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Resistance to Palbociclib in Breast Cancer Cells is Associated with Dysregulation of CCND1 Expression And CDK–RB–E2F Pathway Alteration

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Introduction: Understanding the molecular mechanisms underlying resistance to CDK4/6 inhibitors in breast cancer is crucial. As these drugs target key regulators of the cell cycle and proliferation, genes involved in the cyclin–CDK–RB–E2F signaling pathway are strong candidates for mediating or predicting therapeutic resistance.

Materials and Methods: RNA-Seq data (GSE130437) from MCF7 (HR+/HER2−) and MDA-MB231 (triple-negative) breast cancer cell lines, before and after induction of palbociclib resistance, were analyzed. Gene expression of *CDK4*, *CDK6*, *CCND1*, *RB1*, *E2F1–3*, *FOXM1*, and *PLK1* was evaluated using two-way ANOVA and Pearson correlation to identify transcriptional alterations associated with acquired resistance. FPKM values were used to assess differences in expression.

Results: Gene expression profiling in MCF7 (HR+/HER2−) and MDA-MB231 (triple-negative) breast cancer cell lines before and after developing resistance to palbociclib revealed distinct molecular patterns. In MCF7, resistance was associated with a general downregulation of cell cycle regulators, including *RB1, FOXM1, PLK1*, *E2F1, E2F2,* and the cyclin D–CDK4/6 complex, with *CCND1* showing a significant decrease. In contrast, MDA-MB231 displayed a strong upregulation of *CCND1* ($p < 0.000001$) upon resistance, while other genes showed minimal or non-significant changes. Correlation analyses highlighted *CCND1*, *CDK4*, and *PLK1* as key expression hubs, suggesting subtype-specific transcriptional adaptations to CDK4/6 inhibition.

Conclusions: Resistance to CDK4/6 inhibitors in breast cancer involves distinct, subtype-specific transcriptional changes. MCF7 cells show downregulation of cell-cycle and cyclin D–CDK4/6 pathway genes, whereas MDA-MB231 cells exhibit marked upregulation of CCND1, indicating that CCND1 and related regulators are potential biomarkers and therapeutic targets for overcoming resistance.

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INTRODUCTION

The optimism that emerged with the discovery of targeted cancer therapeutics was challenged by acquired resistance to these treatments. Either gene mutations or changes in the tumor microenvironment can contribute to drug resistance. Identifying the molecular basis for these resistances offers valuable opportunities for more effective treatment [1]. A range of combination therapies is employed to target breast tumor cells, based on the hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) expression [2]. One of the latest strategies for treating HR-positive and HER2-negative breast cancers involves targeted therapy using cell cycle inhibitors, specifically cyclin-dependent kinase 4/6

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(CDK4/6) inhibitors. Considering that a cell does not become cancerous unless it enters the cell cycle abnormally, the significance of these targeted therapies becomes evident. Palbociclib, a CDK4/6 inhibitor, has demonstrated very promising clinical responses in patients with HR-positive breast cancer. However, its effectiveness is not universal, as primary or secondary resistance to treatment can occur [3].

Resistance to CDK4/6 inhibitors in breast cancer involves multiple molecular mechanisms, with E2F transcription factor 1 (E2F1), retinoblastoma (pRb), and cyclin D1 playing pivotal roles in modulating treatment response. pRb is a key tumor suppressor that controls cell cycle progression; its loss of function following gene mutation enables cells to evade the inhibitory effects of CDK4/6 inhibitors. E2F1 is a transcription factor that, along with other family members, E2F2 and E2F3, is regulated by pRb. Overexpression of *E2F1* can promote cell proliferation even when CDK4/6 activity is blocked [4]. The *CCND1* gene encodes cyclin D1, which activates CDK4/6; its amplification or overexpression can lead to excessive CDK4/6 signaling, diminishing the efficacy of inhibitors [5, 6].

Polo-like kinase 1 (PLK1) and Forkhead box M1 (FOXM1) are crucial regulators of the cell cycle process. Their overexpression has been observed across multiple breast cancer subtypes, correlated with metastasis, and resistance to therapy [7, 8].

