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Elucidating the role of lipid metabolism dysregulation in the transition from oral lichen planus to oral squamous cell carcinoma

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Abstract

Background Oral Lichen Planus (OLP) is a chronic inflammatory disorder that may progress to Oral Squamous Cell Carcinoma (OSCC). Lipid metabolism dysregulation has been implicated in tumor development and immune response modulation. This study aims to explore the role of lipid metabolism, particularly the lipids diacylglycerol (DAG), triacylglycerol (TAG), and phosphatidylcholine (PC), in the progression from OLP to OSCC, and to identify potential therapeutic targets for prevention and treatment.

Methods We performed a Mendelian randomization (MR) analysis to investigate the causal relationships between lipid metabolism and the risk of OLP and OSCC. Differential gene expression analysis was conducted to identify key genes related to lipid metabolism. The interactions of lipid species and key genes were examined using drug databases (DrugBank, DGIdb, and TCMSP) to explore potential drug candidates. Enrichment analysis of signaling pathways, including PPAR signaling, was also conducted to understand the underlying mechanisms.

Results Our MR analysis revealed that DAG exerts a protective effect in OLP (OR < 1), but its role shifts to a risk factor in OSCC (OR > 1), potentially by altering the tumor immune microenvironment. TAG and PI dysregulation also plays a critical role in tumorigenesis. Gene expression analysis identified several key lipid metabolism-related genes, including SLC27A6, FABP3, FABP4, ADIPOQ, and PLIN1, whose expression differed between OLP and OSCC, highlighting their importance in tumor progression. These genes were enriched in the PPAR signaling pathway, suggesting its involvement in tumor growth and immune modulation. Potential drug candidates, such as palm acid (PA), Imatinib, and Curcumin, were identified through drug-repurposing strategies.

Conclusion Lipid metabolism dysregulation plays a crucial role in the progression of OLP to OSCC. Targeting key lipid metabolism pathways and genes, such as DAG, TAG, PI, and the PPAR pathway, may offer promising strategies for early diagnosis and therapeutic intervention. This study provides novel insights into the molecular mechanisms of OLP-to-OSCC progression and suggests potential drug candidates, including natural compounds, for future clinical applications. Further research is needed to validate these findings in clinical settings.

Clinical trial number Not applicable.

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Keywords Lichen planus, Oral, Oral squamous cell carcinoma, Diacylglycerol, Mendelian randomization analysis, Phosphatidylcholine, Triacylglycerol, Lipid metabolism, Immune microenvironment

Introduction

Oral Lichen Planus (OLP) is a chronic inflammatory disease affecting the oral mucosa, with its etiology remaining incompletely understood. Current research indicates that cell-mediated immune responses play a pivotal role in the pathogenesis of OLP, with T lymphocytes exhibiting cytotoxicity against antigens expressed on the basal cell layer [1]. Recognized as an oral potentially malignant disorder (OPMD), OLP has garnered significant attention due to its malignant transformation risk, which ranges from 0.04 to 1.74% annually. As the malignant transformation of OLP falls within the spectrum of oral malignant tumors (OMTs), it is noteworthy that a subset of oral squamous cell carcinoma (OSCC) cases originates from the progressive evolution of OPMDs [2].

Oral carcinogenesis is a multistep process, beginning with normal cells, progressing through dysplasia, and culminating in malignancy [3]. Squamous cell carcinoma accounts for 90% of oral malignancies and ranks as the sixteenth leading cause of cancer incidence and mortality globally, representing a significant public health challenge [4–5]. Among OLP cases that undergo malignant transformation, the tongue is the most frequently affected site, followed by the oral mucosa, gingiva, lips, and floor of the mouth [6]. Chronic inflammation may facilitate this progression, potentially involving Candida infections that produce carcinogenic substances capable of penetrating and colonizing the epithelium [7]. Furthermore, aberrant DNA methylation in OLP has been proposed as a driver of its malignant transformation [8]. Concurrently, key biomarkers within the immune microenvironment play a pivotal role in signaling pathways associated with OLP and its progression to malignancy [9].OLP pathogenesis involves immune dysregulation and inflammatory signaling alterations. Its microenvironment is marked by increased CD4 + and CD8 + T cells, dendritic cells, macrophages, and NK cells [10–11]. Pro-inflammatory cytokines like IL-6, TNF-α, and IFN-γ sustain inflammation, promoting epithelial damage and malignancy. Tumour-associated macrophages contribute to OSCC progression by secreting cytokines, such as IL-10 and TGF-β [12], The JAK-STAT pathway modulates immune responses, while NF-κB activation enhances inflammation, cell proliferation, and apoptosis resistance. Additionally, PI3K-Akt signaling, crucial for cell survival and metabolism, is frequently altered in OLP, potentially driving malignant transformation. Understanding these pathways is key to identifying therapeutic targets and elucidating OLP progression [13].Despite these findings, the malignant potential of OLP remains controversial, and its transformation mechanisms and precise risk factors warrant further investigation. Emerging evidence highlights a notable association between OLP and metabolic syndrome [14]. Chronic inflammation in OLP may lead to lipid metabolism abnormalities. Lipid rafts, essential for activating signaling receptors and lymphocytes, particularly during the early stages of T-cell receptor stimulation, play a critical role in this process. Lipid metabolic reprogramming has been identified as a hallmark of cancer [15–16].

In patients with OPMDs such as OLP, alterations in lipid profiles may be closely associated with their malignant transformation process. The malignant potential of OLP, along with its relationship with metabolic syndrome and lipid metabolism abnormalities, presents a compelling avenue for further research. This study aims to elucidate these underlying mechanisms to uncover the metabolic and molecular regulatory pathways critical in the transformation from OLP to OSCC.

Materials and methods

Mendelian Randomization (MR) analysis of genetic factors in OLP and OMT

Data sources

This study utilized data from two primary databases: the GWAS Catalog (https://www.ebi.ac.uk/gwas/) [17] and the FINNGEN database (https://www.finngen.fi/en/access_results) [18]. The FINNGEN database provided detailed clinical information related to OLP and OMT, with OLP samples comprising 587 cases and 411,594 control samples; OMT samples included 832 cases and 314,193 control samples. Additionally, 179 lipid species were identified through searches in the GWAS Catalog.

Analytical strategy

The aim of this research was to investigate the potential causal relationships between lipid species and both OLP and OMT, guided by three core hypotheses: the correlation hypothesis, the exclusion restriction hypothesis, and the independence hypothesis. We screened for single nucleotide polymorphisms (SNPs) associated with lipid exposure, applying a significance threshold of $P < 5e\text{-}6$. Statistical analyses were conducted primarily within the Mendelian Randomization (MR) framework to ensure the robustness of the findings. To guarantee the strength of the instrumental variables, we established an F-value threshold greater than 10. Additionally, linkage disequilibrium was controlled by setting conditions to $r^2 < 0.001$ and a window of 10,000 KB.Potential confounders, including smoking, alcohol consumption, dietary habits,

diabetes, and autoimmune diseases, were excluded from the analysis. Reverse validation was performed to further assess causal relationships.

Statistical models and analysis

In this study, the Mendelian Randomization analysis was conducted using a variety of methods to enhance the reliability and validity of the findings. Data analysis was performed using R version 4.3.2, employing key statistical tools such as the Inverse Variance Weighted (IVW) method and MR-Egger method. Additional approaches, including MR weighted mode, MR weighted median, and MR simple mode, were also utilized. To assess heterogeneity and potential pleiotropy, q-value testing and directional pleiotropy testing were conducted. A leave-one-out method was implemented for each single nucleotide polymorphism (SNP), allowing for the calculation of the meta-effect of the remaining SNPs and observing changes in outcomes with the exclusion of each SNP, thereby ensuring the robustness of the study results.

Database analysis

Acquisition and preprocessing of mRNA-Seq data for OSCC

mRNA-seq data and clinical information were obtained from the TCGA database (https://www.cancer.gov/ccg/) [19] using the Repository interface. Samples were selected from head and neck squamous cell carcinoma (TCGA-HNSC) specifically related to oral cavity sites, including the floor of the mouth, base of the tongue, gum, palate, lip, and other unspecified oral and tongue regions. Non-oral sites such as the hypopharynx, larynx, oropharynx, and tonsils were excluded. As of November 1, 2024, a total of 345 samples were downloaded, comprising 313 OSCC tissue samples and 32 adjacent normal tissue samples. The analysis was performed using the raw counts matrix obtained from TCGA. The RNA-seq data were processed using R version 4.3.1, where missing values and outliers were removed during data cleaning. Gene expression data were normalized and categorized into tumor and normal groups for differential expression analysis using DESeq2 in R, and differentially expressed genes were identified.

Identification of differentially expressed genes in OLP

The transcriptomic dataset GSE131567 from the GEO database (https://www.ncbi.nlm.nih.gov/geo/) [19] was analyzed, comprising data from six untreated OLP patients and six healthy controls. The objective of using this dataset was to identify differentially expressed genes (DEGs) associated with oral lichen planus (OLP), providing insights into the molecular mechanisms underlying the disease. GEO2R was used to perform differential expression analysis, applying thresholds of log-2FoldChange > 1.5 or < -1.5 and a P-value < 0.05.

Identification of diacylglycerol-associated genes

To explore the genetic landscape associated with diacylglycerol (DAG), the Genecards database [20] (https://www.genecards.org/) was utilized. The term "Diacylglycerol" was entered as the query. The selection of diacylglycerol (DAG) for analysis in this study was based on its identified role as a protective factor in oral lichen planus (OLP) and a risk factor in oral malignant transformation (OMT) through Mendelian randomization analysis. Previous studies have indicated that DAG may have significant implications in the development and progression of these conditions. In contrast to other lipid molecules such as triacylglycerol (TAG) and phosphatidylcholine (PC), DAG was chosen due to its specific association with these diseases as observed in the preliminary data. This targeted approach allows for a more focused investigation of DAG's potential as a biomarker and its impact on disease pathogenesis.

Identification of overlapping genes

To pinpoint genes shared among key datasets, the Venny platform (https://bioinfogp.cnb.csic.es/tools/venny/) [21] was employed. This analysis integrated differentially expressed genes (DEGs) from OSCC and OLP datasets with the DAG-associated gene list. By overlapping these three datasets. These shared genes may play pivotal roles in linking DAG-related pathways to the pathophysiology of both OSCC and OLP, providing valuable targets for further functional and therapeutic investigations.

