChaC glutathione specific γ-glutamylcyclotransferase 1; Cys, cysteine; GLUT, glucose transporter; N-WASP, neuronal-Wiscott-Aldrich syndrome protein; NADPH, nicotinamide adenine dinucleotide phosphate; NCKAP1, NCK-associated protein 1; NFE2L2, NFE2 like bZIP transcription factor 2; NRF2, nuclear factor erythroid 2-related factor 2; PPP, pentose phosphate pathway; R5P, ribose 5-phosphate; SLC3A2, solute carrier family 3 member 7; SLC7A11, solute carrier family 7 member 11; TAZ, transcription coactivator with PDZ-binding motif; TEAD, TEA domain transcription factor; WRC, WAVE regulatory complex; YAP, Yes1-associated transcriptional regulator.

alterations in other metabolic pathways that can lead to disulfide death (36). In addition to the Warburg effect, increased glutamine catabolism and *de novo* fatty acid synthesis are key hallmarks of cancer. Glutamine catabolism provides nutrients for the TCA cycle, and supplies nitrogen and carbon for the synthesis of nucleotides and amino acids (36). Furthermore, rapidly dividing cancer cells require increased *de novo* synthesis of fatty acids from acetyl coenzyme A using the reducing power of NADPH for membrane biosynthesis (36). When cysteine availability is limited, some cells utilize the transsulfuration pathway to biosynthesize cysteine from methionine. Specifically, cystathionine β-synthase converts methionine-derived homocysteine to cystathionine, which is then converted to cysteine by cystathionine γ-lyase (37). Activation of the transsulfuration pathway inhibits the disulfide death-dependent pathway by producing cysteine or GSH, acting in conjunction with system X_c^-.

Regulation and modification of SLC7A11. High expression of SLC7A11 is one of the key conditions for disulfide bond formation; its expression is influenced by multiple mechanisms, potentially involving transcriptional regulation by transcription factors and epigenetic regulators. These mechanisms aim to control the mRNA levels, protein stability and subcellular localization and transport protein activity of SLC7A11 (21). The expression of SLC7A11 can be induced under various stress conditions, including oxidative stress, amino acid starvation, metabolic stress and genotoxic stress, likely as an adaptive response enabling cells to restore redox homeostasis and maintain survival under stress condition (22) (Fig. 1).

Activating transcription factor 4 (ATF4) and nuclear factor erythroid 2-related factor 2 (NRF2) are considered to be the main transcription factors that mediate the stress-induced transcription of SLC7A11 (38). ATF4 is a member of the ATF/cAMP response element-binding family that not only serves as a transcription activator but also as a repressor protein, capable of responding to various types of cellular stress including ER stress, oxidative stress, amino acid depletion and the integrated stress response (38). The association of ATF4 and NRF2 has been reported to induce the expression of cyclooxygenase-2 in melanoma, and to regulate amino acid homeostasis via the production of asparagine and serine in non-small cell lung cancer (39-41). In addition, ATF4 promotes NRF2 expression through two pathways. The first pathway involves the depletion of GSH in ChaC glutathione-specific γ-glutamylcyclotransferase 1-dependent cells, and the second

pathway directly promotes the expression of NFE2 like the transcriptional induction of NFE2L2 expression (42). In-depth analyses reveal that NRF2 supports ATF4-induced cells by increasing cystine uptake via the glutamate-cystine antiporter xCT. In addition, NRF2 upregulates genes mediating thioredoxin usage and regeneration, thus balancing the glutathione decrease (42). Ultimately, both pathways promote the transcription of SLC7A11 and the generation of GSH. A study has shown that the expression level of ATF4 in gastric cancer is significantly increased, and that the transcriptional activity of ATF4 accelerates the growth and spread of gastric cancer (43). The antitumor activity of salbutamycin has been demonstrated to proceed via induction of the autophagic degradation of protein disulfide bond isomerase family A member 4 (PDIA4) and attenuation of the eukaryotic translation initiation factor 2 α kinase 3-ATF4-SLC7A11 signaling pathway (44), suggesting that the promotion of PDIA4 and upregulation of SLC7A11 promote the occurrence of disulfide death events. Studies have shown that PDIA4, an enzyme in the ER, is involved in the formation, breakage and rearrangement of protein disulfide bonds, thereby mediating oxidative protein folding (45,46).

ATF4 is known to regulate SLC7A11 via a number of other methods. For example, in hepatocellular carcinoma, Yes1-associated transcriptional regulator (YAP)/transcription coactivator with PDZ-binding motif (TAZ) are key effectors of the Hippo signaling pathway that play a crucial role in the maintenance of the intracellular GSH balance (47). These transcription factors coordinate the ATF4-dependent induction of SLC7A11 expression through interaction with TEA domain transcription factors (TEADs) (47). Research by Gao *et al* (47) indicated that the knockdown of YAP and TAZ resulted in a significant reduction in SLC7A11 expression at both the mRNA and protein levels in hepatocellular carcinoma cells. In the same study, chromatin immunoprecipitation using specific antibodies against YAP or TAZ followed by quantitative PCR (qPCR) showed that YAP and TAZ bind to DNA fragments containing TEAD motifs from the SLC7A11 gene promoter. These findings demonstrate that SLC7A11 is a direct transcriptional target of YAP/TAZ. Further mechanistic experiments showed that YAP/TAZ interacts with ATF4, forming a complex that binds to TEAD motifs, thereby enhancing the nuclear localization of ATF4, further increasing transcriptional activity, and preventing proteasomal degradation and ubiquitination in the cytoplasm. In addition, the study demonstrated that within the nucleus, ATF4 binds to DNA fragments in the amino acid responsive element region of the SLC7A11 promoter, thereby coordinating the expression of SLC7A11 (47). Thus, these findings indicate that a feedback loop between Hippo signaling and ATF4 activation regulates SLC7A11 expression. ATF4 and NRF2 are also involved in SLC7A11 transcription in melanoma, where enzyme activation is predominantly associated with thiol metabolism and oxidative stress (48,49). As aforementioned, NRF2 supports ATF4-induced cells by increasing cystine uptake via system X_c^- component SLC7A11 (42). Mechanistically, the high uptake of cystine by cancer cells, high SLC7A11 expression and reduced glucose metabolism leads to the toxic accumulation of cystine and other disulfide bond-containing molecules in the cell, NADPH depletion and collapse of the redox system. SLC7A11 plays a key role in the synthesis of GSH and negatively regulates ferroptosis, yet is upregulated in disulfide death (50). Promoting the upregulation of SLC7A11 through alternative pathways may also promote the disulfide death process (Fig. 1).

