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Research Article

Omentin-1 is associated with the expression of proliferation, migration, and PI3K/AKT-related genes in breast cancer cells

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Abstract

Background: Breast cancer (BC) progression is regulated not only by intrinsic tumor characteristics but also by the tumor microenvironment, including adipose tissue-derived adipokines. Omentin-1 (intelectin-1) is a visceral adipokine implicated in metabolic regulation and inflammation; however, its role in BC remains controversial and insufficiently defined.

Aims: This study aimed to evaluate the effects of omentin-1 on the proliferation, adhesion, and migration of BC cells and to investigate its association with the expression of PIK3CA/AKT1-related and migration-associated genes.

Methods: MCF-7 (estrogen receptor-positive, weakly invasive) and MDA-MB-231 (estrogen receptor-negative, highly invasive) BC cell lines were treated with 100 and 200 ng/mL of recombinant omentin-1 for 24 and 48 h. Cell proliferation was assessed using the XTT assay, adhesion by an XTT-based method after washing, and migration via a wound-healing assay. The expression levels of PIK3CA, AKT1, and MMP-9 were analyzed by quantitative real-time polymerase chain reaction. Statistical significance was set at $p < 0.05$.

Results: Omentin-1 significantly reduced proliferation in MCF-7 cells at 48 h by 20%–30% relative to control ($p < 0.001$), whereas no significant effect was observed in MDA-MB-231 cells ($p > 0.05$). Adhesion remained unchanged in the two cell lines (94%–100% across all groups, $p > 0.05$). Migration was significantly inhibited in MCF-7 cells at 72 h, with gap closure declining from 85.71% to 62.98% and 58.98% ($p = 0.031$; $p = 0.001$). In contrast, MDA-MB-231 cells responded in a limited, time-dependent manner, with enhanced migration at 24 h and with no variations at 72 h due to complete closure. Gene expression analysis revealed dose- and time-dependent changes in transcription of *PIK3CA*, *AKT1*, and *MMP-9*, with each cell line showing distinct patterns.

Özet

Dayanak: Meme kanseri progresyonu, yalnızca tümöre özgü intrinsik özellikler tarafından değil, aynı zamanda adipoz dokudan kaynaklanan adipokinleri de içeren tümör mikroçevresi tarafından düzenlenmektedir. Omentin-1 (intelectin-1), metabolik düzenleme ve inflamasyon süreçlerinde rol oynadığı bilinen visseral kökenli bir adipokindir; ancak meme kanserindeki rolü hâlen tartışmalı olup yeterince tanımlanmamıştır.

Amaçlar: Bu çalışmada, omentin-1'in meme kanseri hücrelerinde proliferasyon, adezyon ve migrasyon üzerindeki etkilerinin değerlendirilmesi ve PIK3CA/AKT1 ile ilişkili ve migrasyonla ilişkili gen ekspresyonlarıyla olan bağlantısının araştırılması amaçlanmıştır.

Yöntemler: MCF-7 (östrojen reseptörü pozitif ve zayıf invaziv) ve MDA-MB-231 (östrojen reseptörü negatif ve yüksek invaziv) hücre hatları 100 ve 200 ng/mL omentin-1 ile 24 ve 48 saat süreyle muamele edilmiştir. Proliferasyon XTT yöntemiyle, adezyon yıkama sonrası XTT ile, migrasyon ise yara iyileşme testiyle değerlendirilmiştir. PIK3CA, AKT1 ve MMP-9 genlerinin ekspresyon düzeyleri kantitatif gerçek zamanlı polimeraz zincir reaksiyonu yöntemiyle belirlenmiştir. İstatistiksel anlamlılık düzeyi $p < 0,05$ olarak kabul edilmiştir.

Bulgular: Omentin-1, 48. saatte MCF-7 hücrelerinde proliferasyonu anlamlı düzeyde azaltmıştır (kontrole göre %20–30 azalma, $p < 0,001$); buna karşılık MDA-MB-231 hücrelerinde anlamlı bir etki gözlenmemiştir ($p > 0,05$). Adezyon, her iki hücre hattında da değişmeden kalmıştır (tüm gruplarda %94–100, $p > 0,05$). Migrasyon, MCF-7 hücrelerinde 72. saatte anlamlı şekilde baskılanmış ve gap kapanma oranı %85,71'den %62,98 ve %58,98'e düşmüştür ($p = 0,031$; $p = 0,001$). Buna karşılık, MDA-MB-231 hücrelerinde daha sınırlı ve zamana bağlı bir yanıt gözlenmiş; 24. saatte artış görülürken, 72. saatte tüm gruplarda tam kapanma nedeniyle fark izlenmemiştir. Gen ekspresyon analizleri, *PIK3CA*, *AKT1* ve *MMP-9* için doza ve

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Conclusion: Omentin-1 is associated with differential effects on BC cell behavior in a cell line-, dose-, and time-dependent manner, which are observed in parallel with alterations in the expression of PIK3CA/AKT1- and cell migration-related genes.

zamana bağlı değişimler olduğunu ve bu değişimlerin hücre hatlarına özgü farklılıklar gösterdiğini ortaya koymuştur.