Functional and pathway enrichment analysis

The functional roles of the 33 overlapping genes were annotated using the DAVID database (https://david.ncifcrf.gov/) [22], focusing on Gene Ontology (GO) classifications across three categories: biological processes (BP), cellular components (CC), and molecular functions (MF). Additionally, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis was conducted to uncover the biological pathways significantly associated with these genes. This comprehensive analysis highlighted pathways involved in lipid metabolism, cellular signaling, and structural dynamics, shedding light on the potential mechanisms linking DAG-related pathways to OSCC and OLP pathogenesis.

Protein-protein interaction (PPI) network and hub gene identification

To investigate the interactions among the overlapping genes, a PPI network was constructed using the STRING database (https://string-db.org/) [23]. Key net work parameters, including the number of nodes, edges, and average node degree, were calculated to assess the network's complexity. The resulting PPI network was visualized using Cytoscape software, where hub genes

were identified by applying CytoNCA metrics, such as Betweenness Centrality (BC), Closeness Centrality (CC), and Degree Centrality (DC). Following the application of stringent filtering criteria, the most significant hub genes were selected for downstream analyses, providing valuable insights into the molecular mechanisms underlying OSCC and OLP pathogenesis.

Drug target identification and Pharmacological insights

To explore the therapeutic potential of the identified hub genes, queries were conducted in DrugBank (https://go.drugbank.com/) [24], DGIdb (https://dgidb.org/) [25], and TCMSP (https://old.tcmsp-e.com/index.php) [26] databases. These searches aimed to identify druggable targets and their associated compounds, uncovering possible pharmacological interventions. The identified targets and compounds were analyzed to assess their relevance for clinical application in managing OSCC and OLP.

Results

MR analytic result

Relationship between lipid species and OLP

In our analysis, lipid species as the exposure and OLP as the result.The analysis identified five lipid species significantly associated with OLP(Fig. 1A). Among these, diacylglycerol (DAG) (16:0_18:1) (GCST90277258) was confirmed to be a protective factor for OLP. Conversely, other lipid species such as phosphatidylcholine (PC) (16:0_20:3) (GCST90277286), phosphatidylinositol (PI) (16:0_20:4) (GCST90277360), triacylglycerol (TAG) (50:1) (GCST90277387), and triacylglycerol (TAG) (53:2) (GCST90277401) were identified as risk factors (Fig. 1B) (P-value < 0.05).This suggests that specific lipid alterations may influence OLP susceptibility.

Using five analytical methods — IVW, MR-Egger, weighted mode, weighted median, and simple mode — the relationship between lipid species and OLP was systematically examined. The results indicated that diacylglycerol (DAG) (16:0_18:1) (GCST90277258) had an odds ratio (OR) of 0.799, with a 95% confidence interval (CI) ranging from 0.660 to 0.967 ($P = 0.021$), suggesting a protective effect. Conversely, phosphatidylcholine (PC) (16:0_20:3) (GCST90277286) exhibited an OR of 1.253 (95% CI: 1.052–1.493, $P = 0.011$), indicating an increased risk. Similarly, phosphatidylinositol (PI) (16:0_20:4) (GCST90277360) had an OR of 1.232 (95% CI: 1.049–1.446, $P = 0.011$), while triacylglycerol (TAG) (50:1) (GCST90277387) showed an OR of 1.214 (95% CI: 1.024–1.438, $P = 0.026$). Furthermore, triacylglycerol (TAG) (53:2) (GCST90277401) presented an OR of 1.251 (95% CI: 1.053–1.486, $P = 0.011$). These findings underscore distinct roles for specific lipid species in the pathogenesis of OLP, with DAG appearing to confer protection, while the other lipid species were associated with increased risk (Fig. 2).These results highlight a distinct role of lipid metabolism in OLP, suggesting a protective mechanism mediated by DAG, potentially through modulation of inflammatory pathways.

Relationship between lipid species and OMT

In analysis, lipid species as the exposure and OMT as the result.The analysis identified nine lipid

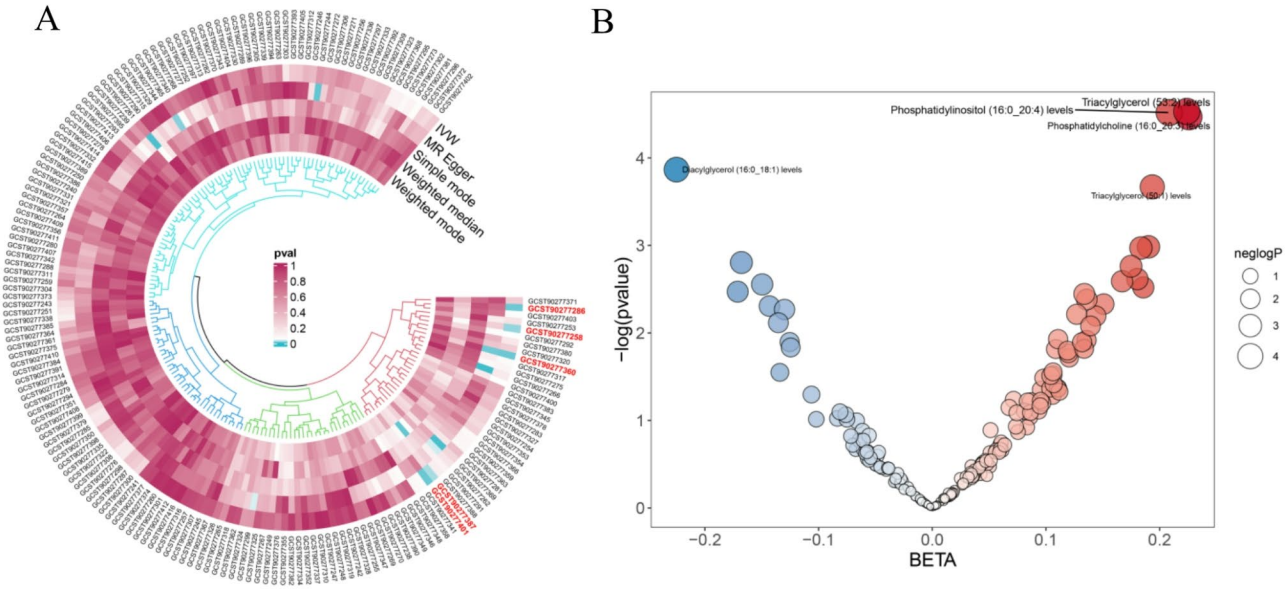


Fig. 1 Visualization of Lipid Species Correlation and Association with OLP. **A**: Heat map of the correlation between lipid species and OLP (Red labels indicate significantly associated lipid species). **B**: Bubble diagram of lipid species and OLP (Blue bubbles represent a negative correlation, and red bubbles represent a positive correlation)

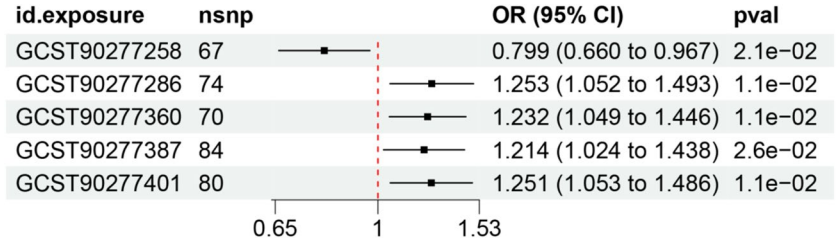


Fig. 2 Comparison of results from different MR methods for lipid and OLP (Five algorithms)

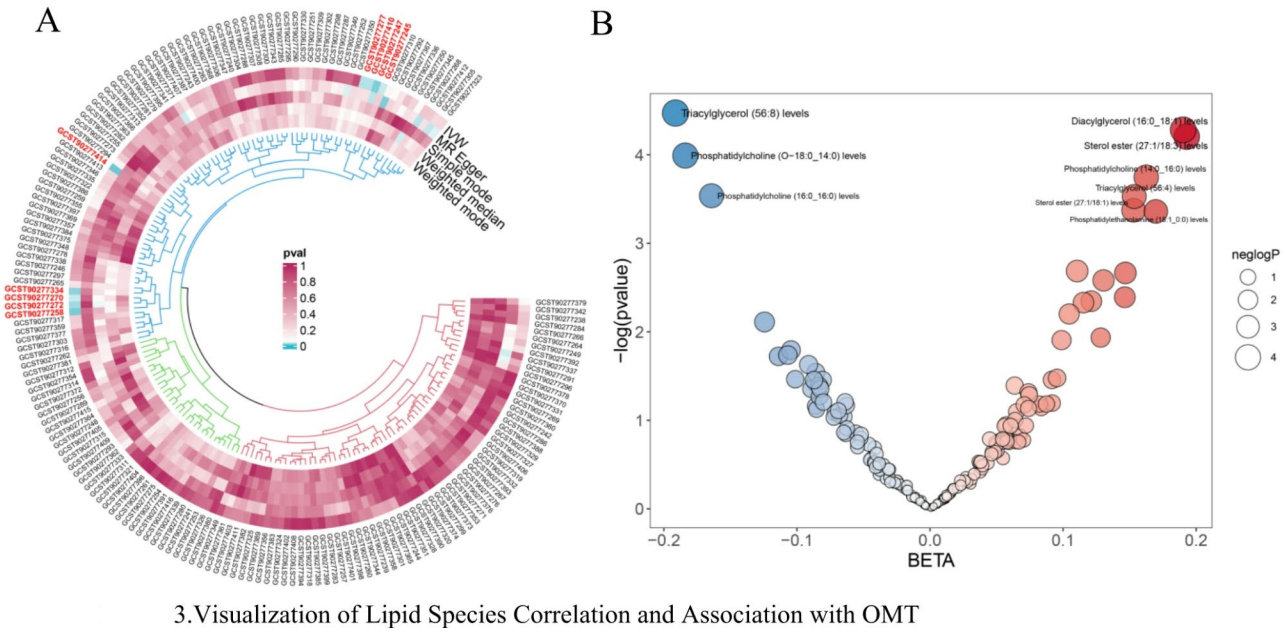


Fig. 3 Visualization of Lipid Species Correlation and Association with OMT. **A**:Heat map of the correlation between lipid species and OMT (Red labels indicate significantly associated lipid species). **B**:Bubble diagram of lipid species and OMT (Blue bubbles represent a negative correlation, and red bubbles represent a positive correlation)

