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Original Article

Evaluation of Ferroptosis-Related Genes in Gastric Cancer via Bioinformatics Analysis

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Abstract

Background: Gastric cancer (GC) ranks among the most prevalent malignancies globally, contributing significantly to both morbidity and mortality. Ferroptosis, a unique iron-dependent form of cell death, has been implicated in various cancers, including GC. This study investigated the association between ferroptosis-related genes (FRGs) and GC using bioinformatics analyses.

Methods: Differentially expressed genes (DEGs) were identified using a publicly available microarray dataset. Genes associated with ferroptosis were then extracted, and their overlap with the DEGs was assessed. To gain further insights, functional enrichment analysis was performed, followed by the prediction of microRNA (miRNA) and transcription factor (TF) interactions. Additionally, a protein-protein interaction (PPI) network was constructed. Key genes were identified using the CytoHubba extension in Cytoscape, and their prognostic value was analyzed through receiver operating characteristic (ROC) curve evaluation.

Results: Overall, 3242 DEGs were identified, of which 78 were ferroptosis-related (DEFRGs). These DEFRGs were enriched in pathways such as ferroptosis and pathways in cancer. Among them, hsa-miR-106a-5p and SP1 were identified as key miRNA and TF, respectively. The PPI network revealed five hub genes: *TP53, MDM2, KRAS, IL6, and PTGS2*. ROC curve analysis demonstrated that all hub genes have excellent prognostic value for GC.

Conclusion: This study highlights the critical association between GC and ferroptosis-related genes using bioinformatics tools. These findings provide insights for future investigations and the development of targeted therapies against GC.

Keywords: Gastric cancer; Ferroptosis; Hub genes; Bioinformatics; Prognostic analysis

Introduction

Gastric cancer (GC) is listed as among the most prevalent and aggressive forms of cancer globally, affecting millions of people each year. It is recognized as an essential public health issue on a global scale and classified as the fourth major cause of cancer-related deaths (1). Gastric cancer, with more than 1 million new cases worldwide, has been neglected as a significant clinical problem. An important part of GC has been connected to an assortment of pathogenic contaminations, including viruses such as Epstein-Barr virus (EBV) or bacteria like Helicobacter pylori (H. pylori) (2). It is a highly heterogeneous malignant disease, both molecularly and phenotypically (3). In terms of response to treatment, gastric cancer faces multiple challenges (4). The exact etiology and molecular mechanisms involved in gastric cancer initiation are still unknown. In the early stages of GC, symptoms are usually not visible; therefore, diagnosing the disease is difficult and occurs in the later stages, leading to a reduced chance of survival (5). In order to reliably determine prognosis, identify therapeutic markers, and ultimately improve the survival rate in GC patients, it is critical to perceive novel and reliable biomarkers. A new form of cell death, in addition to apoptosis, has been described as ferroptosis. Ferroptosis, in terms of its functional mechanism, is distinct from other forms of cell death and is involved in cellular processes such as diffident cancers (5, 6). During cell death, it is commonly linked to two phenomena: severe iron accumulation and lipid peroxidation. (5). The most prominent molecular mechanism involved in ferroptosis is severe lipid peroxidation, releasing damage-associated molecular patterns (DAMPs) and consequently affecting immunological responses (6). Ferroptosis-inducing factors through various mechanisms, either directly or indirectly influence glutathione peroxidase in a variety of pathways. As a result, it reduces antioxidant activity and accumulation of lipid reactive oxygen species (Lipid-ROS) in cells and ultimately leads to cell death (6). A key point is that ferroptosis dysregulation plays a role in various tumor processes, including GC (6, 7). Furthermore, natural bioactive metabolites have promising effects to combat multidrug resistance (MDR) in cancer and inhibit multiple tumor progression by inducing ferroptosis (7). These findings implicate ferroptosis as a novel player regulating tumor suppressor function. For example, inhibition of this pathway in diffident cancers has led to an increase in tumorigenesis (7). Multiple studies demonstrate that key regulators of ferroptosis, such as solute carrier family 7 member 11 (*SLC7A11*), glutathione peroxidase 4 (*GPX4*), nuclear factor erythroid 2-related factor 2 (*NRF2*), and cysteine dioxygenase type 1 (*CDO1*), have been associated with cancer progression and patient prognosis (8). For example, inhibition of genes involved in this pathway can trigger other forms of cell death, such as necroptosis (8, 9). Although ferroptosis plays a crucial role in maintaining the survival of normal cells and tissues, it is becoming gradually evident that certain oncogenic pathways are linked to ferroptosis, rendering cancer cells highly susceptible to ferroptotic cell death (9). In the last few decades, many efforts have been made to search for sensitive biomarkers to identify high-risk patients with poor survival. With the development of transcriptional profiling, several multigene signatures have been developed to assess the prognosis of GC patients (10). Although only a few high-accuracy markers have been identified for the early detection of this disease, further studies are needed to confirm their relevance (11). Further investigation is required to establish whether these ferroptosis-related genes could function as effective diagnostic markers and therapeutic targets for GC, potentially enhancing patient survival rates (12).