Rac-WRC-Arp2/3 signaling pathway regulates disulfide death. Rac has been demonstrated to activate the WRC to promote the formation of lamellipodial protrusions from cells (51,52). Cell migration typically involves the formation of lamellipodia, which are induced by Rac GTPase, and peripheral cell protrusions, which are driven by actin networks formed by the branching activity of the Arp2/3 complex (53,54). NCK-associated protein 1 (NCKAP1) within the WRC is responsible for activating the Arp2/3 complex. This activation drives the formation of branched actin filaments and also promotes the reorganization of actin and the formation of lamellipodia, resulting in the construction of a branched cortical actin network beneath the plasma membrane (55,56). The absence of NCKAP1 has been shown to attenuate the glucose starvation-induced formation of disulfide bonds, contraction of F-actin and detachment of F-actin from the plasma membrane in UMRC6 cells (57). The WAVE-2 catalytic subunit of the WRC facilitates Arp2/3-mediated actin polymerization and lamellipodia formation. The branched network of actin filaments that form the lamellipodia is a critical environment in which disulfide linkages can form between actin cytoskeletal proteins. In a study of melanoma, it was established that WAVE pathway typically involves two key mechanisms, the first being the direct activation of neuronal-Wiskott-Aldrich syndrome protein (N-WASP)-Arp2/3 by the Rac-independent activator cell division control protein 42 to form a plate-like structure, and the second being the WRC-Rac-dependent formation of lamellipodia (58). The deletion of either of these two pathways can disrupt F-actin filament formation and subsequently lead to cellular death (Fig. 1).

Glucose transporter (GLUT) inhibitors. GLUT inhibitors can induce the dimerization of SLC7A11 in GSH-abundant cells and synergize with immune therapies, such as programmed cell death protein 1/programmed cell death ligand 1 antibodies, resulting in enhancing tumor-killing efficacy (59). MutS homolog 3 (MSH3) has been demonstrated to induce disulfide bond deposition in renal cell carcinoma (RCC) cell lines under glucose starvation conditions (60). MSH3 is a DNA mismatch repair protein that binds to MSH2 to form the MutSβ heterodimer, which repairs incorrect base insertions and deletions (61). MSH3 is closely associated with the tumor microenvironment, immune checkpoint genes and immunotherapeutic susceptibility (60). In the aforementioned study, a predictive model of disulfide-related genes was constructed and MSH3 was identified as a key gene, the expression of which was negatively correlated with the number of Tregs, which contribute to the promotion of tumor progression and immune escape (60). The GLUT1 inhibitors BAY-876 and KL-11743 have been utilized to inhibit glucose uptake (62,63), consequently reducing NADPH production and increasing the NADP/NADPH ratio. This inhibition induced the formation of disulfide bonds in the actin cytoskeleton and induced its collapse in highly SLC7A11-expressing UMRC6 RCC

Table I. Expression of genes associated with disulfide death in different types of tumors.

Tumor type	Associated genes	(Refs.)
Lung adenocarcinoma	G6PD	(71)
Breast cancer	NDUFS1, LRPPRC, SLC7A11	(72)
Gastric cancer	APOD, NCKAP1	(93)
Glioblastoma	LRPPRC, RPN1, GYS1	(114)
Bladder cancer	POU5F1, CTSE	(122)
Renal cell carcinoma	MSH3	(123)

APOD, apolipoprotein D; CTSE, cathepsin E; G6PD, glucose-6-phosphate dehydrogenase; GYS1, glycogen synthase 1; LRPPRC, leucine rich pentatricopeptide repeat containing; MSH3, MutS homolog 3; NCKAP1, NCK-associated protein 1; NDUFS1, NADH:ubiquinone oxidoreductase core unit S1; POU5F1, POU class 5 homeobox 1; RPN1, ribophorin I; SLC7A11, solute carrier family 7 member 11.

cells, efficiently leading to cell death (30). In addition, these GLUT inhibitors also significantly reduced colorectal tumor volume in a mouse xenograft model, suggesting that they have potential as a treatment for colorectal cancer (64). Glucose uptake is significantly increased in cancer cells (65), and GLUT inhibition has been shown to be effective in reducing the proliferation and metabolism of human lung and cervical cancer cells (66). In addition, a study demonstrated that GLUT upregulation is associated with 5-fluorouracil resistance, and the inhibition of GLUT significantly improved the outcome in a mouse model of colorectal cancer (67). The upregulation of SLC7A11 expression in colon cancer cells, which may be induced by mutations in tumor suppressor genes such as BRCA1-associated deubiquitinase 1 or kelch-like ECH-associated protein 1, has been shown to promote the sensitivity of the cells to GLUT inhibitors (68,69). In a study by Zhao *et al* (70) in which HCT-116 colorectal cancer cells were treated with the GLUT1 selective inhibitor BAY-876 and the GLUT1/GLUT3 inhibitor KL-11743, sensitivity to these inhibitors was reduced in estrogen-related receptor α knockdown cells compared with control cells, indicating that estrogen-related receptor α sensitizes the cells to GLUT inhibition and ultimately to cell death. Overall, research suggests that the occurrence of disulfide-related death events is promoted by the inhibition of GLUT.

4. Relationship between disulfide death and tumors

Metabolic reprogramming is often regarded as a notable hallmark of cancer, with disulfide death becoming a focal point of research. Studies performed using public databases have detected the expression and mutations of disulfide death-related genes in cancers including lung adenocarcinoma (LUAD) (71), breast cancer (72) and hepatocellular carcinoma (73), as shown in Table I. Our group went from the study of iron death to copper death to the current study of disulfide death, which is an ongoing process of exploration in the field of cancer. Centered on disufidptosis-associated genes, the studies performed cluster subtyping and analyzed the differentially expressed genes associated with disulfide death. Following this, multiple differentially expressed genes were employed to construct prognostic risk models, and the association of these genes with prognosis were analyzed through immune infiltration, immune checkpoint and drug sensitivity analyses, with the aim of determining precise individualized treatments according to different disease types (71-73).

In the study of LUAD, qPCR was utilized to assess the expression of seven core differentially expressed genes in the A549 lung cancer cell line and the BEAS-2B normal bronchial epithelial cell line. Glucose-6-phosphate dehydrogenase (G6PD) had the highest risk coefficient as a disulfide death factor in LUAD among these genes, and western blotting experiments confirmed the elevated expression of G6PD in LUAD cells. Treatment with a G6PD inhibitor effectively reduced the expression of G6PD in the A549 cells, and the results of Ki67 staining and colony formation assays showed that the inhibition of G6PD significantly inhibited the proliferation of these cells (71). G6PD acts as a catalyst in the metabolism of glucose via the PPP, and also contributes to maintenance of the biological redox balance and biosynthesis processes (74). In tumors and other proliferating or developing cells, the rate of glucose uptake significantly increases, leading to the production of lactate, even in the presence of oxygen and fully functioning mitochondria. This process, known as the Warburg effect, has been studied extensively, as summarized in a previous review (75). In addition to meeting the biosynthetic needs of the cell during synthetic metabolic processes, the PPP also provides an antioxidative defense mechanism and generates NADPH (76). G6PD has a rate-limiting role in the PPP and is dynamically modified by O-linked β-N-acetylglucosamine, via a process termed O-GlcNAcylation, under hypoxia (77). This glycosylation activates G6PD and enhances the flux of glucose through the PPP, providing necessary precursors for the biosynthesis of nucleotides and lipids, and reducing agents such as NADPH for antioxidative defense (78). It has been shown that the inhibition of G6PD glycosylation reduces the growth of A549 lung cancer cells *in vitro* and tumor growth *in vivo*, while G6PD O-GlcNAcylation promotes the proliferation and tumor growth of these cells. This highlights that the upregulation of G6PD in LUAD may serve as a new target for LUAD treatment (79). G6PD has also been indicated to regulate ferroptosis through an NADPH-dependent mechanism, while NADPH also affects the disulfide bond formation process (71). A reduction in NADPH levels triggers the formation of disulfide bonds between actin and the cytoskeleton proteins and the contraction of F-actin, which are key steps leading to disulfide death (80).