Sonuç: Omentin-1'in, meme kanseri hücre davranışları üzerinde hücre hattı, doz ve zamana bağlı farklı etkilerle ilişkili olduğu ve bu etkilerin PIK3CA/AKT1 ile ilişkili ve migrasyonla ilişkili gen ekspresyon değişiklikleri ile paralellik gösterdiği saptanmıştır.

Keywords: Omentin-1, breast cancer, PIK3CA, AKT1, MMP-9

Introduction

Breast cancer (BC) is one of the most common tumors among women and remains a leading cause of cancer-related mortality, primarily due to recurrence and metastasis (Riggio et al., 2021). Although advances in diagnosis and treatment have improved patient outcomes, the molecular mechanisms underlying tumor progression and metastasis are incompletely understood. Identifying factors that regulate BC cell proliferation and migration is, therefore, essential for improving prognostic assessment and developing novel therapeutic strategies.

Tumor behavior is influenced by intrinsic gene-level alterations and interactions with the tumor microenvironment (TME) (Dec et al., 2023). The adipose tissue of the breasts is a major component of this microenvironment and functions as an active endocrine organ by secreting adipokines that regulate inflammation, metabolism, angiogenesis, and cell signaling (Kothari et al., 2020). An increasing body of evidence suggests that adipokines can modulate key processes, including cell proliferation, adhesion, and migration, involved in carcinogenesis (Dec et al., 2023; Kothari et al., 2020). Obesity-associated adipose tissue dysfunction has been linked to chronic low-grade inflammation, insulin resistance, and altered adipokine profiles, which may promote the initiation and progression of breast tumors. Specific adipokines, such as leptin and adiponectin, have been extensively implicated in BC biology, with leptin generally exerting pro-tumorigenic effects by promoting proliferation, angiogenesis, and migration; in contrast, adiponectin is more often associated with anti-proliferative and pro-apoptotic impacts. Therefore, the imbalance of adipokine signaling within the obese breast TME is considered an important contributor to BC aggressiveness and determinant of clinical outcomes (Lamabadusuriya et al., 2025; Ma et al., 2025; Verras et al., 2023).

Omentin-1, also known as intelectin-1 (ITLN1), is a visceral adipose tissue-derived adipokine with reported anti-inflammatory, antioxidant, and endothelial-protective properties (Gu et al., 2019; Maruyama et al., 2012; Mylonakis et al., 2025; Yamawaki et al., 2011). At the molecular level, it is associated with the PIK3CA/AKT1 signaling pathway, which plays a central role in regulating cell growth, survival, and motility and is frequently dysregulated in BC. This pathway is one of the most commonly altered signaling cascades in BC, with activating mutations in PIK3CA and aberrant AKT signaling contributing to tumor progression, epithelial–mesenchymal transition (EMT), metastasis, and resistance to endocrine and targeted therapies. Furthermore, its activation leads to downstream signaling through mTOR, forming the PI3K/AKT/mTOR axis, which supports tumor cell growth, survival, and metabolic adaptation (Khorasani et al., 2024; Ortega et al., 2020). Alterations in this pathway have been associated with tumor aggressiveness and metastatic potential (Dec et al., 2023; Li et al., 2015b; Ortega et al., 2020).

Experiments investigating the role of omentin-1 in cancer have yielded inconsistent results. Omentin-1 promotes proliferation, invasion, migration, and angiogenesis in colorectal cancer cells, whereas tumor-suppressive impacts, including reduced proliferation and enhanced apoptosis, have been described in gastric cancer, neuroblastoma, and hepatocellular carcinoma cells (Li et al., 2015a; Li et al., 2015b; Mylonakis et al., 2025; Ye et al., 2019; Zhang & Zhou, 2013; Zhang et al., 2020).

These divergent findings support the notion that the bioeffects of omentin-1 are highly context-dependent and vary according to cancer type and cell environment.