There is a lack of comprehensive bioinformatics analyses to identify ferroptosis-related hub genes associated with GC and evaluate their prognostic significance. Addressing this gap could enhance our understanding of GC pathogenesis and lead

to the identification of novel therapeutic targets. In this study, we intend to use bioinformatics analysis through the Gene Expression Omnibus database (GEO) to investigate microarrays related to gastric cancer. Therefore, we investigated the relationship between GC and genes related to ferroptosis to be able to determine the effective hub genes in prognosis and to identify the prognostic value of the hub gene through subsequent analyses. This study was intended to recognize and characterize essential genes associated with GC to develop a prognostic model. The introduced hub genes may serve as candidate biomarkers for targeted therapy against GC.

Methods

Data acquisition and analysis

The dataset analyzed in this study was selected from the online database GEO (https://www.ncbi.nlm.nih.gov/geo/) (13). The GSE54129 microarray dataset was chosen, including 111 tumor samples from GC patients and 21 normal gastric samples from healthy controls. GSE54129 is based on GPL570. Subsequently, the differentially expressed genes (DEGs) were screened between tumor samples vs healthy control samples using the GEO2R online web tool. The cut-off criteria for DEGs screening were |log fold change|>1.2 and adjusted-*P*-value<0.05. The |log fold change| >1.2 threshold was chosen to capture genes with biologically significant expression changes (greater than 2.29-fold increase or decrease), balancing the need for sensitivity and specificity in identifying key genes. Significant and non-significant DEGs were depicted by volcano plot. Besides, ferroptosis-related genes (FRGs) were extracted from the FerrDb online database (http://www.zhounan.org/ferrdb/) (14). After FRGs downloading, the duplicated value and non-human FRGs were removed and a total of 340 FRGs remained. Then, the differentially expressed ferroptosis-related genes (DEFRGs) were extracted from the intersection between DEGs and FRGs using a Venn diagram (15). DEFRGs were used for subsequent analysis.

Functional enrichment analysis of DEFRGs

Functional enrichment analysis of DEFRGs was performed through EnrichR, a robust web-based resource for gene set analysis (16). These analyses contain gene ontology (GO) (including three categories of biological processes, cellular components, and molecular functions) and analysis of pathways based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) database. The cut-off criteria for analyses were adjusted-*P*-value<0.05.

Analysis of DEFRGs association with regulatory elements

To identify the association between DEFRGs and related microRNAs (miRNAs), miRTarBase database linked to EnrichR. miRTarBase is a comprehensive database of miRNA-target interactions (MTIs) that have been experimentally confirmed using various techniques (17). Besides, the association between DEFRGs and related transaction factors (TFs) was evaluated using TRRUST database linked to EnrichR. TRRUST is a comprehensive database of transcriptional regulatory networks (18). The cut-off criterion was considered adjusted *P*-value <0.05.

Protein-protein interaction (PPI) network establishment and selection of hub genes

DEFRGs were input for PPI network analysis via the STRING database with a confidence score ≥0.4 (19). The STRING is one of the most comprehensive databases that encompass information about information between known proteins. extracted PPI was visualized through Cytoscape software (20). The significant modules, which are the most important in the network, were characterized using the Molecular Complex Detection (MCODE) plug-in. Hub genes were selected based on three centrality algorithms: degree, closeness, and betweenness. The hub genes present in the significant modules were considered as the final FRGs.

