Original Article

ISSN: 1735-0344 *Tanaffos 2025; 24(3): 272-280*

TANAFFOS

Exploring Molecular Mechanism of Ferroptosis in A549 Lung Cancer Cells

Mohammad Rostami-Nejad [1], Zahra Razzaghi [2], Reza M Robati [3], Babak Arjmand [4,5], Vahid Mansouri [6], Maryam Hamzeloo-Moghadam [7], Mitra Rezaei [8], Fatemeh Bandarian [9], Farideh Razi [10], Mostafa Rezaei-Tavirani [6]

[1] Celiac Disease and Gluten Related Disorders Research Center, Research Institute for Gastroenterology and Liver Disease, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [2] Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [3] Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [4] Cell Therapy and Regenerative Medicine Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran, [5] Iranian Cancer Control Center (MACSA), Tehran, Iran, [6] Proteomics Research Center, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [7] Traditional Medicine and Materia Medica Research Center, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [8] Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [9] Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran, [10] Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

Received: 13 July 2024
Accepted: 17 February 2025

Correspondence to: Rezaei-Tavirani M
Address: Proteomics Research Center, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email address: taviranim@gmail.com

Background: Ferroptosis is a non-apoptotic cell death pattern caused by iron-dependent lipid peroxidation injury. It is a new strategy for lung cancer treatment. Molecular mechanism detection of ferroptosis via protein-protein interaction (PPI) network analysis is the main aim of this investigation.

Materials and Methods: To detect gene expression changes related to ferroptosis, Gse247883 from Gene Expression Omnibus (GEO) was a candidate to be analyzed via PPI network analysis. The gene expression profiles of A549 lung cancer cells were compared with those of controls via the GEO2R program. Volcano plot visualized the significantly differentially expressed genes (DEGs). The hubs of up- and downregulated PPI networks were determined and enriched for related biological processes.

Results: Some 14 hubs, including EGFR, TXNRD1, SOD1, TXN, PRDX1, PTGS2, CXCL8, TLR4, CALR, P4HB, UBC, GSR, and VCP, among the 295 recognized significant upregulated DEGs and 13 hubs; PTEN, HNRNPA1, HNRNPA2B1, HSP90AB1, NPM1, XPO1, ANLN, HNRNPC, PPP1CC, NCL, EEF1A1, HSPD1, and MATR3 for the downregulated PPI network of 249 recognized significant DEGs were determined. A total of 11 and 6 groups of various types of biological groups related to the hubs of the up- and downregulated PPI network were identified, respectively.

Conclusion: In conclusion, most effects of ferroptosis are regulation of EGFR, TXNRD1, SOD1, TXN, PRDX1, PTGS2, TLR4, P4HB, UBC, GSR, VCP, PTEN, HNRNPA1, HNRNPA2B1, HSP90AB1, NPM1, XPO1, HNRNPC, NCL, EEF1A1, and HSPD1 genes and "Regulation of oxidative stress-induced cell death", "Telomere maintenance via telomere lengthening", and "RNA-dependent DNA biosynthetic process" groups of biological processes.

Keywords: Ferroptosis; Gene expression; Network analysis; Lung cancer

INTRODUCTION

Lung cancer (LC) is the second most diagnosed cancer in the world, with a high incidence of mortality (1). LC malignant tumors mainly originate in the trachea, bronchus, and lung, such as squamous cell carcinoma, adenocarcinoma, small and large cell carcinoma (2). Traditional therapies such as surgery, radiotherapy, chemotherapy, and immunotherapy could not benefit advanced-stage patients (3). Further explorations into the mechanism of lung cancer are required to find efficient therapeutic methods and effective drugs. Specific genes regulate programmed cell death and play an important role in the maintenance of organisms (2). Ferroptosis (Fr) is a non-apoptotic cell death pattern caused by iron-dependent lipid peroxidation injury (4). Cancer cells need more iron, and the imbalance of iron metabolism can increase cancer risk and promote tumor growth (5).

Fr as a new strategy for LC treatment has been mentioned in recent years. However, the precise mechanism of ferroptosis in lung cancer has not been clarified yet. Fr is a kind of cell death caused by intracellular iron accumulation, cell membrane damage due to the failure of glutathione peroxidase activity, an increase in intracellular lipid peroxidase, and the iron-dependent production of reactive oxygen species (ROS) (4, 6). Morphological changes happened in the mitochondria of Fr cells, such as cristae disappearance and volume reduction, besides changes in characteristic genes such as GPX4, GSS, and TFR1 (7, 8). By promoting Fr in lung tumors, lung cancer development is consequently prohibited. SLC7A11 and PTGS2 are critical in Fr regulation in LC cells (9, 10). Other genes such as FSP1, ACSL4 (11), IREB2, and VDAC2/3 are still being investigated and may vary based on LC subtype (12-14). The interplay between these genes, proteins, and other signaling pathways regulating Fr is complex and undeclared. Genomics techniques, besides network analysis, could be appropriate. In this study, we aim to figure out the genes and proteins involved in lung cancer cell apoptosis mediated by Fr. Network analysis of the original data may help identify potential biomarkers associated with apoptosis in lung cancer cells induced by Fr. Further investigation of the molecular mechanisms underlying Fr-induced apoptosis in lung cancer cells may provide additional insights into the relevant biomarkers and signaling pathways. These findings could contribute to a better understanding of the molecular basis of Fr-induced apoptosis and potentially inform the development of therapeutic strategies for lung cancer and other malignancies.

