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Research article

The effect of paclitaxel on cachexia-related gene *AZGP1* expression during adipocyte differentiation

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Abstract

Cancer cachexia, a syndrome characterized by involuntary weight loss, affects skeletal muscles and leads to adipose tissue loss. Activation of adipose tissue during cancer cachexia may contribute to cachexia through mechanisms like ZAG, a biomarker for adipose atrophy. This study aimed to analyze the effect of paclitaxel on adipogenesis and cachexia-related genes in cancer cachexia. The study involved human preadipocyte cells grown in a commercial medium, with 50 nM paclitaxel applied on different days for differentiation. The 15th day, marking the completion of differentiation was analyzed for lipid accumulation and *PPARγ* and *AZGP1* gene expression. The study found that paclitaxel during adipogenesis suppressed differentiation and lipid accumulation in human preadipocytes. It was determined that there was no change in the expression level of the *AZGP1* gene in day 3 preadipocytes given paclitaxel starting from the 3rd day of differentiation. It was determined that *PPARγ* gene expression was suppressed in day 0 preadipocytes given paclitaxel starting from the first day of differentiation compared to the control group. As a result, it has been determined that paclitaxel may contribute to adipose tissue loss in cancer cachexia by suppressing the differentiation of preadipocytes and lipid accumulation during adipogenesis. The change caused by paclitaxel in the expression of genes such as *AZGP1* and *PPARγ* during adipogenesis needs to be analyzed in further studies.

Keywords: *Adipogenesis; cachexia; paclitaxel; AZGP1; PPARγ*

1. Introduction

Loss of fat and skeletal muscle mass characterizes cachexia, a multifactorial illness that progresses into functional impairment and is not entirely reversible with standard dietary support (Ni and Zhang, 2020). It is a multifaceted systemic illness affecting various organs and tissues (Peixoto da Silva et al., 2020). Cancer cachexia lowers quality of life, lowers responsiveness to treatment, decreases response to anticancer therapy, lowers performance status, and lowers survival (Muliawati et al., 2012).

Primary tumor treatment or anticancer treatments like surgery, chemotherapy, and radiotherapy can contribute to cachexia by altering nutritional and metabolic status and causing tumor-specific damage (Laviano et al., 2011). However, there is conflicting evidence on the direct effect of anticancer drugs on cachexia (Cabrera et al., 2025).

Most cancer patients experience body composition changes the disease. Patients receiving chemotherapy for breast cancer and prostate cancer, for instance, acquire adipose tissue and lose skeletal muscle, which is linked to a higher risk of clinical comorbidities and cancer recurrence. On the other hand, patients with advanced colorectal and lung cancer may lose skeletal muscle in addition to adipose tissue, which is linked to a worse prognosis and a reduced response to treatment (Sebastiano and Mourtzakis, 2012; Choi et al., 2025; Khan et al., 2025).

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Several studies with tumor-bearing animals have reported brown adipose tissue activation via lipolysis during cancer cachexia (Panagiotou et al., 2025). Adipose tissue plays a critical role in the pathophysiology of cancer cachexia, particularly through enhanced lipolysis, browning, and thermogenesis during the early stages of the disease. Although brown adipose tissue contributes to energy expenditure and may exacerbate cachexia, the specific mechanisms and overall role of adipose tissue in human cancer cachexia remain inadequately understood (Mota et al., 2024).

Cancer cachexia involves the remodeling of adipose tissue due to various genetic, metabolic, and inflammatory mechanisms. It's unclear if tumor-derived compounds or the tumor itself cause the loss of adipose tissue. *In vitro* studies show that co-culturing Lewis lung carcinoma cells inhibits adipogenesis in mouse precursor adipocytes, promoting lipid droplet volume reduction (Lopes et al., 2018). Adipocytes and tumor cells secrete pro-inflammatory cytokines and downregulate adipogenic genes, suggesting that tumor cells may interfere with adipocyte formation by inducing an inflammatory response. This could significantly influence metabolic and functional alterations in cachectic adipose tissue (Mannelli et al., 2020).