Investigation of the diagnostic performance of hub genes

The receiver operating characteristic (ROC) curve and related areas under the ROC curves (AUCs) were computed to assess the diagnostic performance of hub genes. These analyses were performed via GraphPad Prism. The cutoff criterion was considered an AUC greater than 0.9 that (excellent performance). AUC values closer to 1.0 suggest excellent classification accuracy in distinguishing between two classes (cancerous vs non-cancerous groups), while a value of 0.5 suggests random chance.

Results

Screening of DEFRGs

First, the GSE54129 microarray dataset was analyzed via the GEO2R online tool. 2212 DEGs, including 1264 up- and 949 down-regulated genes, were obtained (Supplementary file 1). DEGs including significant and non-significant genes were depicted by volcano plot (Fig. 1).

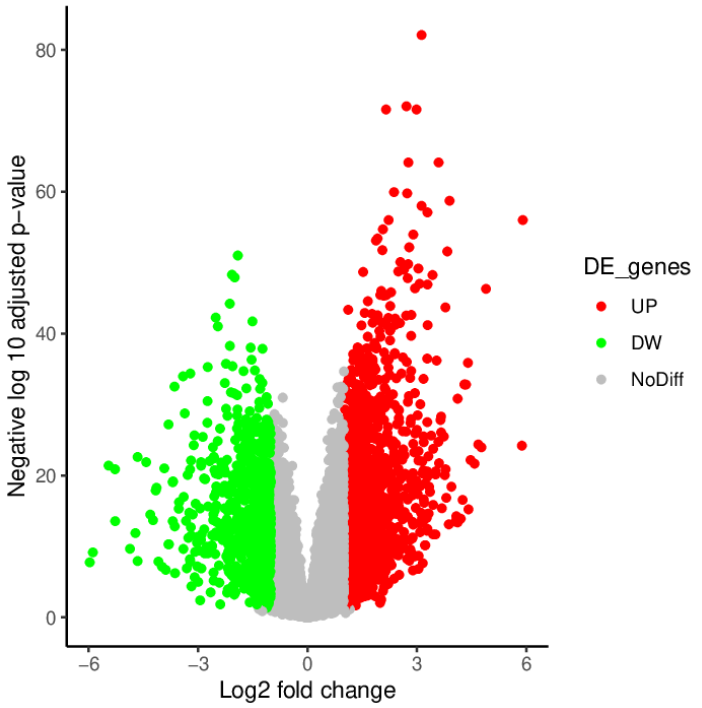

Fig. 1: Volcano plot of DEGs that gray dots show un-significant genes, red dots show up-regulated genes, and blue dots show down-regulated genes

Furthermore, 340 FRGs were retrieved from the FerrDb database (Supplementary file 1). Venn diagram revealed that there were 78 common genes as DEFRGs between DEGs and FGRs (Fig. 2 & Supplementary file 1).

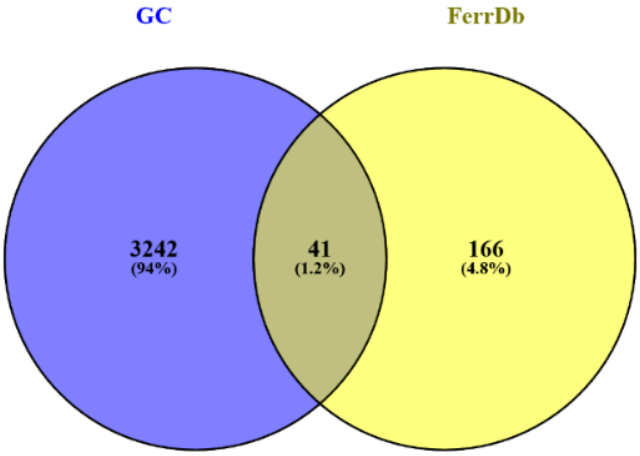

Fig. 2: Venn diagram to select DEFRGs between GC and ferroptosis. altogether, 41 common genes were identified

Functional enrichment analysis of DEFRGs

Functional enrichment analysis of DEFRGs was conducted via EnrichR. In GO analysis, DEFRGs were mainly enriched in "cellular response to lipid", "positive regulation of cell differentiation" and "cellular response to oxygen-containing compound" in the BP category (Fig. 3).

