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An Investigation of TRIM36 Expression in Breast Cancer

Meme Kanserinde TRIM36 Ekspresyonunun İncelenmesi

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Öz

Meme kanseri, dünya genelinde en sık teşhis edilen kanser türü olup, kansere bağlı ölümler arasında ikinci sırada yer almaktadır. *TRIM36*'nın rolü prostat ve akciğer kanseri gibi bazı insan kanserlerinde araştırılmış olsa da bu proteinin işlevleri büyük ölçüde bilinmemektedir. Bu çalışmada, daha önce meme kanseri ile ilişkisi incelenmemiş olan *TRIM36*'nın ifade düzeyi ve meme kanseri patogeneziyle potansiyel ilişkisi analiz edilmiştir. Çalışma kapsamında, 45 meme kanseri hastasının normal ve tümör dokularından RNA izole edilmiştir. İzole edilen RNA'dan tamamlayıcı DNA (cDNA) sentezlenmiş ve *GAPDH* ile *TRIM36*'nın mRNA ifade düzeyleri qRT-PCR yöntemiyle ölçülmüştür. *TRIM36* ifadesinin meme dokularında gözlendiği tespit edilmiştir; ancak, *GAPDH*'ye normalize edilen *TRIM36* mRNA ifade düzeyleri açısından normal ve tümör dokuları arasında istatistiksel olarak anlamlı bir fark bulunamamıştır (p=0.731). Bu çalışma, meme kanseri dokularında *TRIM36* gen ifadesinin normal dokulardan farklı olmadığını öne sürse de sınırlı örneklem boyutu, *TRIM36* geni ile meme kanseri arasındaki ilişkinin daha kapsamlı çalışmalarla aydınlatılması gerekliliğini ortaya koymaktadır.

Anahtar Kelimeler: Gen Ekspresyonu, Meme Kanseri, *TRIM36*

Abstract

Breast cancer is the most frequently diagnosed cancer type worldwide and ranks 2nd among cancers that cause death. While the role of *TRIM36* has been investigated in certain human cancers, such as prostate and lung cancer, its functions remain largely unexplored. In this study, the expression level of *TRIM36*, whose role in breast cancer has not been previously examined, and its potential association with breast cancer pathogenesis were analyzed. RNA was isolated from normal and tumor tissues of 45 breast cancer patients. Complementary DNA (cDNA) was synthesized from the RNA, and mRNA expression levels of *GAPDH* and *TRIM36* were quantified using qRT-PCR. *TRIM36* expression was observed in breast tissues; however, no statistically significant difference was found in *TRIM36* mRNA expression levels, normalized to *GAPDH*, between normal and tumor tissues (p=0.731). Although this study suggests that *TRIM36* gene expression levels in breast cancer tissues do not differ from normal tissues, the limited sample size highlights the need for more comprehensive studies to elucidate the relationship between the *TRIM36* gene and breast cancer.

Keywords: Gene Expression, Breast Cancer, *TRIM36*

Introduction

According to GLOBOCAN data for 2022, breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer-related deaths worldwide, following lung cancer. It has the highest incidence among women (1). The heterogeneous nature of breast cancer, the incomplete understanding of tumorigenesis mechanisms, and the resulting limited availability of specific treatment options for most subtypes contribute to its high incidence and mortality rates. Consequently, the identification of biomarkers with strong diagnostic potential has gained significant attention for improving diagnostic and therapeutic strategies (2).

TRIM (tripartite motif) proteins are a family of E3 ubiquitin ligases comprising more than 70 members. (3,4). The TRIM protein family is defined by the presence of a RING domain, one or two B-box domains, a coiled-coil domain, and a variable C-terminal domain (5). Specific C-terminal domains of TRIM proteins include the COS domain, fibronectin type III repeat (FNIII), PRY domain, SPRY domain, acid-rich domain (ACID), filamin-type IG domain (FIL), NHL domain, PHD domain, bromodomain (BROMO), Meprin and TRAF-homology domain (MATH), ADP-ribosylation factor family domain (ARF), and transmembrane domain (TM) (6).