PPARγ (Peroxisome proliferator-activated receptor gamma) is a crucial regulator of adipogenesis, increasing the expression of adipocyte differentiation markers and lipid accumulation. It plays a significant role in both brown and white adipose tissue differentiation in various regions. *PPARγ* may contribute to the pathogenesis of diseases with irregular lipid metabolism (Kim et al., 2024). The activation of *PPARγ* in white adipose tissue may depend on the NF-κB pathway, potentially modulating inflammation in white adipose tissue, possibly due to cancer cachexia (Mannelli et al., 2020).

ZAG (zinc-α2-glycoprotein) is a secretory protein and is encoded by the *AZGP1* (α2 zinc glycoprotein 1, zinc-binding) gene (Pendás et al., 1994). *AZGP1* plays a crucial role in regulating energy homeostasis and glucose/lipid metabolism by acting on hypothalamic POMC neurons, and its regulation pathway is being investigated in several types of cancer (Yun et al., 2024; Qin et al., 2024; Qiu et al., 2024). ZAG is one of the proteins involved in regulating body weight, glucose levels, and body fat (Zimowska et al., 2024). ZAG's association with metabolic syndrome, including obesity, hypertension, and dyslipidemia, underscores its broader implications for human health (Zhou et al., 2024). The relationship between serum ZAG protein and serum zinc is not fully explained but ZAG levels have regulatory effects on insulin resistance and plasma glucose levels are mediated by zinc and acylated ghrelin (Kurtulus et al., 2024). ZAG is involved in metabolism through various pathways. Recent studies have demonstrated the role of ZAG in energy and lipid metabolism, as well as a possible connection with exercise (Unver et al., 2024). It promotes the browning of white adipose tissue, raising energy expenditure and reducing body weight and fat tissue (Elattar et al., 2018). ZAG supports the proliferation of 3T3-L1 mouse preadipocytes by inhibiting the expression of *PPARγ* and *C/ERBα* (Zhu et al., 2013). Enhanced expression of ZAG in adipose tissue has been linked to elevated lipolytic activity, contributing to fat depletion and body weight reduction. As a key lipid-mobilizing factor, ZAG plays a pivotal role in the metabolic alterations observed in cachectic individuals (Martínez-Navarro et al., 2024). Moreover, increased circulating levels of ZAG protein may serve as a potential biomarker for the early detection of cancer-associated cachexia characterized by adipose tissue wasting (Yeung et al., 2009; Senyigit et al., 2024; Wen et al., 2024). ZAG is upregulated in cachectic people and animal models, and elevated amounts of free fatty acids in the bloodstream have been linked to the acceleration of muscle protein breakdown in cancer cachexia (Burgi and Schmid, 1961).

The study investigated the impact of chemotherapeutic agent paclitaxel on adipogenesis and adipose tissue loss in cancer cachexia. The aim was to determine how effective chemotherapy agents are on the molecular infrastructure of the cachetic state that occurs in cancer. It examined gene expression, lipid accumulation, and cachexia-related gene expression. Results showed that paclitaxel suppressed adipogenesis and preadipocyte differentiation, highlighting the relationship between chemotherapeutic agents and adipose tissue loss.

2. Materials and methods

2.1. Preparation of paclitaxel concentrations

The study used 1 mg paclitaxel (Taxol®, Sigma Aldrich) and prepared a concentration of 1.25 mM main stock and 5 μM intermediate stock for human preadipocyte cells. During differentiation, 1 μL of intermediate stock was applied to cells, with a final concentration of 50 nM, ensuring DMSO did not exceed 0.05% in each well (Choron et al., 2015).

2.2. Culture of human preadipocyte cells

Human preadipocyte cells (HPAD) used in the research were provided by Dr. Sevgin Degirmencioglu. Cells stored as stock at -196°C were cultured in a human preadipocyte growth medium (Thermo Fisher, USA) under appropriate conditions (at 37°C with 5% CO_2). When the cells were fully confluent, they were passaged and multiplied until they reached the ideal number for the experiment.

2.3. Application of paclitaxel and differentiation of preadipocyte cells

Table 1
The experimental groups treated with paclitaxel.