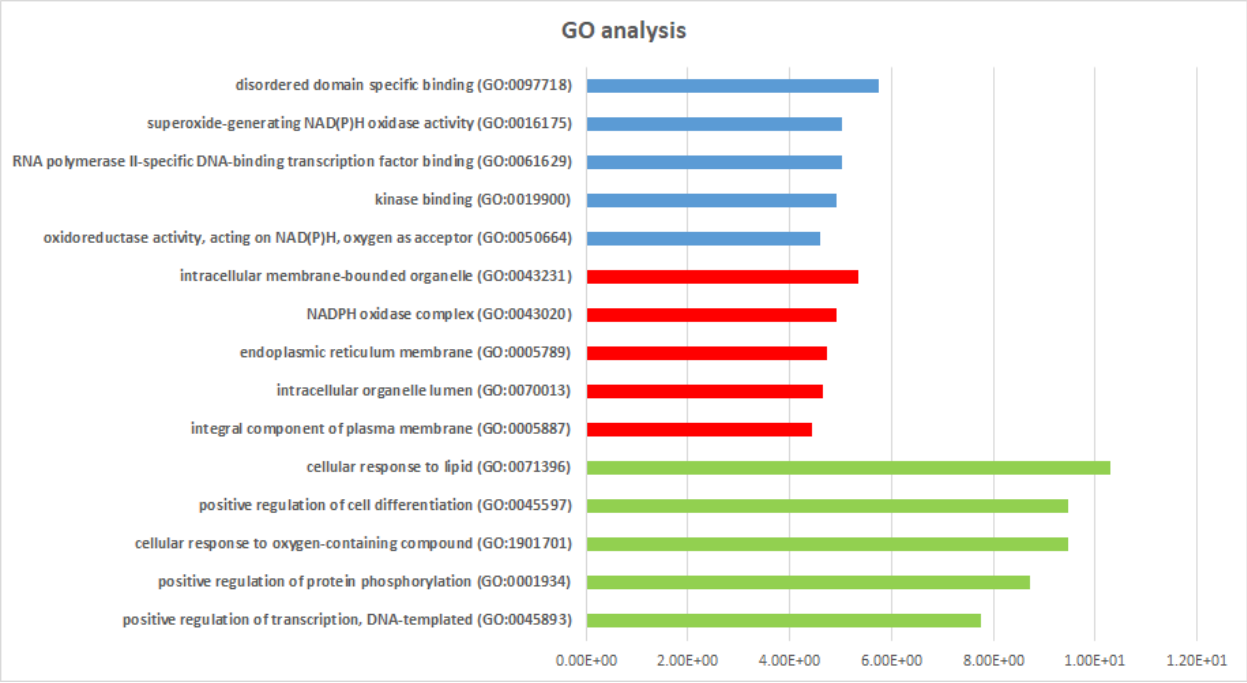

Fig. 3: Gene ontology analysis of DEFRGs. Blue lines indicate Biological Process terms, red lines indicate Cellular Component terms and green liens lines indicate Molecular Function

In terms of CC, DEFRGs were mostly enriched in "intracellular membrane-bounded organelle", "NADPH oxidase complex" and "endoplasmic reticulum membrane". In terms of MF, DEFRGs were predominantly enriched in "disordered domain specific binding", "superoxide-generating NAD (P) H oxidase activity" and "RNA polymerase II-specific DNA-binding transcription

factor binding" (Fig. 3). Finally, KEGG analysis showed that DEFRGs were mostly enriched in "Ferroptosis", "Pathways in cancer" and "Human T-cell leukemia virus 1 infection" (Fig. 4).