The classical molecular subtypes of breast cancer include luminal, HER2 and basal subtypes, which have different prognostic characteristics and drug sensitivities (81). A study identified that NADH:ubiquinone oxidoreductase core unit S1 (NDUFS1), leucine rich pentatricopeptide repeat containing (LRPPRC) and SLC7A11 are differentially expressed and have prognostic value for disulfide death in breast cancer by screening The Cancer Genome Atlas (TCGA) data and the GSE86166 dataset (72). NDUFS1 is the initiating enzyme of the mitochondrial respiratory chain, which is responsible for electron transfer from NADH to coenzyme Q10 and for the

translocation coupling of protons from the matrix to the intermembrane space (82). It is the largest core subunit encoded by nuclear genes, and is part of the eight iron-sulfur clusters that are responsible for the oxidation of NADH (83).

LRPPRC is a leucine-rich PPR motif protein that regulates gene expression at the transcriptional and post-transcriptional levels by binding to target RNAs. It contributes to RNA stabilization, regulation, processing, splicing, translation and editing (84). As a multifunctional protein, LRPPRC regulates energy metabolism and is involved the maturation and stability of nuclear-encoded mRNA, as well as cellular oxidative phosphorylation. It also plays a role in the regulation of signaling pathways and mitochondrial function (84). Mitochondria are important for NADPH synthesis and the regulation of disulfide bond stress; thus, the functional state of mitochondria may be closely associated with the onset and progression of disulfide toxicity. LRPPRC deficiency reduces the stability of mitochondrial mRNAs, resulting in the loss of polyadenylation of these mRNAs and abnormalities in mitochondrial translational (85).

NDUFS1 plays a key role in the mitochondrial fusion pathway. Mitochondrial fusion is an endogenous protective process for mitochondrial quality control and the maintenance of mitochondrial homeostasis and function (86,87). NDUFS1 is the largest core subunit in respiratory chain complex I, and the reduced expression of this subunit leads to reduced homeostasis of respiratory chain complex I and mitochondrial dysfunction (88). It has been demonstrated that significantly reduced levels of LRPPRC and NDUFS1 in ulcerative colitis may disrupt the homeostasis of the relevant subunits from respiratory chain complexes IV and I, causing the respiratory electron transport chain to become dysfunctional and ultimately inhibiting NADPH production and the reduction of disulfide bonds, thereby promoting disulfide death (85).

The LRPPRC gene has been found to be upregulated in a variety of human malignancies, and this upregulation is closely associated with a poor prognosis (89,90). LRPPRC has also been demonstrated to serve as an independent prognostic factor in hepatocellular carcinoma (91). The downregulation of LRPPRC induces apoptosis in cancer cells and reduces their invasive ability, suggesting that LRPPRC may be a promising biomarker and potential molecular target for cancer treatment (84). It has been shown that LRPPRC and NDUFS1 are resistant to disulfide death and that their inactivation synergizes with glucose starvation and regulation of the energy metabolism of NADPH to induce cell death (30). LRPPRC and NDUFS1 have both been observed to be significantly downregulated in breast cancer, and it has been suggested that they may have a notable synergistic role in the induction of disulfide death in breast cancer (92).

Studies of genes associated with disulfide death in gastric cancer have identified that apolipoprotein D (APOD) and NCKAP1 are potential therapeutic targets for this disease (93,94). The NCKAP1 protein is a component of the WAVE complex, along with Abl interactor 1 and 2, BRICK1, cytoplasmic FMR1 interacting proteins 1 and 2, and WASP family members 1 and 2. NCKAP1 deletion has been shown to affect actin nucleation in fibroblast laminar pseudopod formation by affecting the spreading and focal adhesion dynamics of cells, suggesting a role for NCKAP1 in cell migration (95). In addition, NCKAP1 is involved in the formation of the actin network, and has been shown to be a key gene in disulfide death, which regulates a variety of processes such as apoptosis, migration and invasion, and serves a crucial role in pathogenesis (94).

APOD is one of the 22 members of the human APO family, encoded by a gene located on human chromosome 3 (96). APOD is involved in the inflammatory response and lipid metabolism, and plays an important role in a number of cancers (97). For instance, high APOD expression has been shown to be associated with shorter overall survival and recurrence-free survival in patients with non-small cell lung cancer (98). Studies have also shown that elevated expression of APOD in cancer of the breast and central nervous system is closely associated with highly differentiated, non-invasive and non-metastatic cancers, and that APOD reduces the osteopontin-mediated adhesion, invasiveness and proliferation of Rama37 breast cancer cells *in vitro* (99-101). However, APOD has been suggested to be an independent predictor of metastasis-free survival and overall survival in patients with invasive breast cancer, with increased APOD expression being associated with a poor prognosis (102). In gastric cancer, bioinformatics analyses have been used to indicate that APOD may be included as a component of genetic risk models for disulfide death, and is associated with an increased tumor mutational load and immune cell infiltration (103-105). In addition, positive correlations have been identified for APOD with macrophage infiltration and the Wnt signaling pathway in stomach cancer as evaluated by the analysis of CD68 and Wnt family member 2B, respectively (106). In addition to its involvement in the immune response, APOD is also a marker of hypoxia, which has a fundamental role in the immune microenvironment of tumors (107,108). Bioinformatics analysis has also indicated that APOD expression is positively associated with cancer-associated fibroblasts, endothelial cells and hematopoietic stem cells in most cancers, but negatively associated with myeloid-derived suppressor cells. It is hypothesized that APOD may affect formation of the actin cytoskeleton, subsequently influencing the collapse of the cytoskeleton during disulfide death (109).