MATERIALS AND METHODS

Data collection

To explore critical ferroptosis-associated genes, GSE247883 from the GEO database was considered for analysis (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE247883). The gene expression profiles of treated A549 cells with ferrostatin-1 (Fer-1) were compared with those of controls.

Pre-evaluation analysis

Data were assessed to find the significant DEGs via GEO2R; the results were visualized by a volcano plot. The significant DEGs based on adjusted p-value (P_{adj}) < 0.05 were determined. The up- and downregulated DEGs were separately provided to be evaluated via PPI network analysis.

PPI network analysis

The significant up- and downregulated DEGs were included in separate PPI networks via STRING protein query by Cytoscape software v 3.7.2. The constructed PPI networks were formed via undirected edges and were analyzed by the "Network analyzer" application of Cytoscape software. Mean+2SE was considered as a degree cutoff to discover the hub nodes (15).

Descriptions of hubs were extracted from the STRIN database and summarized (https://string-db.org/cgi/input?sessionId=bZhPmsmWoGKB&input_page_show_search=on). The hubs were assessed via the ClueGO application of Cytoscape software to find the affected critical biological processes.

Statistical analysis

$P_{adj} < 0.05$ was considered to explore the significant DEGs. Degree cutoff > mean+2SD was applied to identify hub nodes. P-value of grouping: 0.05, and the correction test, Bonferroni step-down, were applied to analyze the significantly enriched biochemical processes and clusters.

Ethical Approval

This project was approved by Shahid Beheshti University of Medical Sciences with the ethical code of IR.SBMU.RETECH.REC.1402.453.

RESULTS

Significant DEGs were visualized via a volcano plot. As it is shown in Figure 1, there are considerable numbers of up- and downregulated DEGs. It seems the number of upregulated DEGs is more than the number of downregulated DEGs. The up- and down-regulated PPI networks, including 295 and 249 nodes, were created, respectively (Figures 2 and 3).

As it is shown in Tables 1 and 2, EGFR, TXNRD1, SOD1, TXN, PRDX1, PTGS2, CXCL8, TLR4, CALR, P4HB, UBC, GSR, and VCP as upregulated hubs and PTEN, HNRNPA1, HNRNPA2B1, HSP90AB1, NPM1, XPO1, ANLN, HNRNPC, PPP1CC, NCL, EEF1A1, HSPD1, and MATR3 as downregulated hubs are pointed out. The Biological processes related to the upregulated hubs are presented in Figures 4 and 5. As depicted in Figure 5, EGFR, TXNRD1, SOD1, TXN, PRDX1, PTGS2, TLR4, P4HB, UBC, GSR, and VCP appear as associated genes. The Biological processes related to the downregulated hubs are shown in Figures 6 and 7. As it is illustrated in Figure 7, PTEN, HNRNPA1, HNRNPA2B1, HSP90AB1, NPM1, XPO1, HNRNPC, NCL, EEF1A1, and HSPD1 appear as associated genes.

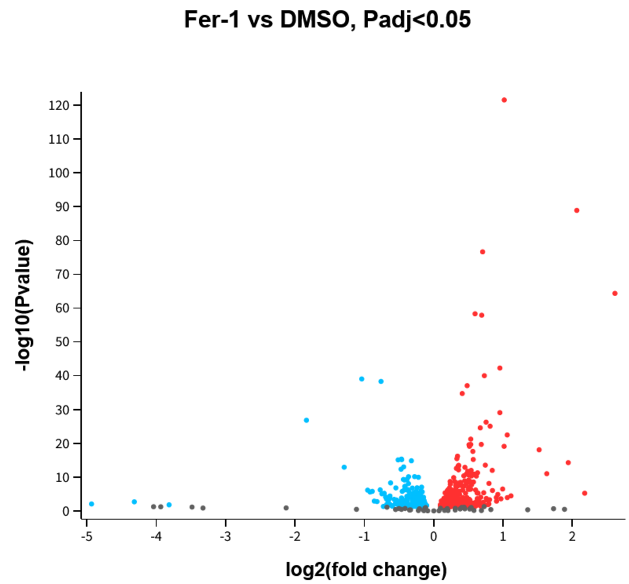

Figure 1. Volcano plot illustration of significantly downregulated DEGs (blue) and upregulated DEGs (red)