Clinical studies evaluating circulating omentin-1 levels in BC have reported conflicting findings, and *in vitro* data addressing its impacts on BC cell behavior remain limited (Abas et al., 2022; Christodoulatos et al., 2021; Panagiotou et al., 2021; Tahmasebpour et al., 2020). In line with this observation, clinical investigations of breast neoplasms have demonstrated altered circulating omentin-1 contents compared with healthy controls, suggesting a role of this adipokine in BC biology that has not yet been fully clarified. Moreover, the potential impacts of omentin-1 on the expression of PIK3CA/AKT1-related and migration-associated genes in BC cells remain poorly elucidated.

Therefore, the present study aimed to investigate the influence of omentin-1 on proliferation, adhesion, and migration in BC cell lines with distinct phenotypic characteristics. In addition, it evaluated the expression of PIK3CA/AKT1- and migration-associated genes, including *PIK3CA*, *AKT1*, and *MMP-9*, to provide insights into the molecular associations underlying the cell-level responses to omentin-1.

Materials and Methods

Cell Culture

MCF-7 (weakly invasive, estrogen positive) and MDA-MB-231 (highly invasive, estrogen negative) BC cell lines were obtained from the American Type Culture Collection (USA) and cultured

in 75 cm^2 flasks containing Dulbecco's Modified Eagle's Medium containing 10% (v/v) fetal bovine serum, penicillin/streptomycin (100 units/mL), and 2 mM L-glutamine at 5% CO_2 and 37 °C temperature. The cultured cells were treated with 100 and 200 ng/mL recombinant omentin-1 (Catalog no: 9137-IN-050, R&D Systems) to evaluate its molecular effects.

Cell Proliferation

Cell proliferation was determined using the 2,3-Bis(2-Methoxy-4-Nitro-5-Sulfophenyl)-2H-Tetrazolium-5-Carboxanilide (XTT) method, which relies on the suppression of mitochondrial enzymes in metabolically active cells. Briefly, 7×10^3 cells were seeded into each well of a 96-well plate. Following the incubation period, 50 µL of XTT solution was added to each well containing 100 µL of medium, and A_{450} was measured after 2 h using a Multiskan GO ELISA reader (Thermo Scientific) following the kit instructions to quantify cell proliferation. Each experiment was repeated at least three times, six wells per repetition.

Adhesion Assay

To evaluate adhesion, 7×10^3 cells were seeded into each well of a 96-well plate. For each experimental group, including adhesion and corresponding control wells, eight wells were allocated. After allowing cell adherence for 24 h, omentin-1 was administered at the previously indicated concentrations. Following incubation, non-adherent cells were removed by washing the wells three times with PBS. Cell adhesion was then quantified via the XTT assay, and absorbance was measured with an ELISA reader. All experiments were performed in triplicate.

Migration Assay

Cell migration was assessed employing a wound-healing assay. Cells were seeded into 35-mm tissue culture dishes at a density of 5×10^5 cells per dish and allowed to attach for 24 h. Subsequently, linear wounds were created by scratching the cell monolayer with a sterile 1-mL pipette tip. Detached cells were removed by washing with fresh culture medium, after which omentin-1 was added. Following 1 h of incubation, baseline images were obtained, and wound widths at all line intersections were measured at 24, 48, and 72 h using an inverted microscope equipped with a µm-level scale. Cell migration was quantified by measuring wound closure in 45 randomly selected areas per sample at each time point. Each experiment was repeated independently three times.

Determination of Gene Expression Levels by Real-Time Polymerase Chain Reaction (PCR)

Total RNA Isolation

Cultured cells were detached from the flask with trypsin and seeded into 6-well culture dishes at a density of 5×10^5 cells per well. After a 24 h incubation period, recombinant omentin-1 was added at 100 and 200 ng/mL, and cells were treated for 24 and 48 h. At the end of each incubation, cells were trypsinized, harvested from the flask bottom, and total RNA was isolated using the Biobasic EZ-10 kit following the manufacturer's protocol. RNA concentration was determined using a spectrophotometer. RNA samples were stored at −80 °C until use.

cDNA Synthesis

cDNA was synthesized using 200 ng of total RNA with the OneScript® cDNA Synthesis Kit (abm) per the manufacturer's protocol. Briefly, random primers, RT buffer, dNTPs, nuclease-free water, and reverse transcriptase were employed under optimized PCR conditions (Techne). The synthesized cDNAs were then stored at −20 °C until further use in qPCR analysis.

qRT-PCR

Expression patterns of the target genes *PIK3CA* (Hs00907957_m1), *AKT1* (Hs00178289_m1), *MMP-9* (Hs00957562_m1), and *18S RNA* (Hs99999901_s1) were analyzed using real-time PCR (Stratagene Mx3000p, California, USA). The qPCR reaction mix was prepared by mixing cDNAs with appropriate primer probes (TaqMan® Gene Expression Assay, 20X), PCR master mix (TaqMan® Gene Expression Master Mix), and nuclease-free water. Gene expression in cells was quantified using gene-specific primer-probe sets and normalized employing the *18S RNA* housekeeping gene. The fold change in transcription was calculated using the $2^{-\Delta\Delta C_T}$ method (Schmittgen & Livak, 2008).

