



LETTER

Comprehensive characterization of cell disulfidptosis in human cancers: An integrated pan-cancer analysis



Excessive accumulation of disulfide molecules, like cystine, can induce disulfide stress and high toxicity in cells, but the reduced form of nicotinamide adenine dinucleotide phosphate can reverse this process and mitigate disulfide stress.^{1,2} One previous study showed that aberrant expression of cystine transporters, such as solute carrier family 7 member 11 (SLC7A11), or excessive cystine uptake, combined with glucose deprivation, could rapidly deplete the nicotinamide adenine dinucleotide phosphate level, leading to excessive disulfide accumulation and subsequent cell death.¹ However, the underlying mechanism is unclear. Recently, Liu and colleagues reported a novel cell death pattern based on disulfide stress, termed “disulfidptosis”, which is distinct from common forms of cell death, including autophagy, apoptosis, and ferroptosis.³ However, so far, no study has been conducted to analyze the roles of disulfidptosis genes in pan-cancer. Insights into disulfidptosis genes in pan-cancers are crucial to clarify disulfidptosis involved tumorigenesis and to develop inhibitors targeting disulfidptosis with a clinical potential as cancer treatment.⁴

In our study, to investigate the mechanisms of disulfidptosis-related tumors and provide new ideas for tumor treatment by controlling disulfidptosis, we identified a total of 10 disulfidptosis-related genes, including six pro-disulfidptosis genes (*NUBPL*, *NDUFA11*, *LRPPRC*, *OXSM*, *NDUFS1*, and *GYS1*) and four anti-disulfidptosis genes (*SLC7A11*, *SLC3A2*, *RPN1*, and *NCKAP1*).³ Then, we performed a systematic pan-cancer analysis of 10 disulfidptosis-related genes across 32 types of cancer through multi-omic profiling data. We comprehensively analyzed the genetic alternation and characterized the expression profile of disulfidptosis-related genes in pan-cancer using multiple public databases. Furthermore, we evaluated the

potential association between disulfidptosis gene expression and tumor microenvironment or tumor stemness. Besides, we also constructed an interaction network of disulfidptosis genes and predicted the potential drugs for targeting the disulfidptosis pathway. Details of these analyses are provided in the [Supplementary Information](#).

Genetic alternations, such as copy number variations (CNVs) and single nucleotide variants (SNVs), are associated with tumor occurrence, progression, and treatment response.⁵ [Figure S1A](#) showed that *LRPPRC* was the most frequently mutated disulfidptosis gene in 32 human cancers, especially in uterine corpus endometrial carcinoma (UCEC, 34%) and skin cutaneous melanoma (SKCM, 16%), both of which had a mutation rate of over 15%. In UCEC, all 10 disulfidptosis genes were screened for SNVs. UCEC had a higher mutation rate in all disulfidptosis genes compared with other cancers. [Figure S2](#) showed that some disulfidptosis genes that have relatively high mutation rates (over 15%) could lead to the activation or inhibition of corresponding proteins in UCEC and SKCM. Notably, 34% and 16% mutation rates of *LRPPRC* are found in UCEC and SKCM, respectively and our analysis showed that the mutations of *LRPPRC* could lead to activation of the protein in UCEC, while inhibition of the protein in SKCM ([Fig. S2](#)). The SNV landscape revealed that SNV changes in disulfidptosis genes occurred in all 570 tumor patients, with a frequency of 100% and missense mutation as the major type of SNV ([Fig. S1B](#)). The profile of disulfidptosis gene SNVs associated with survival showed that kidney renal papillary cell carcinoma and liver hepatocellular carcinoma were the most likely to be associated with disulfidptosis gene SNVs with a strongly positive association in progression-free survival and disease-free interval. However, only a few genes were significant in these cancers, with most of the other cancer types revealing no significant difference ([Fig. S1C](#)). Furthermore, CNV of the disulfidptosis genes had multiple function modes in pan-cancers. The pan-

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have a disparate expression mode in the different cancer subtypes. Subtype analysis showed that expression of disulfidptosis genes showed significant relevance in some cancer subtypes, like breast cancer (Fig. 1D). As shown in Figure 1D, the disulfidptosis genes were also closely associated with the activation or inhibition of various tumorigenesis-related pathways. Based on these results, a pathway regulation network (Fig. S6A) and microRNA-mRNA regulation network of disulfidptosis genes were constructed. Seven of the ten disulfidptosis genes were identified to be regulated by microRNAs. A larger number of microRNAs may be involved in the expression regulation of the disulfidptosis genes, making up the complex miRNA-mRNA regulation network (Fig. S6B). These results provided insights into the potential cross-talks between disulfidptosis and other signaling pathways or non-coding RNAs. Meanwhile, the survival for KIRC had the highest correlation with the expression of disulfidptosis genes. The high expression of three pro-disulfidptosis genes (*NUBPL*, *LRPPRC*, and *NDUFS1*) and the anti-disulfidptosis gene *NCKAP1* were associated with a lower risk of KIRC in patients. We further performed prognosis analysis based on TCGA, GTEx, and TARGET cohorts and found that these 10 genes are closely associated with cancer prognosis (Fig. S4).

To further explore the association between disulfidptosis genes and tumor microenvironment, tumor stemness was analyzed in all types of cancer. The correlation analysis of tumor microenvironment revealed a negative association between the expression of all disulfidptosis genes and the immune score of pancreatic adenocarcinoma, and between *LRPPRC* expression and the immune score of nearly all cancers (Fig. S5A). Besides, *GYS1* and *RPN1* expression were positively associated with the stromal score of brain lower-grade glioma (Fig. S5B). Further correlation analysis indicated that RNAss was negatively correlated with *NCKAP1* expression and positively correlated with *LRPPRC* expression in pan-cancer (Fig. S5C). The expression of disulfidptosis genes was negatively associated with DNAss in cholangiocarcinoma but positively associated with DNAss in ovarian cancer (Fig. S5D). We also analyzed the potential correlation between disulfidptosis gene expression and drug sensitivity in multiple human cancer cell lines. The results suggested that *GYS1* expression was negatively associated with drug sensitivity to many chemotherapy agents, including dasatinib, temsirolimus, and AZD6482 (Fig. S6C). Meanwhile, *NCKAP1* and *SLC7A11* expression were positively associated with drug sensitivity to ABT-737, olaparib, and belinostat (Fig. S6D).

In conclusion, our study revealed that the expression alterations of disulfidptosis genes might be involved in the activation or inhibition of various cancer-related pathways. Meanwhile, our results also highlight that disulfidptosis genes are closely associated with tumor microenvironment and tumor stemness, which may affect patient response to therapy. Importantly, we analyzed the correlations between disulfidptosis and drug sensitivity and found that the disulfidptosis pathway may be crucial in reversing drug resistance. With the increasing interest in disulfidptosis, like ferroptosis in cancer research, these in-time profile analyses will provide new

ideas and useful information for future studies on the potential of disulfidptosis as a treatment strategy in various cancers.

Author contributions

Study concept and design: NL and SW. Data acquisition and data cleaning: GZ. Data analysis and interpretation: GZ, YJ, and YW. Manuscript drafting: GZ, YJ, and YW. Supervision: LM and SZ. Proofreading and revision: NL and SW. Critical revision of the manuscript for important intellectual content: All authors. The authors read and approved the final manuscript.

Conflict of interests

The authors declare that they have no competing interests.

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Data availability

Publicly available datasets were analyzed in this study. These data can be found at: <https://portal.gdc.cancer.gov/>. Please contact the corresponding author for further data requests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gendis.2023.101095>.

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