Experimental Groups	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5
Day 0	PTX+DM	PTX+DM	PTX+DM	PTX+DM	PTX+DM
Day 3	DM	PTX+DM	PTX+DM	PTX+DM	PTX+DM
Day 6	DM	DM	PTX+DM	PTX+DM	PTX+DM
Day 9	DM	DM	DM	PTX+DM	PTX+DM
Day 12	DM	DM	DM	DM	PTX+DM
Control DMSO (+)	DM+DMSO	DM+DMSO	DM+DMSO	DM+DMSO	DM+DMSO
Control (-)	DM	DM	DM	DM	DM

PTX: paclitaxel DM: differentiation medium DMSO: Dimethyl sulfoxide.

The seeded cells were followed until sufficient density was reached in the culture dishes. To determine the effect of paclitaxel on adipogenesis at the determined concentration, the differentiation stage of human preadipocyte cells into mature adipocyte cells was chosen as a model. For this, HPAD cells were counted, 10^5 cells/well in 12-well culture dishes and seeded with 1 ml of growth medium. The cells were incubated and checked regularly until they were 90% confluent. When the cells were 90% confluent, the growth medium was then aspirated from the wells and 1 mL of human adipocyte differentiation medium used to differentiate cells was added. After removing the old medium, 50 nM paclitaxel and 1 mL of fresh human adipocyte differentiation medium were replaced every 3 days for 15 days (Table 1).

2.4. Analysis of gene expression

Following paclitaxel application and the time required for differentiation, cells were collected on day 15 for total RNA isolation, cDNA synthesis, and PCR analyses. Total RNA was obtained from total RNA with the isolation kit (GeneJet RNA Purification Kit, Thermo Scientific, USA) following the manufacturer's recommendations. Purity and concentration analysis of the obtained RNAs was performed using a spectrophotometer (Thermo Scientific, USA). The concentrations of all RNAs were adjusted to 1000 ng/µl. To determine the gene expression level, cDNA synthesis using 1 µg RNA was performed using a commercially available kit (RevertAid First Strand cDNA Synthesis Kit, Thermo Scientific, USA). PCR cycling conditions for cDNA synthesis: 10 min at 25℃, 15 min at 42℃, and 5 min at 85℃. The expression levels of the genes whose primer sequences are given in Table 2 were examined with the cDNAs obtained. *PPARγ* and *AZGP1* genes and GAPDH gene primer sequences as internal control are given in Table 2 and were synthesized by Oligomer Biotechnology (Turkey). SyberGreen Master Mix kit (Real Q Plus 2X Master Mix Green, Amplicon, Denmark) was prepared under the manufacturer's recommendations, and 40 cycles in the quantitative real-time polymerase chain reaction was performed using a 30 sec at 95℃, 30 sec at 55℃, 30 sec 72℃ heat program. The level of expression of each gene compared to control cells was examined using the formula $2^{-\Delta\Delta Ct}$.

2.5. Determination of lipid accumulation

Determination of lipid accumulation in cells was done by the Oil Red O Staining method. To analyze the effect of paclitaxel on lipid accumulation during the adipocyte differentiation process, 105 cells/well of human preadipocyte cells were passaged into 12-well cell culture plates and paclitaxel was applied at the determined concentration every 3 days for the 15 days required for differentiation into mature adipocytes. On day 15, the procedure previously described by You et al. (2014) was applied with minor modifications. Cells were washed 2 times with 1 ml of PBS after the medium was collected. Cells were fixed by incubation for 1 hour with 1 ml of 10% formalin. Following this, the cells were washed 2 times with 1.5ml ddH_2O and incubated for 5 min. It was treated with 1ml of 60% isopropanol. The isopropanol was then withdrawn and left to dry. When drying was observed, it was kept in an Oil Red O (Merck, Germany) working solution for 30 min. Oil Red O dye was aspirated and cells were washed with 1.5 ml of ddH_2O. Cells were photographed under a 10X inverted microscope. After photographing, 1 ml of 60% isopropanol was added to each well and the absorbance of the dye solution at 570 nm was measured in a spectrophotometer.

