

RESEARCH ARTICLE

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Role of PDGF-BB in Oral Squamous Cell Carcinoma through PI3/AKT/mTOR Pathway: An Integrated Computational and Real-Time PCR-Based Approach

Georgia Benitha^{1*}, Pratibha Ramani², Selvaraj Jayaraman³, Abilasha Ramasubramaniam⁴, Sandra Sagar⁵

Abstract

Objective: This study investigates the role of PDGF-BB in oral squamous cell carcinoma (OSCC) and its impact on the *PI3K/AKT/mTOR* pathway. The goal is to elucidate the expression levels analysis of PDGF-BB and signaling molecules in OSCC pathogenesis, potentially identifying novel biomarkers or therapeutic targets. **Methods:** A combined approach involving in silico and experimental methods was employed. Protein sequence data for PDGF-BB were obtained from UniProt, and protein-protein interactions were analyzed using STRING to visualize PDGF-BB's network. Pathway enrichment analysis was conducted via PANTHER to identify relevant signaling pathways. The study included 30 OSCC patients and 30 matched healthy controls. Serum PDGF-BB protein levels were quantified using enzyme-linked immunosorbent assay (ELISA), while mRNA expression of *PI3K*, *AKT*, and *mTOR* was measured in OSCC and adjacent non-tumor tissues using quantitative real-time PCR (RT-qPCR). **Results:** Pathway analysis identified 12 significant signaling pathways associated with PDGF-BB, with the *PI3K/AKT/mTOR* pathway chosen for validation due to its relevance in cancer-related signaling. STRING analysis confirmed PDGF-BB's interaction with this pathway. ELISA revealed significantly elevated serum PDGF-BB levels in OSCC patients (3.44 ng/mL) compared to controls (1.38 ng/mL, $p < 0.05$). RT-qPCR demonstrated significant upregulation of *PI3K*, *AKT*, and *mTOR* mRNA in OSCC tissues, with fold changes of 1.93, 2.1, and 1.9, respectively, relative to adjacent non-tumor tissues. **Conclusion:** PDGF-BB is significantly upregulated in OSCC and likely contributes to OSCC progression by activating the *PI3K/AKT/mTOR* pathway. These findings highlight PDGF-BB's potential as a biomarker and therapeutic target in OSCC. Targeted therapies aimed at disrupting PDGF-BB and *PI3K/AKT/mTOR* signaling may improve OSCC outcomes, offering a promising avenue for future research and clinical applications.

Keywords: Oral squamous cell carcinoma- PDGF-BB, *PI3K/AKT/mTOR* pathway- Protein-protein interaction

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Introduction

Oral squamous cell carcinoma (OSCC) is one of the most common and aggressive cancers of the head and neck, accounting for more than 90% of all oral malignancies. Despite advances in treatment techniques such as surgery, chemotherapy, and radiation, the five-year survival rate for individuals with OSCC remains disappointingly low, especially in the advanced stages of the disease. This limited effectiveness in improving long-term outcomes is mostly attributable to the high rates of recurrence and metastasis found in OSCC patients [1, 2]. The persistent

low survival rates, especially in countries where tobacco and alcohol use are prominent, highlight the need for a greater understanding of OSCC's molecular and genetic origins, which could potentially lead to more successful therapy possibilities [3-5].

OSCC is a complicated disease characterized by several genetic abnormalities, epigenetic alterations, and abnormal cellular pathways. A variety of genes and signaling pathways have been linked to its progression, including the inactivation of tumor suppressor genes, activation of oncogenes, and overexpression of growth factors and receptors [6, 7]. Notably, growth factors like

