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Research Article

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The Role of DHRS2 in the Regulation of BRCA1 Expression in Non-small Cell Lung Cancer

DHRS2'nin Küçük Hücre Dışı Akciğer Kanserinde BRCA1 Ekspresyonunun Düzenlenmesindeki Rolü

Vahideh Zarerajabi [1,2], Burcu Salman Yaylaz [1,2], Sema Sırma Ekmekci [2] & Neslihan Abacı [2]

[1] İstanbul University, Institute of Graduate Studies in Health Sciences, Department of Genetics, İstanbul, Türkiye
[2] İstanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Genetics, İstanbul, Türkiye

Abstract

Objective: Non-small cell lung cancer (NSCLC) is a leading cause of cancer mortality and is often diagnosed late. *DHRS2* regulates lipid metabolism, hormones, and oxidative stress, acting as a tumour suppressor by stabilising p53 and inhibiting *MDM2*. *Tp53* and *BRCA1* are crucial for DNA repair and tumour suppression, with *BRCA1* as a prognostic marker in NSCLC. However, the interaction between *DHRS2* and *BRCA1* in NSCLC remains unclear. This study aimed to examine how *DHRS2* expression influences *BRCA1* levels in NSCLC cells, providing insight into potential therapeutic targets.

Material and Methods: *DHRS2* overexpression was induced in NSCLC cells (A549, H1299) and normal bronchial epithelial cells (BEAS-2B) using an expression vector and confirmed by quantitative PCR (qPCR). The effect of *DHRS2* overexpression on *BRCA1* expression levels was examined. In addition, *BRCA1* expression levels in NSCLC subtypes were analysed using GEPIA2, while genomic alterations in *BRCA1* and *DHRS2* were investigated via cBioPortal-TCGA.

Results: *DHRS2* overexpression led to a decrease *in BRCA1* expression in A549 cells (p53 wild-type) but had no effect in H1299 cells (p53-null). In BEAS-2B cells, *DHRS2* overexpression also resulted in *BRCA1* suppression. GEPIA2 analysis showed significantly higher *BRCA1* expression in tumour tissues. Genomic analysis revealed frequent *BRCA1* alterations, indicating instability, whereas *DHRS2* had fewer mutations, implying a regulatory role.

Conclusion: This study demonstrates that *DHRS2* modulates *BRCA1* expression through a p53-dependent mechanism. Genetic alterations in *BRCA1* and *DHRS2* indicate their potential involvement in NSCLC tumorigenesis. Future studies should further investigate the mechanisms mediated by *DHRS2* and p53 to elucidate their roles in cancer progression.

Keywords *DHRS2* · *BRCA1* · non-small cell lung cancer · DNA damage response

Öz

Amaç: Küçük hücre dışı akciğer kanseri (KHDAK), kansere bağlı ölümlerin önde gelen nedenlerinden biridir ve genellikle ileri evrede teşhis edilir. *DHRS2*, lipid metabolizması, hormon regülasyonu ve oksidatif stresle ilişkili olup, p53 stabilizasyonu ve *MDM2* inhibisyonu yoluyla kanser progresyonunu etkileyen önemli bir tümör baskılayıcıdır. *TP53* ve *BRCA1*, DNA hasar yanıtı ve tümör baskılama süreçlerinde kritik roller oynarken, *BRCA1* aynı zamanda KHDAK'de prognostik bir belirteç olarak öne çıkmaktadır. Bu çalışma, KHDAK hücrelerinde *DHRS2* ekspresyon düzeyleri ile *BRCA1* arasındaki etkileşimleri inceleyerek, moleküler mekanizmalarını daha iyi anlamayı ve yeni terapötik hedefler ile tedavi stratejileri geliştirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Bu çalışmada ekspresyon vektörü kullanılarak akciğer kanser hücre hatları (A549, H1299) ve normal bronş epitel hücre hattında (BEAS-2B), *DHRS2* aşırı ekspresyonu sağlanmış ve quantitative PCR (qPCR) ile doğrulanmıştır. Ardından, *DHRS2* aşırı ekspresyonunun *BRCA1* ekspresyon seviyeleri üzerindeki etkisi incelenmiştir. Ayrıca KHDAK'nin alt tiplerinde *BRCA1* ekspresyon düzeyleri GEPIA2, *BRCA1* ve *DHRS2* genlerindeki genomik değişiklikler ise cBioPortal-TCGA ile incelenmiştir.