Statistical Analysis

All experiments were performed in at least three independent biological replicates, each including technical triplicates. Data are presented as the mean ± standard deviation. Normality of data distribution was assessed using the Shapiro–Wilk test, and homogeneity of variance was evaluated utilizing Levene's test before parametric analyses. For proliferation and adhesion assays involving two independent variables—dose and time—within each cell line, two-way analysis of variance (ANOVA) was applied to evaluate main and synergistic effects. For migration and gene expression analyses, which included three independent variables—cell line, dose, and time—three-way ANOVA was used to assess the effects of these factors and their interactions. Post hoc comparisons were performed employing Tukey's Honestly Significant Difference test. A level of $p < 0.05$ was considered statistically significant. All analyses were performed utilizing IBM SPSS Statistics software.

Results

Cell Proliferation

At 24 h, proliferation of MCF-7 cells did not differ significantly between the control group and 100 ng/mL ($p = 0.914$) or 200 ng/mL ($p = 0.958$) omentin-1 treated groups, and between the 100 and 200 ng/mL groups ($p = 0.992$). However, unlike between the treatment groups ($p = 0.998$), proliferation declined significantly in the 100 ng/mL ($p < 0.001$) or 200 ng/mL ($p < 0.001$) groups compared to the control at 48 h (Figure 1a). Similarly, at 24 h, proliferation in MDA-MB-231 did not differ statistically between the 100 ng/mL ($p = 0.960$) or 200 ng/mL ($p = 0.972$) groups compared to the control, and between the treated groups ($p =$

0.999). Although a slight decrease was observed at 48 h, there was no variation between the treated groups ($p = 0.472$) (Figure 1b).

Adhesion

The effects of omentin-1 on adhesion in MCF-7 and MDA-MB-231 cell lines were evaluated at 24 and 48 h (Figure 1c–d). In MCF-7 cells, adhesion levels were relatively stabilized across treatment groups. At 24 h, these were 98.45% in the control, 98.88% at 100 ng/mL ($p = 0.989$), and 97.50% at 200 ng/mL ($p = 0.947$); at 48 h, these were 95.46%, 96.25% ($p = 0.952$), and 97.82% ($p = 0.654$), respectively. However, no notable differences were observed between the treatment groups, indicating that omentin-1 did not markedly affect adhesion capacity (Figure 1c). In MDA-MB-231 cells, adhesion values were also high and fluctuated only minimally following treatment. At 24 h, adhesion decreased slightly from 100% (control) to 97.17% (100 ng/mL) ($p = 0.630$) and 98.08% (200 ng/mL) ($p = 0.783$). At 48 h, the values were 98.19%, 94.12% ($p = 0.587$), and 98.04% ($p = 0.999$) (Figure 1d). Although 100 ng/mL induced a modest reduction, particularly at 48 h, overall changes remained limited.

Migration

Omentin-1 was more effective in suppressing the migration of MCF-7 than MDA-MB-231 cells (Figure 1e–f). In the control group MCF-7 cells, gap closure increased over time—24 h: 25.65%, 48 h: 58.86%, and 72 h: 85.71%. Omentin-1 did not significantly alter migration at early time points; at 24 h, closure rates were 27.14% (100 ng/mL) ($p = 0.962$) and 27.52% (200 ng/mL) ($p = 0.941$); at 48 h, these were 45.81% and 46.32%, respectively ($p = 0.189$; $p = 0.213$). However, at 72 h, omentin-1 markedly reduced migration, with gap closure decreasing to 62.98% (100 ng/mL; $p = 0.031$) and 58.98% (200 ng/mL; $p = 0.001$) compared to the control (Figure 1e). The control group MDA-MB-231 cells showed enhanced baseline migration levels: 24 h, 30.24%; 48 h, 56.47%; and 72 h, 100%. Omentin-1 caused a more variable response. At 24 h, migration reached 37.67% (100 ng/mL) and 47.79% (200 ng/mL), with statistical significance ($p = 0.047$ and $p < 0.001$, respectively). At 48 h, closure was further increased at 200 ng/mL (68.93%; $p = 0.017$), but did not alter significantly at 100 ng/mL (55.87%; $p = 0.189$). At 72 h, all groups reached 100% closure, indicating no detectable impacts at this time point (Figure 1f).