¹Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, India. ²Department of Oral and Maxillofacial Pathology, Priyadarshini Dental College and Hospitals, India. ³Department of Oral Pathology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, India. ⁴Department of Biochemistry, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India. ⁵Department of Oral and Maxillofacial Pathology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India. *For Correspondence: benithageorge10@gmail.com

epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) are thought to be major drivers in the evolution of OSCC. These growth factors, by their interactions with their respective receptors, can increase cellular proliferation, angiogenesis, and resistance to apoptosis, which are hallmarks of cancer [8]. PDGF, in particular, has emerged as a significant player in OSCC, given its role in regulating various cellular processes within the tumor microenvironment, thus presenting itself as a promising target for further investigation [9, 10]. The PDGF family comprises four distinct polypeptide chains (PDGF-A, -B, -C, and -D) that combine to form five different dimeric isoforms, including PDGF-BB, a homodimer of the B chain [11]. These isoforms exert their biological effects through binding to receptor tyrosine kinases, specifically PDGFR α and PDGFR β , which then activate a series of downstream signaling pathways involved in cell proliferation, survival, and migration [12]. PDGF-BB, in particular, has been identified as a potent mitogen and chemoattractant for mesenchymal cells, such as fibroblasts and pericytes, which play crucial roles in supporting the structure and function of tissues. In the context of cancer, PDGF-BB has been shown to promote angiogenesis, facilitate the recruitment of cancer-associated fibroblasts, and enhance the invasive capabilities of tumor cells [13, 14].

The *PI3K/AKT/mTOR* pathway is a major signaling cascade that regulates cell growth, survival, and metabolism, all of which cancer cells frequently exploit to promote unrestrained proliferation. This system is strictly regulated in healthy cells; nevertheless, in cancer, mutations and overactivation of components within this pathway can result in uncontrolled cell proliferation and resistance to cell death mechanisms [15]. The *PI3K/AKT/mTOR* pathway is often activated first by receptor tyrosine kinases such as PDGFR. When PDGFR binds to PDGF-BB, it dimerizes and autophosphorylates, triggering a cascade of phosphorylation events that eventually activate *PI3K*. *PI3K* then phosphorylates PIP2 to form PIP3, which acts as a docking site for *AKT*, a serine/threonine kinase that is crucial in supporting cell survival and proliferation [16].

Once activated, *AKT* phosphorylates and activates *mTOR*, a kinase that controls cell development by increasing protein synthesis and suppressing autophagy. *mTOR* activation also improves cellular metabolism, allowing cancer cells to continue multiplying. The *PI3K/AKT/mTOR* pathway is typically elevated in OSCC, and abnormal activation has been linked to increased tumor aggressiveness, treatment resistance, and poorer clinical outcomes. Understanding the link between PDGF-BB and the *PI3K/AKT/mTOR* pathway in OSCC may provide novel therapeutic targets for this complex disease [17, 18].

PDGF-BB interacts with PDGFR β and activates the *PI3K/AKT/mTOR* pathway, promoting cancer cell survival, proliferation, and migration. In OSCC, the connection between PDGF-BB and the *PI3K/AKT/mTOR* pathway is very important because it may promote the cancer's aggressiveness, making it more resistant to standard treatments. Studies have revealed that targeting

the PDGF-BB/*PI3K/AKT/mTOR* axis may potentially hamper the tumor's ability to sustain its development and elude apoptosis, offering a promising option for future therapeutic interventions in OSCC [19, 20].

The purpose of this study is to examine the involvement of PDGF-BB in OSCC and its effects on the *PI3K/AKT/mTOR* pathway. This study seeks to provide a thorough understanding of how PDGF-BB contributes to OSCC pathogenesis at the molecular level by combining computational analysis and real-time PCR validation. The study specifically intends to unravel the methods by which PDGF-BB stimulates the *PI3K/AKT/mTOR* pathway in OSCC to potentially identify novel biomarkers or therapeutic targets that could enhance OSCC patient treatment. Given the important role of PDGF-BB and the *PI3K/AKT/mTOR* pathway in OSCC progression, insights acquired from this work should pave the way for new, tailored therapy options aiming to disrupt this signaling axis and improve outcomes for patients with OSCC.

Materials and Methods

In Silico analysis

Protein sequences and functional annotations for PDGF BB were obtained from UniProt (<https://www.uniprot.org/>) by searching each protein by name and filtering results to Homo sapiens. FASTA sequences and functional data, including domains and localization, were downloaded for each protein to support pathway and interaction analyses. In this study, the STRING database (<https://string-db.org/>) was utilized to examine the interactions of the PDGF BB protein with other related proteins. STRING serves as a resource to collect, evaluate, and combine publicly accessible protein-protein interaction information and further enhances it with computational interaction predictions. This approach allowed for a comprehensive analysis of the network of proteins potentially associated with PDGF-BB within relevant signaling pathways. In this study, the PANTHER database (v17.0; Protein ANalysis THrough Evolutionary Relationships) was applied to carry out gene ontology analysis. This analysis provides insight into the biological processes, molecular functions, and subcellular localization of gene products. User-defined gene lists from the dataset were uploaded in batch mode to categorize gene functions. Additionally, pathway-based classification was performed to identify significant pathways potentially linked to PDGF-BB. Among the enriched pathways, the *PI3K/AKT/mTOR* pathway was selected for validation due to its relevance in OSCC (Figure 1).