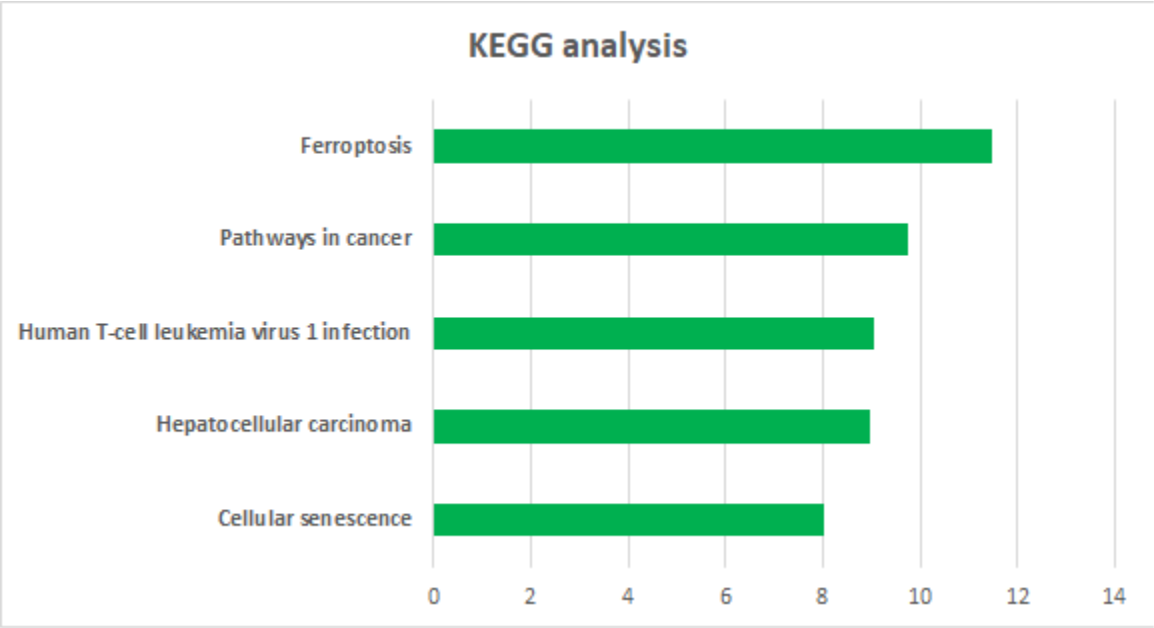

Fig. 4: KEGG pathway analysis of DEFRGs. The top 5 terms are shown

Analysis of DEFRGs association with regulatory elements

First, the association of DEFRGs and related miRNAs were assessed. hsa-miR-106a-5p significantly interacted with DEFRGs as key miRNA. Similarly, the association of DEFRGs and related TFs were evaluated. SP1 significantly interacted with DEFRGs as key TF. The top 10 miRNAs and TFs associated with hub genes are shown in (Supplementary file 2).

Protein-protein interaction (PPI) network establishment and selection of hub genes

The PPI network of DEFRGs was produced via the STRING database and depicted through Cytoscape (Fig. 5).

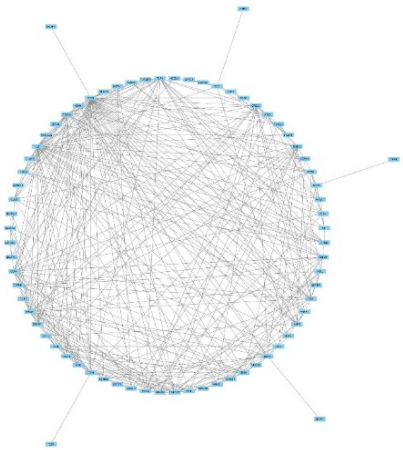

Fig. 5: PPI network of DEFRGs. Blue rectangles indicate genes and black lines indicate an interaction between them

The network consists of 73 "nodes," representing individual genes/proteins, and 341 "edges," indicating the interactions between them. MCODE analysis showed that one significant module that has 13 nodes and 61 edges (Fig. 6). Then, hub genes were determined using the cytoHubba plugin. Six genes, including, *TP53, IL6, KRAS, PTGS2, CDH1,* and *MDM2 TP53* were selected based on Degree, Closeness, and Betweeness methods. Except for CDH1, other hub genes were present in the significant module and are considered as final hub FRGs (Fig. 6).