A study of glioblastoma identified three genes that were significantly associated with disulfide death in this type of cancer, namely LRPPRC, ribophorin I (RPN1) and glycogen synthase 1 (GYS1). These three genes were demonstrated to be located in the mitochondria, cytosol and microtubules, respectively, of U-251MG glioblastoma cells (110). TCGA glioma dataset analysis revealed that LRPPRC is downregulated in glioma, whereas RPN1 and GYS1 are upregulated. In addition, a Kaplan-Meier survival analysis showed that high LRPPRC expression was positively associated with a good prognosis while the high expression of RPN1 and GYS1 was positively associated with a poor prognosis in patients with glioma (110). RPN1 contributes to protein synthesis and glycoprotein formation in the ER (111,112). It acts as a receptor and regulator of protein translocation in the ER, helping to direct and anchor nascent proteins to the ER membrane, thereby facilitating their proper folding and glycan modification (113). In a study aiming to evaluate RPN1 as a pan-cancer marker, wild-type (WT) and RPN1 knockout (KO) MDA-MB-231 breast cancer and A549 lung cancer cells cultured in glucose-containing or -deficient

medium were analyzed by flow cytometry to evaluate cell death. In addition, F-actin in the cells was immunofluorescently labeled to visualize changes in the actin cytoskeleton under different glucose conditions. The results indicated that cell death and cytoskeletal breakdown occurred under glucose deprivation. This cytoskeletal breakdown was inhibited in RPN1 KO cells, suggesting that RPN1 mediates cell death through the degradation of cytoskeletal proteins. In addition, protein extraction and western blotting analyses performed using non-reducing and reducing methods indicated that when these cells are deprived of glucose, RPN1 KO contributes to the stabilization of cytoskeletal proteins. This suggests that RPN1 deletion promotes cytoskeletal integrity. These findings suggest that RPN1 plays a role in the mediation of disulfide death in breast and lung cancer, possibly through a mechanism involving the induction of cytoskeletal protein degradation (114). It is possible that this pathway may also be associated with disulfide death in glioblastoma. GYS1 is the most important rate-limiting enzyme in the last step of glycogen synthesis (115). A lack of GYS1 has been shown to cause type 0 myoglycogen storage disease that may lead to death (116,117). GYS1 is rapidly induced under hypoxic conditions and is positively associated with the accumulation of glycogen in glioblastoma (118). A hypoxic environment is favorable for the growth, development and infiltration of tumors, and the upregulation of hypoxia-induced factors has been verified as a basic pathway in most tumors (119). Notably, glycogen metabolism is a metabolic pathway that is upregulated by hypoxia (120). Carbon and sulfur from glycogen breakdown can enter the PPP and contribute to the production of NADPH, which serves as a reducing agent to scavenge ROS and maintain immune cell survival (121). GSH and thioredoxin are two major cellular antioxidants that scavenge intracellular ROS and rely on NADPH, produced via the PPP, as an electron donor. Therefore, it may be hypothesized that GYS1 regulates disulfide death by influencing the production of NADPH by the PPP.

In summary, the current literature supports that disulfide death occurs in tumors, and G6PD, LRPPRC, SLC7A11, APOD, NCKAP1, RPN1 and GYS1 have been demonstrated to serve as predictive target genes in different tumor types. Among these, SLC7A11 serves as a key link to disulfide death and is also a promising target for research in a variety of cancer types.

5. Summary and outlook

In summary, cell death is known to progress via various processes, including apoptosis and necrosis, as well as ferroptosis, copper-induced death and disulfide death. While cellular respiration in the form of oxidative phosphorylation is not essential for all cells, tumor cells commonly rely on the Warburg effect, an alternative pathway. In disulfide death, blocking the PPP prevents the supply of NADPH, resulting in the abnormal accumulation of disulfide bonds, which ultimately leads to cell death. Tumor cells require the glycolysis pathway to supply energy for survival, which can be inhibited by GLUT inhibitors to impede tumor growth. Among the solid tumors studied to date, most of the genes on disulfide death are associated with mitochondrial regulation, and respiratory chain 1 occupies an important role in mitochondria. SLC7A11 is a key channel protein associated with disulfide death, and also serves as a therapeutic target for tumor cells. The expression of SLC7A11 has been found to be downregulated in ferroptosis and upregulated in disulfide death, suggesting a certain association between the two mechanisms. Potential means of regulating the relationship between these mechanisms and identifying a suitable target in tumor cells merit exploration in future studies.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

XL conceptualized and designed the article, conducted the literature search and chart preparation and wrote the manuscript. DZ reviewed the manuscript and supervised the study. Data authentication is not applicable. Both authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Kerr JF, Wyllie AH and Currie AR: Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 26: 239-257, 1972.
2. Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, Alnemri ES, Altucci L, Amelio I, Andrews DW, *et al*: Molecular mechanisms of cell death: Recommendations of the Nomenclature Committee on Cell Death 2018. Cell Death Differ 25: 486-541, 2018.
3. Jiang X, Stockwell BR and Conrad M: Ferroptosis: Mechanisms, biology and role in disease. Nat Rev Mol Cell Biol 22: 266-282, 2021.
4. Tsvetkov P, Coy S, Petrova B, Dreishpoon M, Verma A, Abdusamad M, Rossen J, Joesch-Cohen L, Humeidi R, Spangler RD, *et al*: Copper induces cell death by targeting lipoylated TCA cycle proteins. Science 375: 1254-1261, 2022.
5. Liu X, Zhuang L and Gan B: Disulfidptosis: Disulfide stress-induced cell death. Trends Cell Biol 34: 327-337, 2024.
6. Ravilious GE and Jez JM: Structural biology of plant sulfur metabolism: from assimilation to biosynthesis. Nat Prod Rep 29: 1138-1152, 2012.
7. Wanders D, Hobson K and Ji X: Methionine restriction and cancer biology. Nutrients 12: 684, 2020.