2.6. Statistical analysis of data

Two-tailed distribution and two-sample homoscedastic t-test analysis were used for data analysis. The statistical significance of the results obtained was evaluated over a p-value of 0.05, and values with a p-value of ≤0.05 were considered reliable.

3. Result

3.1. Paclitaxel reduced lipid accumulation

As a result of the analysis of 50 nM paclitaxel applied to preadipocytes with Oil Red O staining, it was determined that lipid accumulation was reduced in the group compared to the control group (Fig. 1A). After staining, the absorbance measurements of the dye obtained from the cells were normalized with the absorbance value of the control cells. Preadipocytes differentiated by administering paclitaxel were compared with those in the control group. Considering that paclitaxel was applied to the cells in the day 0 group throughout the differentiation period, it was determined that paclitaxel suppressed lipid accumulation, and the day 0 group was followed by the cells in the days 3, 6, 9, and 12 group, respectively. According to the results, absorbance measurements were obtained at values of 0.67, 0.86, 0.87, 1.05, and 1.19 on days 0, 3, 6, 9, and 12, respectively. The results were found to be statistically significant for all groups (p<0.05). (Fig. 1B).

3.2. Effect of paclitaxel on AZGP1 and PPARγ gene expression

It was observed that there was no change in the expression level of the *AZGP1* gene in day 3 preadipocytes given 50 nM paclitaxel starting from the 3rd day of differentiation, compared to the control group (cells that were not treated with any substance). When the on days 0, 6, 9, and 12 preadipocyte groups were compared with the control group, it was observed that gene expression levels were suppressed up to 0.44, 0.42, 0.5,

Table 2
Primer sequences used for RT-PCR.

Gene		Primer Sequences	Temperature of Annealing (°C)	GC Content (%)
AZGP1	**Forward (F)**	5'-TACAACGACAGTAACGGGTCT-3'	58	48
	Reverse (R)	5'-TATTTCCAGAATGCTCCGCTG-3'	58	48
PPARγ	**Forward (F)**	5'-TCGGTTTCAGAAATGCCTTG-3'	55	45
	Reverse (R)	5'-AGGTCAGCGGACTCTGGATT-3'	59	55
GAPDH	**Forward (F)**	5'-CGAGATCCCTCCAAAATCAA-3'	55	45
	Reverse (R)	5'-TTCACACCCATGACGAACAT-3'	55	45