Bulgular: *DHRS2*'nin aşırı ekspresyonu, A549 hücrelerinde (p53 wild type) *BRCA1* ekspresyonunu azaltırken, H1299 hücrelerinde (p53 null) herhangi bir değişikliğe neden olmamaktadır. BEAS-2B hücre hattında ise *DHRS2*'nin aşırı ekspresyonu *BRCA1* ekspresyonunu baskılamaktadır. GEPIA2 verileri, *BRCA1*'in tümör dokularında normal dokulara kıyasla belirgin şekilde arttığını göstermektedir. Genomik değişiklik analizi, *BRCA1*'deki amplifikasyonlar ve delesyonlar, genomik instabiliteyi işaret ederken, *DHRS2*'nin daha az mutasyon sergilemesi, düzenleyici rolünü ortaya koymaktadır.

Sonuç: Elde ettiğimiz bulgular *DHRS2*'nin *BRCA1* ekspresyonunu modüle edebileceğini ve p53'ün bu süreçte kritik rol oynayabileceğini göstermektedir. *BRCA1* ve *DHRS2*'deki genetik değişiklikler, KHDAK tümörigenezinde etkili olduğunu düşündürmektedir, gelecekteki çalışmalarla *DHRS2* ve p53 aracılı mekanizmaları daha ayrıntılı incelemelidir.

Anahtar Kelimeler *DHRS2* · *BRCA1* · Küçük hücreli dışı akciğer kanseri · DNA hasar yanıtı

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Corresponding author: Neslihan Abacı neslihan.abaci@istanbul.edu.tr

INTRODUCTION

Lung cancer is one of the most common types of cancer, accounting for approximately 26% of cancer-related deaths worldwide (1). Non-small cell lung cancer (NSCLC) accounts for 80% of lung cancer, and NSCLC is divided into lung squamous cell carcinoma (LUSC) and lung adenocarcinoma (LUAD). NSCLC is a group of diseases that exhibit genetic and cellular heterogeneity, but early diagnosis is difficult as there are usually no obvious symptoms in the early stages. NSCLC follows an aggressive course, often leading patients to be diagnosed with locally advanced or metastatic disease. While surgical intervention is preferred in early-stage patients, multimodal treatment modalities such as radiotherapy and chemotherapy combination are used in advanced-stage patients (2).

The Short-Chain Dehydrogenase/Reductase (SDR) superfamily plays important roles in the metabolism of lipids, amino acids, carbohydrates, steroid hormones, and xenobiotics and participates in redox sensing mechanisms. *DHRS2*, a member of the SDR family, has a structural domain that interacts with the coenzyme NADP. The organelle localisation of *DHRS2* protein is mainly in the cytoplasm, nucleus, and mitochondria. When it is in the nucleus, it is found mainly in the karyoteca (3). The highest levels of *DHRS2* are found in the parotid gland and ovary, and relatively low expressions are found in the liver, placenta, mammary glands, and testis (4). As an NADPH-dependent carbonyl reductase, *DHRS2* reduces dicarbonyl compounds and protects cells against carbonyl cytotoxicity. *DHRS2*, which plays an important role in lipid metabolism and hormone regulation, is also associated with mitochondrial oxidative stress and protects cells against oxidative damage. It contributes to cancer progression, particularly through p53 stabilisation and *MDM2* inhibition. The high expression of *DHRS2* may increase sensitivity to treatment in some types of cancer (e.g. Hodgkin's lymphoma, gastric cancer and colorectal cancer) and shows a protective function against oxidative stress. Furthermore, the inhibition of *DHRS2* offers an approach to combat resistance in cancer therapy. It is important to study the regulatory mechanisms of *DHRS2* to better understand its potential in cancer therapy. Although *DHRS2* has become prominent primarily for its tumour suppressor functions, its regulatory role in DNA repair processes and these mechanisms are not yet fully understood, and the function of *DHRS2* in cancer biology stands out as a research area that needs to be examined in more depth (5).

