MARMARA
MEDICAL JOURNAL

Original Article

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The effect of epigenetic regulation on apoptosis and ferroptosis in A549 and MRC-5 cell lines

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Submitted: 16.07.2025 **Accepted:** 05.03.2026

ABSTRACT

Objective: Lung cancer represents the second most prevalent form of malignancy on a global scale and is associated with the highest mortality rate of all cancers. The objective of this study is to investigate the gene expression profiles of various cell death pathways in healthy lung cells and lung cancer cells. Furthermore, the study seeks to establish how epigenetically associated genes regulate these pathways.

Materials and Methods: The MRC-5 and A549 cell lines were cultivated under the optimal conditions for their growth. The isolation of RNA, the subsequent synthesis of cDNA, and the analysis of quantitative real-time PCR were performed in order to measure the expression levels of EZH2, DNMT1, caspase-3, and GPX4 genes in the cells.

Results: The findings of this study indicate an upregulation of the epigenetic regulators DNMT1 and EZH2, as well as the ferroptosis inhibitor GPX4, in A549 lung cancer cells. Concurrently, a decrease in caspase-3 gene expression was observed.

Conclusion: Our results indicate that the expression levels of the epigenetic regulators DNMT1 and EZH2 are elevated in lung cancer cells, which is associated with reduced apoptotic signaling, as indicated by decreased caspase-3 expression, and suppression of ferroptosis through increased GPX4 expression.

Keywords: Lung cancer, Apoptosis, Ferroptosis, Epigenetics, A549, MRC-5

1. INTRODUCTION

Lung cancer is among the most prevalent types of cancer and the foremost cause of cancer-related mortality [1, 2]. The higher incidence rates observed in developing countries can be attributed to the prevalence of air pollution. Notwithstanding considerable progress in surgical, radiotherapy, and chemotherapy methodologies over the preceding two decades, the disease persists as a considerable problem. The five-year survival rate for non-small cell lung cancer (NSCLC), the most common type, is approximately 15%. The occurrence of distant metastasis serves to compound the severity of the situation. Consequently, further research into the molecular mechanisms of lung cancer is imperative to identify more effective treatment methods for this disease [3]. In this study, the human lung adenocarcinoma A549 cell line (Alveolar Basal Epithelial cell line from a 1973 lung carcinoma patient) was utilised as a model system to investigate the effects of ferroptosis, epigenetics and apoptosis. These cells are extensively employed as a model in research pertaining to lung cancer [4, 5]. The fibroblast-based diploid cell culture line known as Medical Research Council cell strain 5 (MRC-5) was first established from lung tissue and represents healthy lung cells [6]. The study of heritable variations in gene expression not caused by changes in the DNA sequence is known as epigenetics, in contrast to the process of mutation. The principal epigenetic mechanisms encompass DNA methylation, chromatin structural changes, loss of imprinting, and non-coding RNA. Furthermore, epigenetic control of gene expression is a pivotal mechanism in the pathophysiology of numerous diseases, including cancer. [7, 8]. The prospect of novel biomarkers for the early diagnosis,

How to cite this article: Gurbuz Can V, Kusat T. The effect of epigenetic regulation on apoptosis and ferroptosis in A549 and MRC-5 cell. Marmara Med J 2026;39 (2): 146-150. doi: 10.5472/marumj.1951321

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ISSN: 1309-9469

http://doi.org/10.5472/marumj.1951321
Marmara Med J 2026;39(2): 146-150

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prognosis, prediction and response to therapy of cancer is provided by epigenetic changes in DNA. Additionally, reversing epigenetic modifications is a possible target for innovative treatment approaches and drug development [7, 9]. The primary process of development and programmed cell death, apoptosis has been the subject of much research over the last three decades [10]. In addition to encouraging the growth of tumors, abnormalities in apoptotic pathways can also render cancer cells resistant to therapy. Thus, apoptosis irregularity is a significant indication of malignancy [11]. Caspases represent a class of proteases that are indispensable for the process of apoptotic signaling. Caspase-3, a cysteine protease, has been identified as a key player in the process of apoptotic cell death. The therapeutic relevance of apoptosis in cancer treatment has been the subject of several studies, and caspase-3 is closely associated with apoptosis. Consequently, numerous conventional cancer therapies are designed to trigger apoptosis, with the objective of eradicating cancerous cells. It can thus be posited that the Caspase-3 induction process may hold significant importance in the context of tumour therapy [12].

Our study aims to determine the different cell death pathways that occur in healthy lung cells versus lung cancer cells, and how genes associated with epigenetics regulate these pathways.