Gene Expression Levels

The effect of omentin-1 on the expression levels of *PIK3CA*, *AKT1*, and *MMP-9* was investigated (Figure 2). In MCF-7 cells, treatment with 100 ng/mL omentin-1 induced statistically significant decreases in the transcription of *PIK3CA* ($p < 0.001$), *AKT1* ($p < 0.001$), and *MMP-9* ($p < 0.001$) at 24 h, but with all genes enhanced at 48 h ($p < 0.001$). Conversely, with 200 ng/mL omentin-1, the expression of *PIK3CA* ($p < 0.05$), *AKT1* ($p < 0.001$), and *MMP-9* ($p < 0.01$) was elevated at 24 h; however, transcription of all genes declined significantly at 48 h ($p < 0.001$). Additionally, transcription of all three genes increased at 24 h and then decreased at 48 h in the 100 and 200 ng/mL groups ($p < 0.001$).

In MDA-MB-231 cells treated with 100 ng/mL omentin-1, *AKT1* ($p < 0.05$) and *MMP-9* ($p < 0.001$) expression declined significantly at 24 h, whereas the transcription of all three increased significantly at 48 h ($p < 0.01$; $p < 0.001$; and $p < 0.001$). In cells treated with 200 ng/mL omentin-1, *PIK3CA* expression was elevated ($p < 0.05$). Additionally, *MMP-9* expression was reduced at 24 h ($p < 0.001$); transcription of all three genes increased significantly at 48 h ($p < 0.001$). Notably, at 24 h, the expression of *PIK3CA* ($p < 0.01$) and *AKT1* ($p < 0.05$) was higher with 200 ng/mL omentin-1 than with 100 ng/mL; at 48 h, transcription of all genes was significantly greater with 200 ng/mL omentin-1 ($p < 0.001$).

Discussion

The present study identified omentin-1 to be associated with differential effects on BC behavior depending on cell type, concentration, and exposure time. The most prominent findings were the inhibition of omentin-1 on proliferation and migration in MCF-7 cells, which were limited or absent in the more invasive MDA-MB-231 cells. These observations suggest that biological responses to omentin-1 may vary according to the molecular characteristics of BC cells. One possible explanation may involve estrogen receptor (ER) status. MCF-7 cells are ER-positive, whereas MDA-MB-231 cells are ER-negative, representing distinct subtypes of BC (Ford et al., 2011). The unique responses of these cell lines may be associated with variations in signaling environments linked to ER status (Khatpe et al., 2021; Lee et al., 2005; Mohamood, 1995). ERα interacts with the PI3K/AKT/mTOR axis through genomic and non-genomic mechanisms. In particular, membrane-associated ERα can interact with the p85 regulatory subunit of PI3K, leading to AKT activation independent of transcriptional regulation (Lee et al., 2005; Simoncini et al., 2000). Such ligand-sensitive regulation may maintain the PI3K/AKT/mTOR axis in a more dynamic and modulatable state in ER-positive cells, potentially rendering MCF-7 cells more responsive to external stimuli, such as omentin-1 (Gil, 2014; Khatpe et al., 2021). In contrast, ER-negative BC cells exhibit a more constitutive activation of PI3K/AKT signaling, which may suppress their responsiveness to upstream regulatory inputs. In line with this result, the limited response in MDA-MB-231 cells observed in the present study may reflect a less modulatable signaling environment associated with this phenotype (Fruman et al., 2017; Glaviano et al., 2023; Lee et al., 2005). Together, these findings suggest that ER status may contribute to a framework associated with PI3K/AKT/mTOR signaling dynamics and adipokine responsiveness in BC cells.

The PI3K/AKT/mTOR axis represents a central signaling network in BC, regulating cell growth, survival, and metastasis. Its dysregulation, frequently driven by alterations such as *PIK3CA* mutations and *PTEN* loss, contributes to tumor progression and therapeutic resistance. Moreover, the bidirectional crosstalk between ER signaling and the PI3K/AKT/mTOR pathway further highlights its role in subtype-specific tumor behavior and treatment response. In this context, the differential impacts of omentin-1 in MCF-7 and MDA-MB-231 cells may be associated with ER-