The p53 protein is a crucial tumour suppressor that responds to DNA damage by regulating genes involved in the DNA damage response (DDR) (6). While *BRCA1* was previously associated with breast and ovarian cancer, it has recently gained interest as a prognostic and predictive marker in other tumours like NSCLC. *BRCA1* is recognised as a multifunctional tumour suppressor protein that plays an essential role in a range of critical cellular processes, including cell cycle regulation, DNA replication, mitotic spindle assembly, transcriptional control, and the higher-order organisation of chromatin (7). Additionally, *BRCA1* is integral to the DDR and apoptosis. Beyond its tumour-suppressive functions, *BRCA1* also modulates cellular responses to cytotoxic chemotherapy. Therefore, *BRCA1* is being investigated as a potential predictive marker in NSCLC treatment (8).

This study aimed to investigate possible interactions between *DHRS2* expression levels and *BRCA1*. To determine the effects of the *DHRS2* gene on NSCLC and the associated molecular mechanisms, *BRCA1* expression levels were examined in one non-cancerous human lung epithelial cell line (BEAS-2B) and two NSCLC cell lines [A549 (p53 wild type) and H1299 (p53 deficiency)] which were induced with the *DHRS2* expression vector. Investigating the interactions between *BRCA1* and *DHRS2* in the context of NSCLC may provide valuable insights into novel therapeutic targets and treatment pathways against this deadly disease.

MATERIAL AND METHODS

Expression of the *BRCA1* gene in NSCLC

Gene expression levels were analysed using the GEPIA2 database. Tumour tissues from LUAD and LUSC patients were compared with corresponding normal tissues. Data were expressed in Transcripts Per Million (TPM) units, and statistically significant differences were assessed using appropriate statistical analyses.

Genomic Alteration Analysis of *BRCA1* and *DHRS2* in the LUAD and LUSC samples

Genomic alterations in *the BRCA1* and *DHRS2* genes in LUAD and LUSC were analysed using the cBioPortal for Cancer Genomics (https://www.cbioportal.org/). Data from the TCGA (The Cancer Genome Atlas) Firehose Legacy and TCGA Nature 2014 datasets were used for this analysis. The genomic alterations, including missense mutations, splice mutations, truncating mutations, amplifications, and deep deletions, were identified and visualised by the OncoPrint tool.

Cell culture

The human non-small cell lung cancer cell lines (A549 and H1299) and the regular bronchial epithelial cell line (BEAS-2B), which were stored in a liquid nitrogen tank (-196°C), were obtained from the Istanbul University Aziz Sancar Institute of

Experimental Medicine. Both the H1299 and BEAS-2B cell lines were cultured in RPMI-1640 medium (Thermo Fisher Gibco, ABD) supplemented with 10% heat-inactivated fetal bovine serum (sourced from South America; Capricorn, Germany) and 1% penicillin-streptomycin (P/S) (Capricorn, Germany). The cells were incubated at 37°C with 5% CO_2. Similarly, A549 cells were grown in DMEM/F12 medium (Thermo Fisher Gibco, ABD) formulated by ATCC, supplemented with 10% FBS and 1% P/S, and incubated at 37°C in a 5% CO_2 ambiance.