A research team investigated gene expression profiles in palbociclib-resistant ER-positive MCF7 and ER-negative MDA-MB-231 cell lines. The RNA-seq results in the Gene Expression Omnibus (GEO) database (accession GSE130437) revealed distinct transcriptional changes associated with resistance. In MCF7 cells, resistance correlated with the upregulation of genes involved in the cell cycle and DNA replication, while in MDA-MB-231 cells, it was mainly tied to metabolic pathways [9, 10]. Accordingly, in this study, we examined the expression of the RB1, CDK4, CDK6, FOXM1, PLK1, E2F1-3, and CCND1 genes using data from GSE130437 to assess their association with palbociclib resistance. These genes were selected based on previous studies that highlighted them as important factors in palbociclib resistance in breast cancer. Our goal was to investigate the differences in their expression patterns and the correlation between HR-positive and triple-negative breast cancer cells.

Materials and Methods

RNA-Seq Data and Cell Lines

Gene expression data with accession number GSE130437 were downloaded from the GEO database (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE130437). The study included 12 RNA-Seq samples from MCF7 and MDA-MB-231 cell lines, categorized into four groups, before and after induction of palbociclib resistance. Each group consisted of three biological replicates. The MCF7 cell line represented invasive ductal carcinoma (IDC) with HR+/HER2- expression, while MDA-MB-231 belonged to the mesenchymal stem-like (MSL) subtype with no HR or HER2 expression. The cell lines were continuously exposed to 0.1-4uM palbociclib for six months and maintained at 1uM palbociclib. RNA-Seq analysis was conducted using the GPL18573 platform, and the results were presented as raw Fragments Per Kilobase of transcript per Million mapped reads (FPKM) values.

Gene expression data extraction

We specifically extracted gene expression data for CDK4, CDK6, and cyclin D1 (CCND1), which are components of the cyclin D-CDK4/6 complex. The expression of RB1, as the main target of this complex, and E2F1, E2F2, and E2F3 were also considered in the analysis. To further understand additional proteins involved in palbociclib resistance, we also included FOXM1 and PLK1 gene expression. To strengthen the validation of the results, the PUM1 gene was used as an internal control. Information on the genes studied, including Ensembl ID and chromosomal location, is provided in Table 1.

Statistical Analysis

Raw GEO data were exported as Excel spreadsheets and then imported into GraphPad Prism V.8.4.3 to create input data files. To compare gene expression among groups, Two-way ANOVA and Multiple t-tests were used. The correlation between genes within each group was studied using Pearson's Correlation, and the findings were presented as regression graphs.

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Table 1. Data showing the genes analyzed in this study, including their names, corresponding Ensembl Gene IDs, and chromosomal locations.

Gene name	Ensembl Gene ID	Chromosome Location
RB1	ENSG00000139687	13: 48,303,735-48,599,436 forward strand
FOXM1	ENSG00000111206	12: 2,857,676-2,877,174 reverse strand
PLK1	ENSG00000166851	16: 23,677,656-23,690,367 forward strand
CDK4	ENSG00000135446	12: 57,747,722-57,756,013 reverse strand
CDK6	ENSG00000105810	7: 92,604,921-92,836,591 reverse strand
CCND1(Cyclin D1)	ENSG00000110092	11: 69,641,143-69,654,474 forward strand
E2F1	ENSG00000101412	20: 33,675,477-33,686,385 reverse strand
E2F2	ENSG00000007968	1: 23,506,438-23,531,233 reverse strand
E2F3	ENSG00000112242	6: 20,401,847-20,493,714 forward strand
PUM1	ENSG00000134644	1: 30,931,505-31,065,991 reverse strand

P-values below 0.05 were deemed statistically significant.

To assess the discriminatory potential of the selected gene signature between parental and Palbociclib-treated states, we performed Receiver Operating Characteristic (ROC) curve analysis using expression data from three independent cell culture replicates per condition. Gene set performance was quantified by calculating the Area Under the Curve (AUC) and corresponding confidence intervals (CIs), estimated using the StatsKingdom ROC Calculator (https://www.statskingdom.com/roc-calculator.html).

RESULTS

Gene expression in MCF7 cells upon palbociclib resistance

For a more detailed examination, genes were categorized into three groups: cell cycle regulators, E2F transcription factors, and components of the cyclin D-CDK4/6 complex. It was evident that the expression of selected genes decreased after the cell became resistant to palbociclib. In the cell cycle regulators category, which included *RB1*, *FOXM1*, and *PLK1*, all three genes were expressed in the MCF7 cell line before resistance induction. Evaluation of resistant cells revealed a significant decrease in all three genes (Figure 1a). In the E2F transcription factor group, significant changes were observed in the *E2F1* and *E2F2* genes, whereas E2F3 expression showed no significant change (Figure 1b). In the third group, which included *CDK4*, *CDK6*, and *CCND1* genes, only the decrease in *CCND1* was significant compared to the parental cell line. The expression level of *CDK6* was much lower than that of the other genes, close to the detection limit (Figure 1c).

