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# Exploring the Impact of Fatty Acids on Ovarian Cancer Progression

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## ABSTRACT

Ovarian cancer (OC) stands as a formidable challenge in women's health, constituting a significant portion of gynecological-related deaths. The aggressive nature of epithelial ovarian cancer (EOC) manifests as a major hindrance to effective treatment. This study delves into the complex interplay between fatty acid stimuli, cellular signaling pathways, and subsequent cellular responses in the context of ovarian cancer, employing mouse ovarian cancer cell lines ID8 with distinct genetic backgrounds—those harboring BRCA2/p53 mutations and those with solely p53 mutations. Despite the well-established role of fatty acids in cancer cell growth, invasion, and metastasis, the intricate dynamics of how these molecules modulate signaling pathways and influence cellular outcomes, particularly in ovarian cancer with specific genetic mutations, remain less explored. In this context, the study aims to elucidate the differential responses observed in cell signaling activation and cell proliferation, shedding light on the unique sensitivity of ID8 cells with both p53 and BRCA2 mutations to odd chain fatty acids. Additionally, the investigation underscores the correlation between fatty acid types and lipid accumulation, offering valuable insights into the potential mechanisms driving ovarian cancer aggressiveness. These findings emphasize the importance of considering genetic backgrounds in tailoring therapeutic strategies, paving the way for more effective and personalized approaches in the treatment of ovarian cancer.

## Introduction

Epithelial ovarian cancer, originating in the fallopian tube epithelium, stands as the primary cause of gynecological-related fatalities. Unfortunately, a substantial 70% of EOC cases are diagnosed in advanced stages, marked by extensive peritoneal spread to the omentum. The late-stage diagnosis predicament is exacerbated by the insidious nature of EOC symptoms, resembling those of gastrointestinal issues, leading to frequent misinterpretations. Despite ongoing efforts, the survival rates for late-stage EOC remain dishearteningly low, underscoring the urgency to address the challenges associated with its delayed detection (Desai et al., 2014; Lheureux et al., 2019).

Delving into the molecular intricacies of EOC initiation within the fallopian tube epithelium reveals a complex interplay of genetic alterations, signaling pathways, and biomarkers orchestrating the transition from normal epithelium to malignancy (Otsuka, 2021). This deeper understanding offers potential targets for early detection strategies, aiming to intervene at a precancerous stage.

The dismal survival rates associated with ovarian cancer can be largely attributed to the extensive metastasis of tumors within the pelvic and abdominal regions during advanced stages of the disease. Conventional approaches such as standard debulking surgery and chemotherapy exhibit limited efficacy in eliminating tumors at this critical juncture. The origin of ovarian tumors within the peritoneal cavity, their subsequent spread to adjacent organs like the fallopian tubes and uterus, and dissemination through various routes, including transcoelomic, hematogenous, and lymphatic pathways, contribute to the formidable challenges faced in late-stage OC management (Gaitskell et al., 2022). The movement of peritoneal fluid emerges as a significant facilitator

of tumor metastasis, acting as a passive carrier that transports tumors to the peritoneum and omentum, further complicating therapeutic interventions (Cortés-Guiral et al., 2021).

While glycolysis has long been regarded as the primary pathway for fueling cancer cell growth, recent investigations highlight the crucial role of lipid metabolism in driving ovarian cancer cell proliferation, invasion, and metastasis (Schiliro and Firestein, 2021). This emerging understanding positions lipid metabolism as a potential target for therapeutic interventions in OC. Studies reveal the upregulation of key molecules associated with both endogenous and exogenous lipid metabolism, including CD36, fatty acid binding protein 4 (FABP4), fatty acid synthase (FASN), and Stearoyl-CoA desaturase 1 (SCD1), at tumor sites (Kim et al., 2023). Fatty acid oxidation, a process that provides essential fuel for cells, is heightened in cancer, serving to meet the increased energy demands of tumor cells and fostering chemoresistance. Notably, dietary influences on lipid metabolism have been elucidated in a study demonstrating that high-fat diets contribute to significantly elevated tumor weights in mice, underscoring the pivotal role of nutrients in modulating lipid metabolism (Zhao et al., 2019).