2. MATERIALS and METHODS

Cell culture

In the present study, cell lines obtained from the American Type Culture Collection (ATCC) were utilised, and the multiplication of the A549 and MRC-5 cell lines was achieved by following the recommended method for seeding, as outlined by ATCC. The MRC-5 (ATCC: CCL-171 P:8) and A549 (ATCC: CCL-185 P:15) cell lines were cultivated under the appropriate conditions and subsequently seeded into sterile 25 cm^2 flasks containing Dulbecco's Modified Eagle Medium (DMEM medium), which was supplemented with 10% fetal bovine serum (FBS), 1% penicillin-streptomycin and 2 mM L-glutamine. The cells were then incubated at 37°C within a 5% CO2 incubator, continuing until a sufficient number of cells had been achieved. Following this, RNA isolation was carried out.

RNA isolation

The predetermined number of cells was then added to 6-well plates, with each plate containing three replicates. Following the incubation period, the cells were collected in accordance with the specified conditions and subjected to centrifugation at 2000 rpm at 4°C for a duration of 10 minutes. Following centrifugation, the samples were transferred to 1.5 mL Eppendorf tubes for the RNA isolation stage. In order to initiate the process of RNA isolation, it was first necessary to lyse the cells. For this purpose, TRIzol reagent (RiboEx Kit; catalogue number: 301-001, GeneAll Biotechnology, Seoul, Korea) was employed. Subsequent to this, RNA isolation was performed using a spin column-based RNA isolation kit (GeneAll Biotechnology, Hybrid-R, catalogue number: 305-101, Seoul, Korea) in accordance with the manufacturer's instructions. The concentration and purity of the isolated RNA were measured using a Qubit device (Invitrogen, Qubit4 Fluorometer), after which the samples proceeded to the cDNA synthesis stage.

cDNA Synthesis

The cDNA synthesis was conducted according to the protocols stipulated by the manufacturer (ABT, cDNA Synthesis Kit with Rnase Inh. catalogue number: C03-01-05, High Capacity, Turkey). A master mix was prepared, with a total volume of 20 µl, and reverse transcription was performed. The process was analysed on a ProFlex thermal cycler (Applied Biosystems™) at a temperature of 25 °C for five minutes, at a temperature of 50 °C for 15 minutes, and at a temperature of 85 °C for five minutes (1 cycle). The synthesised cDNA samples were stored at – 80 °C.

Quantitative Real-Time PCR analysis

The master mix was assembled, adhering to the manufacturer's guidelines (i.e., ABT, 2X SYBR Mastermix, catalogue number: Q03-01-05, Turkey) for real-time PCR analysis. The total volume of the master mix amounted to 10 µL. The reaction was performed on a Drawell Real-Time Quantitative PCR device, with an initial denaturation at 95 °C for 5 minutes (1 cycle), followed by 40 cycles of denaturation at 95 °C for 30 seconds, annealing at 60 °C for 30 seconds, and elongation at 72 °C for 1 minute. The samples were analysed in triplicate. The primers utilised are delineated in Table I. The glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH) gene was used for standardization.

Table I. *Primer sequences of genes*

Primer Name	Primer sequences (5' to 3')
EZH2_F	CCAAGGAAAAAGAAGAGGAAA
EZH2_R	CTATCACACAAGGGCACGAA
DNMT1_F	TTGGTGGATGAATGTGAGGA
DNMT1_R	CTCTGTTGGCTGGGTTTTTG
Caspase-3_F	ATTTGGAACCAAAGATCATACATGG
Caspase-3_R	TTCCCTGAGGTTTGCTGCAT
GPX4_F	AGTTTTCCGCCAAGGACATC
GPX4_R	TCTTCATCCACTTCCACAGC
GAPDH_F	ACCCACTCCTCCACCTTTGAC
GAPDH_R	TGTTGCTGTAGCCAAATTCGTT

EZH2: Enhancer of Zeste Homolog 2, DNMT1: DNA (Cytosine-5)-Methyltransferase 1, Caspase-3: Cysteine-aspartic acid protease-3, GPX4: Glutathione Peroxidase 4, GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase, F: Forward, R: Reverse

Statistical Analysis

GraphPad Prism 8 software (San Diego, CA, USA) and the IBM SPSS 25.0 software package (Chicago, IL, USA) were used to perform the statistical analyses and generate the graphs. All data were obtained from at least three independent experiments and are shown as mean ± standard deviation (SD). The data were determined to be normally distributed using the Shapiro-Wilk

test (p>0.05) and were also found to be homogeneous using the Levene test. The statistical evaluation of gene expression between the two cell lines (A549 and MRC-5) was achieved by employing the Student's t-test. Two-way analysis of variance (ANOVA) followed by Tukey's post hoc test was used to evaluate the effects of cell type and gene on expression levels when multiple genes were analyzed simultaneously. A p-value of less than 0.05 was considered statistically significant.