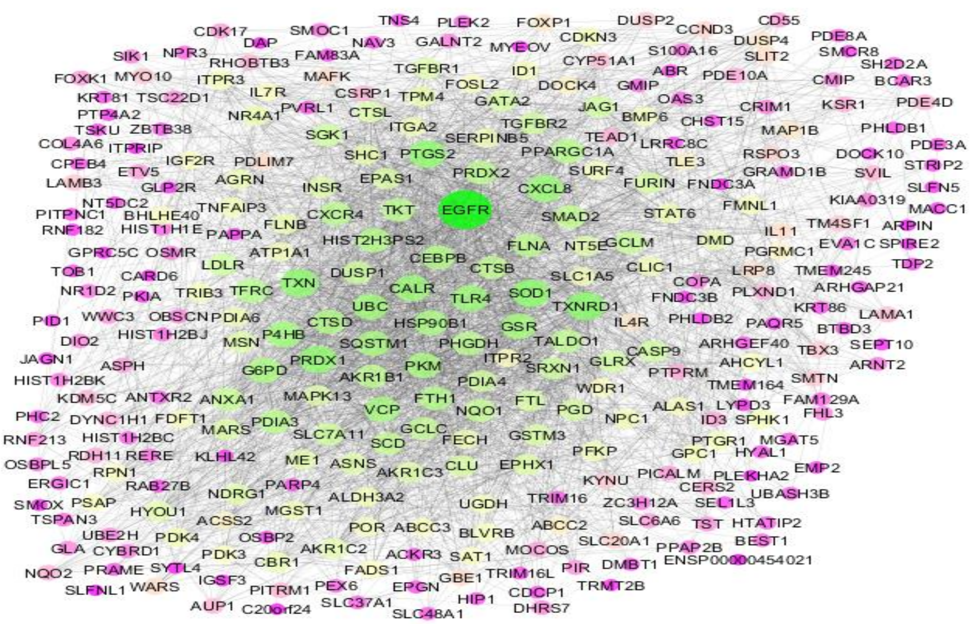

Figure 2. Upregulated PPI network of 295nodes and 3260 edges. The nodes are laid out by degree value. Red to green corresponds to an increment of degree value