Plasmids and Transfection

A commercially purchased expression vector containing the *DHRS2* gene (OriGene, USA) was used. We established three groups: 1. *DHRS2-overexpressing* group, 2. non-target (NT) control group (in which cells were transfected with the same vector but with the gene region removed), and 3. no template control (NTC) group (a group without transfection treatment). Commercially available E. coli strains (DH5α) were used as competent cells to replicate the expression vector. The vectors were transformed into cells according to the protocol and then selected according to antibiotic resistance. After the selected colonies had been grown in LB medium, we isolated the vectors using the Miniprep isolation kit (Invitrogen, ABD). We transfected *DHRS2* containing vector and empty vector into cells separately according to the manufacturer's protocol of Lipofectamine™ 3000 (Invitrogen, ABD) transfection agent. The cells were harvested 24 and 48 h after transfection. RNA was then isolated from these cells for analysis, and the overexpression efficiency was evaluated using qPCR.

Quantitative PCR (qPCR)

Total RNA was extracted using the PureLink® RNA Mini Kit (Invitrogen-Thermo Fisher, ABD). Subsequently, complementary DNA (cDNA) was synthesised from RNA using the High Capacity cDNA Reverse Transcription Kit (Thermo Scientific, Massachusetts, USA), following the manufacturer's protocol. Quantitative PCR was performed in quintuplicate on the LightCycler 480 system using the Bioline SensiFast SYBR® No-Rox kit ((Meridian, Bioline, ABD). QPCR was performed under the following conditions: Fluorescence signals were acquired during pre-denaturation at 95°C for 5 min, followed by amplification at 95°C for 10 s, 64°C for 20 s, and 72°C for 10 s for 45 cycles. The melting curve analysis was then performed at 95°C for 5 s and 65°C for 1 min, with a final hold at 4°C for 30 s. Target gene expression levels were normalised to the internal control gene TATA-binding protein and then calculated using the $2^{-\Delta\Delta Ct}$ method. The primer sequences are provided in Table 1.

Table 1. Primer sequences of the target genes

Gene	Primer Sequence	
	Forward 5'– 3'	Reverse 5'– 3'
DHRS 2	GCT GTC ATC CTG GTC TCT TCC	CTG GAA CCA CGC AGT TTA CC
BRCA1	CCG AAG AGG GGC CAA GAA AT	ACA GAC ACT CGG TAG CAA CG
TBP	ACT TGA CCT AAA GAC CAT TGC AC	CTT GAA GTC CAA GAA CTT AGC TGG

Statistical analysis

Statistical analyses were performed using SPSS version 25.0 (IBM SPSS Corp., Armonk, NY, USA) and GraphPad Prism (version 8.0.2, Boston, USA). The expression levels of the *DHRS2* and *BRCA1* genes were compared using Student's t-test, Mann–Whitney U test, and one-way analysis of variance (ANOVA). A p-value of less than 0.05 was considered statistically significant.

RESULTS

Expression Levels of the *BRCA1* Gene in the LUAD and LUSC Samples

Gene expression analysis using the TCGA dataset in GEPIA revealed that *BRCA1* expression levels were significantly elevated in LUAD and LUSC tumour tissues compared with normal tissues. In both the LUAD and LUSC groups, the gene expression levels were higher in tumour tissues, whereas the normal tissues exhibited lower expression levels (Figure 1).

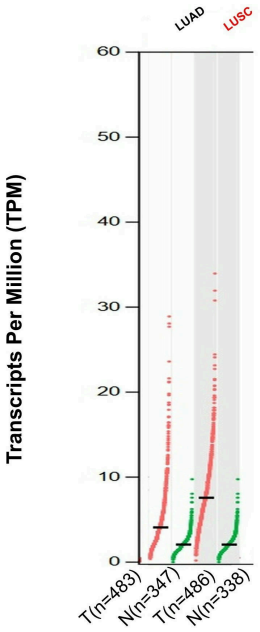

Figure 1. The expression levels of the *BRCA1* gene in the LUAD and LUSC samples and normal tissues in the GEPIA database.