3. RESULTS

We selected Enhancer of Zeste 2 (EZH2), DNA methyltransferase 1 (DNMT1), caspase-3, and glutathione peroxidase 4 (GPX4) genes to see how different types of cell death pathways work in normal lung tissue cell lines and lung cancer cell lines, and how epigenetic regulation of these genes affects these pathways. Figure 1 shows the changes in gene expression in both cell lines. The statistical results indicate that all genes, except for caspase-3, were overexpressed in A549 cells compared to MRC-5 cells, and this increase was found to be statistically significant (p<0.05). Unlike other genes, in comparison to MRC-5 cells, caspase-3 expression was downregulated in A549 lung cancer cells, and this decrease was statistically significant (p<0.05)

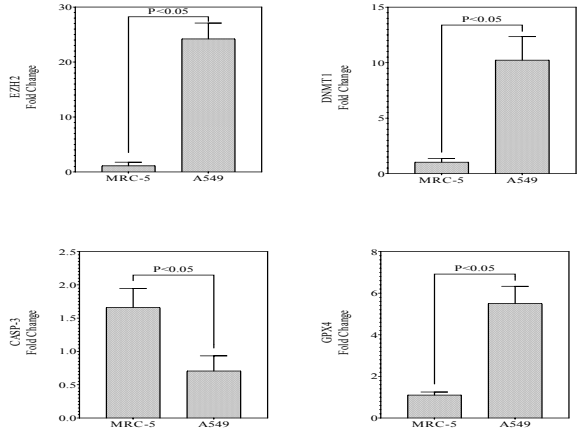


Figure 1 *Alterations in the level of EZH2, DNMT1, caspase-3, and GPX4 gene expression in MRC-5 and A549 cell lines*

Examining the interactions and relationships between genes in the same cell line revealed no statistically significant relationships between the EZH2 and DNMT1, DNMT1 and caspase-3, EZH2 and caspase-3, EZH2 and GPX4, and DNMT1 and GPX4 genes in the MRC-5 cell line (p>0.05) (Figure 2). Nevertheless, a significant relationship was found only between the caspase-3 and GPX4 genes in the MRC-5 cell line. In contrast, statistically significant relationships were found between all genes in the A549 cell line (p<0.05).

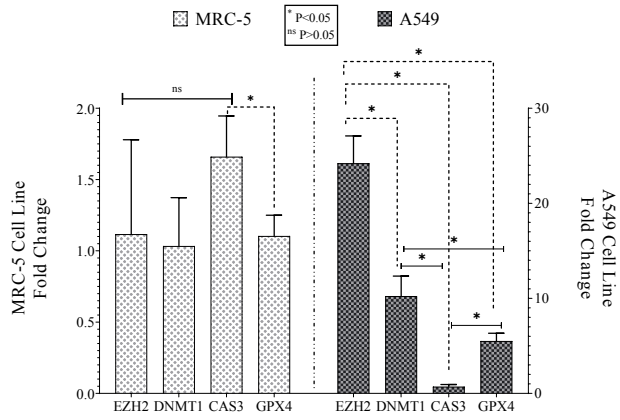


Figure 2. *The bar graph demonstrating gene interactions in MRC-5 and A549 cell lines*

4. DISCUSSION

Current treatment methods for lung cancer have a low overall survival rate due to the metastatic nature of the disease and its resulting resistance to drugs and radiation. Therefore, new treatment strategies and effective new drugs are urgently needed. GPX4 is a target of ferroptosis in lung cancer [13]. Apoptosis is the most frequent and well-investigated kind of programmed cell death. Recent research has revealed that ferroptosis is a new type of programmed cell death. Inhibition of GPX4 is required to activate ferroptosis, whereas activation of caspase-3 is required for apoptosis [14]. Regarding cancer, ferroptosis might be a natural way of stopping tumors from growing. This process is linked to p53 [15]. GPX4 levels are increased in lung cancer cells, which is necessary for cancer cells' survival [16-19]. GPX4 has also previously been shown to inhibit apoptosis [16, 20]. Studies have demonstrated that caspase-3 is downregulated in lung cancer, as in many other types of cancer [21, 22]. Similar to these studies, our study detected a significant increase in GPX4 expression levels in lung cancer cells compared to normal lung cells. Consistent with the results, caspase-3 expression, a key marker of apoptosis, was significantly reduced in A549 lung cancer cells compared to MRC-5 cells. Furthermore, we identified a significant relationship only between the caspase-3 and GPX4 genes within the MRC-5 normal lung cell line. This finding suggests a potential molecular-level association between apoptotic and ferroptotic pathways under physiological conditions.