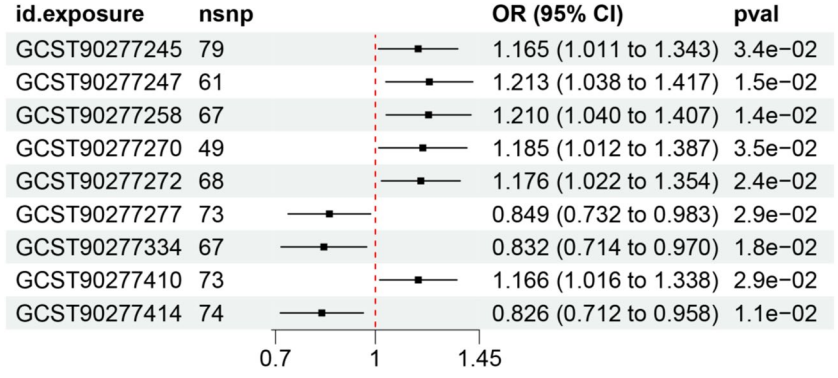


Fig. 4 Comparison of results from different MR methods for lipid and OMT (Five algorithms)

species significantly associated with OLP (Fig. 3A). The analysis of OMT revealed significant associations with nine lipid species. Triacylglycerol (56:8) (GCST90277414), phosphatidylcholine (PC) (O-18:0_14:0) (GCST90277334), and phosphatidylcholine (PC) (16:0_16:0) (GCST90277277) were identified as protective factors. On the other hand, sterol ester (27:1/18:1) (GCST90277245), sterol ester (27:1/18:3) (GCST90277247), diacylglycerol (DAG) (16:0_18:1) (GCST90277258), phosphatidylethanolamine (PE) (18:1_0:0) (GCST90277270), phosphatidylcholine (PC)

(14:0_16:0) (GCST90277272), and triacylglycerol (56:4) (GCST90277410) were identified as risk factors (Fig. 3B).

Using a combination of five analytical approaches—IVW, MR-Egger, weighted mode, weighted median, and simple mode—the association between lipid species and OLP was comprehensively analyzed. The findings revealed that triacylglycerol (TAG) (56:8) (GCST90277414) had an odds ratio (OR) of 0.826, with a 95% confidence interval (CI) of 0.712–0.958 ($P = 0.011$), suggesting a protective effect. Similarly, Phosphatidylcholine (PC) (O-18:0_14:0) (GCST90277334) demonstrated an OR of 0.832 (95% CI: 0.714–0.930, $P = 0.018$), and Phosphatidylcholine (PC) (16:0_16:0) (GCST90277277) exhibited an OR of 0.849 (95% CI: 0.732–0.983, $P = 0.029$).In contrast, lipids such as Sterol Ester (27:1/18:1) (GCST90277245) had an OR of 1.165 (95% CI: 1.011–1.343, $P = 0.034$), and Sterol Ester (27:1/18:3) (GCST90277247) showed an OR of 1.213 (95% CI: 1.038–1.417, $P = 0.015$), both indicating elevated risk. Moreover, Diacylglycerol (DAG) (16:0_18:1) (GCST90277258) displayed an OR of 1.210 (95% CI: 1.040–1.407, $P = 0.014$), and Phosphatidylethanolamine (18:1_0:0) (GCST90277270) had an OR of 1.185 (95% CI: 1.012–1.387, $P = 0.035$). Similarly, Phosphatidylcholine (PC) (14:0_16:0) (GCST90277272) exhibited an OR of 1.176 (95% CI: 1.022–1.354, $P = 0.024$), and triacylglycerol (TAG) (56:4) (GCST90277410) presented an OR of 1.166 (95% CI: 1.016–1.338, $P = 0.029$), further underscoring their potential role as risk factors.Notably, DAG (16:0_18:1) (GCST90277258) demonstrated a dual biological role, functioning as a protective factor in OLP but serving as a risk factor in OMT.This dual role suggests that DAG may play different roles in inflammation versus tumor progression, potentially shifting from an anti-inflammatory mediator to a pro-tumorigenic factor under certain conditions.

Causal relationship between DAG (16:0_18:1) and OLP supported by multiple analyses

The analysis provides strong evidence supporting a potential protective role of DAG (16:0_18:1) against the risk of OLP.In Fig. 5A, the red solid line from the IVW method is entirely to the left of zero, indicating that an increase in DAG (16:0_18:1) levels is associated with a reduced risk of OLP. Additionally, the heterogeneity test (IVW, $Q = 74.6$, $P = 0.220$) and the horizontal pleiotropy test (Egger intercept = 0.03, $P = 0.901$) further support these findings (Table 1). Figure 5B illustrates data points representing SNP loci, which align with the assumption that strong genetic effects of DAG correlate with a strong protective effect against OLP, suggesting a negative causal relationship. Figure 5C demonstrates that excluding individual SNPs has minimal impact on the overall error line, which consistently remains to the left of zero, reinforcing the reliability of the results. The funnel plot exhibits a symmetrical distribution, suggesting minimal bias (Fig. 5D). These analyses collectively highlight the potential causal relationship between DAG and OLP. However, reverse validation, where OLP was treated as the exposure and DAG (16:0_18:1) as the outcome, did not identify any significant association. indicating that while DAG may influence OLP risk, OLP does not significantly alter DAG levels, further supporting the directionality of the causal effect.

Causal relationship between DAG (16:0_18:1) and OMT supported by multiple analyses

Positive analysis: DAG as a potential risk factor for OMT This analysis provides compelling evidence supporting the role of DAG (16:0_18:1) as a potential risk factor for OMT. DAGs play a crucial role in cellular signaling, particularly in pathways involved in proliferation and apoptosis, which are key processes in tumorigenesis. The observed association suggests that elevated DAG levels may contribute to oncogenic signaling, thereby promoting OMT development.As illustrated in Fig. 6A, the red solid line representing the IVW method lies entirely to the right of zero, indicating that elevated levels of DAG (16:0_18:1) are associated with an increased risk of OMT. Further statistical support is provided by the heterogeneity test (IVW, $Q = 60.3$, $P = 0.641$) and horizontal pleiotropy test (Egger intercept = 0.031, $P = 0.121$), suggesting minimal bias or confounding factors (Table 1). Figure 6B displays the scatterplot of SNPs, where each data point corresponds to a single SNP locus. The overall upward slope aligns with the hypothesis that strong genetic effects of DAG (16:0_18:1) are positively associated with the risk of OMT, indicating a positive causal relationship. This finding implies that genetic variations influencing DAG metabolism may predispose individuals to OMT, potentially through mechanisms involving altered lipid homeostasis and inflammation. Figure 6C confirms the robustness of this finding, showing that excluding individual SNPs has minimal impact on the overall trend, as the error bars consistently remain to the right of zero. This robustness is further emphasized by the funnel plot in Fig. 6D, which exhibits a symmetrical shape, indicating minimal publication bias or systematic errors. Together, these results suggest that DAG (16:0_18:1) may actively contribute to the malignant transformation process, highlighting its potential as a biomarker or therapeutic target in OMT.

Reverse validation: OMT as an exposure To further probe the relationship, a reverse validation was performed with OMT treated as the exposure variable and DAG (16:0_18:1) as the outcome. Reverse causality test-