Genomic alteration analysis of the *BRCA1* and *DHRS2* genes in LUAD and LUSC

The genomic alteration analysis revealed distinct mutation patterns in *BRCA1* and *DHRS2* across the LUAD and LUSC samples. *BRCA1* exhibited frequent amplifications (red) and deep deletions (blue), indicating potential genomic instability and its role in tumour progression. Additionally, various mutations, including missense (green), splice (orange), and truncating mutations (yellow), were observed, demonstrating possible functional disruptions. In contrast, *DHRS2* primarily showed amplification events (red), with fewer detected mutations, including some missense mutations (green). Overall, the alteration frequency for both genes was approximately 3% among the analysed samples, highlighting their potential involvement in NSCLC tumorigenesis (Figure 2a). Additionally, Figure 2b demonstrates the differences in the types and frequencies of genetic alterations in the *BRCA1*

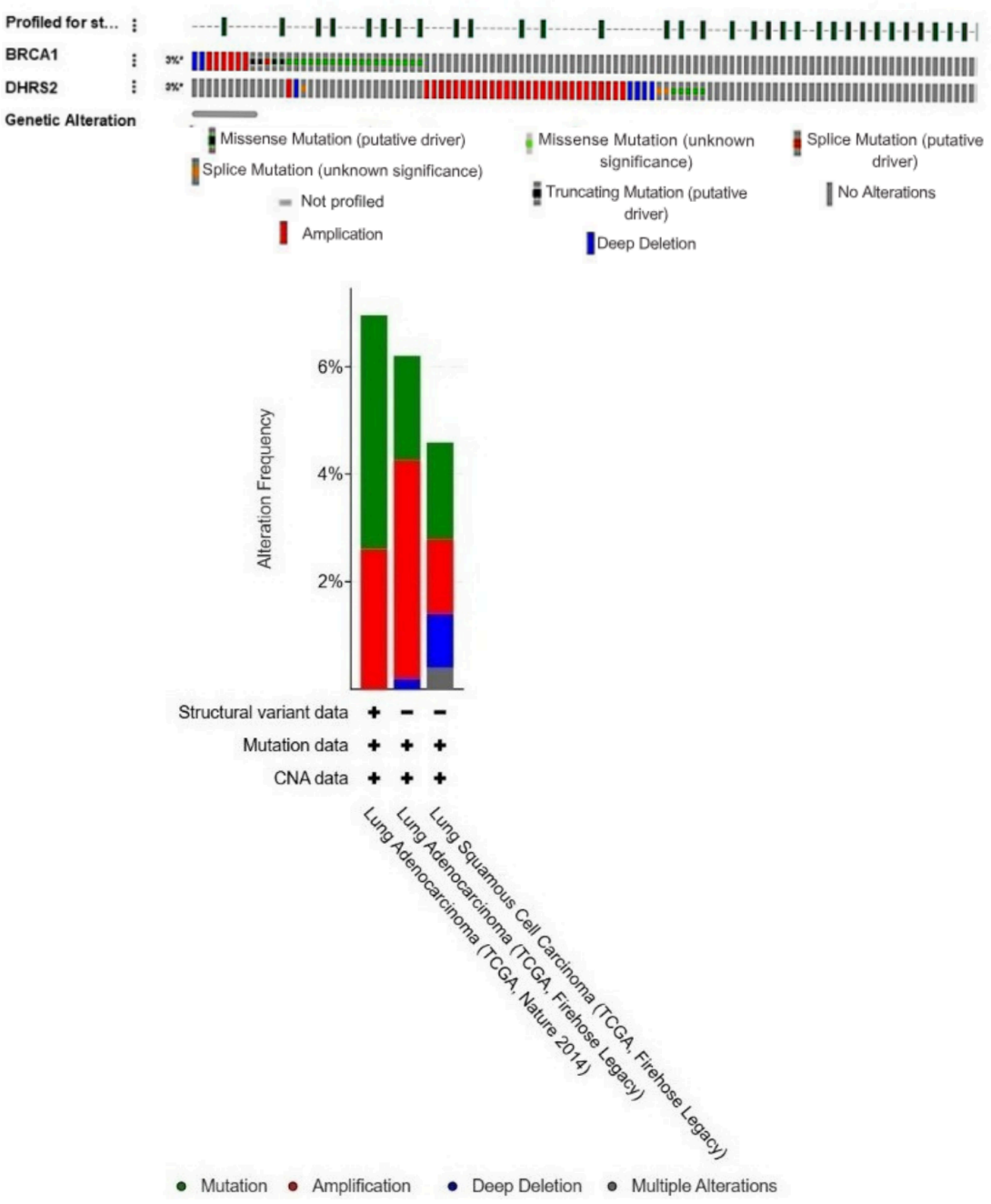

Figure 2. Genomic alterations in the *BRCA1* and *DHRS2* genes in NSCLC analysed by the cBioPortal database. (a) OncoPrint of the gene alterations in these two genes in the LUAD and LUSC cohorts (the different colours indicate different types of genetic alterations, of which amplification accounts for the largest proportion). (b) Details of the gene alteration types in the *BRCA1* and *DHRS2* in the LUAD and LUSC cohorts. CNA, copy number alteration; TCGA, The Cancer Genome Atlas; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma.