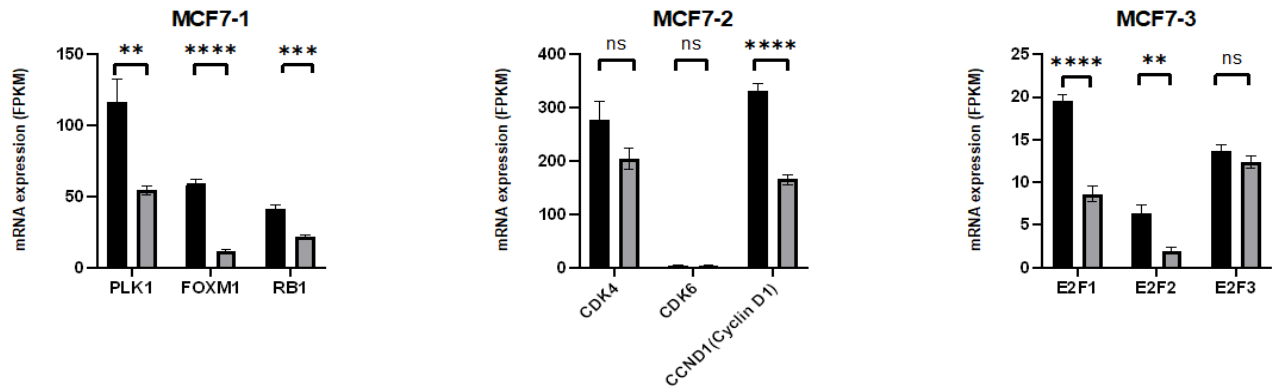

Figure 1. Gene expression changes in MCF7 cells upon palbociclib resistance. (a) Cell cycle regulators *RB1*, *FOXM1*, and *PLK1* show significant downregulation after resistance. (b) E2F transcription factors *E2F1* and *E2F2* decrease significantly, while *E2F3* remains unchanged. (c) Cyclin D–CDK4/6 complex components show a significant reduction in *CCND1*, with *CDK6* expression near the detection limit.

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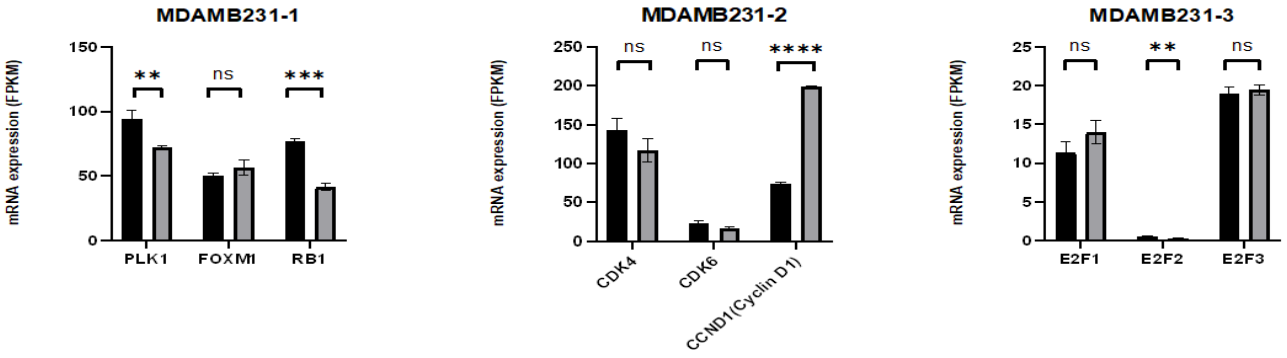

Figure 2. Gene expression changes in MDA-MB-231 cells upon palbociclib resistance. (a) Cell cycle regulators *RB1* and *PLK1* show significant downregulation, while *FOXM1* exhibits a slight, non-significant increase. (b) *E2F* transcription factors display variable changes, with *E2F1* slightly increased, *E2F3* slightly decreased, and *E2F2* dimly expressed. (c) Cyclin D–CDK4/6 complex components show a pronounced and significant upregulation of *CCND1*, while *CDK4* and *CDK6* remain largely unchanged.