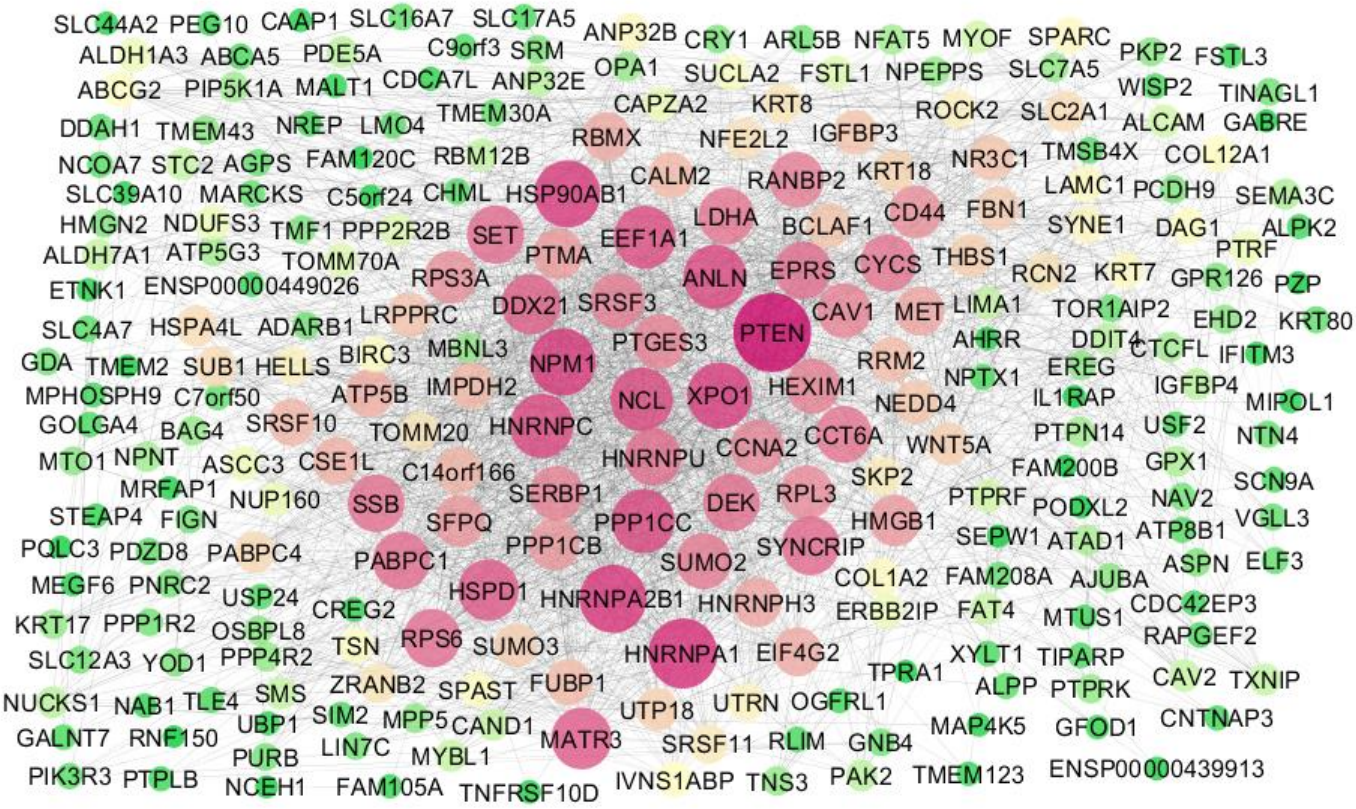

Figure 3. Downregulated the PPI network of 249 nodes and 2446 edges. The nodes are laid out by degree value. Green to red corresponds to an increment of degree value

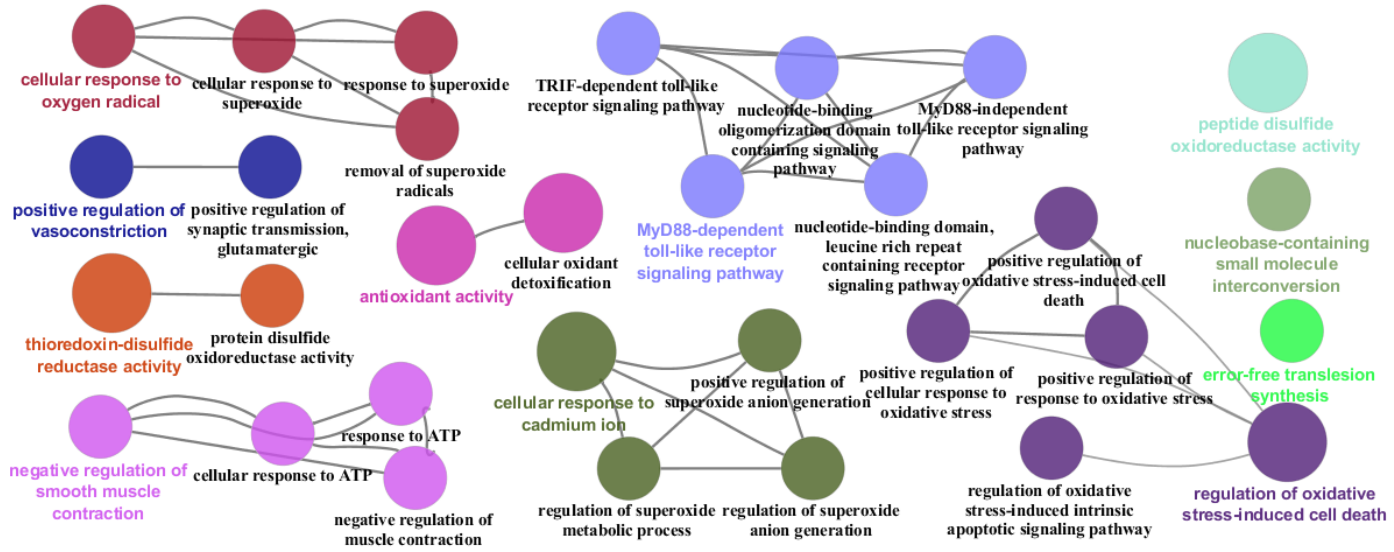

Figure 4. Biological processes related to the upregulated DEGs. The groups are labeled in colors

Table 1. List of upregulated hubs; descriptions are extracted from the STRING database and summarized, K: degree