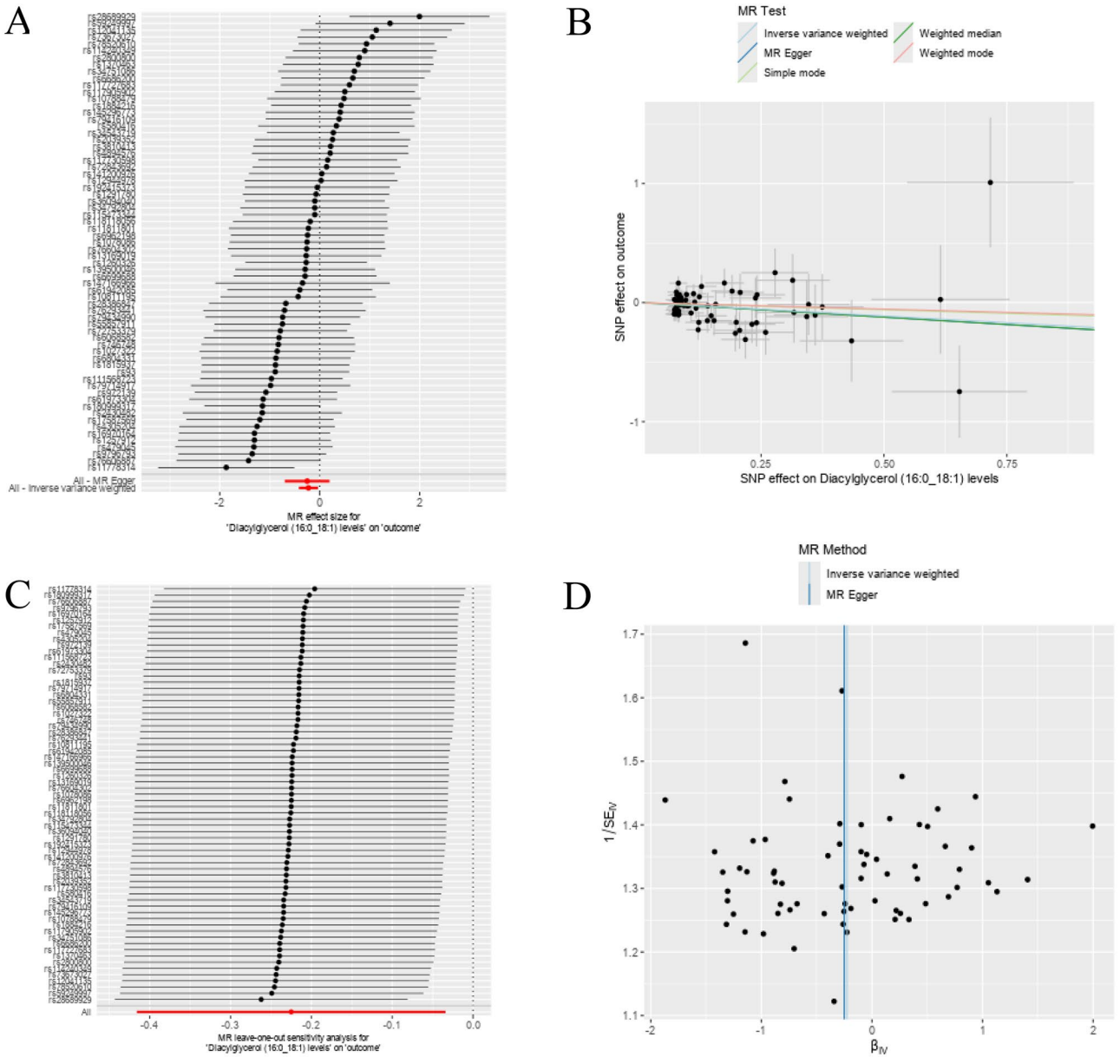


Fig. 5 Visualizing the Causal Relationship Between DAG (16:0_18:1) and OLP. **A**: Forest plot illustrating the causal relationship between DAG (16:0_18:1) and OLP (The red solid line from the IVW method lies entirely to the left of zero, indicating that an increase in DAG (16:0_18:1) levels is associated with a reduced risk of OLP). **B**: Scatter plot showing the causal relationship between DAG (16:0_18:1) and OLP (Each data point represents an SNP, and the overall downward slope indicates a negative causal relationship). **C**: Leave-one-out forest plot for DAG (16:0_18:1) and OLP (The error bars consistently remain to the left of zero, demonstrating the robustness of the results). **D**: Funnel plot for the causal relationship between DAG (16:0_18:1) and OLP (The symmetrical shape of the funnel plot suggests minimal bias)

Table 1 Sensibility analysis

Exposure	outcome	Heterogeneity tests						Horizontal pleiotropic		
		MR Egger			IVW			egger intercept	se	pval
		Q	Q_df	Q_pval	Q	Q_df	Q_pval			
DAG	OLP	74.6	65	0.195	74.6	66	0.220	0.003	0.025	0.901
DAG	OMT	60.3	65	0.641	62.8	66	0.589	0.031	0.02	0.121
OMT	DAG	5.98	5	0.308	6.20	6	0.401	0.017	0.04	0.688

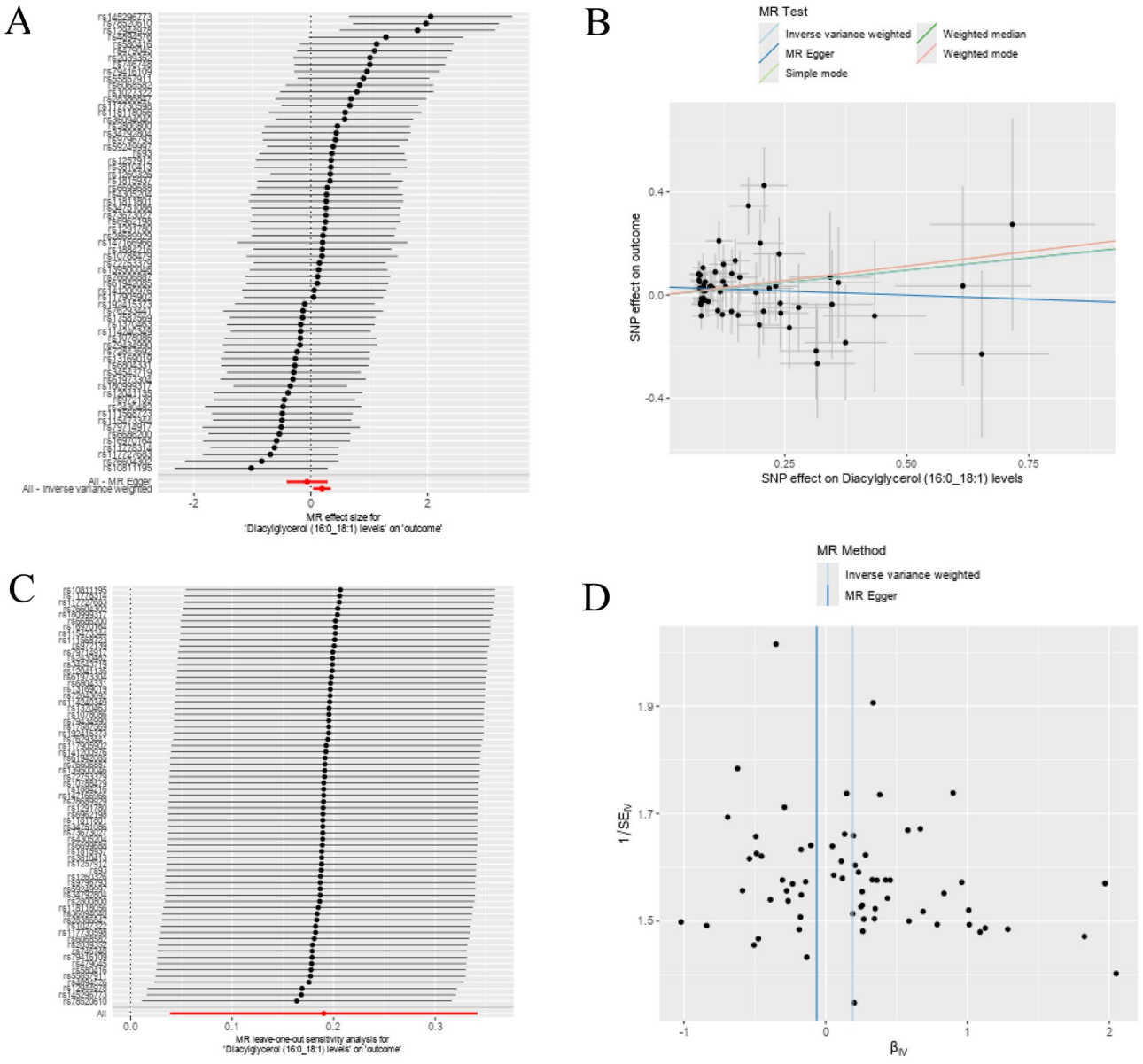


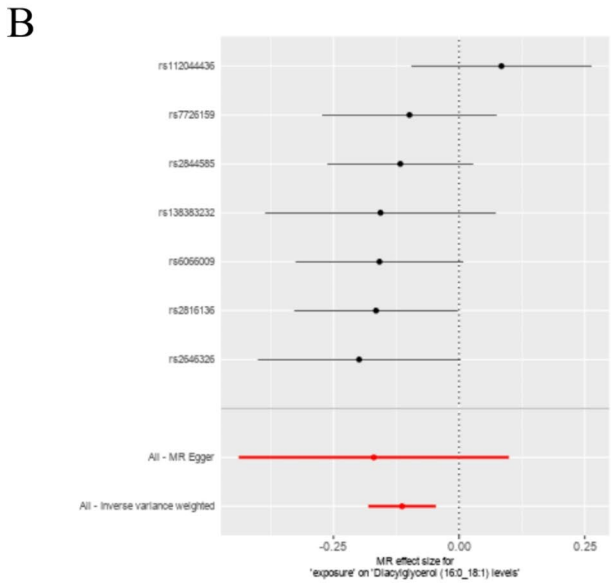
Fig. 6 Visualization of the Causal Relationship Between DAG (16:0_18:1) and OMT. **A**: The forest plot illustrates the causal association between DAG (16:0_18:1) and OMT, with the red solid line from the IVW method positioned entirely to the right of zero. This suggests that increased levels of DAG (16:0_18:1) are linked to a higher risk of OMT occurrence. **B**: The scatter plot depicts the causal relationship between DAG (16:0_18:1) and OMT, where each data point represents an SNP. The overall upward slope indicates a positive causal relationship. **C**: The leave-one-out forest plot for DAG (16:0_18:1) and OMT shows that the error bars consistently remain to the right of zero, underscoring the robustness of the results. **D**: The funnel plot visualizes the causal relationship between DAG (16:0_18:1) and OMT, with its symmetrical shape indicating minimal bias

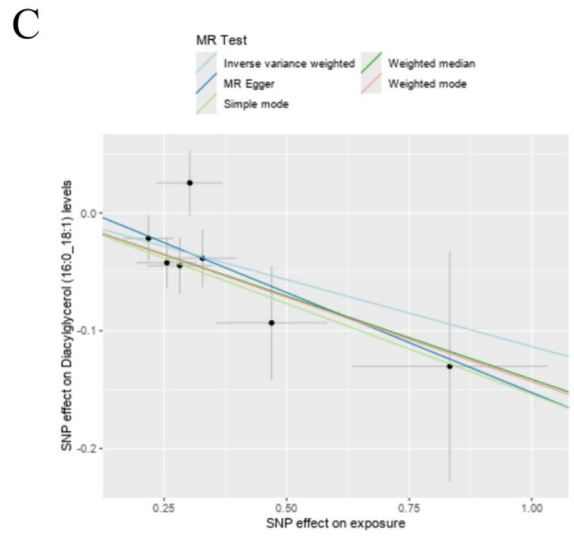
ing is crucial to determine whether OMT itself influences DAG metabolism, which could suggest a feedback mechanism or compensatory biological response.The MR analysis yielded varying results: the IVW method produced an odds ratio (OR) of 0.893 (95% CI: 0.835–0.955, $P = 0.001$). The MR-Egger method showed an OR of 0.844 (95% CI: 0.645–1.104, $P = 0.271$), while the weighted mode yielded an OR of 0.867 (95% CI: 0.774–0.971, $P = 0.048$). The simple median method gave an OR of 0.855 (95% CI: 0.778–0.940, $P = 0.001$), and the weighted median method reported an OR of 0.857 (95% CI: 0.759–0.969, $P = 0.049$), as shown in Fig. 7A.