EZH2 is a histone methyltransferase that functions as a core component of the Polycomb Repressor Complex 2 (PRC2) that adds methyl groups to lysine 27 of histone H3 (H3K27), which is linked to gene silencing [23]. EZH2 is involved in cell cycle, apoptosis, autophagy, DNA damage repair and cell differentiation. [24]. DNMT1 and EZH2 are crucial to the epigenetic control of genes [25]. Upregulation of DNMT1 and EZH2 has been connected to increased proliferation and aggressive metastatic activity, leading to a poor prognosis

http://doi.org/10.5472/marumj.1951321
Marmara Med J 2026;39(2): 6-150

in many types of cancer. Therefore, targeting DNMT1 and EZH2 could benefit patients with certain malignancies [26]. Studies have shown that EZH2 is overexpressed in various solid tumors, including lung cancer, and in this study, prognostic significance of EZH2 expression has been emphasised [27, 28]. The overexpression of EZH2 correlates with a worse prognosis for individuals diagnosed with NSCLC [27, 29]. Research has demonstrated a link between EZH2 and DNMT1, two epigenetic regulators and oncogenes, and the development and progression of tumors. The development and progression of various tumour cells are affected by the epigenetic regulation of EZH2 and DNMT1 [26]. Our study found that the EZH2 and DNMT1 genes, which act as epigenetic regulators in lung cancer, showed high expression levels.

Previous studies have reported that EZH2 – and DNMT1-mediated epigenetic regulation may influence ferroptosis-related pathways, including GPX4, under different conditions [30, 31]. In this study, epigenetic regulator expression patterns were found to be associated with GPX4 expression. Furthermore, the study revealed that GPX4 expression is co-upregulated with DNMT1 and EZH2 in lung cancer. The present findings indicate the likelihood of the existence of additional epigenetic or genetic molecular pathways that could lead to an increase in GPX4 expression in lung cancer, when the genes in question are evaluated in their entirety. Furthermore, studies have identified that the inhibition of EZH2 and DNMT1 genes can result in increased caspase-3 levels [32, 33]. In alignment with the aforementioned studies, our research revealed an inverse relationship between the expression of epigenetic regulators in lung cancer and the apoptosis-inducing enzyme, caspase-3.

In the present study, the interaction among all the genes under investigation in the context of lung cancer was evaluated. The results obtained revealed high expression of the epigenetic regulators EZH2 and DNMT1, as well as the ferroptosis inhibitor GPX4. In addition, low expression of the apoptosis inducer caspase-3 was identified. In summary, increased expression of epigenetic regulators was associated with reduced apoptotic signaling and suppression of ferroptosis, as indicated by decreased caspase-3 expression and increased GPX4 expression, respectively. This finding indicates that both death pathways are operational in lung cancer and interact with each other. Despite the existence of studies in the literature demonstrating the ability of the epigenetic regulators EZH2 and DNMT1 separately to induce GPX4 inhibition (with no studies investigating this phenomenon in the context of lung cancer), as outlined in the preceding discussion, there are also studies indicating that GPX4 is elevated in cases of lung cancer. In the review of the literature, there are no studies that evaluate these genes together in cancer. Consequently, the present study provides significant insights that address this knowledge gap in the existing literature.

Conclusions

In summary, the present study demonstrates that the expression levels of the epigenetic regulators DNMT1 and EZH2 are elevated in lung cancer cells. This is associated with reduced apoptotic signaling, as indicated by decreased caspase-3 expression, and suppression of ferroptosis through increased GPX4 expression in A549 lung cancer cells. Furthermore, the expression patterns of these genes suggest a complex and dynamic regulatory association in lung cancer cells. It is anticipated that these data will yield significant biomarkers, facilitating the diagnosis, treatment, and prognosis of lung cancer. To develop effective therapeutic strategies, there is an urgent need to conduct more in vivo and in vitro studies on how epigenetic modifications affect ferroptosis and apoptosis, and on their roles in cancer. The study is subject to certain limitations due to its in vitro cell culture design. No methodology at the protein level is available; therefore, the results do not offer direct insight into protein activity or pathway activation, and the study was conducted using a single lung cancer cell line, which may have limited its generalisability. Nevertheless, given that the present study is based on in vitro cell culture models and transcriptional analyses, the clinical relevance and generalisability of these findings must be validated through in vivo experiments and patient-based studies.

Compliance with Ethical Standards

Ethical statement: Ethics Committee approval was not required as this is a cell line-based study.

Conflict of interest: The authors declare that there is no conflict of interest.

Financial support: This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions: VGC: Responsible for the design of the study, research conceptualization, writing, review, editing, funding acquisition and performance, TK: performed the methodology and statistical analysis. VGC and TK have confirmed the authenticity of the raw data. Both authors confirm that they have read and approved of the final manuscript.

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