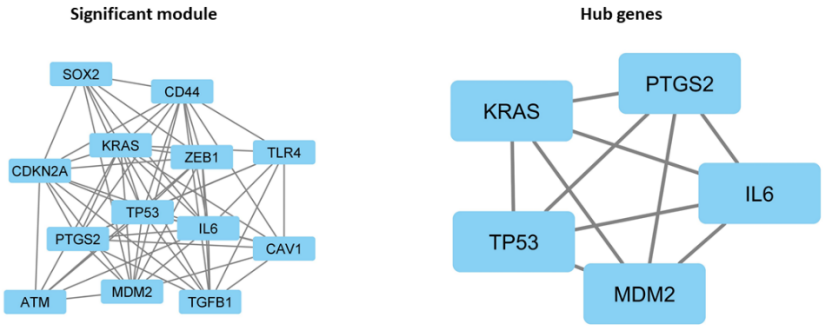

Fig. 6: The significant module and hub genes of DEFRGs; significant module was chosen using the MCODE plugin of Cytoscape. Five hub genes were selected using gene intersection between three algorithms (degree, closeness, and betweenness) and significant modules

Investigation of the diagnostic performance of hub genes

ROC curves and corresponding AUC for the identified hub genes (*TP53, IL6, KRAS, PTGS2,* and *MDM2*) were evaluated. The results showed that all hub genes had AUCs >0.90, which demonstrated excellent prediction performance (Fig. 7).

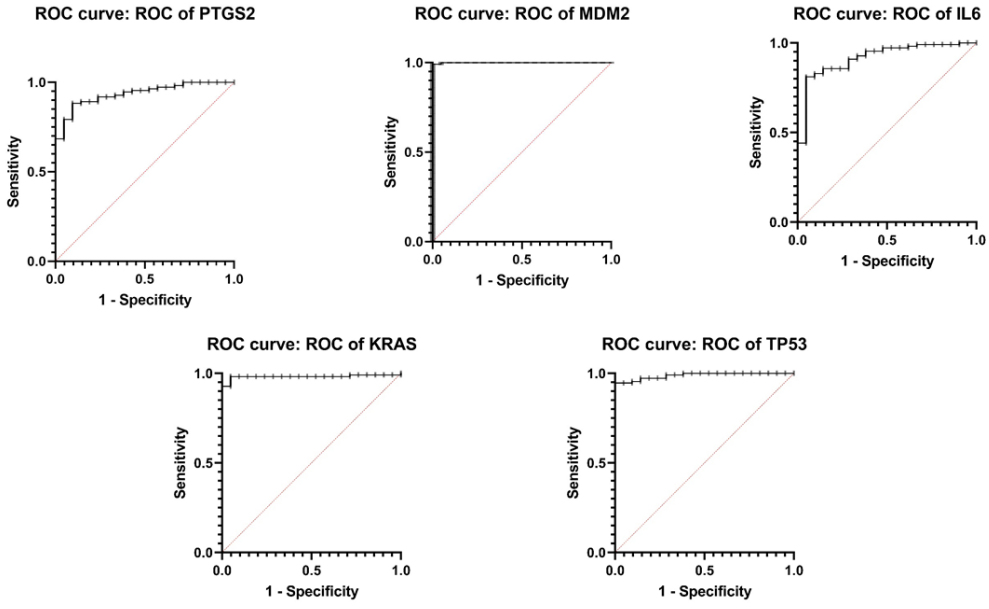

Fig. 7: ROC curve analysis of hub genes; all hub genes had AUCs >0.90, which demonstrated excellent prediction performance

Discussion

Gastric cancer continues to be a leading cause of cancer mortality, accounting for 8% of all cancer-related deaths in 2020 despite reducing trends (21). Recent developments in genome analysis have led to the identification of biomarkers that are clinically significant for GC diagnosis, therapy, and prognosis. These includes molecules associated with growth factor signaling, key regulators of cell cycle progression and programmed cell death, such as the tumor suppressor *p53*, along with immune checkpoint modulators like PD-1 and PD-L1, and components involved in cell adhesion (22). Radiation treatment and chemotherapy for cancer are significantly hampered by the high antioxidant concentrations in cancer cells. An iron-dependent form of regulated cell death known as ferroptosis is brought on by increased in lipid peroxidation products (23).

This study identified 78 DEFRGs from the GSE54129 microarray dataset, highlighting their significant role in various biological processes. Functional enrichment analysis revealed that these DEFRGs are primarily involved in cellular responses to lipids and oxygen-containing compounds, as well as positive regulation of cell differentiation. Additionally, key interactions with miRs, particularly hsa-miR-106a-5p, and transcription factors like SP1 were established. The construction of a PPI network led to the identification of hub genes including *TP53, IL6, KRAS, PTGS2*, and *MDM2*, which demonstrated excellent diagnostic potential with AUC values exceeding 0.90. These findings underscore the importance of DEFRGs in understanding ferroptosis mechanisms and their potential implications in cancer biology and therapeutic strategies.