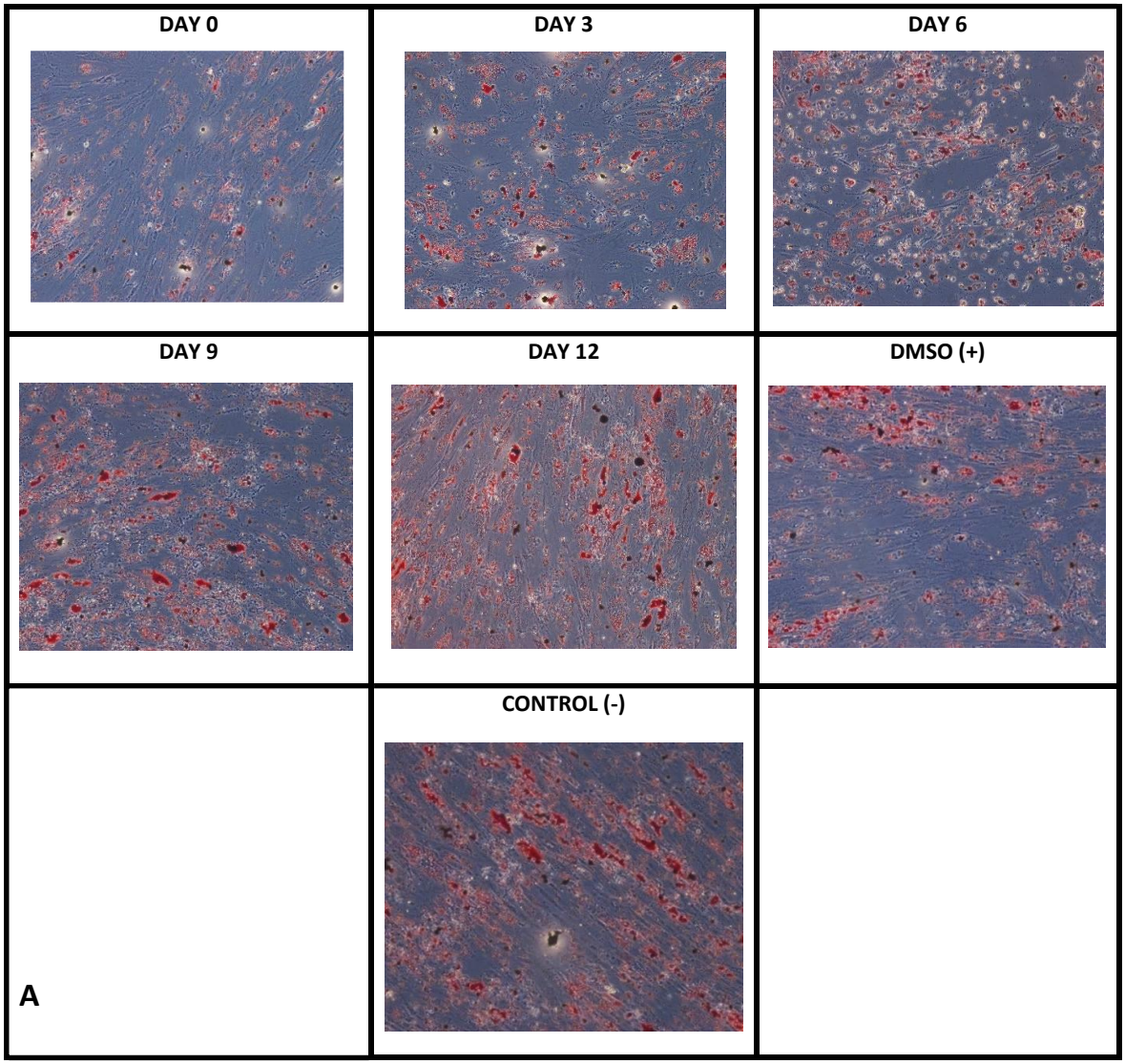

Fig. 1A. Effect of paclitaxel on differentiation of human preadipocyte cells. Lipid accumulation was detected by Oil Red O staining. (A) Microscope images of differentiated adipocytes after Oil Red O staining (scale bar=100 μm).

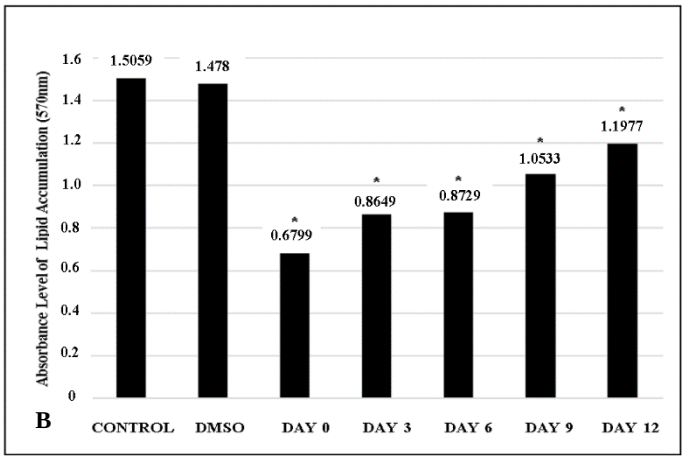

Fig. 1B. Effect of paclitaxel on differentiation of human preadipocyte cells. Lipid accumulation was detected by Oil Red O staining. (B) Comparison of optical absorbance values at 570 nm of the dye recollected from adipocytes.