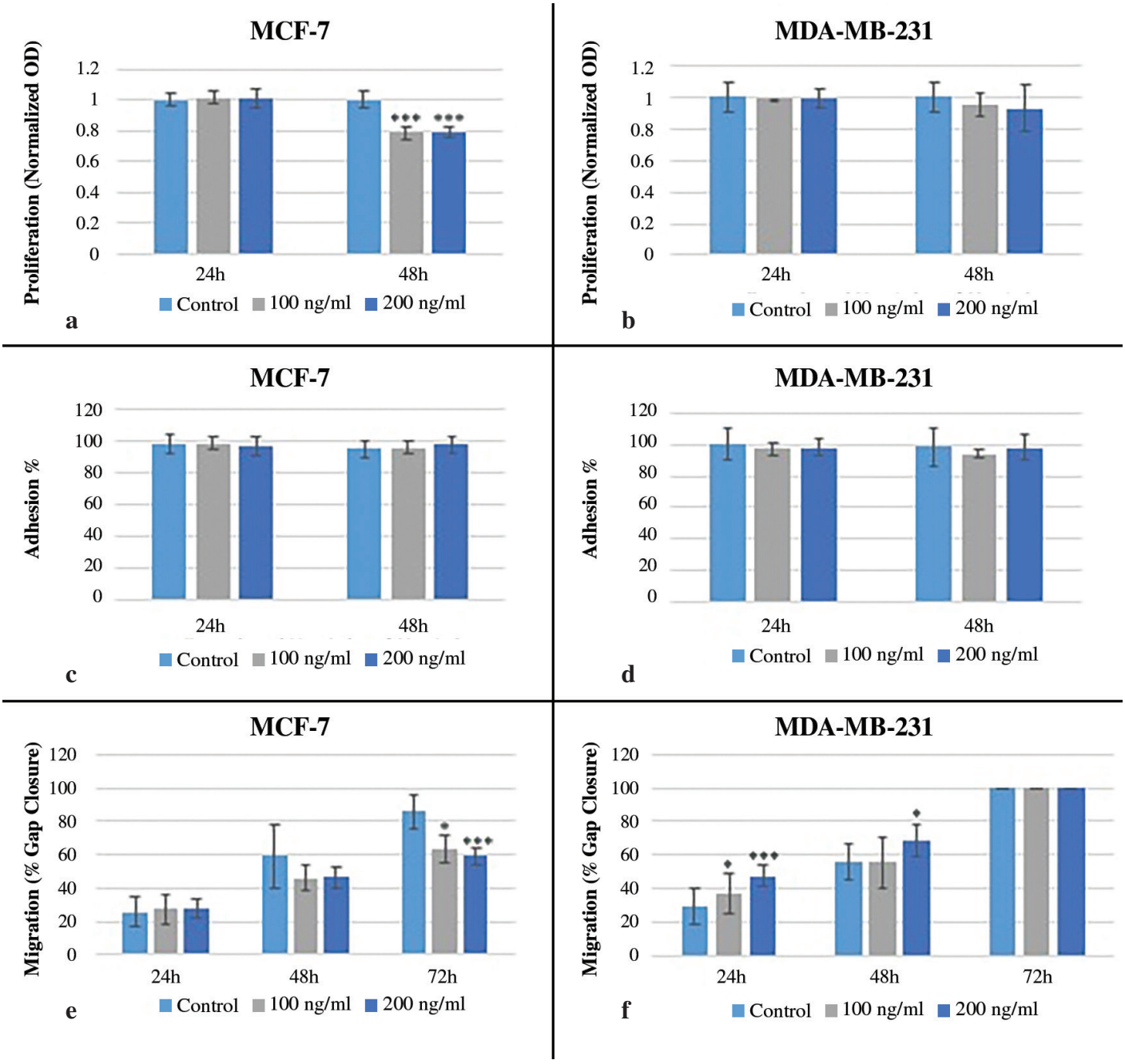

Figure 1. Effect of omentin-1 on proliferation (a, b); adhesion (c, d); and migration (e, f) in cell lines (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$).

related variations in PI3K/AKT signaling dynamics (Dec et al., 2023; Dong et al., 2021; Gil, 2014; Glaviano et al., 2023; Khatpe et al., 2021; Khorasani et al., 2024; Li et al., 2015b; Ortega et al., 2020; Zhang et al., 2024).

A complementary mechanism may involve ER-associated differences in adipokine signaling. Adiponectin, an adipokine of the same functional class as omentin, exerts ER-dependent effects in BC, demonstrating predominantly antiproliferative and pro-apoptotic actions in ER-negative cells; in contrast, its role in ER-positive cells remains controversial and may involve growth-promoting impacts through ERα signaling crosstalk (Naimo et al., 2020). In addition, variations in adipokine receptor expression across BC subtypes have been reported, with lower receptor levels associated with ER-negative and more aggressive phenotypes (Llanos et al., 2020). Although a direct relationship between ER status and omentin receptor (ITLN1) expression has not been clearly established, adipokine signaling may vary with cell context, and ER status may influence this response. In this context, the differential reactions to omentin-1 observed in this study may reflect ER-associated variations in adipokine signaling and downstream pathway responsiveness.