and *DHRS2* genes across various LUAD and LUSC databases. According to the results, alterations in these genes were observed in approximately 5% of the total patient population. The most common type of alteration was mutation (green), which was detected in both cancer types. An increase in the copy number (red) was observed in certain patient groups, while in some patients, the *BRCA1* and *DHRS2* genes were completely deleted (blue, deep deletion). The proportion of samples with multiple alterations was low (grey). Furthermore, differences in the rates of genetic alterations were observed between LUAD and LUSC, with *BRCA1* amplifications being more frequent in LUSC (Figure 2b). Together, these results suggest that the genomic alterations of these genes might play an essential role in cancer onset and progression.

DHRS2 Modulates *BRCA1* Expression in Lung Cancer and Normal Bronchial Epithelial Cells

DHRS2 overexpression was performed in A549, H1299 and BEAS-2B cells and confirmed the successful construction of A549 *DHRS2* OE, H1299 *DHRS2* OE and BEAS-2B *DHRS2* OE cell lines by qPCR analysis.

In this study, we evaluated the changes in *BRCA1* expression levels in A549, H1299, and BEAS-2B cell lines overexpressing the *DHRS2* gene (Figure 3). The findings suggest that the effect of *DHRS2* on *BRCA1* regulation is related to the cell type, p53 levels, and transfection method used:

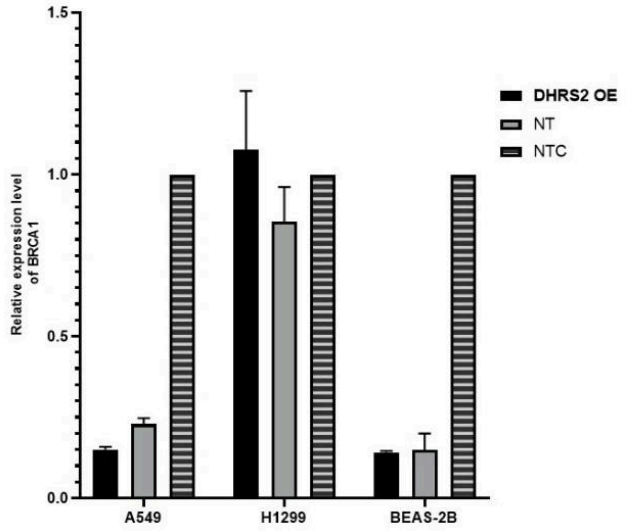

Figure 3. Relative expression level of the *BRCA1* gene in the A549 *DHRS2* OE, H1299 *DHRS2* OE and BEAS-2B *DHRS2* OE, groups ($p<0.001$).

A549 cell line (p53 wild type): *BRCA1* expression was significantly reduced in the *DHRS2* overexpressed group, but the expected difference between the NT and the overexpressed groups was not observed. This suggests that lipofectamine affects *BRCA1* expression.

H1299 cell line (p53 null): *BRCA1* expression was unchanged between the control and DHRS2-overexpressing groups. This result supports that p53 deficiency may abrogate the effect of *DHRS2* on *BRCA1*.