This study investigates the influence of various fatty acid types, including omega-3 and omega-6 fatty acids, as well as odd chain and even chain fatty acids, on mouse ovarian cancer cell lines with distinct mutations, specifically the ID8 cell lines. The research aims to compare the effects of these fatty acids on lipid accumulation, cell proliferation, and the activation of molecular signaling pathways regulating lipid metabolism and cell growth. Surprisingly, the findings indicate that different fatty acid types do not significantly impact cell proliferation. However, a noteworthy distinction emerges in lipid accumulation, with omega-6 fatty acids promoting greater storage compared to omega-3 fatty acids, and odd chain fatty acids inducing more lipid accumulation than even chain fatty acids. These results suggest that manipulating dietary lipid components could play a role in influencing ovarian cancer progression and therapeutic efficacy, offering insights for potential dietary interventions in the management of ovarian cancer patients.

## The Pathology of Ovarian Cancer

### The Diagnosis of Ovarian Cancer

Ovarian carcinoma, arising from the ovarian epithelium, fallopian tube, or the mesothelium cells lining the peritoneal cavity, exhibits distinct subtypes with varying progression patterns. Type I ovarian tumors evolve slowly into well-differentiated carcinomas, often harboring mutations in genes such as BRAF, KRAS, and ERBB2, accompanied by the activation of mitogen-activated kinases. Conversely, Type II ovarian tumors, notably high-grade serous ovarian carcinomas (HGSOC), are marked by heightened aggressiveness and genetic instability. HGSOC, the most prevalent histological subtype, displays unstable DNA copy number changes and mutations in the p53 gene, occurring in 50-80% of cases. The subtype stands out with its distinctive features, including cells with large nuclei and brisk mitotic activity, that lead to its aggressive nature (Khashaba et al., 2022). Cooperative actions of various mutations, including BRCA1 and BRCA2 mutations, recognized for their roles in ovarian and breast cancers, further contribute to tumorigenesis. Additionally, amplifications of AKT2 kinase and PI3K genes play a role in the pathogenesis of HGSOC (Koshiyama et al., 2014).

Ovarian cancer presents with a spectrum of signs and symptoms that necessitate keen attention for timely diagnosis. Notable indicators include abnormal vaginal bleeding, abdominal pain or pressure, back pain, bloating, difficulty eating, and alterations in bathroom habits (Bankhead et al., 2008). Unfortunately, the diagnosis often occurs at an advanced stage, where the disease has extended into the pelvic region, involving reproductive organs and the sigmoid colon. The advancement of the tumor is frequently accompanied by local and systemic inflammatory responses, further complicating the clinical presentation of ovarian carcinoma (Bankhead et al., 2008).

Histologically, epithelial ovarian cancer is categorized into distinct subtypes, including serous carcinoma, endometrioid carcinoma, mucinous carcinomas, and clear-cell carcinoma, each exhibiting unique mutation profiles (Kobel and Kang, 2022). These subtypes, characterized by their heterogeneity, are further stratified into grades. Low-grade tumors display low mitotic activity, smaller nuclei, and a resemblance to corresponding normal tissue, while high-grade tumors exhibit structures significantly deviating from the norm. The characterization of these histological and molecular aspects provides a comprehensive understanding of the intricate landscape of ovarian cancer, paving the way for targeted diagnostic and therapeutic strategies.

### The Therapies of Ovarian Cancer

The primary treatment modalities for advanced-stage epithelial ovarian cancer currently involve debulking surgery and chemotherapy. The objective of debulking surgery is to remove the tumor until it is no longer visible or reduced to a size of one centimeter, a state termed optimally debulked. However, this surgical intervention may impact other organs, potentially leading to complications, and the removal of the ovary and uterus can result in infertility, posing significant challenges for patients (Cummings et al., 2022). Subsequently, platinum-based and taxane-based chemotherapy regimens are commonly administered to address residual cancer cells and prevent recurrence. Despite these efforts, approximately 50-70% of patients experience cancer recurrence associated with chemoresistance after initial treatment (Coleridge et al., 2021).