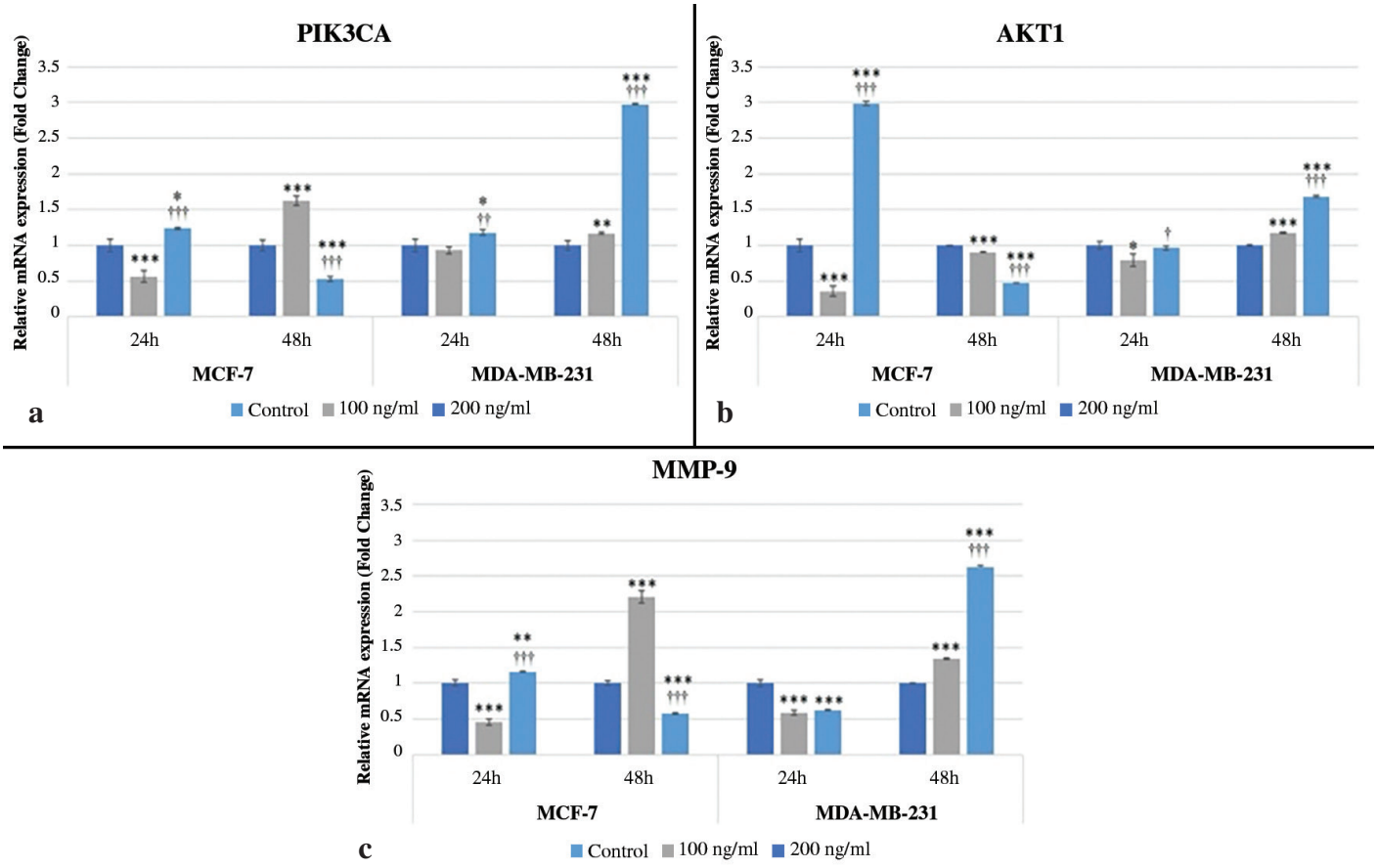

Figure 2. Effect of omentin-1 on the expression of *PIK3CA* (a), *AKT1* (b), and *MMP-9* (c) in cell lines compared to the control (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; 100 ng/mL vs. 200 ng/mL; $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$, $^{\dagger\dagger\dagger}p < 0.001$).