8. Kaplowitz N, Aw TY and Ookhtens M: The regulation of hepatic glutathione. Annu Rev Pharmacol Toxicol 25: 715-744, 1985.
9. Lu SC: Glutathione synthesis. Biochim Biophys Acta 1830: 3143-3153, 2013.
10. Diotallevi M, Checconi P, Palamara AT, Celestino I, Coppo L, Holmgren A, Abbas K, Peyrot F, Mengozzi M and Ghezzi P: Glutathione Fine-Tunes the Innate Immune Response toward Antiviral Pathways in a Macrophage Cell Line Independently of Its Antioxidant Properties. Front Immunol 8: 1239, 2017.
11. Chen YJ, Lu CT, Lee TY and Chen YJ: dbGSH: A database of S-glutathionylation. Bioinformatics 30: 2386-2388, 2014.
12. Lermant A and Murdoch CE: Cysteine Glutathionylation Acts as a Redox Switch in Endothelial Cells. Antioxidants (Basel) 8: 315, 2019.
13. Kurniawan H, Franchina DG, Guerra L, Bonetti L, -Baguet LS, Grusdat M, Schlicker L, Hunewald O, Dostert C, Merz MP, *et al*: Glutathione Restricts Serine Metabolism to Preserve Regulatory T Cell Function. Cell Metab 31: 920-936.e7, 2020.
14. Gai X, Liu Y, Lan X, Chen L, Yuan T, Xu J, Li Y, Zheng Y, Yan Y, Yang L, *et al*: Oncogenic KRAS induces arginine auxotrophy and confers a therapeutic vulnerability to SLC7A1 inhibition in non-small cell lung cancer. Cancer Res 84: 1963-1977, 2024.
15. You S, Zhu X, Yang Y, Du X, Song K, Zheng Q, Zeng P and Yao Q: SLC7A1 overexpression is involved in energy metabolism reprogramming to induce tumor progression in epithelial ovarian cancer and is associated with immune-infiltrating cells. J Oncol 2022: 5864826, 2022.
16. Shen C and Wang Y: Ferroptosis biomarkers for predicting prognosis and immunotherapy efficacy in adrenocortical carcinoma. Arch Med Res 54: 45-55, 2023.
17. Lei S, Chen C, Han F, Deng J, Huang D, Qian L, Zhu M, Ma X, Lai M, Xu E and Zhang H: AMER1 deficiency promotes the distant metastasis of colorectal cancer by inhibiting SLC7A11- and FTL-mediated ferroptosis. Cell Rep 42: 113110, 2023.
18. Ouyang S, Li H, Lou L, Huang Q, Zhang Z, Mo J, Li M, Lu J, Zhu K, Chu Y, *et al*: Inhibition of STAT3-ferroptosis negative regulatory axis suppresses tumor growth and alleviates chemoresistance in gastric cancer. Redox Biol 52: 102317, 2022.
19. Yang J, Zhou Y, Xie S, Wang J, Li Z, Chen L, Mao M, Chen C, Huang A, Chen Y, *et al*: Metformin induces Ferroptosis by inhibiting UFMylation of SLC7A11 in breast cancer. J Exp Clin Cancer Res 40: 206, 2021.
20. Wang Z, Shen N, Wang Z, Yu L, Yang S, Wang Y, Liu Y, Han G and Zhang Q: TRIM3 facilitates ferroptosis in non-small cell lung cancer through promoting SLC7A11/xCT K11-linked ubiquitination and degradation. Cell Death Differ 31: 53-64, 2024.
21. Koppula P, Zhuang L and Gan B: Cystine transporter SLC7A11/xCT in cancer: ferroptosis, nutrient dependency, and cancer therapy. Protein Cell 12: 599-620, 2021.
22. Koppula P, Zhang Y, Zhuang L and Gan B: Amino acid transporter SLC7A11/xCT at the crossroads of regulating redox homeostasis and nutrient dependency of cancer. Cancer Commun (Lond) 38: 12, 2018.
23. Wang L, Liu Y, Du T, Yang H, Lei L, Guo M, Ding HF, Zhang J, Wang H, Chen X and Yan C: ATF3 promotes erastin-induced ferroptosis by suppressing system Xc. Cell Death Differ 27: 662-675, 2020.
24. Xiao H, Jedrychowski MP, Schweppe DK, Huttlin EL, Yu Q, Heppner DE, Li J, Long J, Mills EL, Szpyt J, *et al*: A Quantitative Tissue-Specific Landscape of Protein Redox Regulation during Aging. Cell 180: 968-983.e4, 2020.
25. Musaogullari A and Chai YC: Redox Regulation by Protein S-Glutathionylation: From Molecular Mechanisms to Implications in Health and Disease. Int J Mol Sci 21: 8113, 2020.
26. Machesky LM: Deadly actin collapse by disulfidptosis. Nat Cell Biol 25: 375-376, 2023.
27. Yan Y, Teng H, Hang Q, Kondiparthi L, Lei G, Horbath A, Liu X, Mao C, Wu S, Zhuang L, *et al*: SLC7A11 expression level dictates differential responses to oxidative stress in cancer cells. Nat Commun 14: 3673, 2023.
28. Xia N, Guo X, Guo Q, Gupta N, Ji N, Shen B, Xiao L and Feng Y: Metabolic flexibilities and vulnerabilities in the pentose phosphate pathway of the zoonotic pathogen Toxoplasma gondii. PLoS Pathog 18: e1010864, 2022.
29. El Mjiyad N, Caro-Maldonado A, Ramírez-Peinado S and Muñoz-Pinedo C: Sugar-free approaches to cancer cell killing. Oncogene 30: 253-264, 2011.