Patient Selection and Sample Collection

This study included 30 patients diagnosed with OSCC and 30 healthy controls matched for age and sex. OSCC tumor tissues and adjacent non-tumor tissue samples were obtained from OSCC patients undergoing surgical resection at the Department of Oral Maxillofacial Surgery, Saveetha Dental College and Hospitals, Chennai, India. Healthy control tissue samples were collected from individuals with no history of oral disease or malignancy

during routine dental procedures or oral biopsies. OSCC samples and control samples were confirmed through histopathological examination by certified pathologists. Additionally, blood samples were drawn from both OSCC patients and healthy controls. Blood samples were allowed to clot at room temperature for 30 minutes before being centrifuged at $1,500 \times g$ for 10 minutes to separate the serum, which was then collected and stored at -80°C until further analysis. All participants provided informed consent, and the study was approved by the Institutional Ethics Committee of Saveetha Dental College and Hospitals. IHEC/SDC/OPATH-2004/24/176

RNA Extraction

Total RNA was extracted from OSCC tumor tissues, adjacent non-tumor tissues, and control tissues using the TRIzol Reagent (Invitrogen, USA) according to the manufacturer's protocol. Briefly, tissue samples were homogenized in a TRIzol reagent, and chloroform was added to separate the aqueous phase containing RNA. Following centrifugation, the aqueous layer was transferred to a fresh tube, and RNA was precipitated using isopropanol. The RNA pellet was washed with 75% ethanol, air-dried, and resuspended in RNase-free water. RNA concentration and purity were assessed using a NanoDrop™ spectrophotometer (Thermo Scientific, USA), and RNA integrity was confirmed on a 1.5% agarose gel electrophoresis.

Reverse Transcription and Quantitative Real-Time PCR (RT-qPCR)

mRNA expression levels of key genes involved in the *PI3K/AKT/mTOR* pathway were analyzed using quantitative real-time PCR (RT-qPCR). Complementary DNA (cDNA) synthesis was performed using the iScript™ cDNA Synthesis Kit (Bio-Rad, USA) following the manufacturer's protocol. Briefly, 1 µg of total RNA was reverse-transcribed in a 20 µL reaction volume containing oligo(dT) primers and reverse transcriptase enzyme. For qPCR, gene-specific primers were designed for *PI3K*, *AKT*, *mTOR*, and a housekeeping gene (*GAPDH*) as an internal control. The qPCR reactions were set up in PCR tubes with a reaction volume of 20 µL, containing 10 µL of SYBR Green PCR Master Mix (Applied Biosystems, USA), 2 µL of cDNA template, 0.5 µL each of forward and reverse primers (10 µM), and 6 µL of nuclease-free water. Amplification was performed on a Bio-Rad Opus 96 RT-qPCR System (Bio-Rad) with the following thermal cycling conditions: initial denaturation at 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. Relative mRNA expression levels were calculated using the $2^{-\Delta\Delta C_t}$ method, where the C_t (cycle threshold) values of target genes were normalized to the C_t values of the housekeeping gene (*GAPDH*). Fold changes in gene expression were calculated by comparing the relative expression in OSCC tissues to that in control tissues.