TRIM proteins are implicated in various diseases, including cancer, infectious diseases, developmental disorders, and neuropsychiatric conditions (7). Many TRIM proteins have been identified as playing dual roles in human cancers, functioning as both tumor suppressors and oncogenes. For instance, translocation of *TRIM19* is involved in acute promyelocytic leukemia (APL) (8). TRIM24 acts as an oncogenic transcription activator, promoting cell growth in prostate cancer cells and regulating proliferation in gastric cancer and hepatocellular carcinoma (9, 10). TRIM22 and TRIM24 target TP53 for degradation (11, 12), whereas TRIM13 overexpression stabilizes TP53, leading to apoptosis induction (13).

Additionally, *TRIM29* regulates the Wnt/β-catenin signaling pathway and acts as an oncogene in gastric cancer (14). In contrast, *TRIM8* is downregulated in glioma tissues and interacts with

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activated STAT protein inhibitors, such as PIAS3, negatively regulating their activity (15, 16).

TRIM36 is an RBCC (RING, B-box, Coiled-Coil) protein that belongs to the C-I TRIM subfamily. It is encoded by a 55 kb genomic sequence comprising 10 exons, localized on chromosome 5q22.3. First identified in 2001 (5), *TRIM36* was cloned and characterized by Balint et al. in 2004. According to this study, the TRIM36 protein, consisting of 728 amino acids, includes a RING finger, two B-boxes, a coiled-coil domain, a fibronectin type III motif, and a C-terminal domain. Although TRIM36 contains a putative nuclear localization signal, it was exclusively detected in the cytoplasm (17).

TRIM36 expression has been shown to be high in testis, prostate, and brain tissues, while being low in kidney, lung, and heart tissues. Despite being synthesized in many cell types, TRIM36 is notably absent in mitotic cells (17). Additionally, TRIM36 has been reported to be associated with homodimerization and microtubules (6). In a study conducted in 2009, TRIM36 overexpression was observed to decelerate the cell cycle and limit cell growth (18).

In this study, we investigated the expression levels of *TRIM36*, a gene that has not been previously studied in the context of breast cancer, and its potential association with breast cancer pathogenesis.

Material and Method

Tissue Samples

Fine needle aspiration biopsies were collected from both tumor tissue and normal tissue (approximately 50 mg in weight) from the same individual, with normal tissue sampled at least 5 cm away from the tumor site. These samples were obtained from 45 breast cancer patients undergoing mastectomy at Zonguldak Bülent Ecevit University Faculty of Medicine, Department of General Surgery. The collected tissues were preserved in TRIzol™ reagent (Thermo Fisher Scientific) and stored at -80°C until RNA isolation. Written informed consent was obtained from all participants prior to their inclusion in the study. The study protocol was approved by the Zonguldak Bülent Ecevit University Non-Interventional Clinical Research Ethics Committee on February 10, 2021 (Approval No. 2021/03).

RNA Isolation

RNA isolation from tissue samples was carried out using the PureLink™ RNA Mini Kit (Invitrogen, Thermo Fisher Scientific, Cat. No: 12183018A) according to the manufacturer's protocol. The concentration and purity of the isolated RNA samples were measured using a microplate and µDrop plate reader (Thermo Scientific Multiskan™ Sky, Cat. No: 51119600DP). Measurements were performed at 230, 260, and 280 nm wavelengths. RNase-free water provided in the PureLink™ RNA Mini Kit was used as a blank control. The isolated RNA samples were stored at -80°C until further use.

cDNA Synthesis

cDNA synthesis was carried out using the cDNA Synthesis Kit with RNase Inhibitor (High Capacity) (A.B.T.™). The reaction was prepared in a final volume of 20 µl according to the manufacturer's protocol, consisting of 1X Reaction Buffer, 2.5 mM dNTP mix, 50 µM random hexamers, 200 U/µl reverse transcriptase, 0.5 µl RNase inhibitor, 10 µl RNA, and 3.5 µl RNase-free water. The reaction mixture was incubated at 25°C for 10 minutes, 37°C for 120 minutes, and 85°C for 5 minutes. The resulting cDNA concentrations and purities were measured using the same microplate and µDrop plate reader (Thermo Scientific Multiskan™ Sky, Cat. No: 51119600DP) and stored at -80°C until further use.

Real-Time PCR (qRT-PCR)

Real-time PCR (qRT-PCR) experiments were conducted using the synthesized cDNAs and 2X qPCR SYBR-Green MasterMix (without ROX) (A.B.T.™) on a CFX96 Touch™ Real-Time PCR Detection System.