30. Liu X, Nie L, Zhang Y, Yan Y, Wang C, Colic M, Olszewski K, Horbath A, Chen X, Lei G, *et al*: Actin cytoskeleton vulnerability to disulfide stress mediates disulfidptosis. Nat Cell Biol 25: 404-414, 2023.
31. Chen J, Ma B, Yang Y, Wang B, Hao J and Zhou X: Disulfidptosis decoded: A journey through cell death mysteries, regulatory networks, disease paradigms and future directions. Biomark Res 12: 45, 2024.
32. Fregoso FE, van Eeuwen T, Simanov G, Rebowski G, Boczkowska M, Zimmet A, Gautreau AM and Dominguez R: Molecular mechanism of Arp2/3 complex inhibition by Arpin. Nat Commun 13: 628, 2022.
33. Wicks EE and Semenza GL: Hypoxia-inducible factors: Cancer progression and clinical translation. J Clin Invest 132: e159839, 2022.
34. Rozpedek W, Pytel D, Mucha B, Leszczynska H, Diehl JA and Majsterek I: The Role of the PERK/eIF2α/ATF4/CHOP signaling pathway in tumor progression during endoplasmic reticulum stress. Curr Mol Med 16: 533-544, 2016.
35. Zhang Y, Lin C, Liu Z, Sun Y, Chen M, Guo Y, Liu W, Zhang C, Chen W, Sun J, *et al*: Cancer cells co-opt nociceptive nerves to thrive in nutrient-poor environments and upon nutrient-starvation therapies. Cell Metab 34: 1999-2017.e10, 2022.
36. Ma Y, Temkin SM, Hawkridge AM, Guo C, Wang W, Wang XY and Fang X: Fatty acid oxidation: An emerging facet of metabolic transformation in cancer. Cancer Lett 435: 92-100, 2018.
37. Wang L, Cai H, Hu Y, Liu F, Huang S, Zhou Y, Yu J, Xu J and Wu F: A pharmacological probe identifies cystathionine β-synthase as a new negative regulator for ferroptosis. Cell Death Dis 9: 1005, 2018.
38. Tang H, Kang R, Liu J and Tang D: ATF4 in cellular stress, ferroptosis, and cancer. Arch Toxicol 98: 1025-1041, 2024.
39. Jessen C, Kreß JKC, Baluapuri A, Hufnagel A, Schmitz W, Kneitz S, Roth S, Marquardt A, Appenzeller S, Ade CP, *et al*: The transcription factor NRF2 enhances melanoma malignancy by blocking differentiation and inducing COX2 expression. Oncogene 39: 6841-6855, 2020.
40. DeNicola GM, Chen PH, Mullarky E, Sudderth JA, Hu Z, Wu D, Tang H, Xie Y, Asara JM, Huffman KE, *et al*: NRF2 regulates serine biosynthesis in non-small cell lung cancer. Nat Genet 47: 1475-1481, 2015.
41. Gwinn DM, Lee AG, Briones-Martin-Del-Campo M, Conn CS, Simpson DR, Scott AI, Le A, Cowan TM, Ruggero D and Sweet-Cordero EA: Oncogenic KRAS Regulates Amino Acid Homeostasis and Asparagine Biosynthesis via ATF4 and Alters Sensitivity to L-Asparaginase. Cancer Cell 33: 91-107.e6, 2018.
42. Kreß JKC, Jessen C, Hufnagel A, Schmitz W, Xavier da Silva TN, Ferreira Dos Santos A, Mosteo L, Goding CR, Friedmann Angeli JP and Meierjohann S: The integrated stress response effector ATF4 is an obligatory metabolic activator of NRF2. Cell Rep 42: 112724, 2023.
43. Wang Y, Ali M, Zhang Q, Sun Q, Ren J, Wang W, Tang D and Wang D: ATF4 transcriptionally activates SHH to promote proliferation, invasion, and migration of gastric cancer cells. Cancers (Basel) 15: 1429, 2023.
44. Kang L, Wang D, Shen T, Liu X, Dai B, Zhou D, Shen H, Gong J, Li G, Hu Y, *et al*: PDIA4 confers resistance to ferroptosis via induction of ATF4/SLC7A11 in renal cell carcinoma. Cell Death Dis 14: 193, 2023.
45. Wang Z, Zhang H and Cheng Q: PDIA4: The basic characteristics, functions and its potential connection with cancer. Biomed Pharmacother 122: 109688, 2020.
46. Lee CH, Chiang CF, Lin FH, Kuo FC, Su SC, Huang CL, Li PF, Liu JS, Lu CH, Hsieh CH, *et al*: PDIA4, a new endoplasmic reticulum stress protein, modulates insulin resistance and inflammation in skeletal muscle. Front Endocrinol (Lausanne) 13: 1053882, 2022.
47. Gao R, Kalathur RKR, Coto-Llerena M, Ercan C, Buechel D, Shuang S, Piscuoglio S, Dill MT, Camargo FD, Christofori G and Tang F: YAP/TAZ and ATF4 drive resistance to Sorafenib in hepatocellular carcinoma by preventing ferroptosis. EMBO Mol Med 13: e14351, 2021.
48. Chen D, Fan Z, Rauh M, Buchfelder M, Eyupoglu IY and Savaskan N: ATF4 promotes angiogenesis and neuronal cell death and confers ferroptosis in a xCT-dependent manner. Oncogene 36: 5593-5608, 2017.
49. Sasaki H, Sato H, Kuriyama-Matsumura K, Sato K, Maebara K, Wang H, Tamba M, Itoh K, Yamamoto M and Bannai S: Electrophile response element-mediated induction of the cystine/glutamate exchange transporter gene expression. J Biol Chem 277: 44765-44771, 2002.