Enzyme-linked immunosorbent Assay (ELISA) for PDGF BB Protein Quantification

Serum levels of PDGF-BB in OSCC patients and

healthy controls were quantified using a commercially available PDGF-BB ELISA kit. Serum samples were thawed on ice and diluted as necessary based on the ELISA kit's recommendations. For the assay, 100 µL of each serum sample, standard, or blank was added to the wells of a 96-well ELISA plate precoated with a PDGF BB-specific antibody. The plate was incubated at room temperature for 2 hours, followed by washing with a wash buffer to remove unbound proteins. A biotinylated secondary antibody specific to PDGF BB was added to each well and incubated for 1 hour at room temperature. After washing, streptavidin-horseradish peroxidase (HRP) conjugate was added, and the plate was incubated for 30 minutes at room temperature in the dark. The wells were then washed, and 100 µL of TMB substrate solution was added to each well, followed by a 15-minute incubation. The reaction was stopped with 50 µL of stop solution, and the optical density (OD) was measured at 450 nm using a microplate reader. PDGF BB concentrations in the serum samples were calculated by comparing their OD values to a standard curve generated from known concentrations of recombinant PDGF BB provided with the ELISA kit. All samples were run in duplicate, and the average protein levels were recorded.

Statistical Analysis

Data were analyzed using GraphPad Prism 9.0 software (GraphPad Software, USA). The relative mRNA expression levels and PDGF BB protein concentrations in OSCC tissues and control tissues were compared using a two-tailed Student's t-test. A p-value of < 0.05 was considered statistically significant. Results were presented as mean $\pm$ standard deviation (SD) to account for variability within sample groups.

Results

Pathway Analysis

The PDGF BB protein structure was retrieved from UniProt (Figure 1). STRING helps to visualize the network of proteins, which is potentially linked to various proteins, including *PI3K/AKT/mTOR* (Figure 2). Pathway

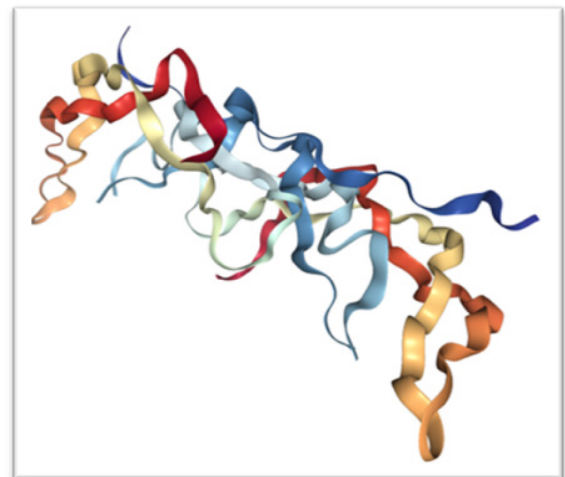


Figure 1. Represents the PDGF BB Protein Structure Retrieved from UniProt

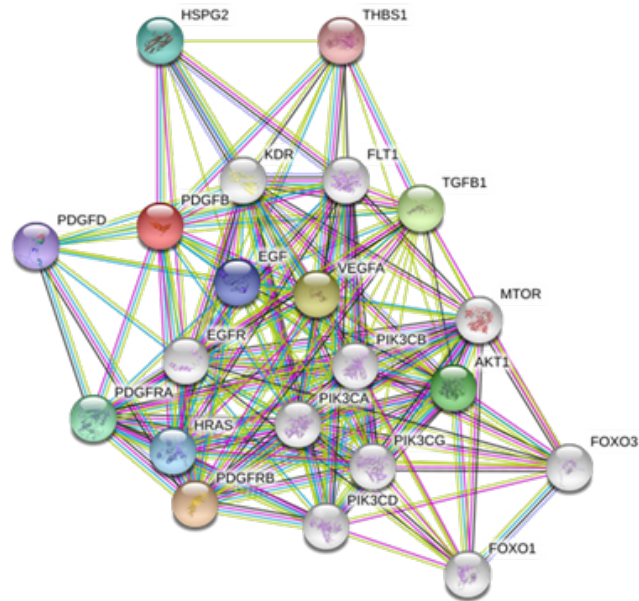


Figure 2. STRING Helps to Visualize the Network of Proteins

analysis was conducted using PANTHER software to identify key signaling pathways associated with PDGF BB in OSCC. The analysis revealed a total of 12 significant pathways potentially involved in PDGF BB signaling (Figure 3). Among these, the *PI3K/AKT/mTOR* signaling pathway was selected for validation due to its relevance in cell survival, growth, and proliferation. This pathway was chosen based on its high statistical significance within the identified pathways and its documented role in cancer-related signaling.