No.	DEG	K	STRING database description
1	EGFR	144	Receptor tyrosine kinase binding ligands of the EGF family activate several signaling cascades to convert extracellular cues into appropriate cellular responses. Plays a role in enhancing learning and memory performance.
2	TXNRD1	79	Gene associated with retinoic and interferon-induced mortality 12 protein; Isoform 1 induces actin and tubulin polymerization, leading to the formation of cell membrane protrusions.
3	SOD1	77	Destroys radicals that are normally produced within the cells and which are toxic to biological systems.
4	TXN	77	Surface-associated sulphydryl protein; Participates in various redox reactions and contributes to the response to intracellular nitric oxide. Induces the FOS/JUN AP-1 DNA-binding activity in ionizing radiation (IR) cells.
5	PRDX1	75	Thioredoxin-dependent peroxide reductase 2; Thiol-specific peroxidase that catalyzes the reduction of hydrogen peroxide and organic hydroperoxides to water and alcohols, respectively. Plays a role in cell protection against oxidative stress by detoxifying peroxides. Reduces an intramolecular disulfide bond in GDPD5 that gates the ability of GDPD5 to drive postmitotic motor neuron differentiation.
6	PTGS2	75	Converts arachidonate to prostaglandin H2 (PGH2), a committed step in prostanoid synthesis. Constitutively expressed in some tissues in physiological conditions, such as the endothelium, kidney, and brain, and in pathological conditions, such as in cancer. PTGS2 is responsible for the production of inflammatory prostaglandins. Up-regulation of PTGS2 is also associated with increased cell adhesion, phenotypic changes, resistance to apoptosis, and tumor angiogenesis.
7	CXCL8	72	IL-8 is a chemotactic factor that attracts neutrophils, basophils, and T-cells, but not monocytes. It is also involved in neutrophil activation. It is released from several cell types in response to an inflammatory stimulus.
8	TLR4	70	Cooperates with LY96 and CD14 to mediate the innate immune response to bacterial lipopolysaccharide (LPS). Acts via MYD88, TIRAP, and TRAF6, leading to NF-kappa-B activation, cytokine secretion, and the inflammatory response. It promotes sterile inflammation in monocytes/macrophages in response to oxidized low-density lipoprotein (oxLDL) or amyloid-beta 42.
9	CALR	69	It promotes folding, oligomeric assembly, and quality control in the endoplasmic reticulum. Interacts with the DNA-binding domain of NR3C1 and mediates its nuclear export. Involved in maternal gene expression regulation. May participate in oocyte maturation via the regulation of calcium homeostasis.
10	P4HB	67	This multifunctional protein catalyzes the formation, breakage, and rearrangement of disulfide bonds. It involves enhancing cell migration.
11	UBC	66	It is involved in DNA repair, endoplasmic reticulum-associated degradation, cell-cycle regulation, lysosomal degradation, kinase modification, protein degradation via the proteasome, and endocytosis.
12	GSR	65	Maintains high levels of reduced glutathione in the cytosol.
14	VCP	63	Necessary for the fragmentation of Golgi stacks during mitosis and for their reassembly after mitosis. Involved in the formation of the transitional endoplasmic Vesicle budding from the tER is an ATP-dependent process. It involves sterol-mediated ubiquitination and endoplasmic reticulum-associated degradation. Also involved in DNA damage response. Essential for the maturation of ubiquitin- containing autophagosomes and the clearance of ubiquitinated protein by autophagy. Acts as a negative regulator of type I interferon production.

Table 2. List of downregulated hubs; descriptions are extracted from the STRING database and summarized, K: degree

No.	DEG	K	STRING database description
1	PTEN	78	Tumor suppressor. It inhibits cell migration and integrin-mediated cell spreading and focal adhesion formation. Plays a role in the process of newborn neurons' integration during adult neurogenesis, including correct neuron positioning, dendritic development, and synapse formation. May be a negative regulator of insulin signaling and glucose metabolism in adipose tissue.
2	HNRNPA1	69	Involved in the packaging of pre-mRNA into hnRNP particles, the transport of poly(A) mRNA from the nucleus to the cytoplasm, and may modulate splice site selection. May bind to specific miRNA hairpins.
3	HNRNPA2B1	67	Plays a role in various processes such as transcription, pre-mRNA processing, RNA nuclear export, subcellular location, mRNA translation, and stability of mature mRNAs. Involved in the transport of specific mRNAs to the cytoplasm in oligodendrocytes and neurons.
4	HSP90AB1	66	Promotes the maturation, structural maintenance, and proper regulation of specific target proteins involved, for instance, in cell cycle control and signal transduction. Apart from its chaperone activity, it also plays a role in the regulation of the transcription machinery.
5	NPM1	66	Involved in diverse cellular processes such as ribosome biogenesis, centrosome duplication, protein chaperoning, histone assembly, cell proliferation, and regulation of tumor suppressors p53/TP53 and ARF.
6	XPO1	65	Mediates the nuclear export of cellular proteins (cargos) bearing a leucine-rich nuclear export signal (NES) and of RNAs.
7	ANLN	63	Required for cytokinesis. Essential for the structural integrity of the cleavage furrow and for completion of cleavage furrow ingression. Plays a role in bleb assembly during metaphase and anaphase of mitosis. May play a significant role in podocyte cell migration.
8	HNRNPC	63	May play a role in the early steps of spliceosome assembly and pre-mRNA splicing.
9	PPP1CC	63	It associates with over 200 regulatory proteins to form highly specific holoenzymes, which dephosphorylate hundreds of biological targets. It is involved in cell division, regulation of glycogen metabolism, muscle contractility, protein synthesis, determining circadian period length, and rendering Treg cells functionally defective.
10	NCL	62	It is the major nucleolar protein of growing eukaryotic cells. It induces chromatin decondensation by binding to histone H1. It is thought to play a role in pre-rRNA transcription and ribosome assembly.
11	EEF1A1	61	It plays a role in protein biosynthesis and Th1 cytokine production.
12	HSPD1	59	Chaperonin implicated in mitochondrial protein import and macromolecular assembly.
13	MATR3	59	May play a role in transcription or may interact with other nuclear matrix proteins to form the internal fibrogranular network. It may play a role in nuclear retention of defective RNAs. Plays a role in the regulation of DNA virus-mediated innate immune response.