For the *GAPDH* gene, primer and template concentrations were optimized according to the manufacturer's instructions, and single-site amplification was confirmed through melting curve analysis. The reaction mixture included 1X Master Mix, 0.5 µM forward and reverse primers, and 2 µl cDNA in a total volume of 20 µl. The PCR cycling conditions were as follows: 95°C for 10 minutes, followed by 40 cycles of 15 seconds at 95°C and 45 seconds at 62°C. Primer sequences used; *GAPDH* forward: 5′-GGTGGTCTCCTCTGACTTCAACA-3′, *GAPDH* reverse: 5′-GTGGTCGTTGAGGGCAATG-3′

For the *TRIM36* gene, primer and template concentrations were similarly optimized, and single-site amplification was verified through melting curve analysis. The reaction mixture included 1X Master Mix, 0.4 µM forward and reverse primers, and 1.8 µl cDNA in a total volume of 20 µl. The PCR cycling conditions were as follows: 95°C for 5 minutes, followed by 40 cycles of 15 seconds at 95°C and 45 seconds at 62°C. Primer sequences used; *TRIM36* forward: 5′-CGTCGGTCCTCCTCCAGAGTTTGTG-3′, *TRIM36* reverse: 5′-GTGGCAAGTTCCGTCGTCGTCTTCC-3′

Primer sequences were designed using Primer3 software (19). All qRT-PCR experiments were performed in triplicate. The relative expression of *TRIM36* in tumor and normal tissues was calculated

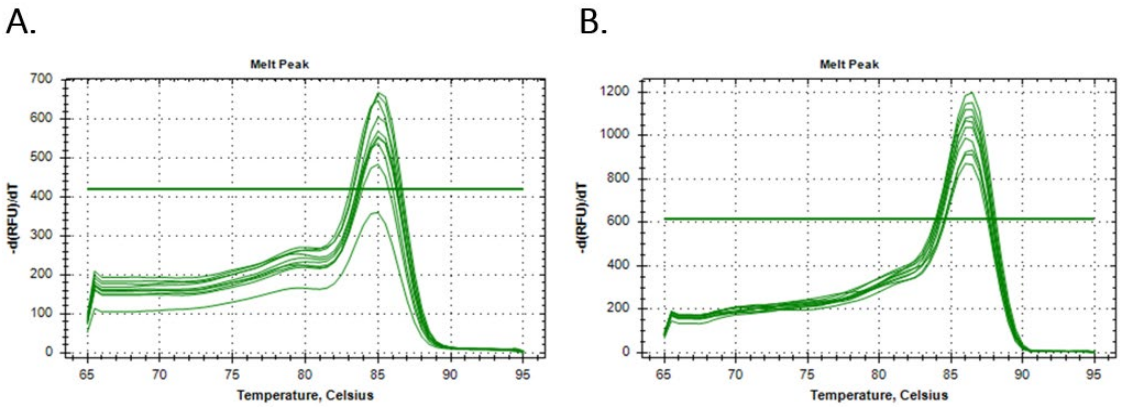

Figure 1. (A) Melting curve analysis showing the melting peak obtained from amplification using primers designed for the GAPDH gene. (B) Melting curve analysis showing the melting peak obtained from amplification using primers designed for the TRIM36 gene.

using the 2^-ΔΔCT method (20), with *GAPDH* serving as the reference gene.

Statistical Analysis

The sample size of the study was calculated using a medium effect size (Cohen's d = 0.5). A minimum of 78 samples (n = 39 per group) were required to achieve 80% power and a confidence level of α <0.05, as calculated using the GPower 3.1.9.7 software. However, we analyzed a total of 90 samples (n = 45 per group). Statistical analyses were performed using SPSS software (Version 29.0). The normality of the data distribution was assessed using the Shapiro-Wilk test. Descriptive statistics are presented as median (minimum–maximum). The Wilcoxon signed-rank test was employed to compare *TRIM36* mRNA expression levels between the two paired groups. A p-value of <0.05 was considered statistically significant.

Results

In this study, *TRIM36* expression levels were analyzed in tumor and adjacent normal breast tissues from 45 breast cancer patients. The primer pairs used for detecting *GAPDH* and *TRIM36* mRNA levels were validated for specificity by melting curve analysis, confirming single-site amplification (Figure 1).