Protein Expression Analysis of PDGF-BB

ELISA was used to quantify PDGF BB protein levels in serum samples collected from OSCC patients and healthy controls. The analysis showed that the mean

PDGF BB concentration in OSCC patients was 3.44 ng/mL, compared to 1.38 ng/mL in healthy controls (Figure 4). The elevated levels of PDGF BB in OSCC samples indicate a significant increase in this protein in the patient group compared to the control group. The measured concentrations exhibited consistency across OSCC samples, with a clear and statistically significant difference ($p < 0.05$) between OSCC and control groups.

mRNA Expression Analysis of PI3K, AKT, and mTOR

Quantitative real-time PCR (RT-qPCR) analysis was conducted to evaluate the mRNA expression levels of *PI3K*, *AKT*, and *mTOR* in OSCC tissues in comparison to adjacent histologically confirmed tumor-free margin tissues. The expression data indicated a



Figure 3. Represents the PANTHER Analysis Revealed a Total of 12 Significant Pathways Potentially Involved in PDGF BB Signaling. The pathway found was associated with PDGF BB using the PANTHER DATABASE.

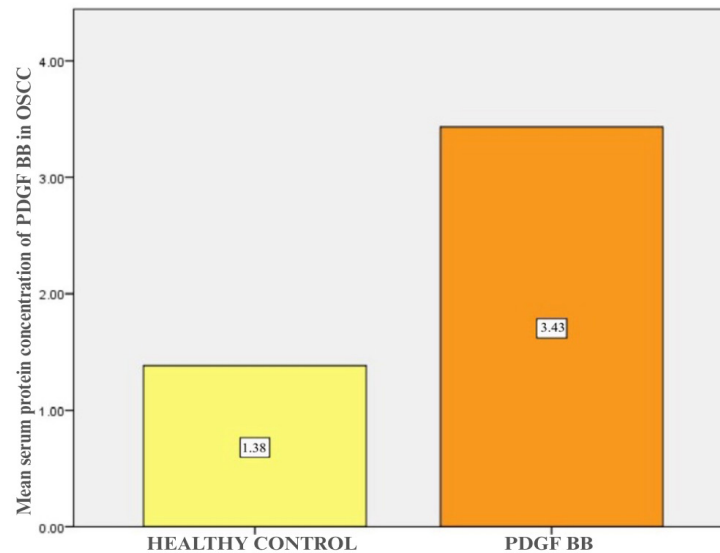


Figure 4. Indicates the Graph Mean Serum Concentration of PDGFBB in OSCC. Statistically significant difference with $p\text{-value} = 0.023^*$ [$p < 0.05$] was noted between OSCC and control groups.

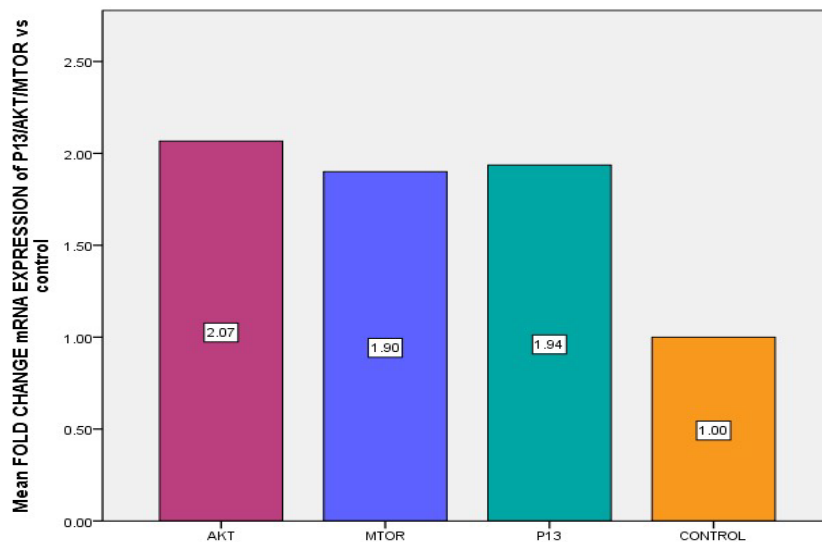


Figure 5. Indicates Upregulation of All three Key Genes in OSCC Samples of the *PI3K/AKT/mTOR* Pathway.

notable upregulation in OSCC samples across all three key genes of the *PI3K/AKT/mTOR* pathway (Figure 5).