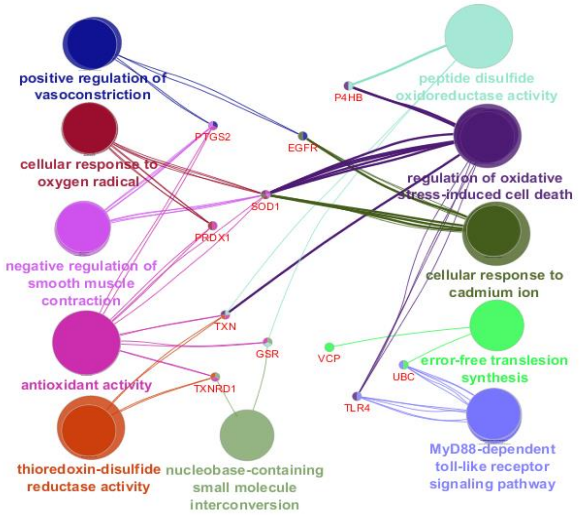

Figure 5. Groups of biological processes related to the upregulated DEGs. The associated genes are labeled in red

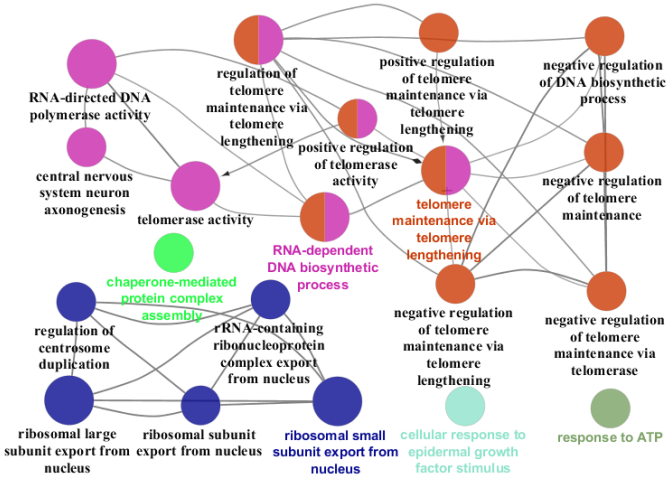

Figure 6. Biological processes related to the downregulated DEGs. The groups are labeled in colors

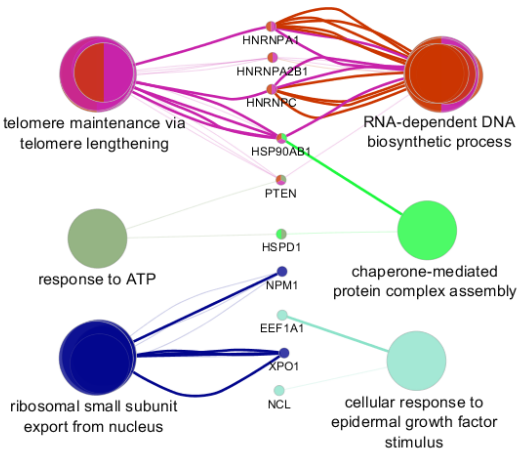

Figure 7. Groups of biological processes related to the downregulated DEGs. The associated genes are arranged in the middle column

DISCUSSION

Ferroptosis has been implicated as a potential anticancer mechanism in non-small cell lung cancer (NSCLC) (16), whereas ferrostatin-1 effectively inhibits ferroptosis (17) and may consequently affect gene expression in A549 lung cancer cells. To detect the molecular mechanism of ferroptosis, it is inhibited by ferrostatin-1. The effective role of ferrostatin-1 in the dysregulation of many genes of A549 lung cancer cells is visualized in Figure 1. As it is shown in Figure 1, there are many significantly dysregulated genes. Investigations indicate that PPI network analysis is a suitable method to screen large numbers of genes or proteins to detect the critical individuals (18, 19). The PPI networks of up- and downregulated DEGs include central nodes (see the nodes with a bigger size in Figures 2 and 3), which can play a role as hubs. Hub nodes are used as key genes to interpret the molecular mechanism of many diseases and the effect of drugs (20, 21). Epidermal growth factor receptor (EGFR) appears as a potent upregulated hub. The significant role of EGFR in the activation of several signaling cascades to convert extracellular signals into appropriate cellular responses is highlighted in Table 1. EGFR is connected to "positive regulation of vasoconstriction" and "cellular response to cadmium ion" groups of biological processes (Figures 4 and 5). "Positive regulation of superoxide anion generation" is a related biological process which affected by EGFR. Investigation indicates that superoxide anion generation promotes or is related to several pathologies in humans and has also been implicated in the aging process (22). There are several documents about the upregulation of EGFR in different forms of cancer, which is positively associated with cancer progression and poor prognosis (23). It can be concluded that inhibition of ferroptosis is accompanied by upregulation of EGFR and lung cancer promotion.