Targeted therapies for ovarian cancer include drugs such as bevacizumab, PARP inhibitors, and agents targeting the FR-alpha protein and cells with NTRK gene changes. While these therapies offer promising outcomes, they are associated with side effects of varying severity, including dizziness, nausea, vomiting, lung disease, and nerve damage (Lim and Ledger, 2016). Although radiotherapy is not the standard for OC, it may be employed in areas where the tumor has spread. Immunotherapy, represented by drugs like pembrolizumab, focuses on targeting checkpoints to treat specific types of OC. However, both radiotherapy and immunotherapy can induce side effects such as fatigue, nausea, diarrhea, and skin problems (Voronova et al., 2022). The quest for a more balanced and effective therapeutic approach remains imperative in advancing ovarian cancer treatment, aiming to mitigate adverse effects while maximizing treatment efficacy.

## The Lipid Metabolism in Ovarian Cancer

### The Effect of Lipids in Ovarian Cancer Metastasis

The role of lipids in ovarian cancer metastasis is a subject of growing interest, as studies delve into the intricate mechanisms through which lipid metabolism fuels the dissemination of ovarian tumors. Elevated fatty acid oxidation emerges as a contributing factor to various aspects of tumor progression, including the modulation of tumor immunity, oncogenic signal transduction, and the structural integrity of cell membranes (Chaudhry et al., 2022; Zhao et al., 2019). As ovarian tumors metastasize through the peritoneal cavity with the flow of malignant ascites, lipid intermediates within the ascites impede the function of T-cells, thereby suppressing the anti-tumor responses of the immune system (Rickard et al., 2021). The impact of secreted fatty acids extends beyond T-cells, influencing other immune cells such as macrophages, neutrophils, and natural killer cells (Zhao et al., 2019).

Notably, the omentum, a primary metastatic destination in OC, consists predominantly of adipocytes. These cancer-associated adipocytes establish an almost symbiotic relationship with OC cells, providing essential nutrition to facilitate the seeding and growth of ovarian cancer cells (Li et al., 2023). The intricate interaction between adipocytes and OC cells is mediated by FABP4, a protein found to be upregulated in metastatic sites. This molecular interplay sheds light on the pivotal role of lipids, particularly FABP4, in fostering the dynamic

relationship between ovarian cancer cells and the adipocyte-rich microenvironment of the omentum, highlighting potential therapeutic targets for disrupting this symbiotic connection and impeding ovarian cancer metastasis (Mukherjee et al., 2020).

### The Regulation of Lipid Metabolism in Ovarian Cancer

The intricate regulation of lipid metabolism in ovarian cancer encompasses various key players governing lipid absorption, synthesis, and fatty acid oxidation. Fatty acid translocase, also known as CD36, assumes a pivotal role by transporting lipoproteins across the cell membrane, and its upregulation has been identified in the context of peritoneal metastasis in ovarian tumors (Koundouros and Poulogiannis, 2020). FABP4, as mentioned earlier, is highly expressed in metastatic ovarian cancer cells, exerting regulatory control over lipid accumulation. Notably, the knockout of FABP4 has demonstrated a reduction in tumor burden and the invasive capability of ovarian cancer carcinoma facilitated by adipocytes (Mukherjee et al., 2020).

Acetyl-CoA Carboxylase (ACC) stands as a key regulator in the initial step of lipid synthesis, and its activity is intricately linked with FASN, which, in turn, is associated with resistance to cytotoxic stress. FASN drives endogenous de novo lipid synthesis when coupled with ACC. SCD1 plays a crucial role in converting saturated fatty acids to unsaturated fatty acids, mitigating lipotoxicity risks detrimental to cells. Beyond promoting ovarian cancer cell growth in the absence of exogenous fatty acids, SCD1 also contributes to resistance against ferroptosis, highlighting its multifaceted role in ovarian cancer progression (Koundouros and Poulogiannis, 2020).

Carnitine Palmitoyl Transferase (CPT), the rate-limiting enzyme responsible for converting long-chain fatty acids to acyl chains for beta-oxidation, assumes a critical role in controlling cell proliferation. The facilitated utilization of CPT by ovarian cancer cells provides substantial survival advantages, and the depletion of CPT1 has been demonstrated to induce apoptosis and cell cycle arrest (Qu et al., 2016). Additionally, Salt-Inducible Kinase 2 (SIK2) exerts control over ACC-mediated fatty acid oxidation, supporting ovarian cancer metastasis to the omentum (Sun et al., 2020). This comprehensive network of lipid metabolism regulators underscores their significance in ovarian cancer progression, offering potential avenues for targeted therapeutic interventions.