In OSCC tissues, the mRNA expression of *PI3K* showed a mean fold-change increase of 1.9367 relative to the non-tumor margin tissues, which were normalized to a baseline expression value of 1.0. This elevated *PI3K* expression was consistently observed in all OSCC samples tested, suggesting a reproducible trend of increased transcriptional activity for this gene in cancerous tissues. Similarly, *AKT* mRNA levels in OSCC tissues exhibited a 2.1-fold increase compared to the adjacent non-cancerous margin tissues. The upregulation of *AKT* was uniform across the OSCC samples, showing minimal variation among individual specimens, thus indicating a stable pattern of *AKT* overexpression in tumor tissue compared to healthy tissue. For *mTOR*, a mean fold-change increase of 1.9 was observed in OSCC tissues compared to the histologically normal adjacent tissues. Like *PI3K* and

AKT, the elevated expression of *mTOR* was consistent among the OSCC samples analyzed, further supporting a trend of higher *mTOR* transcript levels in cancerous tissues. The RT-qPCR results collectively demonstrate significant upregulation of *PI3K*, *AKT*, and *mTOR* mRNA in OSCC tissues relative to non-tumor margins.

Discussion

The findings of this study underline the importance of PDGF-BB in OSCC, particularly its interaction with the *PI3K/AKT/mTOR* signaling pathway. Our strategy combined pathway and protein interaction analysis with gene and protein expression research to look into the role of PDGF-BB in OSCC progression. The findings, including higher serum PDGFBB protein levels in OSCC patients and overexpression of *PI3K*, *AKT*, and *mTOR* mRNA in OSCC tissues, shed light on the molecular

pathways by which PDGF BB may contribute to OSCC pathogenesis.

The PANTHER pathway analysis found 12 important PDGF BB signaling pathways, highlighting the protein's distinct significance in cellular signaling and cancer biology. Among these pathways, the *PI3K/AKT/mTOR* signaling pathway was of special interest because of its known involvement in supporting cell survival, proliferation, and metabolism, which are key activities frequently hijacked by cancer cells for tumor development and survival [17, 21]. This pathway was subsequently verified using STRING network analysis, which enabled the visualization of the PDGFBB protein in relation to other signaling proteins. STRING's network analysis revealed that PDGFBB interacts with a variety of proteins involved in this pathway, highlighting the significance of *PI3K/AKT/mTOR* signaling in OSCC.

In cancer cells, *PI3K* activation triggers a cascade that phosphorylates and activates *AKT*, a protein kinase known to mediate several downstream effects, including the inhibition of apoptosis and the enhancement of cell growth [22]. *AKT*, in turn, activates *mTOR*, a critical regulator of cell proliferation, protein synthesis, and angiogenesis [18]. The upregulation of *PI3K*, *AKT*, and *mTOR* mRNA levels in OSCC samples, as observed in this study, suggests that PDGFBB may facilitate OSCC progression by amplifying the *PI3K/AKT/mTOR* signaling axis. This pathway's activation is consistent with other studies on head and neck squamous cell carcinomas, where *PI3K/AKT/mTOR* dysregulation has been frequently associated with poor prognosis and enhanced metastatic potential [15, 20, 23]. The significant increase in PDGFBB protein levels in the serum of OSCC patients compared to healthy controls adds another layer of evidence supporting the involvement of PDGFBB in OSCC. The mean PDGFBB concentration of 3.44 ng/mL in OSCC patients, compared to 1.38 ng/mL in healthy controls, indicates a strong association between elevated PDGFBB levels and OSCC presence. This increase aligns with prior studies that have implicated PDGFBB as a key player in tumorigenesis due to its role in promoting angiogenesis and recruiting stromal cells, such as fibroblasts and pericytes, into the tumor microenvironment [8, 9, 13, 24]. Elevated PDGFBB may enhance vascularization within the tumor, which can support increased nutrient supply and facilitate tumor growth and invasion.