The antiproliferative influence of omentin-1 was evident in MCF-7 cells at 48 h, whereas no marked changes were observed at earlier time points or in MDA-MB-231 cells. This finding was consistent with previous reports demonstrating that omentin-1 exerts divergent effects on proliferation depending on cancer type (Li et al., 2015a; Li et al., 2015b; Mylonakis et al., 2025; Ye et al., 2019; Zhang & Zhou, 2013; Zhang et al., 2020). Such a limited response in MDA-MB-231 cells may be associated with sustained activation of oncogenic pathways, particularly PI3K/AKT, which can reduce sensitivity to upstream regulatory signals (Fruman et al., 2017; Glaviano et al., 2023).

Omentin-1 did not prominently affect adhesion in either cell line, suggesting a limited role in early attachment-associated processes. In contrast, migration assays demonstrated that omentin-1 reduced migratory capacity more prominently in MCF-7 than in MDA-MB-231 cells, particularly at later time points. However, in addition to potential changes in migratory capacity, remarkably reduced wound closure observed at 72 h in MCF-7 cells may partly reflect decreased proliferative activity at earlier time points. Studies have reported inhibitory or promotive effects of omentin-1 on migration depending on cancer type, supporting a context-dependent response (Dec et al., 2023; Li et al., 2015a; Li et al., 2015b; Ye et al., 2019; Zheng et al., 2012).

To further evaluate the molecular associations underlying these responses, the expression patterns of *PIK3CA*, *AKT1*, and *MMP-9* were analyzed. In the present study, omentin-1 was associated with concentration- and time-dependent changes in gene expression in the two cell lines. Lower or higher concentrations of omentin-1 resulted in opposite temporal expression patterns in MCF-7 cells, whereas the responses were less uniform and increased at later time points in MDA-MB-231 cells.

Clinical evidence suggests a possible involvement of omentin-1 in PIK3CA/AKT1-related processes, indicating a potential association between omentin-1 and tumor behavior in a cancer-type-dependent manner (Borowski & Siemińska, 2020). In addition, clinical studies investigating circulating omentin-1 levels in patients with BC have reported inconsistent findings, with increased or decreased contents observed depending on disease stage and metabolic status (Abas et al., 2022; Christodoulatos et al., 2021; Panagiotou et al., 2021; Tahmasebpour et al., 2020). These discrepancies may reflect the heterogeneous nature of BC and suggest that the bioeffects of omentin-1 are influenced by tumor subtype and cell context.

In line with these observations, our findings suggest that omentin-1 is associated with cell line-specific and time-dependent changes in

BC cell behavior. The alterations observed in the expression of proliferation, migration, and PIK3CA/AKT1-related genes suggest a context-dependent association rather than a uniform effect. Collectively, these results support the notion that omentin-1 may modulate the transcription of genes related to tumor progression. Thus, changes in the expression of PI3K/AKT/mTOR-related genes may contribute to the variable effects of adipokines in BC.

Study Limitations

This study has several drawbacks that must be acknowledged. First, the findings are based on *in vitro* experiments conducted in two BC cell lines, which may not fully reflect the complexity of tumor behavior *in vivo*. Second, molecular analysis was limited to the transcription of select PIK3CA/AKT1- and migration-associated genes, without translation-level validation. Additionally, circulating or tissue levels of omentin-1 and functional pathway inhibition were not included. Furthermore, cell migration may be influenced by concurrent effects on proliferation, particularly in MCF-7 cells, where reduced proliferative activity may have suppressed wound closure at later time points. Therefore, these results should be interpreted within the context of these experimental constraints, and further *in vivo* and mechanistic studies are warranted to confirm and extend their universality.

Conclusion

In conclusion, the present study demonstrates that omentin-1 exerts cell line-specific and time-dependent effects on BC cell behavior. Omentin-1 reduced proliferation and migration predominantly in MCF-7 cells, whereas its effects were limited in the more invasive MDA-MB-231 cells, accompanied by differential changes in PIK3CA/AKT1-related and migration-associated gene expression. These findings suggest that omentin-1 may be associated with the contextual modulation of BC cell behavior. However, further *in vivo* and *in vitro* studies, as well as comprehensive investigations of tissue and circulating omentin-1 levels specific to cancer type and disease stage, are needed to clarify its diagnostic, prognostic, and therapeutic relevance.

Ethics

Ethics Committee Approval: Since this study was conducted using commercially available cell lines and did not involve human participants or experimental animals, ethics committee approval was not required.

Data Sharing Statement: All data are available within the study.

Footnotes

Authorship Contributions: Conceptualization: A.S.; Design/methodology: A.S.; Execution/investigation: A.S.; Resources/materials: A.S.; Data analysis/interpretation: A.S. and Gü.K.; Writing – original draft: A.S.; Writing – review & editing/critical revision: A.S., Gü.K., and Gö.K.

Conflict of Interest: The author(s) have no conflicts of interest to declare.

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