## Research Methods

### Cell Culture and Treatment

In this study, mouse ovarian cancer cell lines CD8 with BRCA2/p53 mutation or only p53 mutation were utilized. These tumor cells were sourced from the American Type Culture Collection (ATCC) and sustained in Dulbecco's Modified Eagle Medium (DMEM), enriched with 10% fetal bovine serum (FBS), and 1% Penicillin-Streptomycin antibiotics. The cells underwent cultivation in a controlled environment with 5% $CO_2$ at 37 degrees Celsius to ensure optimal conditions for growth and maintenance.

To investigate the specific impact of different types of fatty acids on these cancer cells, a targeted experimental approach was implemented. The cells were cultured in DMEM supplemented with 10% dialyzed FBS, a process that involves removing small molecules, including fatty acids, from the serum. Subsequently, the cells were subjected to treatment with 30μM concentrations of fatty acids conjugated with albumin, simulating conditions relevant to the tumor microenvironment. This treatment protocol was maintained for a period of 5 days, allowing for a comprehensive evaluation of the cellular response to the diverse fatty acid stimuli. The utilization of this experimental setup enables a nuanced exploration of how various fatty acids may influence

the behavior and characteristics of ovarian cancer cells with distinct genetic mutations, shedding light on potential mechanisms relevant to ovarian cancer progression.

## Cell Proliferation Measurement

To assess and compare the cell proliferation of cancer cells exposed to various fatty acids, a structured experimental protocol was followed. Initially, the tumor cells were treated with the different fatty acids for a period of 3 days. Subsequently, 500 cells were seeded into 96-well plates, maintaining the same fatty acid treatment conditions for an additional 4 days. This extended exposure period allowed for a comprehensive evaluation of the sustained impact of the specific fatty acid stimuli on cell proliferation.

The quantification of cell mass was achieved using CCK-8, a widely utilized assay for assessing cell viability and proliferation. This assay provides a reliable measure of the cellular metabolic activity, serving as an indicator of the overall cell health and proliferation rate. By employing CCK-8, the study aimed to obtain quantitative data on the extent of cell proliferation under the influence of distinct fatty acids, enabling a comparative analysis of their effects on the cancer cells. This meticulous experimental design ensures a thorough exploration of the potential variations in cell proliferation dynamics induced by the diverse fatty acid treatments, contributing valuable insights to the understanding of the impact of lipid metabolism on ovarian cancer cells.

## Oil Red O Staining

In this study, the tumor cells were subjected to a specific experimental regimen to assess the impact of fatty acids on lipid content. Initially, the cells were cultured in the presence of fatty acids for a duration of 3 days. Subsequently, these treated cells were seeded into a 12-well plate and continued to be cultured with the same fatty acids for an additional 2 days. Following this incubation period, the tumor cells were fixed with a 4% formaldehyde solution to preserve their structural integrity.

The subsequent step involved staining the fixed tumor cells with Oil Red O, a dye commonly used to visualize and quantify lipid content within cells. After the staining procedure, the excess dye reagent was removed, and the tumor cells were thoroughly washed with PBS (phosphate-buffered saline) three times. To extract the Oil Red O reagent for quantitative analysis, isopropanol was employed. Subsequently, a plate reader was utilized to measure the absorbance, providing a quantitative measure of the amount of Oil Red O retained by the tumor cells. This absorbance reading serves as an indicator of lipid content, allowing for the quantification of lipid amounts and providing valuable insights into the influence of different fatty acids on lipid metabolism in the studied tumor cells.