The elevation of PDGFBB could also potentially serve as a biomarker for OSCC, as its significant difference from control levels suggests a potential diagnostic or prognostic application. In previous cancer studies, increased levels of PDGFBB have been linked to aggressive tumor behavior and poorer clinical outcomes, suggesting that PDGFBB could be explored not only as a biomarker but also as a therapeutic target [9-16]. However, additional research is necessary to fully establish PDGFBB's clinical utility in OSCC diagnosis or prognosis.

The mRNA expression analysis of *PI3K*, *AKT*, and *mTOR* genes in OSCC tissues compared to adjacent non-cancerous tissues provided further insights into the mechanistic involvement of PDGFBB in OSCC progression. *PI3K* mRNA was upregulated with a fold

change of 1.9367, while *AKT* and *mTOR* exhibited fold changes of 2.1 and 1.9, respectively. These consistent increases across all three genes strongly suggest an active *PI3K/AKT/mTOR* signaling axis in OSCC tissues [9, 25].

This overexpression is most likely the result of tumor cells adapting to meet their increased metabolic demands while avoiding apoptosis, which is a crucial feature of cancer cells. The mechanism supports cellular survival and proliferation by activating *AKT*, which inhibits pro-apoptotic proteins and upregulates cell cycle proteins. *mTOR* activation boosts protein synthesis and cell proliferation, promoting tumor growth and contributing to an aggressive phenotype. These findings support recent studies that *PI3K/AKT/mTOR* signaling is frequently hyperactivated in head and neck malignancies and may play a role in resistance to current therapy [8, 15].

The persistent overexpression observed in the OSCC samples shows that *PI3K/AKT/mTOR* could be a reliable therapeutic target. Targeted inhibitors of this pathway, such as *PI3K* or *mTOR* inhibitors, have the potential to decrease tumor growth by disrupting the signaling network that promotes cancer cell survival and proliferation. Current research in other tumors has yielded good results with *PI3K/AKT/mTOR* inhibitors, and similar approaches could be used in OSCC. Further study, including preclinical and clinical studies, is required to determine the efficacy of targeting this path in OSCC patients.

The combined elevation of PDGF-BB protein and the upregulation of *PI3K/AKT/mTOR* mRNA expression highlight the potential of this pathway as both a biomarker and therapeutic target in OSCC. The *PI3K/AKT/mTOR* pathway's relevance in multiple cellular functions essential for tumor maintenance suggests that interventions targeting this pathway could yield beneficial effects for OSCC patients. Therapeutic strategies that combine *PI3K/AKT/mTOR* pathway inhibition with existing OSCC treatments might enhance treatment efficacy and improve patient outcomes.

Additionally, since PDGFBB plays a role in regulating tumor-associated stromal cells, its inhibition could have dual benefits: directly impacting tumor cells and altering the tumor microenvironment to make it less supportive of cancer progression. Further studies investigating the effects of PDGF-BB inhibition on the tumor microenvironment, angiogenesis, and immune cell infiltration could offer insights into combination therapies that address multiple facets of OSCC biology [26].

This study's limitations include a relatively small sample size, which may affect generalizability, and a focus on mRNA rather than protein-level analysis of the *PI3K/AKT/mTOR* pathway in OSCC tissues. Additionally, reliance on computational tools like STRING and PANTHER provides predictive rather than experimentally validated interactions. Further studies with larger cohorts, protein-level analyses, and experimental validation of pathway interactions are needed to confirm PDGFBB's role in OSCC and assess its therapeutic potential more comprehensively.

Conclusion

This study underscores the relevance of PDGFBB and the *PI3K/AKT/mTOR* pathway in OSCC progression.

The elevated PDGFBB levels in OSCC patients and the upregulation of *PI3K*, *AKT*, and *mTOR* in OSCC tissues suggest that PDGFBB promotes tumor growth and survival through this signaling pathway. Future research focusing on targeted inhibition of PDGFBB or *PI3K/AKT/mTOR* components may pave the way for more effective OSCC treatments, with PDGFBB also holding promise as a diagnostic biomarker. These findings contribute to our understanding of OSCC biology and provide a foundation for potential clinical applications in diagnosis and therapy.

Author Contribution Statement

All authors contributed equally in this study.

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Conflict of interest

None.

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