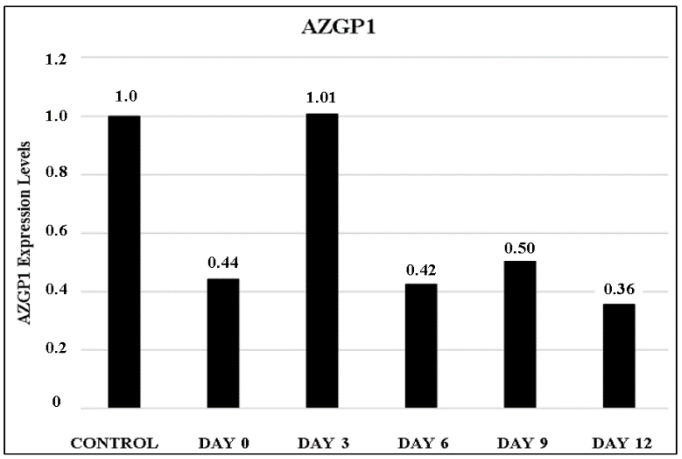

Fig. 2. *AZGP1* gene expression level (*: statistically significant).

and 0.36, respectively (Fig. 2). p values were found to be 0.12, 0.78, 0.703, 0.177, and 0.068 for on days 0, 3, 6, 9 and 12, respectively.

When comparing day 0 preadipocytes given 50 nM paclitaxel from the first day of differentiation with the control group (cells not applied any substance), it was determined that *PPARγ* gene expression was suppressed (p=0.000). In the day 3 and day 6 preadipocyte groups, gene expression levels were observed to be suppressed up to 0.65 and 0.9, respectively, when compared to the control group (0.100, 0.604, respectively). However, it was observed that gene expression levels in day 9 and day 12

preadipocyte cells increased to 2.29 and 3.99, respectively, compared to the control group (p=0.015, 0.003, respectively) (Fig. 3).

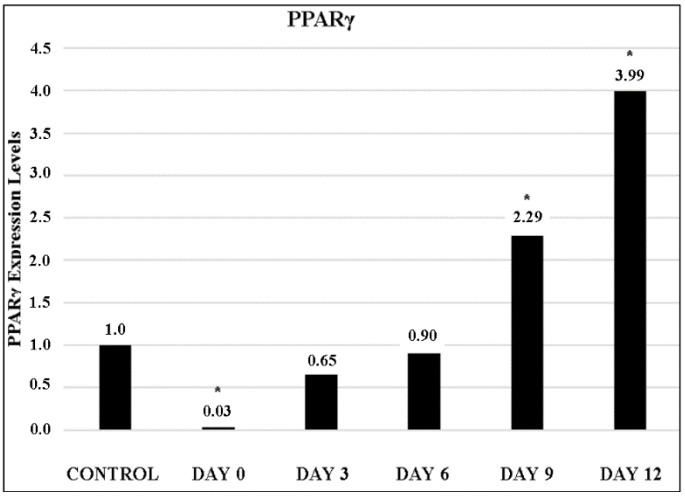

Fig. 3. *PPARγ* gene expression level (*: statistically significant).

4. Discussion

Cancer cachexia is a syndrome characterized by involuntary weight loss, affecting skeletal muscles and adipose tissue (Fearon et al., 2011). Chemotherapeutic agents also cause body weight loss (Huang et al., 2019). ZAG, a marker of fat catabolism and cachexia, is highly expressed in cachectic patients and promotes browning of adipocytes, triggers fat oxidation, increases energy expenditure, and inhibits adipocyte differentiation by inhibiting *PPARγ* and *C/ERBα* expression in preadipocytes (Mracek et al., 2011; Zhu et al., 2013).

Cancer cachexia can impair the regulation of adipogenesis and adipogenic factors (Batista et al., 2013; Bing et al., 2006). A study found that co-culture of lung carcinoma cells with mouse preadipocyte 3T3-L1 cells negatively affected adipogenesis by promoting reduced lipid accumulation and volume, leading to downregulation of adipogenic and lipolytic gene expressions (Lopes et al., 2018). Another study found that the downregulation of ZAG was accompanied by a decrease in lipid droplet formation, thus suggesting that inhibition of ZAG may reduce lipid synthesis in colorectal cancer cells (Xu et al., 2024). This is the first study to examine the effects of paclitaxel on the differentiation of human preadipocyte cells, adipogenesis, and cachexia-related genes like *AZGP1* in cancer cachexia.