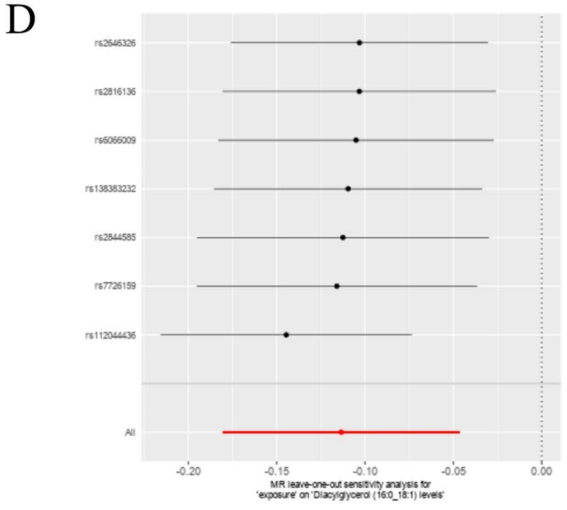
In Fig. 7B, the red solid line from the IVW method is entirely to the left of zero, suggesting a negative causal relationship where OMT might reduce DAG (16:0_18:1) levels. This result implies that OMT could influence lipid metabolism pathways, potentially through increased lipid turnover or enhanced degradation of DAG molecules, which may serve as an adaptive response to malignancy. The heterogeneity test (IVW, $Q = 5.98$, $P = 0.308$)

A

id.exposure	method	nsnp	OR (95% CI)	pval
	MR Egger	7	0.844 (0.645 to 1.104)	0.271
ID	MR IVW	7	0.893 (0.835 to 0.955)	0.001
	Weighted mode	7	0.867 (0.774 to 0.971)	0.048
	Simple median	7	0.855 (0.778 to 0.940)	0.001
	Simple mode	7	0.857 (0.759 to 0.969)	0.049







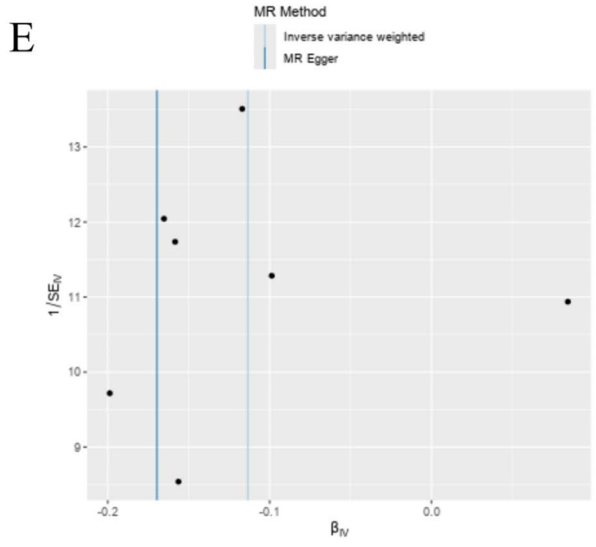


Fig. 7 Visualization of the Causal Relationship Between OMT and DAG (16:0_18:1). **A**: Comparison of results across different MR methods for assessing the relationship between OMT and DAG (16:0_18:1) (five algorithms). **B**: Forest plot illustrating the causal relationship between OMT and DAG (16:0_18:1) (the red solid line from the IVW method lies entirely to the right of zero, indicating that the occurrence of OMT is associated with metabolic changes in DAG (16:0_18:1)). **C**: Scatter plot showing the causal relationship between OMT and DAG (16:0_18:1) (each data point represents an SNP, with an overall upward slope suggesting a negative causal association). **D**: Leave-one-out forest plot for OMT and DAG (16:0_18:1) (the error lines consistently remain to the left of zero, reinforcing the robustness of the results). **E**: Funnel plot for the causal relationship between OMT and DAG (16:0_18:1) (the symmetrical distribution of the funnel plot indicates minimal bias)

and horizontal pleiotropy test (Egger intercept = 0.17, $P = 0.688$) provide additional support for these findings (Table 1). Figure 7C presents the scatterplot of SNP loci, with data points showing a consistent trend in which strong genetic effects of OMT are associated with a significant impact on DAG (16:0_18:1). The negative causal relationship is reinforced by the consistency of the error bars in Fig. 7D, which remain to the left of zero even after excluding individual SNPs. Additionally, the funnel plot in Fig. 7E displays a symmetrical distribution, further confirming minimal bias in the analysis.

These findings suggest a complex bidirectional relationship between DAG (16:0_18:1) and OMT, where elevated DAG levels increase the risk of OMT, while OMT may inversely suppress DAG levels. This inverse relationship may reflect metabolic reprogramming in tumor cells, which alters lipid biosynthesis and utilization as part of their adaptation to a proliferative state. These observations highlight the need for further exploration of the underlying mechanisms and temporal dynamics, particularly in the context of lipid signaling pathways in cancer progression.

Data analysis results

Differential expression analysis of mRNA in OSCC

Using the DESeq2 package in R, differential expression analysis was performed on mRNA-seq data from the TCGA database, encompassing a total of 59,427 genes from OSCC and adjacent normal tissues. After removing 3,030 genes with missing values (NA), the analysis yielded a comprehensive dataset including metrics such as baseMean, log2FoldChange, lfcSE, stat, p-value, and adjusted p-value (padj). Applying stringent criteria of log2FoldChange > 1.5 or < -1.5 and p-value < 0.05, 950 differentially expressed genes (DEGs) were identified. Among these, 47 genes were downregulated, while 903 genes were upregulated, demonstrating significant transcriptional alterations in OSCC compared to normal tissues (Fig. 8).

The X-axis represents the log2 fold change (OSCC vs. Normal), while the Y-axis typically denotes -log10(p-value). Red dots indicate upregulated genes, blue dots represent downregulated genes, and gray dots signify non-significant genes.

Differential gene expression analysis from the GEO database

Analysis of the GSE131567 dataset from the GEO database identified 21,601 genes in transcriptomic data from

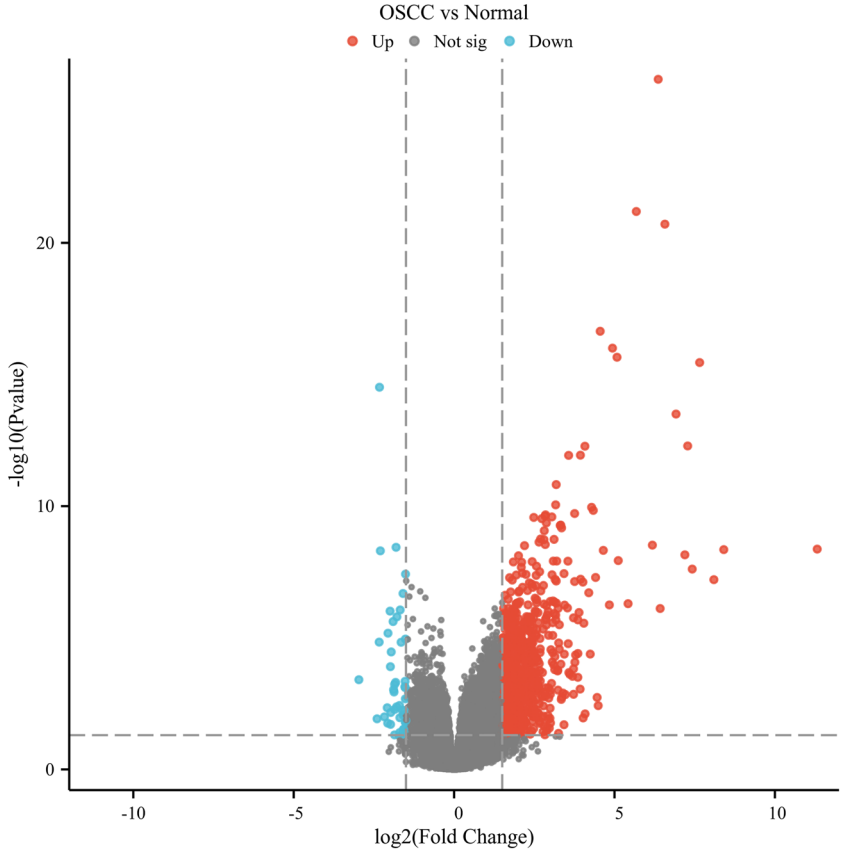


Fig. 8 Volcano Plot of Differentially Expressed Genes (DEGs) in OSCC

OLP and healthy controls. After removing 287 genes with missing values (NA), differential expression analysis was performed using criteria of log2FoldChange > 1.5 or < -1.5 and p-value < 0.05. A total of 3,874 differentially expressed genes (DEGs) were identified, including 1,260 downregulated and 2,614 upregulated genes, highlighting significant transcriptional differences between OLP tissues and normal oral mucosa (Fig. 9).

The X-axis represents the log2 fold change (OLP vs. Normal), while the Y-axis typically denotes -log10(p-value). Red dots indicate upregulated genes, blue dots represent downregulated genes, and gray dots signify non-significant genes.

Identification of diacylglycerol-associated genes

To explore genes associated with diacylglycerol (DAG), a comprehensive search was conducted using the Genecards database. By employing "Diacylglycerol" as the keyword, a total of 4021 genes related to DAG metabolism, signaling, and associated biological processes were identified.

Identification of overlapping genes

The Venny platform was utilized to identify common genes across three datasets: differentially expressed genes (DEGs) from OSCC, DEGs from OLP, and DAG-associated genes. By performing intersection analysis, a total of 33 overlapping genes were identified (Fig. 10).