The relative mRNA expression level of *TRIM36* was normalized to *GAPDH* mRNA expression levels in the same tissues. The median of fold change of *TRIM36* expression relative to *GAPDH* was 0.5218 (0.05-8.73) in normal tissues and 0.5775 (0.01-3.94) in tumor tissues. Desciptive statistics are presented in Table 1.

qRT-PCR results indicated that *TRIM36* is expressed in human breast tissue. However, no statistically significant difference was observed in *TRIM36* expression levels between normal and tumor tissues (p = 0.731, Table 1, Figure 2).

Table 1. Statistics of TRIM36 mRNA expression fold changes in normal and tumor tissues.

Descriptive statistics	Normal tissue (n=45)	Tumor tissue (n=45)	Total (n=90)	p value / significance
Median	0.5218	0.5775	0.5252	
Minimum	0.05	0.01	0.01	0.731[w]
Maximum	8.73	3.94	8.73	

[w]Wilcoxon Signed ranks test.

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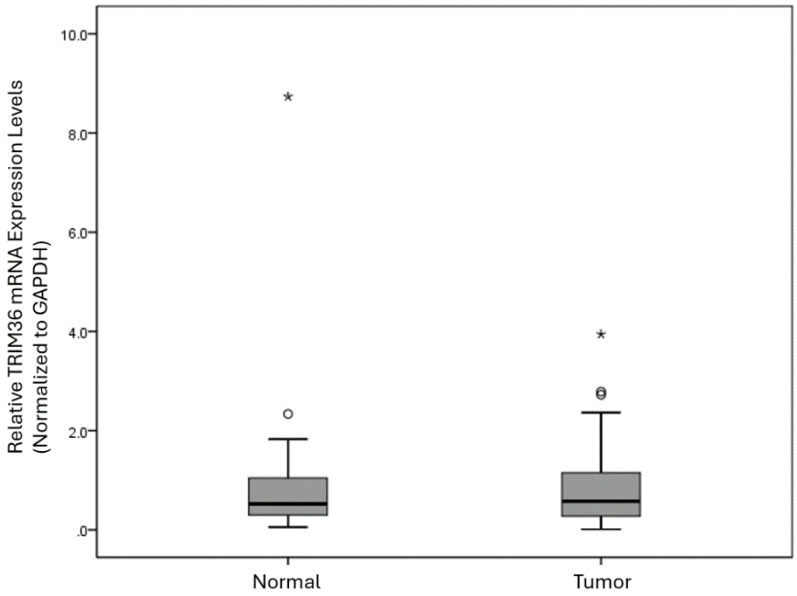

Figure 2. Fold changes in TRIM36 mRNA expression in normal and tumor tissues.

Discussion

Breast cancer, the most commonly diagnosed and one of the most lethal cancers worldwide, is among the malignancies in which the roles of TRIM family members have been extensively studied. For instance, *TRIM25* is expressed in female organs through estrogen action (21). Its high expression levels in human breast cancer cells (MCF7) were shown to accelerate tumor growth, while its silencing slowed tumor progression. Additionally, overexpression of *TRIM25* was found to promote breast cancer development by degrading the cell cycle inhibitor 14-3-3σ (22).

Similarly, *TRIM24* overexpression has been associated with poor prognosis and reduced survival in breast cancer patients (23). TRIM29, which transcriptionally inhibits TP53 (24), has been shown to enhance cell proliferation and metastatic activity in pancreatic cancer cells (25). In contrast, decreased TRIM29 expression in MCF10A human breast cells led to increased cell growth, enhanced cell motility, and impaired 3D acinar formation in vitro. Conversely, in MCF7 cells, overexpression of TRIM29, which is normally expressed at low levels, resulted in reduced cell division rates (26).

Furthermore, silencing TRIM47 in breast cancer cell lines was found to inactivate the PI3K/Akt signaling pathway, leading to the inhibition of cell proliferation, migration, and invasion (27).

In addition, several TRIM proteins are known to play distinct roles in breast cancer. For example, TRIM3, TRIM6, TRIM11, TRIM14, TRIM27, TRIM32, TRIM37, TRIM39, TRIM44, TRIM59, and TRIM63 have been identified as oncogenic, whereas TRIM16, TRIM21, TRIM31, TRIM35, and TRIM62 function as tumor suppressors (28).