Chemotherapeutic agents can disrupt adipogenesis in adipose tissue by inhibiting the differentiation of human adipocyte stem cells (Ebadi and Mazurak, 2014). In our study, paclitaxel administered to human preadipocyte cells suppressed lipid accumulation and adipogenesis. The study conducted by Choron et al. (2015) demonstrated that treatment with 1 μM paclitaxel significantly inhibited adipogenesis in human adipose-derived stem cells (hASCs). Although adipose tissue-derived mesenchymal stem cells (ADSC) could differentiate into adipocytes, asteroids, and chondrocytes, their adipogenic differentiation ability was significantly reduced after cisplatin treatment (Dasari and Tchounwou, 2014). Chang et al. (2017) studied the ability of ADSCs to differentiate *in vivo* after 9 receiving chemotherapy based on cisplatin, finding that chemotherapy significantly decreased the donor capacity to differentiate into adipogenic, osteogenic, and chondrogenic cells. However, combinations of radiotherapy, chemotherapy, and surgical intervention are used in cancer treatment, and *in vitro* chemotherapeutic agent treatments may not fully represent the clinical situation of cachectic patients (Dasari and Tchounwou, 2014).

Bao et al. (2005) found that ZAG mRNA levels increased gradually after induction and peaked on the 8th day, regulated through TNF-α and PPARγ receptors. Zhu et al. (2013) reported that after ZAG expression plasmid transfection into 3T3-L1 mouse preadipocytes, lipid accumulation decreased, adipocyte differentiation was inhibited, and ZAG down-regulated *PPARγ* and *C/EBPα* mRNA levels in the middle and late differentiation phases. In intrahepatic cholangiocarcinoma treated with the anticancer agent lenvatinib, it has been shown that low expression of *AZGP1* is associated with a poor prognosis in patients (Deng et al., 2023).

In our study, paclitaxel applied from day 3 of differentiation did not change *AZGP1* expression in human preadipocytes compared to the control but reduced *AZGP1* expression from day 0, day 6, day 9, and day 12. More *in vitro* and *in vivo* studies are needed to determine the molecular pathways involved in cancer cachexia and to better analyze these findings at the gene level by determining the change in ZAG protein level and possible cachexia pathways.

Recent studies have shown that *PPAR* agonists may be a useful adjuvant therapy to preserve tissue mass (Langer et al., 2024; Beluzi et al., 2015; Goncalves et al. 2018). Our study found that paclitaxel, given from day 0 of differentiation, significantly reduced *PPARγ* expression in human preadipocyte cells, suggesting that chemotherapeutic agents may be effective in developing cancer cachexia. This is in line with the theory that factors involved in downregulating genes involved in adipocyte differentiation may play a key role in metabolic and functional changes in cachectic adipose tissue. *PPARγ* is a transcription factor required for adipogenesis and maintenance of the differentiated state (Chu et al., 2014). In the late stage of adipocyte differentiation, there is an increase in the expression of *PPARγ* and *CEBPα,* necessary for the completion of differentiation. Suppression of *PPARγ* reduces triglyceride accumulation in adipocytes (Chu et al., 2014). However, paclitaxel significantly increased *PPARγ* expression in the late stage of differentiation compared to the control. This increase may be due to *PPARγ* being active in the late stage of adipogenesis or paclitaxel application. Further studies are needed to determine the possible effects of paclitaxel and other chemotherapeutic agents on adipogenesis in the setting of cachexia.

5. Conclusion

This study was conducted to provide a better understanding of how chemotherapeutic agents affect adipose tissue at the molecular level during cachexia. The expression of the adipogenesis-related gene *PPARγ* and the cachexia biomarker *AZGP1* was examined the effects of paclitaxel administered at each stage of preadipocyte differentiation into mature adipocytes. It decreased *PPARγ* expression and lipid accumulation in a dose-dependent manner. The results demonstrated that paclitaxel when employed as a chemotherapeutic treatment for cachectic tumors, has a negative effect on adipocyte differentiation that is dose dependent. It is thought that these findings contribute to the literature for further analysis. Basic data has been provided for the steps to be taken to increase the quality of life of cachectic cancer patients.

Conflict of interest: The authors declare that they have no conflict of interests.

Informed consent: The authors declare that this manuscript did not involve human or animal participants and informed consent was not collected.

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