In the BEAS-2B cell line (normal human bronchial epithelial cell): *BRCA1* expression was found at lower levels in the *DHRS2* overexpressing group compared with the control groups. This indicates that *DHRS2* can suppress *BRCA1* expression in healthy cells.

DISCUSSION

Non-small cell lung cancer is one of the most common cancers worldwide and has a high risk of developing metastases at later stages. The prognosis of these patients is generally poor and their response to treatment is limited (2). Therefore, early diagnosis and treatment is of great importance in NSCLC patients.

In recent years, there has been a growing interest in the role of the SDR (dehydrogenase/reductase) enzyme family in the carcinogenesis and progression of cancers. In particular, the *DHRS2* gene is located on chromosome 14q11.2 and the loss of this region is a common chromosomal alteration in various cancers, suggesting that *DHRS2* may be a tumour suppressor gene. However, whether *DHRS2* functions as an oncogene or a tumour suppressor gene varies depending on the specific cancer type (9). Overexpression of *DHRS2* in some cancer types, particularly breast cancer, is associated with poor prognosis. This may increase the invasion of cancer cells and lead to accelerated metastatic processes. The catalytic and non-catalytic effects of *DHRS2* in metabolic processes also play an important role in cancer progression and the development of resistance to treatment. Increased expression of *DHRS2* may enhance the resistance of cancer cells to oxidative stress and inhibit cellular invasion. However, decreased expression of *DHRS2* has also been observed in some cancers. Decreased *DHRS2* expression in oesophageal, ovarian, gastric cancer and leukaemia cells leads to increased oxidative stress, disruption of the cell cycle and inhibition of cancer cell proliferation. This may weaken the tumour suppressor function of *DHRS2* and contribute to developing resistance to therapy (10). Furthermore, *DHRS2* has been reported to be associated with tumour genomic instability, and this mechanism plays a critical role in cancer progression (11). *DHRS2*'s regulation of p53 and inhibition of *MDM2*'s E3 ubiquitinate activity is one of the crucial mechanisms affecting the biological behaviour of cancer cells (9). *DHRS2* increases the stability of p53 by binding with *MDM2*, which contributes to the maintenance of cellular homeostasis. This interaction may lead to attenuation of tumour suppressive

effects, especially in cancer types where the function of p53 is impaired (12). *DHRS2* has NADPH-dependent dicarbonyl reductase activity, which plays a role in neutralising ROS. It has been shown that the NADP/NADPH ratio decreases in cells overexpressing *DHRS2* and increases in cells in which *DHRS2* is inactivated. In parallel, a decrease in mitochondrial ROS levels was observed in cells lacking *DHRS2* expression. Increased ROS levels can promote DNA damage and lead to oxidative stress in the cell. High levels of oxidative stress can cause cell death, whereas low levels of stress activate DNA repair mechanisms, promoting cell growth, migration, and invasion. ROS-induced DNA damage is frequently observed in cancer cells (9).

Interactions between *BRCA1* and p53 also play an important role in cancer development. *BRCA1* plays a critical role in maintaining genetic stability, whereas p53 regulates the cell cycle and apoptosis and exerts tumour suppressive effects. However, p53 dysfunction can lead to impaired *BRCA1* function and increased cellular resistance to DNA damage. This may lead to increased resistance to therapy, especially in sporadic breast cancer (13). The interaction of *DHRS2* with *BRCA1* and p53 may play an important role in tumour suppression. The fact that *DHRS2* regulates the homeostasis of cancer cells by increasing p53 stability may allow further potentiation of its tumour suppressive effects. However, the interactions of *DHRS2* with *BRCA1* and p53 need to be examined in more detail.

The findings indicate that *BRCA1* gene expression is elevated in LUAD and LUSC tumours, indicating its potential role in the tumorigenesis of these lung cancer subtypes. Given *BRCA1*'s established function in DNA repair mechanisms, its involvement in lung cancer pathogenesis should be further explored.