On the other hand, phosphatase and tensin homolog (PTEN) appears as a potent downregulated hub gene. As it is depicted in Table 2, PTEN is a well-known tumor suppressor. As it is shown in Figures 6 and 7, PTEN is associated with important groups of biological processes. Low expression value of PTEN in lung cancer is reported by researchers (24). This finding supports the positive role of ferroptosis in cancer development.

Overexpression of TXNRD1, SDO1, and TXN, the 2TH to 4TH upregulated hub genes in lung cancer, is investigated and confirmed by researchers (25-27). These finding are corresponded to the role of upregulated DEGs in promoting lung cancer. HNRNPA1, HNRNPA2B1, and HSP90AB1are the downregulated hubs. Han P et al investigation revealed that HNRNPA1 Knockdown promotes non-small cell lung cancer (NSCLC) metastasis (28). The results correspond with the advantages of ferroptosis. In contrast, it is reported that overexpression of HSP90 is a factor in tumorigenesis (29). This finding can be considered a defect of ferroptosis.

"Regulation of oxidative stress-induced cell death" is a group of biological processes, including "positive regulation of oxidative stress-induced cell death", and three other related biological processes, which are shown in Figure 4, indicating that prevention of oxidative stress is a key function of ferroptosis. Regulation of oxidative stress is connected to P4HB, SOD1, TXN, and TLR4. These genes are linked to the "peptide disulfide oxidoreductase activity", "cellular response to oxygen radical", "negative regulation of smooth muscle contraction", "antioxidant

activity", and "MyD88-dependent toll-like receptor" groups of biological processes (Figure 5).

"Telomere maintenance via telomere lengthening" and "RNA-dependent DNA biosynthetic process" groups of biological processes appear as the significant biological processes related to the downregulated DEGs (Figures 6 and 7). The mentioned biological processes are associated with PTEN, HSP90AB1, HNRNPC, HNRNPA2B1, and HNRNPA1, the top downregulated hubs.

CONCLUSION

In conclusion, the anticancer effects of ferroptosis appear to be largely associated with the regulation of EGFR, TXNRD1, SOD1, TXN, PRDX1, PTGS2, TLR4, P4HB, UBC, GSR, VCP, PTEN, HNRNPA1, HNRNPA2B1, HSP90AB1, NPM1, XPO1, HNRNPC, NCL, EEF1A1, and HSPD1. However, the negative effects, such as downregulation of HSP90AB1, are complicated by the advantages of ferroptosis as an anticancer mechanism. "Regulation of oxidative stress-induced cell death", "Telomere maintenance via telomere lengthening", and "RNA-dependent DNA biosynthetic process" are the main affected groups of biological processes.

Conflict of interest

There is no conflict of interest.

Acknowledgment

This project is supported by Shahid Beheshti University of Medical Sciences.

Funding

Shahid Beheshti University of Medical Sciences supported this research.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. ***CA Cancer J Clin*** 2021;71(3):209-49.
2. Xing N, Du Q, Guo S, Xiang G, Zhang Y, Meng X, et al. Ferroptosis in lung cancer: a novel pathway regulating cell death and a promising target for drug therapy. ***Cell Death Discov*** 2023;9(1):110.
3. Zukotynski KA, Hasan OK, Lubanovic M, Gerbaudo VH. Update on Molecular Imaging and Precision Medicine in Lung Cancer. ***Radiol Clin North Am*** 2021;59(5):693-703.
4. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. ***Cell*** 2012;149(5):1060-72.
5. Manz DH, Blanchette NL, Paul BT, Torti FM, Torti SV. Iron and cancer: recent insights. ***Ann N Y Acad Sci*** 2016;1368(1):149-61.
6. Kinowaki Y, Taguchi T, Onishi I, Kirimura S, Kitagawa M, Yamamoto K. Overview of Ferroptosis and Synthetic Lethality Strategies. ***Int J Mol Sci*** 2021;22(17):9271.
7. Li J, Cao F, Yin HL, Huang ZJ, Lin ZT, Mao N, et al. Ferroptosis: past, present and future. ***Cell Death Dis*** 2020;11(2):88.
8. Cao JY, Dixon SJ. Mechanisms of ferroptosis. ***Cell Mol Life Sci*** 2016;73(11-12):2195-209.
9. Dixon SJ, Patel DN, Welsch M, Skouta R, Lee ED, Hayano M, et al. Pharmacological inhibition of cystine-glutamate exchange induces endoplasmic reticulum stress and ferroptosis. ***Elife*** 2014;3:e02523.
10. Li L, Gao Q, Wang J, Gu L, Li Z, Zhang S, et al. Induction of Ferroptosis by Ophiopogonin-B Through Regulating the Gene Signature *AURKA* in NSCLC. ***Front Oncol*** 2022;12:833814.
11. Zhu J, Xiong Y, Zhang Y, Wen J, Cai N, Cheng K, et al. The Molecular Mechanisms of Regulating Oxidative Stress-Induced Ferroptosis and Therapeutic Strategy in Tumors. ***Oxid Med Cell Longev*** 2020;2020:8810785.
12. Xie Y, Hou W, Song X, Yu Y, Huang J, Sun X, et al. Ferroptosis: process and function. ***Cell Death Differ*** 2016;23(3):369-79.
13. Doll S, Proneth B, Tyurina YY, Panzilius E, Kobayashi S, Ingold I, et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. ***Nat Chem Biol*** 2017;13(1):91-8.
14. Vu NT, Kim M, Stephenson DJ, MacKnight HP, Chalfant CE. Ceramide Kinase Inhibition Drives Ferroptosis and Sensitivity