Gene expression in MDA-MB231 cells upon palbociclib resistance

Maintaining the same grouping, gene expression was examined in MDA-MB-231 cells. The overall decrease observed in MCF7 was not evident in this triple-negative cell line. In the first group, *RB1* and *PLK1* continued to decrease significantly, while FOXM1 showed a slight, though non-significant, increase (Figure 2a). Interpreting the results of the E2Fs was challenging, as E2F2 was much lower than the other E2Fs and was undetectable in MDA-MB-231 even before exposure to palbociclib. *E2F3*, as seen in MCF7, had a slight, non-significant decrease, but *E2F1* showed a non-significant increase (Figure 2b). Our most interesting finding is a strong, statistically significant increase in CCND1 expression ($p < 0.05$). No significant change was observed in CDK4 and CDK6, and the expression level of CDK6 in MCF7 was much lower than that of other genes (Figure 2c).

Correlation of the gene expression changes induced by palbociclib

Gene expression correlation levels were analyzed using Pearson correlation, yielding r-values. As shown in the figure, we observed that *CCND1*, *CDK4*, and *PLK1* had the highest expression levels in both cell lines (Figure 3). In the MCF7 cell line, the changes in gene expression before and after induction of resistance to palbociclib showed a proportional pattern across all genes, with values closely aligned along the diagonal (Figure 3a). In contrast, significant changes in *CCND1* were observed in MDA-MB-231, unlike the

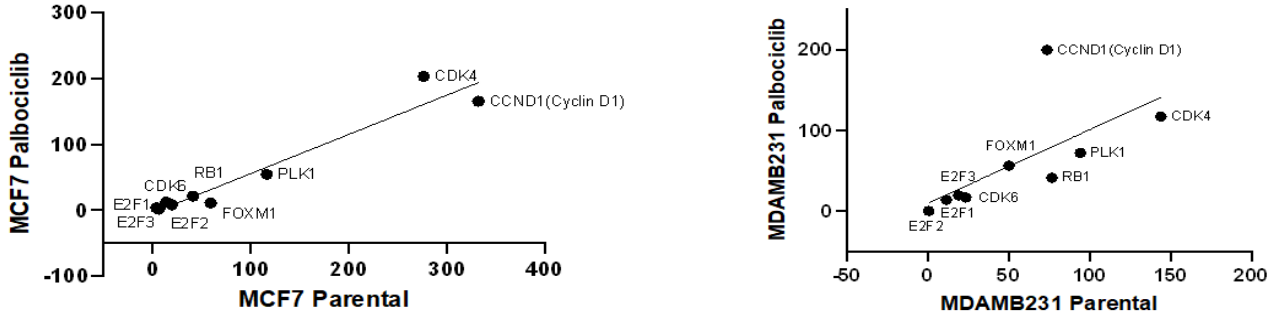

Figure 3. Correlation of gene expression in MCF7 and MDA-MB-231 cells upon palbociclib resistance. (a) In MCF7, gene expression changes before and after resistance show a proportional pattern with values closely aligned along the diagonal. (b) In MDA-MB-231, *CCND1* exhibits significant changes, while other genes display minimal variation. Overall, *CCND1*, *CDK4*, and *PLK1* show the highest expression levels in both cell lines.

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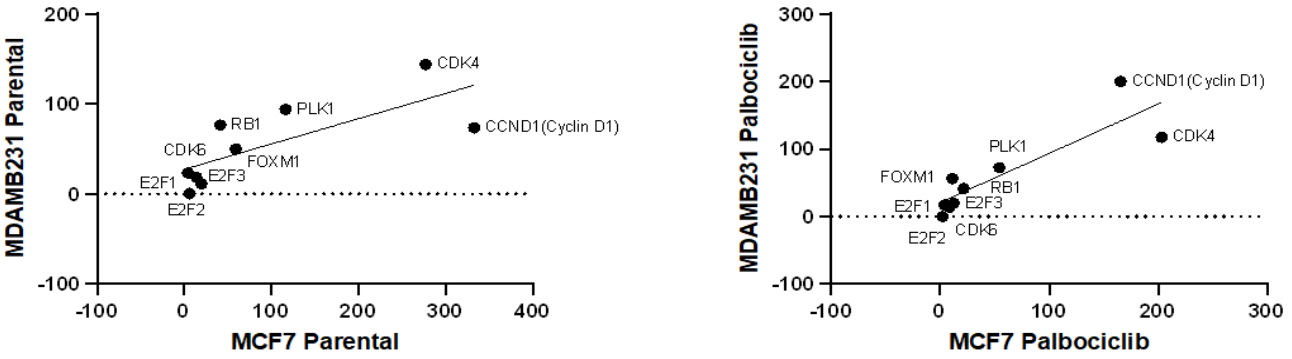