To date, no studies have specifically investigated the relationship between *TRIM36*, the focus of this study, and breast cancer. However, a study using tumor tissues from mice injected with human breast cancer cells reported a decrease in *TRIM36* expression levels in breast tissue (39).

Although the roles of *TRIM36* in human cancers are gradually being elucidated, further research is necessary. For instance, *TRIM36* expression has been found to be elevated in prostate cancer, suggesting a potential role in carcinogenesis (17). Interestingly, however, a study reported that high TRIM36 expression levels were associated with favorable prognosis in prostate cancer, inhibiting cell proliferation and migration. Furthermore, it was proposed that TRIM36, which also promotes apoptosis, functions as a tumor suppressor (30).

In another study published in the same year, high TRIM36 expression levels were observed in prostate cancer tissues. Interestingly, TRIM36 was shown to inhibit the MAPK/ERK phosphorylation pathway, which plays a critical role in tumor survival and development (31).

Conversely, *TRIM36* expression levels were reported to be significantly lower in non-small cell lung cancer and esophageal cancer compared to healthy controls (32,33). In human neuroblastoma patients, *TRIM36* was found to be hypermethylated and expressed at lower levels in individuals with a more aggressive disease course (34).

A study suggested that TRIM36 may influence glycolysis by regulating the expression of the glycolysis-related protein HK2 and neuroendocrine differentiation in prostate cancer. This regulatory mechanism was shown to be inhibited by glycolytic and HK2 inhibitors (35).

More recently, in 2023, TRIM36 was reported to directly interact with and suppress FOXA2, thereby activating the Nrf2/GPX4 ferroptosis signaling

pathway. This interaction suggests a tumor suppressor role for TRIM36 in colorectal cancer (36).

TRIM36 is recognized as an androgen-responsive gene and has been shown to enhance the efficacy of anti-androgen drugs in prostate cancer (31). Androgen signaling is essential for the development and maintenance of male sexual characteristics, including muscle mass, strength, bone mineral density, prostate enlargement, spermatogenesis, hair distribution, and neuronal remodeling. Moreover, it plays a pivotal role in female physiology and reproduction.

Androgen signaling has been implicated in several diseases, including prostate cancer, breast cancer, diabetes, metabolic syndrome, and Alzheimer's disease (37). Notably, androgens have been reported to inhibit human breast cancer cell proliferation both in vitro and in vivo, and clinical observations suggest that androgens or androgenic compounds may exert protective effects against breast cancer growth in women (38).

In this context, TRIM36 may have significant and unexplored roles in breast cancer, potentially influenced by its interaction with androgen signaling pathways.

In this study, we analyzed the relative mRNA expression levels of *TRIM36* in female breast cancer patients by normalizing them to *GAPDH* mRNA levels. We evaluated whether *TRIM36* expression differs between tumor and normal breast tissues. Our findings confirm that *TRIM36* is expressed in breast tissues; however, no statistically significant difference was observed in its expression levels between normal and tumor tissues.

The qRT-PCR analyses further supported that *TRIM36* gene expression in breast cancer tissues does not significantly differ from that in normal tissues. These findings suggest that additional molecular mechanisms should be explored to elucidate the potential role of *TRIM36* in breast cancer development.

Notably, this study was conducted with a limited number of patient samples. Although no significant differences in *TRIM36* expression were identified, larger-scale studies are required to validate these findings in a broader patient population and to fully understand the involvement of *TRIM36* in breast cancer pathogenesis.

Conclusion

In this study, the expression levels of *TRIM36* mRNA in normal and tumor breast tissues were investigated. While *TRIM36* was found to be expressed in breast tissues, no statistically significant differences were observed between normal and tumor tissues. These findings suggest that *TRIM36* may not play a direct role in breast cancer development. However, larger-scale studies with more comprehensive datasets are needed to further evaluate the potential involvement of *TRIM36* in breast cancer and its relationship with other molecular mechanisms.

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Conflict of interest statement

The authors declare no conflict of interest.

Ethics Committee Approval: The study protocol was approved by the Zonguldak Bülent Ecevit University Non-Interventional Clinical Research Ethics Committee. (Zonguldak / February 10, 2021/Approval No:2021/03).

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