Integrating the GEPIA2 database analysis with our cell culture experiments supports the notion that *BRCA1* plays a crucial role in LUAD and LUSC, while *DHRS2*'s regulatory influence on this mechanism is context-dependent. Our data demonstrate that *BRCA1* and *DHRS2* interactions may serve as potential biomarkers or therapeutic targets in lung cancer, warranting further investigation into their clinical relevance.

Genomic Alterations in *BRCA1* and *DHRS2*

The observed genetic alterations in *BRCA1* and *DHRS2* reveal their potential implications in NSCLC tumorigenesis. Frequent copy number variations, including amplifications and deletions in *BRCA1*, indicate its role in genomic instability and tumour progression. This aligns with previous studies highlighting *BRCA1*'s involvement in DNA damage response and repair pathways. Interestingly, *DHRS2* exhibited fewer mutations, implying that its function in NSCLC may be modulated through regulatory mechanisms rather than direct genetic alterations. Further studies are required to elucidate whether *DHRS2*'s tumour-suppressive role directly influences *BRCA1* expression and how these alterations correlate with patient prognosis and therapeutic responses.

Functional Role of *DHRS2* in *BRCA1* Regulation

Our results show that *DHRS2*'s effect on *BRCA1* regulation may be associated with a p53-dependent mechanism and is highly cell type-specific. In A549 cells (p53 wild-type), *DHRS2* overexpression significantly downregulated *BRCA1* expression, supporting a potential p53-mediated regulatory mechanism. The absence of this effect in H1299 cells (p53-null) reinforces the hypothesis that p53 may be required for *DHRS2*-induced *BRCA1* suppression.

Additionally, the lack of expected differences between the NT and *DHRS2*-overexpressing groups in A549 cells implies that Lipofectamine, the transfection reagent, may independently influence *BRCA1* expression. This highlights the necessity of evaluating transfection methods when studying gene regulation. Future studies should validate *DHRS2*'s precise effect on *BRCA1* using alternative transfection strategies to minimise confounding variables.

Finally, *BRCA1* downregulation in BEAS-2B cells upon *DHRS2* overexpression indicates that *DHRS2* may regulate *BRCA1* even in normal bronchial epithelial cells. This indicates that *DHRS2* exerts regulatory functions in normal and cancerous cells through distinct mechanisms, which may have important implications for tumour biology.

This study highlights the differential genetic alterations in *BRCA1* and *DHRS2* across the LUAD and LUSC subtypes. The observed mutation and copy number variations demonstrate that these genes play key roles in lung cancer pathogenesis. The higher frequency of *BRCA1* amplifications in specific patient cohorts further supports its association with DNA repair processes and tumour-suppressive mechanisms. Meanwhile, the role of *DHRS2* in cancer progression remains to be elucidated, particularly regarding its potential tumour-suppressive or oncogenic functions in different cancer types.

Our findings indicate that *BRCA1* and *DHRS2* alterations may serve as potential biomarkers and therapeutic targets in lung cancer. However, validation in patient cohorts and functional studies is necessary to confirm their clinical utility. Future research should focus on elucidating the interactions between *DHRS2*, *BRCA1*, and p53, as well as optimising experimental designs to eliminate potential technical biases.

Ethics Committee Approval: This study was conducted using a cell line and does not require ethics committee approval.
Peer Review: Externally peer-reviewed.
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Author Details

Vahideh Zarerajabi
[1] İstanbul University, Institute of Graduate Studies in Health Sciences, Department of Genetics, İstanbul, Türkiye
[2] İstanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Genetics, İstanbul, Türkiye
0009-0003-0527-297X

Burcu Salman Yaylaz
[1] İstanbul University, Institute of Graduate Studies in Health Sciences, Department of Genetics, İstanbul, Türkiye
[2] İstanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Genetics, İstanbul, Türkiye
0000-0002-9144-3899

Sema Sırma Ekmekci
[2] İstanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Genetics, İstanbul, Türkiye
0000-0002-1201-7542

Neslihan Abacı
[2] İstanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Genetics, İstanbul, Türkiye
0000-0002-9962-4010 neslihan.abaci@istanbul.edu.tr

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