Functional and pathway enrichment analysis

Functional and pathway enrichment analysis was conducted using the DAVID database to explore the biological significance of the 33 overlapping genes.GO analysis revealed enrichment in BP such as brown fat cell differentiation, long-chain fatty acid transport, muscle contraction, regulation of fatty acid oxidation, cholesterol homeostasis, glucose homeostasis, cellular response to tumor necrosis factor, adult heart development, and actin filament organization. In the CC category, genes were enriched in sarcolemma, extracellular exosome, sarcomere, cytoplasmic side of plasma membrane, striated muscle thin filament, and Z disc. For MF, significant terms included cytoskeletal protein binding, calmodulin binding, NAD+-protein-arginine ADP-ribosyltransferase

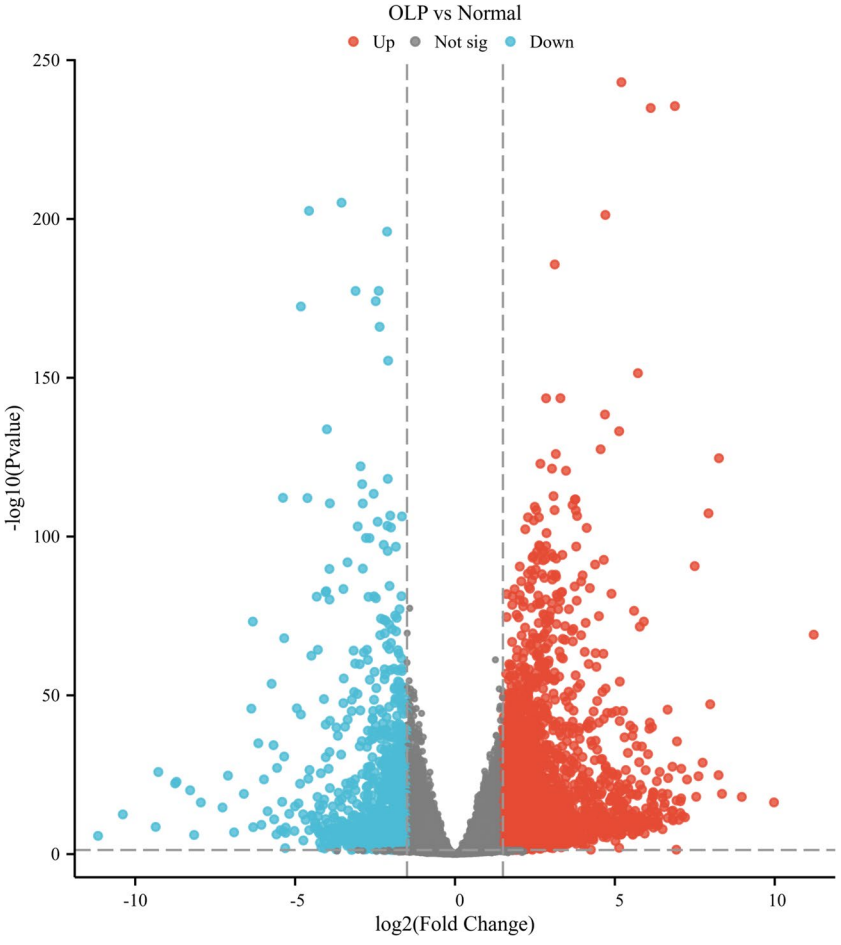


Fig. 9 Volcano Plot of Differentially Expressed Genes (DEGs) in OLP

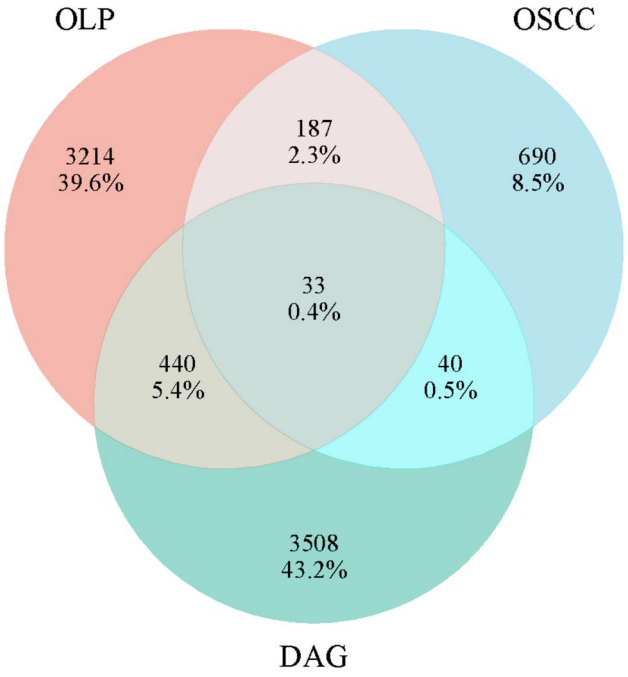


Fig. 10 Venn Diagram Depicting Overlapping Genes Among OSCC DEGs, OLP DEGs, and DAG-Associated Genes

activity, long-chain fatty acid binding, structural constituent of cytoskeleton, long-chain fatty acid transmembrane transporter activity, ankyrin binding, and calmodulin-dependent protein kinase activity (Fig. 11).

Bubble size corresponds to the number of genes associated with each term, with larger bubbles representing more enriched genes. Bubble color indicates the significance level, where redder bubbles denote smaller p-values, reflecting higher enrichment significance.

Pathway enrichment analysis using the KEGG database highlighted several critical pathways, including the PPAR signaling pathway, cytoskeleton in muscle cells, cGMP-PKG signaling pathway, calcium signaling pathway, AMPK signaling pathway, and vascular smooth muscle contraction (Fig. 12A). Notably, five genes (FABP3, FABP4, ADIPOQ, SLC27A6, PLIN1) were enriched in the PPAR signaling pathway, emphasizing its potential role in OSCC and OLP pathophysiology (Fig. 12B).

PPI network and hub gene identification

The 33 overlapping genes were analyzed using the STRING database to construct a PPI network. The analysis revealed 21 interacting genes, as 12 genes lacked connections. Key network metrics included 33 nodes, 32 edges, an average node degree of 1.94, and a PPI enrichment p-value of 2.22e-16, indicating a significant level of