Figure 4. Comparative gene expression analysis between HR-positive MCF7 and triple-negative MDA-MB-231 cells before and after palbociclib resistance. (a) In parental cells, *CCND1* and *CDK4* are higher in MCF7, while other genes show similar expression. (b) After resistance, *CDK4* remains elevated in MCF7, whereas *FOXM1* and *CCND1* are higher in MDA-MB-231, with other genes showing no significant differences.

patterns observed for the other genes (Figure 3b).

Correlation of gene expression changes between MDA-MB-231 and MCF7

To compare the specificity of HR-positive versus triple-negative breast cancer, we conducted a correlation analysis between the two cell lines before and after developing resistance to palbociclib. The results shown in the figure indicated a dispersion of gene expression in the two cell lines (Figure 4). The expression of CCND1 and *CDK4* was higher in parental MCF7 than in MDA-MB-231, whereas the remaining genes showed relatively equal expression in both parental cell lines (Figure 4a). Regarding resistance to palbociclib, *CDK4* showed high expression in MCF7, whereas *FOXM1* and *CCND1* were expressed at higher levels in MDA-MB-231. The other genes had no significant difference between the two treated cell lines (Figure 4b).

Discrimination between parental and palbociclib-treated cells

We first evaluated the combined expression profile of all selected genes across parental and Palbociclib-treated conditions in both MCF7 and MDA-MB-231 cells. This analysis revealed that the full gene set lacked statistically significant discriminatory power in either cell line.

Subsequent optimization identified a minimal panel of five genes—*PLK1, FOXM1, CDK4, CCND1,* and *E2F1*—in MCF7 cells that achieved the strongest and statistically significant discriminatory ability, whereas no comparable panel was observed in palbociclib-resistant MDA-MB-231. The ROC curve for the optimized 5-gene panel is shown in Figure 5. The model yielded an AUC of 0.716 with a 95% CI of 0.435–0.996. Importantly, the significance test for the AUC produced a p-value of 0.0443, confirming that this panel effectively discriminates between

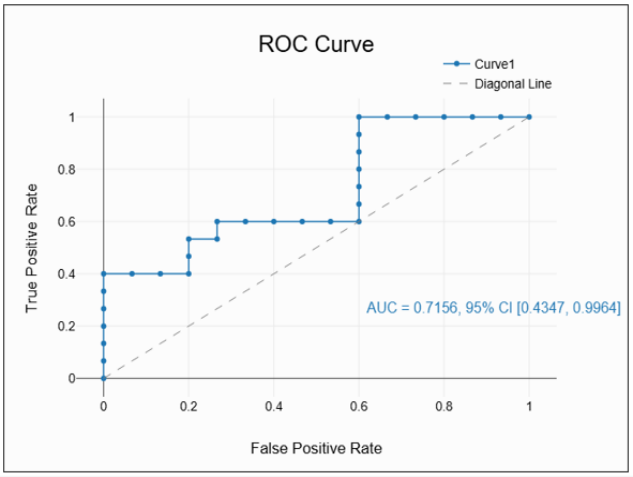

Figure 5. Receiver Operating Characteristic (ROC) Curve for the optimized 5-gene (*PLK1, FOXM1, CDK4, CCND1, E2F1*) signature distinguishing MCF7 parental cells from MCF7 cells treated with Palbociclib. The Area Under the Curve (AUC) was 0.716±0.09552. Analysis performed using the StatsKingdom ROC Calculator.

MCF7 parental and Palbociclib-treated states.