## Western Blotting

In the Western blotting analysis, the treated cells underwent a systematic procedure, starting with washing in ice-cold PBS and subsequent lysis in RIPA buffer with protease and phosphatase inhibitors. The resulting cell lysates were centrifuged, and the BCA Protein Assay Kit was employed to determine total protein concentrations, ensuring equal loading onto SDS-PAGE gels for electrophoresis. The separated proteins were then transferred to PVDF membranes and blocked with 5% non-fat milk in TBST. Following blocking, the membranes were probed overnight at 4°C with specific primary antibodies targeting proteins such as p-AKT, p-ERK1/2, ERK1/2, p-S6, and Vinculin. After washing, the membranes were exposed to suitable horseradish peroxidase-conjugated secondary antibodies, and protein bands were visualized and quantified using the LI-COR Odyssey CLx Imaging System. Densitometric analysis enabled the quantification of PDL1 expression, normalized to the loading control vinculin. This comprehensive Western blotting approach provided insights into the molecular alterations induced by the treatment, elucidating the activation status of crucial signaling pathways and protein

expression levels.

## Results

### The Effect of Fatty Acids On Tumor Cell Proliferation

Despite the absence of significant differences in cell proliferation, as indicated by CCK-8 (Figure 1), following treatment with various fatty acids, intriguing insights were gleaned from the Western blot analyses. Initially, we conducted a comparison of the impacts of omega-3 and omega-6 fatty acids. Our findings revealed that omega-6 fatty acids have a significant capacity to boost the activation of mTOR signaling in ID8 tumor cells with BRCA2 and P53 double mutation, as opposed to tumor cells with only p53 mutation. Nonetheless, omega-6 fatty acids enhanced the phosphorylation of ERK in both types of tumor cells. We then proceeded to compare the effects of odd-chain fatty acid and even-chain fatty acid. We observed no substantial difference in p53 single mutant tumor cells. However, heptadecanoic acid inhibited the phosphorylation of AKT in double mutant cells. Interestingly, both odd-chain and even-chain fatty acids demonstrated the ability to increase ERK phosphorylation. This molecular level of investigation uncovered a nuanced and differential response to fatty acid stimuli between the two types of ID8 cells—with BRCA2/p53 mutation and those with only p53 mutation (Figure 2). Particularly noteworthy was the observation that odd-chain fatty acid treatment induced more pronounced changes in the double mutation tumor cells. This distinction implies a unique sensitivity or altered response profile in the presence of both BRCA2 and p53 mutations, adding a layer of complexity to the understanding of how fatty acids influence signaling pathways and cellular responses in the context of ovarian cancer. These findings underscore the necessity of considering the genetic landscape when exploring the intricate interplay between fatty acids and cancer cell behavior.