One of the hub genes for this study is the *TP53* gene, which according to previous work by scientists, may be one of the genes involved in the ferroptosis pathway. In 2015, Gu and colleagues proposed that ferroptosis could play a critical role in tumor suppression mediated by the p53 protein (24). SLC7A11 is upregulated in the cancer cell by using transcription factors like nuclear factor erythroid 2-like 2 (*NFE2L2/NRF2*) on the transcriptional level. *SLC7A11* may also be downregulated by specific transcription factors, such as tumor protein p53 (TP53) (25). The capacity of p53 to transcriptionally curb *SLC7A11* has appeared to reduce cystine import, resulting in diminished glutathione production and expanded ROS, a key component of ferroptosis (24).

IL6 is one of the other important hub genes obtained from this study involved in ferroptosis. The role of IL-6 in inducing or inhibiting ferroptosis varies depending on the disease context. For instance, a study has demonstrated that IL-6 can promote tumor progression in head and neck squamous cell carcinoma (HNSCC) by inducing resistance to ferroptosis through upregulation of *xCT* (*SLC7A11*). Conversely, IL6 advances ferroptosis in bronchial epithelial cells through actuating ROS-based lipid peroxidation and disturbing press homeostasis (26, 27).

Another hub gene, *KRAS* can up-regulate ROS through different mechanisms. A good illustration of this is *KRAS* which controls the target genes hypoxia-inducible factor (*HIF*)*-1a* and *HIF-2a* to regulate mitochondrial metabolism, and therefore the controller of ferroptosis, transferrin receptor (TFRC), to regulate mitochondrial respiration, and ROS generation. *KRAS* will moreover actuate Rac1-NOX4 signaling to vary NADPH oxidase action. Moreover, the NADPH oxidase (NOX) family plays a significant part in lipid peroxidation in ferroptosis (28-30).

Ferroptosis is related to expanded *PTGS2* expression and prostaglandin E2 (PGE2) discharge. Ferroptosis could straightforwardly increment the expression of *PTGS2* (which encodes cyclooxygenase 2 (COX2)), advance AA metabolism, and advance the secretion of inflammatory signaling molecules (31). GPX4 applies a clear cytoprotective impact by stifling the levels of cellular lipid hydroperoxides that contribute to inflammation (32). In this study, this gene can play a significant role in ferroptosis.

The negative regulators of the tumor suppressor *p53, MDM2* and *MDMX*, act independently and as a heteromeric complex that limits *p53* function. MDM2 and *MDMX* altered the lipid profile of cells to promote ferroptosis. Hindrance *MDM2* or *MDMX* increases the level of ferroptosis suppressor protein 1 (FSP1) protein, which increases the level of coenzyme Q10, a lipophilic antioxidant (33).

The interplay between *TP53, IL6, KRAS, PTGS2,* and *MDM2* highlights a complex network of regulatory mechanisms governing ferroptosis in GC. Targeting these pathways could provide novel therapeutic strategies to enhance ferroptotic cell death and overcome chemotherapy resistance in GC patients. Ferroptosis-related genes hold significant therapeutic potential in GC, as targeting these genes could enhance tumor cell death and overcome resistance to conventional treatments. Future research should focus exploring the role of ferroptosis-related biomarkers in predicting treatment response and developing personalized therapeutic strategies could improve patient outcomes in gastric cancer management.

Conclusion

The findings of this study are primarily derived from bioinformatics analyses and associations, lacking experimental validation of the identified genes in the context of gastric cancer. Further in vitro and in vivo studies are essential to affirm their functional significance. This study should be regarded as a foundational step for further research, as it offers valuable insights but requires subsequent studies to delve deeper into the intricate mechanisms linking ferroptosis-related genes and gastric cancer.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

The data generated and analyzed in this study have been deposited and are available in the GEO (Gene Expression Omnibus) database, which can be accessed at https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE54129. Supplementary files may be requested from the corresponding author based on reasonable application.

Conflict of interest

The authors declare that there is no conflict of interests.

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