50. Dixon SJ, Patel DN, Welsch M, Skouta R, Lee ED, Hayano M, Thomas AG, Gleason CE, Tatonetti NP, Slusher BS and Stockwell BR: Pharmacological inhibition of cystine-glutamate exchange induces endoplasmic reticulum stress and ferroptosis. Elife 3: e02523, 2014.
51. Miki H, Suetsugu S and Takenawa T: WAVE, a novel WASP-family protein involved in actin reorganization induced by Rac. EMBO J 17: 6932-6941, 1998.
52. Steffen A, Rottner K, Ehinger J, Innocenti M, Scita G, Wehland J and Stradal TE: Sra-1 and Nap1 link Rac to actin assembly driving lamellipodia formation. EMBO J 23: 749-759, 2004.
53. Kage F, Döring H, Mietkowska M, Schaks M, Grüner F, Stahnke S, Steffen A, Müsken M, Stradal TEB and Rottner K: Lamellipodia-like actin networks in cells lacking WAVE regulatory complex. J Cell Sci 135: jcs260364, 2022.
54. Rotty JD, Wu C and Bear JE: New insights into the regulation and cellular functions of the ARP2/3 complex. Nat Rev Mol Cell Biol 14: 7-12, 2013.
55. Alekhina O, Burstein E and Billadeau DD: Cellular functions of WASP family proteins at a glance. J Cell Sci 130: 2235-2241, 2017.
56. Ibarra N, Pollitt A and Insall RH: Regulation of actin assembly by SCAR/WAVE proteins. Biochem Soc Trans 33: 1243-1246, 2005.
57. Zhu A, Zong Y, Wei S, Li Y, Fan Y, Liu S and Gao X: Pan-cancer Analysis of the Disulfidptosis-related Gene NCKAP1 and Its Prognostic Value for Lung Adenocarcinoma. J Cancer 14: 3351-3367, 2023.
58. Tang H, Li A, Bi J, Veltman DM, Zech T, Spence HJ, Yu X, Timpson P, Insall RH, Frame MC and Machesky LM: Loss of Scar/WAVE complex promotes N-WASP- and FAK-dependent invasion. Curr Biol 23: 107-117, 2013.
59. Koppula P, Olszewski K, Zhang Y, Kondiparthi L, Liu X, Lei G, Das M, Fang B, Poyurovsky MV and Gan B: KEAP1 deficiency drives glucose dependency and sensitizes lung cancer cells and tumors to GLUT inhibition. iScience 24: 102649, 2021.
60. Xu K, Zhang Y, Yan Z, Wang Y, Li Y, Qiu Q, Du Y, Chen Z and Liu X: Identification of disulfidptosis related subtypes, characterization of tumor microenvironment infiltration, and development of DRG prognostic prediction model in RCC, in which MSH3 is a key gene during disulfidptosis. Front Immunol 14: 1205250, 2023.
61. Sakellariou D, Bak ST, Isik E, Barroso SI, Porro A, Aguilera A, Bartek J, Janscak P and Peña-Diaz J: MutSβ regulates G4-associated telomeric R-loops to maintain telomere integrity in ALT cancer cells. Cell Rep 39: 110602, 2022.
62. Siebeneicher H, Cleve A, Rehwinkel H, Neuhaus R, Heisler I, Müller T, Bauser M and Buchmann B: Identification and optimization of the first highly selective GLUT1 Inhibitor BAY-876. ChemMedChem 11: 2261-2271, 2016.
63. Olszewski K, Barsotti A, Feng XJ, Momcilovic M, Liu KG, Kim JI, Morris K, Lamarque C, Gaffney J, Yu X, *et al*: Inhibition of glucose transport synergizes with chemical or genetic disruption of mitochondrial metabolism and suppresses TCA cycle-deficient tumors. Cell Chem Biol 29: 423-435.e10, 2022.
64. Li Y, Tang M, Dang W, Zhu S and Wang Y: Identification of disulfidptosis-related subtypes, characterization of tumor microenvironment infiltration, and development of a prognosis model in colorectal cancer. J Cancer Res Clin Oncol 149: 13995-14014, 2023.
65. Vander Heiden MG, Cantley LC and Thompson CB: Understanding the Warburg effect: The metabolic requirements of cell proliferation. Science 324: 1029-1033, 2009.
66. Shriwas P, Roberts D, Li Y, Wang L, Qian Y, Bergmeier S, Hines J, Adhicary S, Nielsen C and Chen X: A small-molecule pan-class I glucose transporter inhibitor reduces cancer cell proliferation in vitro and tumor growth in vivo by targeting glucose-based metabolism. Cancer Metab 9: 14, 2021.
67. Chang CK, Chiu PF, Yang HY, Juang YP, Lai YH, Lin TS, Hsu LC, Yu LC and Liang PH: Targeting colorectal cancer with conjugates of a glucose transporter inhibitor and 5-fluorouracil. J Med Chem 64: 4450-4461, 2021.
68. Zhang Y, Koppula P and Gan B: Regulation of H2A ubiquitination and SLC7A11 expression by BAP1 and PRC1. Cell Cycle 18: 773-783, 2019.
69. Zhang Y, Shi J, Liu X, Feng L, Gong Z, Koppula P, Sirohi K, Li X, Wei Y, Lee H, *et al*: BAP1 links metabolic regulation of ferroptosis to tumour suppression. Nat Cell Biol 20: 1181-1192, 2018.
70. Zhao M, Xu C and Zhu H: Efficacy of glucose transporter inhibitors for the treatment of ERRα-overexpressed colorectal cancer. Acta Biochim Pol 69: 567-572, 2022.
71. Qi C, Ma J, Sun J, Wu X and Ding J: The role of molecular subtypes and immune infiltration characteristics based on disulfidptosis-associated genes in lung adenocarcinoma. Aging (Albany NY) 15: 5075-5095, 2023.
72. Xia Q, Yan Q, Wang Z, Huang Q, Zheng X, Shen J, Du L, Li H and Duan S: Disulfidptosis-associated lncRNAs predict breast cancer subtypes. Sci Rep 13: 16268, 2023.
73. Zhao J, Luo Z, Fu R, Zhou J, Chen S, Wang J, Chen D and Xie X: Disulfidptosis-related signatures for prognostic and immunotherapy reactivity evaluation in hepatocellular carcinoma. Eur J Med Res 28: 571, 2023.
74. Yang HC, Wu YH, Yen WC, Liu HY, Hwang TL, Stern A and Chiu DT: The Redox Role of G6PD in Cell Growth, Cell Death, and Cancer. Cells 8: 1055, 2019.
75. Liberti MV and Locasale JW: The Warburg Effect: How does it benefit cancer cells? Trends Biochem Sci 41: 211-218, 2016.
76. Patra KC and Hay N: The pentose phosphate pathway and cancer. Trends Biochem Sci 39: 347-354, 2014.
77. Hart GW, Housley MP and Slawson C: Cycling of O-linked beta-N-acetylglucosamine on nucleocytoplasmic proteins. Nature 446: 1017-1022, 2007.
78. Chen L, Zhang Z, Hoshino A, Zheng HD, Morley M, Arany Z and Rabinowitz JD: NADPH production by the oxidative pentose-phosphate pathway supports folate metabolism. Nat Metab 1: 404-415, 2019.
79. Rao X, Duan X, Mao W, Li X, Li Z, Li Q, Zheng Z, Xu H, Chen M, Wang PG, *et al*: O-GlcNAcylation of G6PD promotes the pentose phosphate pathway and tumor growth. Nat Commun 6: 8468, 2015.
80. Liu X, Zhang Y, Zhuang L, Olszewski K and Gan B: NADPH debt drives redox bankruptcy: SLC7A11/xCT-mediated cystine uptake as a double-edged sword in cellular redox regulation. Genes Dis 8: 731-745, 2020.
81. Holm J, Eriksson L, Ploner A, Eriksson M, Rantalainen M, Li J, Hall P and Czene K: Assessment of breast cancer risk factors reveals subtype heterogeneity. Cancer Res 77: 3708-3717, 2017.
82. Ni Y, Hagras MA, Konstantopoulou V, Mayr JA, Stuchebrukhov AA and Meierhofer D: Mutations in ndufs1 cause metabolic reprogramming and disruption of the electron transfer. Cells 8: 1149, 2019.
83. Zhu J, Vinothkumar KR and Hirst J: Structure of mammalian respiratory complex I. Nature 536: 354-358, 2016.
84. Cui J, Wang L, Ren X, Zhang Y and Zhang H: LRPPRC: A multifunctional protein involved in energy metabolism and human disease. Front Physiol 10: 595, 2019.
85. Song H, Zhang F, Bai X, Liang H, Niu J and Miao Y: Comprehensive analysis of disulfidptosis-related genes reveals the effect of disulfidptosis in ulcerative colitis. Sci Rep 14: 15705, 2024.
86. Tilokani L, Nagashima S, Paupe V and Prudent J: Mitochondrial dynamics: Overview of molecular mechanisms. Essays Biochem 62: 341-360, 2018.
87. Youle RJ and van der Bliek AM: Mitochondrial fission, fusion, and stress. Science 337: 1062-1065, 2012.
88. Wan S, Maitiabula G, Wang P, Zhang Y, Gao X, Zhang L, Gao T and Wang X: Down regulation of NDUFS1 is involved in the progression of parenteral-nutrition-associated liver disease by increasing Oxidative stress. J Nutr Biochem 112: 109221, 2023.
89. Yang Y, Yuan H, Zhao L, Guo S, Hu S, Tian M, Nie Y, Yu J, Zhou C, Niu J, *et al*: Targeting the miR-34a/LRPPRC/MDR1 axis collapse the chemoresistance in P53 inactive colorectal cancer. Cell Death Differ 29: 2177-2189, 2022.
90. Wei WS, Wang N, Deng MH, Dong P, Liu JY, Xiang Z, Li XD, Li ZY, Liu ZH, Peng YL, *et al*: LRPPRC regulates redox homeostasis via the circANKHD1/FOXM1 axis to enhance bladder urothelial carcinoma tumorigenesis. Redox Biol 48: 102201, 2021.
91. Yang L, Zhang W and Yan Y: Identification and characterization of a novel molecular classification based on disulfidptosis-related genes to predict prognosis and immunotherapy efficacy in hepatocellular carcinoma. Aging (Albany NY) 15: 6135-6151, 2023.
92. Zeng M, Wu B, Wei W, Jiang Z, Li P, Quan Y and Hu X: Disulfiram: A novel repurposed drug for cancer therapy. Chin Med J (Engl) 137: 1389-1398, 2024.
93. Li Q and Yin LK: Comprehensive analysis of disulfidptosis related genes and prognosis of gastric cancer. World J Clin Oncol 14: 373-399, 2023.