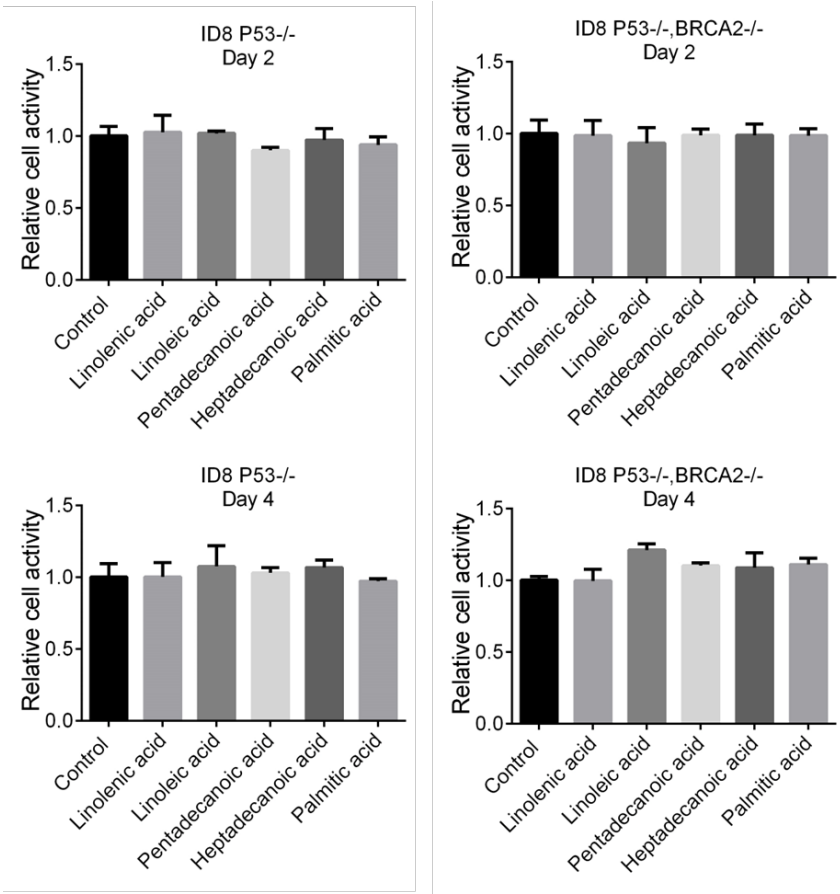


**Figure 1.** The proliferation of tumor cells after treatment with various fatty acids. The tumor cells were treated with fatty acids for 2 days or 4 days. Then the cell activity was measured through CCK-8 assay.

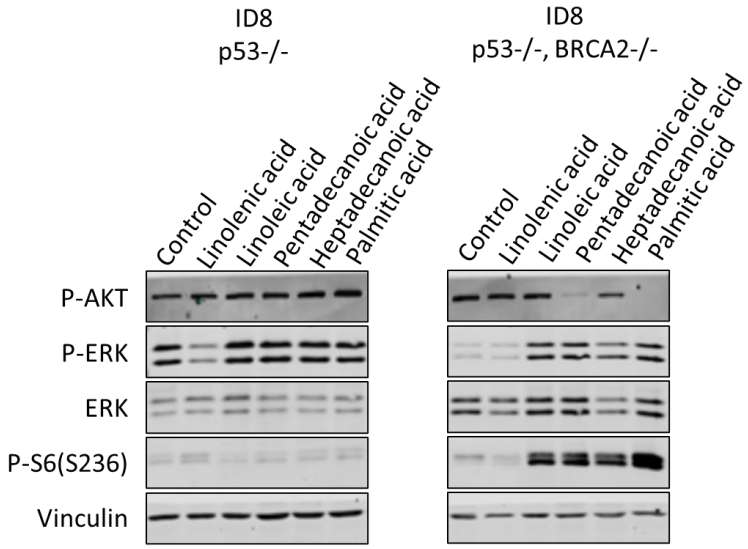


**Figure 2.** The signaling activation of tumor cells. Tumor cells were treated with various fatty acids for 2 days. The total protein was extracted from the tumor cells to measure the activation of mTOR signaling pathway.

### The Effect of Fatty Acids On Lipid Droplet Accumulation

The intricate interplay between lipid content and the aggressiveness of ovarian cancer cells adds a layer of complexity to our understanding of cellular dynamics. Traditionally housed in lipid droplets, lipids, predominantly in the form of fatty acids, transcend their role as mere storage entities. Beyond constituting the structural components of lipid droplets, fatty acids emerge as influential regulators of signaling pathways, exerting a profound impact on the overall lipid accumulation within cells. Our research outcomes bring forth compelling evidence, highlighting the distinct effects of different fatty acids on this intricate balance. First, when comparing the effect of omega-3 and omega-6 fatty acids, only omega-6 fatty acids can promote lipid accumulation. There is no significant difference under omega-3 fatty acid treatment. Furthermore, odd chain fatty acid induces more lipid accumulation than even chain fatty acid. These results underscore the specificity of these fatty acid subtypes in modulating cellular lipid dynamics. These findings not only deepen our understanding of the nuanced relationship between fatty acid composition and lipid regulation but also provide valuable insights into potential mechanisms driving the aggressiveness of ovarian cancer cells within the intricate landscape of lipid metabolism.

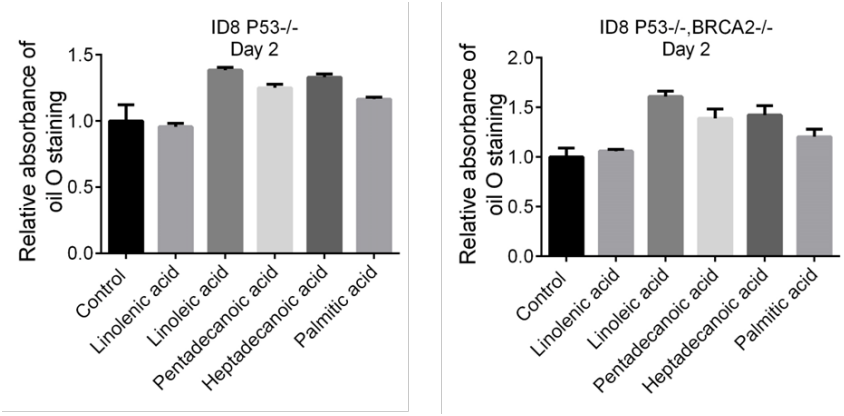


**Figure 3.** The lipid droplet amount in the tumor cells. The tumor cells were treated with various fatty acids for 4 days and then were stained with Oil O Red to indicate the lipid amount in the tumor cells.