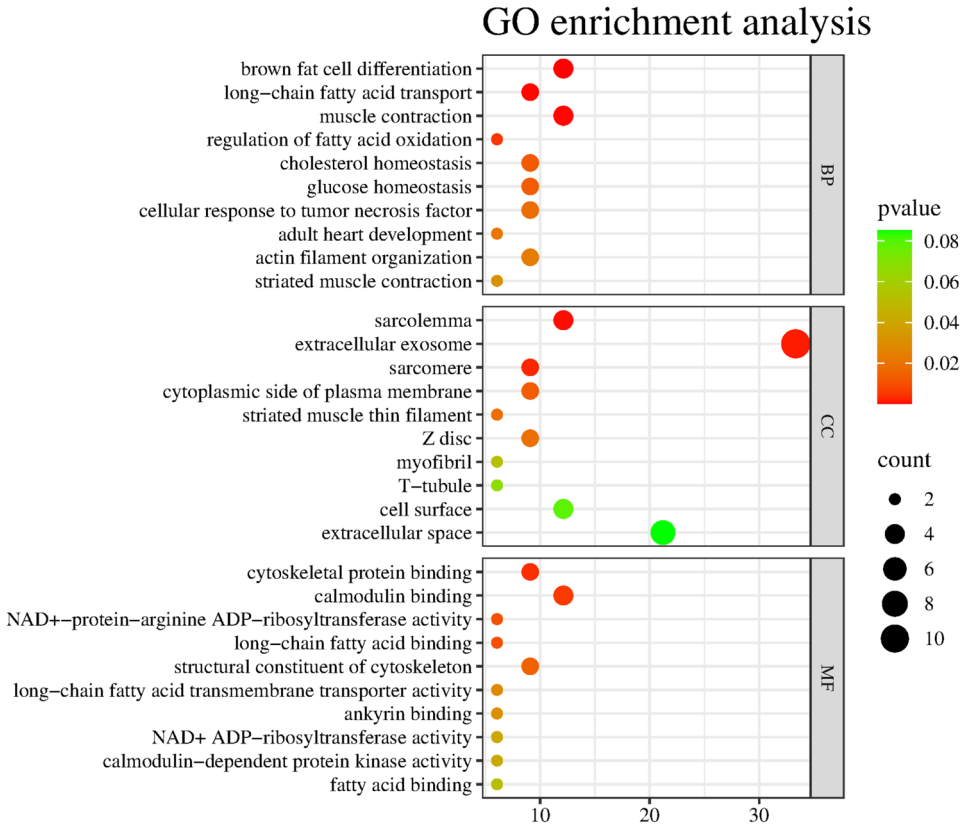


Fig. 11 Bubble plot of GO enrichment analysis

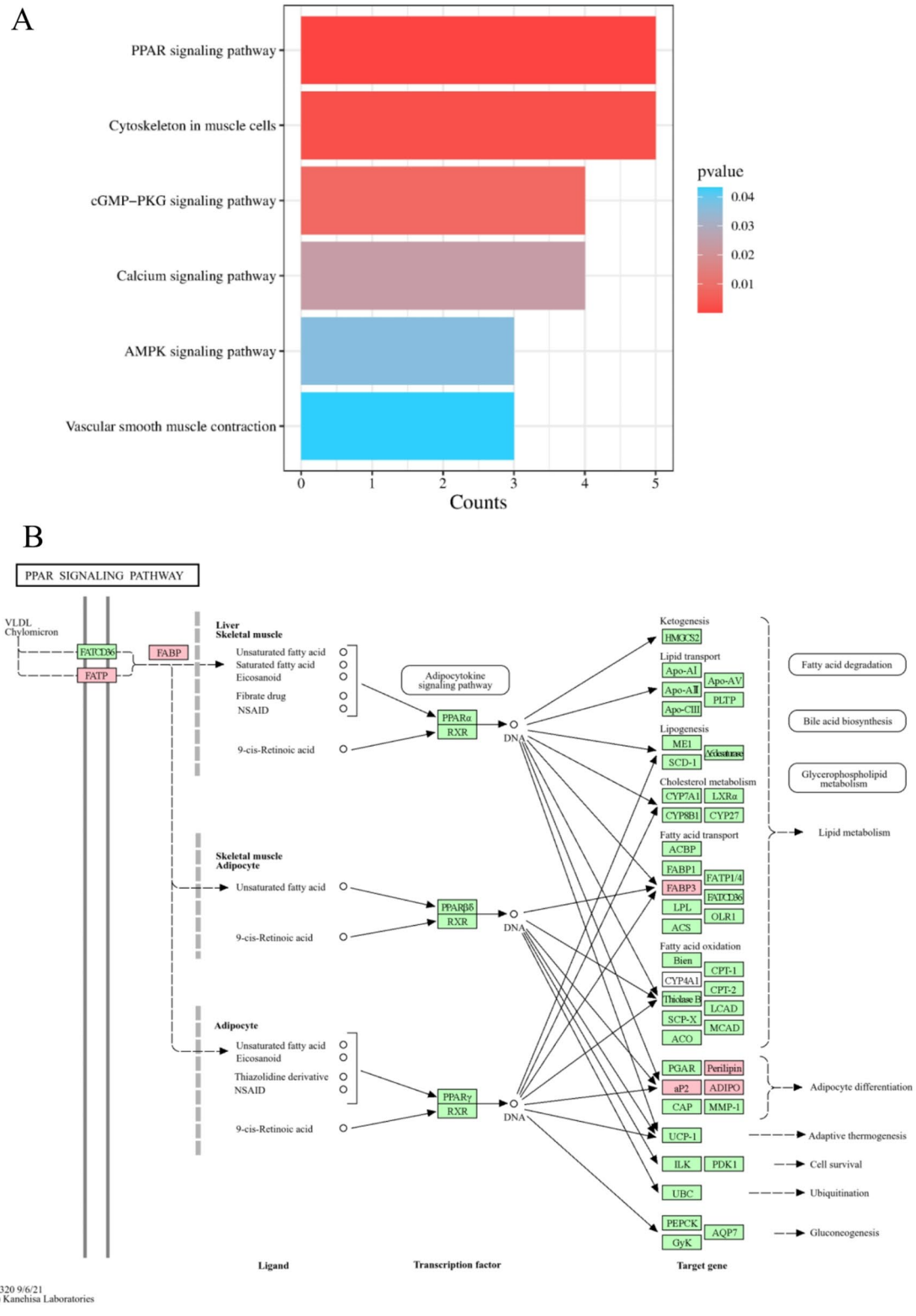


Fig. 12 KEGG path analysis. **A**:Bar chart map of KEGG path analysis **B**:PPAR signaling pathway

interaction among the genes (Fig. 13). The network data were imported into Cytoscape for further visualization and analysis. Using the CytoNCA plugin, centrality measures such as BC, CC, and DC were calculated. Based on these metrics, 17 hub genes were identified after excluding nodes with fewer connections (Fig. 14).

Subsequently, these 17 hub genes were highlighted in a volcano plot, revealing that SLC27A6 was downregulated in OLP (Fig. 15A)(Table 2), while the remaining hub genes were upregulated in both OLP and OSCC (Fig. 15A, B). This analysis underscores the potential role of these hub genes in the progression of OSCC and OLP.

Drug target identification and Pharmacological insights

To explore potential therapeutic strategies, the intersecting hub genes were queried across three major drug databases: DrugBank, DGIdb, and TCMSP. Results from the DrugBank database revealed that FABP3, FABP4, PDK4, SLC2A4, GPD1, MYLK2, and GPIHBP1 were associated with nine pharmacological compounds, including Oleic Acid, Palmitic Acid, Linoleic Acid, Tretinoin, Ascorbic Acid, NADH, Metformin, Fostamatinib, and Cabazitaxel. Similarly, analysis through DGIdb identified seven additional compounds—Etoposide, Imatinib, Streptozocin, Curcumin, Sodium Dichloroacetate, Citric Acid, and Toremifene—targeting genes such as SLC2A4, PDK4, and PLIN1. Lastly, in the TCMSP database, ADIPOQ was linked to traditional Chinese medicine compounds, including Polygoni Cuspidati Rhizoma Et Radix, Mori Cortex, and Smilacis Glabrae Rhixoma. These findings highlight a range of druggable targets and associated compounds with potential clinical applications in OSCC and OLP (Table 3).

Discussion

OLP is a prevalent chronic inflammatory disease of the oral mucosa, with a complex pathogenesis involving T-cell-mediated immune responses, changes in the oral microbiota, and hormonal levels. In severe cases, OLP may progress to OSCC [27], suggesting that under certain conditions, OLP may promote carcinogenesis. In recent years, dysregulated lipid metabolism has been

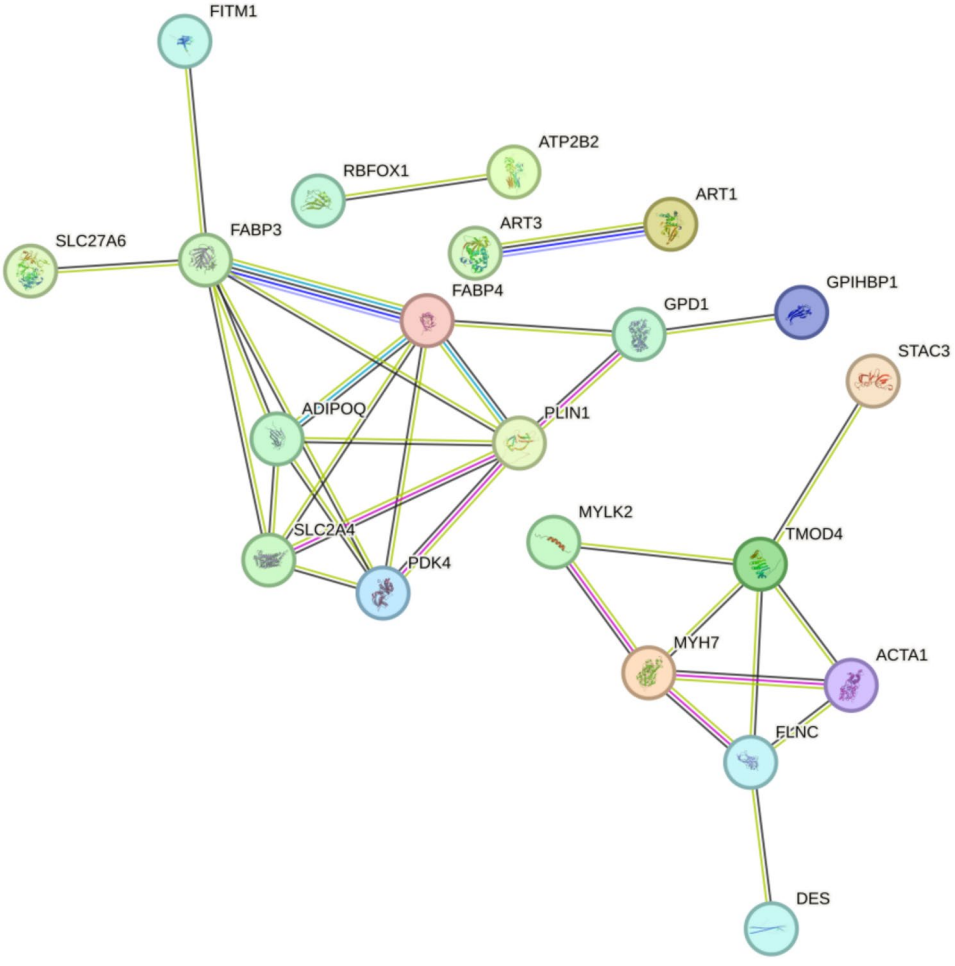


Fig. 13 Protein-protein network construction

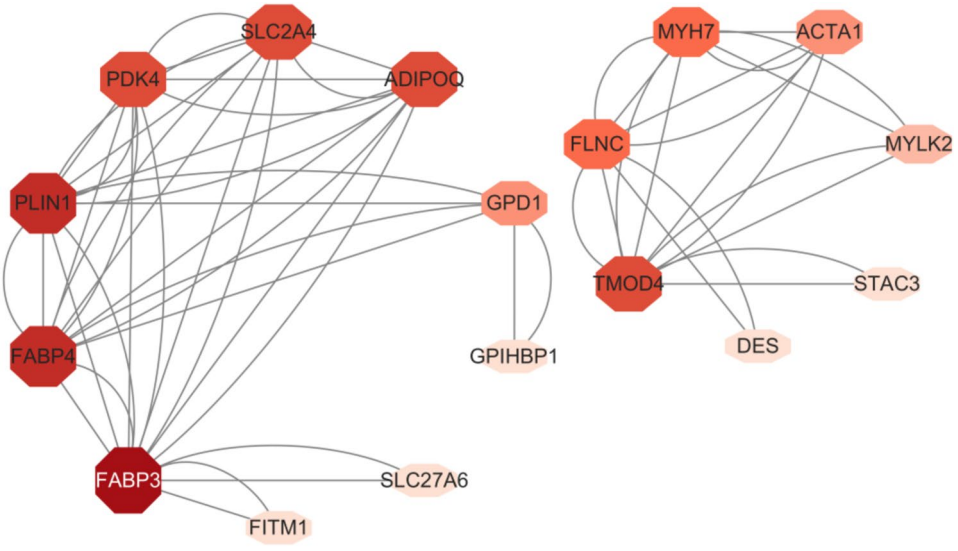
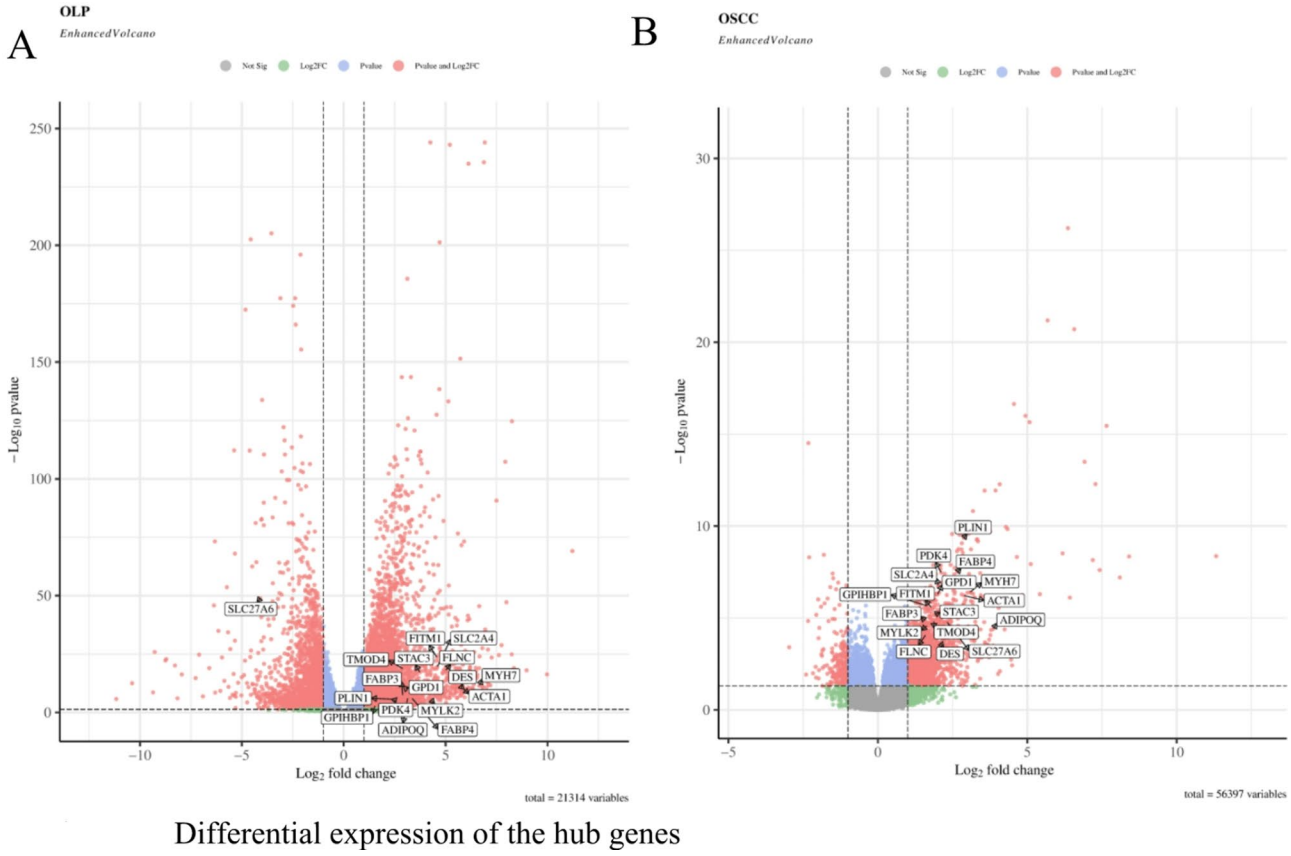