94. Yan J, Fang Z, Shi M, Tu C, Zhang S, Jiang C, Li Q and Shao Y: Clinical Significance of Disulfidptosis-related Genes and Functional Analysis in Gastric Cancer. J Cancer 15: 1053-1066, 2024.
95. Whitelaw JA, Swaminathan K, Kage F and Machesky LM: The WAVE Regulatory Complex Is Required to Balance Protrusion and Adhesion in Migration. Cells 9: 1635, 2020.
96. Drayna DT, McLean JW, Wion KL, Trent JM, Drabkin HA and Lawn RM: Human apolipoprotein D gene: Gene sequence, chromosome localization, and homology to the alpha 2u-globulin superfamily. DNA 6: 199-204, 1987.
97. Ren L, Yi J, Li W, Zheng X, Liu J, Wang J and Du G: Apolipoproteins and cancer. Cancer Med 8: 7032-7043, 2019.
98. Cury SS, de Moraes D, Freire PP, de Oliveira G, Marques DVP, Fernandez GJ, Dal-Pai-Silva M, Hasimoto ÉN, Dos Reis PP, Rogatto SR and Carvalho RF: Tumor Transcriptome Reveals High Expression of IL-8 in Non-Small Cell Lung Cancer Patients with Low Pectoralis Muscle Area and Reduced Survival. Cancers (Basel) 11: 1251, 2019.
99. Hunter S, Young A, Olson J, Brat DJ, Bowers G, Wilcox JN, Jaye D, Mendrinos S and Neish A: Differential expression between pilocytic and anaplastic astrocytomas: Identification of apolipoprotein D as a marker for low-grade, non-infiltrating primary CNS neoplasms. J Neuropathol Exp Neurol 61: 275-281, 2002.
100. Porter D, Lahti-Domenici J, Keshaviah A, Bae YK, Argani P, Marks J, Richardson A, Cooper A, Strausberg R, Riggins GJ, *et al*: Molecular markers in ductal carcinoma in situ of the breast. Mol Cancer Res 1: 362-375, 2003.
101. Jin D, El-Tanani M and Campbell FC: Identification of apolipoprotein D as a novel inhibitor of osteopontin-induced neoplastic transformation. Int J Oncol 29: 1591-1599, 2006.
102. Jankovic-Karasoulos T, Bianco-Miotto T, Butler MS, Butler LM, McNeil CM, O'Toole SA, Millar EKA, Sakko AJ, Ruiz AI, Birrell SN, *et al*: Elevated levels of tumour apolipoprotein D independently predict poor outcome in breast cancer patients. Histopathology 76: 976-987, 2020.
103. Yu J, Zhang Q, Wang M, Liang S, Huang H, Xie L, Cui C and Yu J: Comprehensive analysis of tumor mutation burden and immune microenvironment in gastric cancer. Biosci Rep 41: BSR20203336, 2021.
104. Guo X, Liang X, Wang Y, Cheng A, Zhang H, Qin C and Wang Z: Significance of Tumor Mutation Burden Combined With Immune Infiltrates in the Progression and Prognosis of Advanced Gastric Cancer. Front Genet 12: 642608, 2021.
105. Huo J, Wu L and Zang Y: Construction and Validation of a Universal Applicable Prognostic Signature for Gastric Cancer Based on Seven Immune-Related Gene Correlated With Tumor Associated Macrophages. Front Oncol 11: 635324, 2021.
106. Khan M, Lin J, Wang B, Chen C, Huang Z, Tian Y, Yuan Y and Bu J: A novel necroptosis-related gene index for predicting prognosis and a cold tumor immune microenvironment in stomach adenocarcinoma. Front Immunol 13: 968165, 2022.
107. Beemelmanns A, Zanuzzo FS, Xue X, Sandrelli RM, Rise ML and Gamperl AK: The transcriptomic responses of Atlantic salmon (Salmo salar) to high temperature stress alone, and in combination with moderate hypoxia. BMC Genomics 22: 261, 2021.
108. Shida M, Kitajima Y, Nakamura J, Yanagihara K, Baba K, Wakiyama K and Noshiro H: Impaired mitophagy activates mtROS/HIF-1α interplay and increases cancer aggressiveness in gastric cancer cells under hypoxia. Int J Oncol 48: 1379-1390, 2016.
109. Wang Z, Chen H, Sun L, Wang X, Xu Y, Tian S and Liu X: Uncovering the potential of APOD as a biomarker in gastric cancer: A retrospective and multi-center study. Comput Struct Biotechnol J 23: 1051-1064, 2024.
110. Wang X, Yang J, Yang F and Mu K: The disulfidptosis-related signature predicts prognosis and immune features in glioma patients. Sci Rep 13: 17988, 2023.
111. Ding J, Xu J, Deng Q, Ma W, Zhang R, He X, Liu S and Zhang L: Knockdown of Oligosaccharyltransferase Subunit Ribophorin 1 Induces Endoplasmic-Reticulum-Stress-Dependent Cell Apoptosis in Breast Cancer. Front Oncol 11: 722624, 2021.
112. Qin SY, Hu D, Matsumoto K, Takeda K, Matsumoto N, Yamaguchi Y and Yamamoto K: Malectin forms a complex with ribophorin I for enhanced association with misfolded glycoproteins. J Biol Chem 287: 38080-38089, 2012.
113. Wilson CM, Roebuck Q and High S: Ribophorin I regulates substrate delivery to the oligosaccharyltransferase core. Proc Natl Acad Sci USA 105: 9534-9539, 2008.
114. Wang X, Zhu HQ, Lin SM, Xia BY and Xu B: RPN1: A pan-cancer biomarker and disulfidptosis regulator. Transl Cancer Res 13: 2518-2534, 2024.
115. López-Ramos JC, Duran J, Gruart A, Guinovart JJ and Delgado-García JM: Role of brain glycogen in the response to hypoxia and in susceptibility to epilepsy. Front Cell Neurosci 9: 431, 2015.
116. Cameron JM, Levandovskiy V, MacKay N, Utgikar R, Ackerley C, Chiasson D, Halliday W, Raiman J and Robinson BH: Identification of a novel mutation in GYS1 (muscle-specific glycogen synthase) resulting in sudden cardiac death, that is diagnosable from skin fibroblasts. Mol Genet Metab 98: 378-382, 2009.
117. Pederson BA, Chen H, Schroeder JM, Shou W, DePaoli-Roach AA and Roach PJ: Abnormal cardiac development in the absence of heart glycogen. Mol Cell Biol 24: 7179-7187, 2004.
118. Favaro E, Bensaad K, Chong MG, Tennant DA, Ferguson DJ, Snell C, Steers G, Turley H, Li JL, Günther UL, *et al*: Glucose utilization via glycogen phosphorylase sustains proliferation and prevents premature senescence in cancer cells. Cell Metab 16: 751-764, 2012.
119. Wigerup C, Påhlman S and Bexell D: Therapeutic targeting of hypoxia and hypoxia-inducible factors in cancer. Pharmacol Ther 164: 152-169, 2016.
120. de Heer EC, Zois CE, Bridges E, van der Vegt B, Sheldon H, Veldman WA, Zwager MC, van der Sluis T, Haider S, Morita T, *et al*: Glycogen synthase 1 targeting reveals a metabolic vulnerability in triple-negative breast cancer. J Exp Clin Cancer Res 42: 143, 2023.
121. Ma R, Ji T, Zhang H, Dong W, Chen X, Xu P, Chen D, Liang X, Yin X, Liu Y, *et al*: A Pck1-directed glycogen metabolic program regulates formation and maintenance of memory CD8(+) T cells. Nat Cell Biol 20: 21-27, 2018.
122. Chen H, Yang W, Li Y, Ma L and Ji Z: Leveraging a disulfidptosis-based signature to improve the survival and drug sensitivity of bladder cancer patients. Front Immunol 14: 1198878, 2023.
123. Zhang D, Zhang X, Liu Z, Han T, Zhao K, Xu X, Zhang X, Ren X and Qin C: An integrative multi-omics analysis based on disulfidptosis-related prognostic signature and distinct subtypes of clear cell renal cell carcinoma. Front Oncol 13: 1207068, 2023.