to Cisplatin in Mutant KRAS Lung Cancer by Dysregulating VDAC-Mediated Mitochondria Function. ***Mol Cancer Res*** 2022;20(9):1429-42.

15. Rezaei-Tavirani M, Rezaei-Tavirani S, Ahmadi N, Naderi N, Abdi S. Pancreatic adenocarcinoma protein-protein interaction network analysis. ***Gastroenterol Hepatol Bed Bench*** 2017;10(Suppl1):S85-S92.
16. Tai F, Zhai R, Ding K, Zhang Y, Yang H, Li H, et al. Long non-coding RNA lung cancer-associated transcript 1 regulates ferroptosis via microRNA-34a-5p-mediated GTP cyclohydrolase 1 downregulation in lung cancer cells. ***Int J Oncol*** 2024;64(6):64.
17. Miotto G, Rossetto M, Di Paolo ML, Orian L, Venerando R, Roveri A, et al. Insight into the mechanism of ferroptosis inhibition by ferrostatin-1. ***Redox Biol*** 2020;28:101328.
18. Abbaszadeh HA, Peyvandi AA, Sadeghi Y, Safaei A, Zamanian-Azodi M, Khoramgah MS, et al. Er:YAG Laser and Cyclosporin A Effect on Cell Cycle Regulation of Human Gingival Fibroblast Cells. ***J Lasers Med Sci*** 2017;8(3):143-9.
19. Zamanian-Azodi M, Rezaei-Tavirani M, Hasanzadeh H, Rahmati Rad S, Dalilan S. Introducing biomarker panel in esophageal, gastric, and colon cancers; a proteomic approach. ***Gastroenterol Hepatol Bed Bench*** 2015;8(1):6-18.
20. Hao M, Liu W, Ding C, Peng X, Zhang Y, Chen H, et al. Identification of hub genes and small molecule therapeutic drugs related to breast cancer with comprehensive bioinformatics analysis. ***PeerJ*** 2020;8:e9946.
21. Gaiteri C, Ding Y, French B, Tseng GC, Sibille E. Beyond modules and hubs: the potential of gene coexpression networks for investigating molecular mechanisms of complex brain disorders. ***Genes Brain Behav*** 2014;13(1):13-24.
22. Sun J, Trumpower BL. Superoxide anion generation by the cytochrome bc1 complex. ***Arch Biochem Biophys*** 2003;419(2):198-206.
23. Talukdar S, Emdad L, Das SK, Fisher PB. EGFR: An essential receptor tyrosine kinase-regulator of cancer stem cells. ***Adv Cancer Res*** 2020;147:161-88.
24. Xun G, Hu W, Li B. PTEN loss promotes oncogenic function of STMN1 via PI3K/AKT pathway in lung cancer. ***Sci Rep*** 2021;11(1):14318.
25. Delgobo M, Gonçalves RM, Delazeri MA, Falchetti M, Zandoná A, Nascimento das Neves R, et al. Thioredoxin reductase-1 levels are associated with NRF2 pathway activation and tumor recurrence in non-small cell lung cancer. ***Free Radic Biol Med*** 2021;177:58-71.
26. Liu S, Li B, Xu J, Hu S, Zhan N, Wang H, et al. SOD1 Promotes Cell Proliferation and Metastasis in Non-small Cell Lung Cancer via an miR-409-3p/SOD1/SETDB1 Epigenetic Regulatory Feedforward Loop. ***Front Cell Dev Biol*** 2020;8:213.
27. Liu X, Dong X, Hu Y, Fang Y. Identification of thioredoxin-1 as a biomarker of lung cancer and evaluation of its prognostic value based on bioinformatics analysis. ***Front Oncol*** 2023;13:1080237.
28. Han P, Cao P, Yue J, Kong K, Hu S, Deng Y, et al. Knockdown of hnRNPA1 Promotes NSCLC Metastasis and EMT by Regulating Alternative Splicing of LAS1L exon 9. ***Front Oncol*** 2022;12:837248.
29. Birbo B, Madu EE, Madu CO, Jain A, Lu Y. Role of HSP90 in Cancer. ***Int J Mol Sci*** 2021;22(19):10317.