## Discussion

In our results, we did see some changes at the cell signaling activation but did not see significant difference at the cell number, as measured by CCK-8, despite distinct effects on lipid accumulation, suggesting that alterations in lipid content may not be directly proportional to changes in cell proliferation. This underscores the multifaceted nature of cancer cell responses to different environmental stimuli.

The discrepancy between changes in cell signaling activation and the absence of a significant impact on cell number in our study may stem from cellular adaptations and compensatory mechanisms that maintain cell proliferation despite alterations in signaling. The intricate and context-dependent nature of signaling pathways, along with potential temporal dynamics and multifactorial regulation of cell proliferation, could contribute to the observed complexities. Additionally, genetic heterogeneity within the ovarian cancer cell population may result in diverse subpopulations with distinct responses to signaling changes, further contributing to the overall lack of uniformity in cellular outcomes. A more thorough exploration, including extended observation periods and analyses of downstream effectors, may provide a deeper understanding of the intricate interplay

between signaling pathways and cellular behavior in ovarian cancer.

The distinct response observed between ID8 cells with p53/BRCA2 mutation and those with p53 mutation alone in our study suggests intricate interactions within the cellular signaling network. The coexistence of p53 and BRCA2 mutations may lead to synergistic or antagonistic effects, contributing to a unique cellular sensitivity to odd chain fatty acids. The absence of BRCA2 might trigger compensatory mechanisms or alternative pathways in cells with only p53 mutation, partially mitigating the effects of odd chain fatty acids. However, the presence of both mutations may disrupt these compensatory mechanisms, resulting in a more pronounced cellular response. Additionally, the distinct molecular landscape and potential synthetic lethality in cells with both mutations could further influence their susceptibility to perturbations. Deeper exploration into the specific molecular mechanisms and downstream effectors is essential to unravel the complex dynamics shaping the differential response to odd chain fatty acids in the context of p53/BRCA2 mutation (Guo et al., 2021).

Our Western blot analyses revealed differential effects on crucial signaling pathways, with omega-6 fatty acids notably promoting mTOR signaling activation and odd chain fatty acids increasing ERK phosphorylation, which plays a part in the mitogen-activated protein kinase (MAPK) pathway and whose overexpression may lead to increased cell proliferation. The distinct response patterns observed in ID8 cells with BRCA2/p53 mutation compared to those with only p53 mutation further emphasize the intricate relationship between genetic backgrounds and cellular responses to fatty acid stimuli. The heightened sensitivity of double mutation tumor cells to odd chain fatty acids underscores the need for personalized considerations in therapeutic strategies, particularly in the context of ovarian cancer with specific genetic mutations.

Moreover, our results shed light on the correlation between lipid accumulation and the aggressiveness of ovarian cancer cells. The ability of odd chain fatty acids to significantly induce greater lipid accumulation than even chain fatty acids, and the propensity of omega-6 fatty acids to induce more lipid accumulation compared to omega-3 fatty acids, highlight the potential role of specific fatty acid subtypes in modulating the lipid landscape of ovarian cancer cells. This may have implications for understanding the mechanisms driving tumor progression and could inform targeted therapeutic approaches.

The intricate regulation of lipid metabolism, as evidenced by our findings, emphasizes the need for a nuanced understanding of the role of fatty acids in ovarian cancer progression. The cellular response to these fatty acids is not solely reflected in cell proliferation but extends to the modulation of key signaling pathways and lipid dynamics. These results contribute to the growing body of knowledge surrounding ovarian cancer biology, offering potential avenues for further exploration in the development of targeted therapies and personalized treatment strategies tailored to the genetic profile of individual patients.

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