DISCUSSION

Identifying gene alterations that enable tumor cells to maintain growth and survival despite CDK4/6 inhibition could inform the design of biomarker-based

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therapeutic strategies for combination therapies in breast cancer [11]. Through in silico studies of palbociclib-resistant MCF7 and MDA-MB231 cell lines, we found that the expression of various cell cycle regulator genes decreases with prolonged drug treatment. Our finding of a significant reduction in *RB1* in both cell lines confirmed previous studies showing that this gene contributes to the low response to CDK4/6 inhibitors. Polyclonal mutations in the *RB1* gene were identified in metastatic HR-positive breast cancer patients who developed acquired resistance to CDK 4/6 inhibitors. These mutations were detected through liquid biopsies and suggest that the loss of *RB1* function is a mechanism of resistance to CDK4/6 inhibitor therapy [12]. Heterozygous loss of *RB1* has been reported to be associated with resistance to CDK4/6 inhibitors in HR-positive breast cancer, and it has been found that *RB1* is often completely lost during treatment, leading to further resistance [13]. It has also been demonstrated that when intact *pRb* is present in breast cancer cells, treatment with a CDK4/6 inhibitor prior to radiotherapy significantly increases radiosensitivity, whereas RB1 knockdown abolishes this radiosensitizing effect [14].

Another important result of our study was the significant increase in *CCND1* expression after exposure to palbociclib in the MDA-MB-231 cell line. It is important to note that this was the only gene with significantly increased expression after palbociclib resistance in either cell line. Amplification of the *CCND1* gene is a frequent event in breast cancer. A study of 526 primary breast cancers revealed that around 16.0% of tumors exhibited a median gene copy number of ≥ 4 [6]. Another study on *CCND1* gene amplification in early-stage HER2-negative, HR-positive breast cancer revealed that about 12.9% of tumors displayed amplification, with CCND1 levels ≥ 2.0 [5]. Using data from more than 2,000 patients with over 15 years of follow-up, it was found that tumors with *CCND1* amplifications had a more aggressive phenotype. In survival analyses, patients whose tumors were *CCND1*-amplified had significantly worse breast cancer-specific survival [15].

A recent study was performed on 93 patients with HER2-negative, HR-positive metastatic breast cancer. These patients had experienced disease progression after initial treatment with a CDK4/6 inhibitor in combination with endocrine therapy. The study found that 10.8% of patients (10 out of 93) in the post-CDK4/6 inhibitor group had *CCND1* copy number variations (CNVs). The authors concluded that analyzing ctDNA after CDK4/6 inhibitor treatment can help identify important alterations, such as *CCND1* CNVs, that may have prognostic significance [16]. However, there are conflicting results regarding the role of CCND1 in sensitivity to CDK4/6 inhibition. By emphasizing DNA content-based proliferation assays, it has been shown that tumors or cell lines with high expression of *CCND1* or amplification of the *CCND1* gene, often accompanied by intact *RB1*, showed high sensitivity to CDK4/6 inhibition [17].

In our results, in addition to *CCND1*, we observed only limited increases in FOXM1 after MDA-MB-231 cells developed resistance to palbociclib. In an earlier study, it was demonstrated that *FOXM1* and *CCND1* have distinct yet related functions in the response of pancreatic cancer models to CDK4/6 inhibition. When pancreatic cancer cell lines were exposed to a CDK4/6 inhibitor, FOXM1 protein levels were consistently reduced, suggesting that *FOXM1* is a downstream target of CDK4/6 signaling. Additionally, inhibiting *CCND1* in conjunction with a CDK4/6 inhibitor had an additive impact on reducing cell proliferation [18]. In experiments with multiple human bladder cancer cell lines, these cells were found to be sensitive to CDK4/6 inhibition independently of *RB1*. The transcription factor *FOXM1* was shown to have a crucial role in controlling the response to CDK4/6 inhibition in bladder cancer. Treatment with a CDK4/6 inhibitor led to decreased *FOXM1* phosphorylation both in vitro and in vivo, suggesting that CDK4/6 inhibition disrupts oncogenic signaling downstream of *FOXM1* [19].

CONCLUSIONS

Overall, our study showed that changes in cell cycle genes following resistance to CDK4/6 inhibitors are not universal and pervasive. The 5-gene panel

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effectively discriminates between MCF7 parental and Palbociclib-treated states. However, the sample size of our study was limited and could be improved by including more breast cancer cell lines and patient samples. Furthermore, studying other cellular pathways involved in the development of resistance could be valuable. Using patient-derived xenograft (PDX) models and breast cancer cell lines, a study revealed substantial deregulation of immune-related pathways in palbociclib-resistant tumors. Specifically, genes associated with antigen presentation, cytokine signaling, and immune cell infiltration showed altered expression [20]. Examining cell-cycle cross-links and immune and biochemical pathways can provide a more precise understanding of the context of CDK4/6 inhibitor resistance.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS APPROVAL

This study was approved by the ethics committee and financially supported through a research grant by the Pasteur Institute of Iran (IR.PII.REC.1400.057).

FUNDING

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