Fig. 14 PPI core target



Differential expression of the hub genes

Fig. 15 Differential expression of the hub genes. **A**: Differential expression of hub genes in OLP. **B**: Differential expression of hub genes in OSCC

widely recognized as a key feature of the tumor microenvironment, playing a crucial role in tumor cell proliferation, survival, metastasis, and immune evasion [28–29]. Aberrant lipid metabolism not only affects the function of tumor cells but may also influence the immune microenvironment, thereby promoting tumor progression [30]. This study uses MR analysis, combined with differential gene expression and drug prediction data, to explore the complex role of specific lipid species in the progression of OLP to OSCC. Notably, lipid metabolism

Table 2 Core targets

Number	Protein Names	Gene Names	Uniprot ID
1	Fatty acid-binding protein, heart	FABP3	P05413
2	Fatty acid-binding protein, adipocyte	FABP4	P15090
3	Perilipin-1	PLIN1	O60240
4	Adiponectin	ADIPOQ	Q15848
5	[Pyruvate dehydrogenase (acetyl-transferring)] kinase isozyme 4, mitochondrial	PDK4	Q16654
6	Solute carrier family 2, facilitated glucose transporter member 4	SLC2A4	P14672
7	Tropomodulin-4	TMOD4	Q9NZQ9
8	Myosin-7	MYH7	P12883
9	Filamin-C	FLNC	Q14315
10	Glycerol-3-phosphate dehydrogenase [NAD(+)], cytoplasmic	GPD1	P21695
11	Actin, alpha skeletal muscle	ACTA1	P68133
12	Myosin light chain kinase 2, skeletal/cardiac muscle	MYLK2	Q9H1R3
13	Fat storage-inducing transmembrane protein 1	FITM1	A5D6W6
14	Long-chain fatty acid transport protein 6	SLC27A6	Q9Y2P4
15	SH3 and cysteine-rich domain-containing protein 3	STAC3	Q96MF2
16	Desmin	DES	P17661
17	Glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1	GPIHBP1	Q8IV16

Table 3 Drug prediction

Drug Target	Drug Name	classification	DRUG GROUP
FABP3	Oleic Acid	DrugBank	approved, investigational, vet_approved
	Palmitic Acid		approved
FABP4	Palmitic Acid	GDIdb	approved
	Linoleic acid		approved, experimental
	Oleic Acid		approved, investigational, vet_approved
PDK4	Tretinoin	DrugBank	approved, investigational, nutraceutical
	SODIUM DICHLOROACETATE	GDIdb	approved
SLC2A4	Ascorbic acid	DrugBank	approved, nutraceutical
	ETOPOSIDE	GDIdb	approved
	IMATINIB		approved
	STREPTOZOCIN		approved
	CURCUMIN		approved
GPD1	NADH	DrugBank	approved, nutraceutical
	Metformin		approved
MYLK2	Fostamatinib	DrugBank	approved, investigational
GPIHBP1	Cabazitaxel	DrugBank	approved
PLIN1	CITRIC ACID	GDIdb	approved
	TOREMIFENE		approved
ADIPOQ	*Polygoni Cuspidati Rhizoma Et Radix*	TCMSP	Not approved
	Mori Cortex		
	Smilacis Glabrae Rhixoma		

not only governs immune responses but may also serve as a key catalyst for carcinogenesis.

Lipid metabolism is a complex physiological process that involves the synthesis, breakdown, and oxidation of various lipids, maintaining cellular energy balance and metabolic homeostasis [27]. It plays a critical role in cancer progression, with various tumors, including esophageal squamous cell carcinoma, gastric cancer, and colorectal cancer, relying on alterations in lipid metabolism for energy production, membrane synthesis, and cellular signaling [31]. In recent years, increasing attention has been given to the importance of lipids in immune cell function, particularly in their crucial role in regulating T-cell function. T lymphocytes constitute a major component of the inflammatory infiltrate, where CD4 + T cells induce overall DNA hypomethylation, thereby regulating type 1 T helper immune responses and leading to immune dysregulation in OLP. Both CD8 + and CD4 + T lymphocytes are highly expressed in undifferentiated squamous cell carcinoma samples [32]. Lipid metabolism not only serves as a vital regulator of immune responses but may also promote tumorigenesis by modulating inflammation and immune cell function. T cells play a pivotal role in tumor immunity, not only recognizing and eliminating tumor cells through specific immune responses but also influencing immune effectors by altering their metabolic state [33]. The metabolic state of T cells is closely related to their immune function, and dysregulated lipid metabolism affects their differentiation, survival, and effector functions, potentially leading to immune evasion and tumor development [34].This study reveals the dual role of diacylglycerol (DAG) in OLP. In OLP, DAG exhibits significant protective effects ($OR < 1$, $P < 0.05$), likely by modulating immune responses or maintaining epithelial barrier function to exert anti-inflammatory effects. This finding is consistent with previous research, which indicates that DAG, as a lipid second messenger, plays a key role in immune responses by regulating T cell function [35]. It may suppress inflammation by regulating immune cell infiltration. However, as the lesion progresses to OSCC, the role of DAG shifts from a protective factor to a risk factor ($OR > 1$, $P < 0.05$),

and this transition may be associated with lipid metabolism dysregulation in the tumor immune microenvironment, thereby promoting immune evasion in tumors [36]. Therefore, the mechanisms of DAG's action at different disease stages may be closely linked to changes in intracellular lipid signaling. Further understanding of the specific mechanisms of DAG in these two states will provide new targets and strategies for clinical intervention.

Additionally, this study identifies the significant roles of TAG and phospholipids (such as PC) in both OLP and OSCC. TAG plays an important regulatory role in lipid metabolism, involved in fatty acid synthesis and related to cell growth, development, and stress responses [37–38]. Dysregulated TAG metabolism may contribute to tumorigenesis by increasing oxidative stress or activating pro-inflammatory signaling pathways [39]. In this study, TAG was identified as a risk factor for OLP, and its role in OSCC may be related to tumor cell membrane stability and the increased energy demand of the cells. PC and phosphatidylethanolamine (PE), as essential components of cell membranes, are involved in cell signaling and energy storage. In cancer, dysregulated PC metabolism is closely linked to tumor cell surface exposure and immune evasion [40, 41]. In this study, both PC and TAG were identified as risk factors for OLP, possibly contributing to lesion formation through the stimulation of oxidative stress or activation of pro-inflammatory signaling pathways.

This study highlights the biphasic role of DAG in OLP and OSCC, where it exerts a protective effect in OLP but appears to drive cancer progression in OSCC. This paradoxical function may be attributed to DAG's involvement in cell signaling, immune regulation, and metabolic homeostasis, which are context-dependent and influenced by the disease state. In OLP, DAG might support cellular homeostasis and immune surveillance by modulating T-cell activation and anti-inflammatory responses, thereby preventing excessive inflammation and tissue damage [42].Additionally, DAG plays a crucial role in maintaining epithelial integrity, which may contribute to its protective effect in OLP.However, the role of DAG shifts toward a pro-tumorigenic function, potentially due to its influence on oncogenic signaling pathways such as PKC (protein kinase C) and Ras/MAPK (mitogen-activated protein kinase) [43]. DAG is a well-established activator of PKC, a signaling cascade known to promote cell proliferation, migration, and survival in various cancers [44]. Elevated DAG levels in OSCC may enhance PKC-mediated phosphorylation of downstream targets, leading to increased tumor growth and metastasis [45]. Additionally, DAG influences lipid raft dynamics within the plasma membrane, affecting receptor-mediated signaling that may favor an immunosuppressive tumor microenvironment [46].Another possible mechanism for DAG's tumor-promoting role in OSCC is its effect on immune cell polarization and metabolic reprogramming. DAG has been implicated in shifting macrophages from an M1 (pro-inflammatory, tumor-suppressive) to an M2 (anti-inflammatory, tumor-promoting) phenotype, fostering an environment conducive to tumor progression [47].Similarly, DAG accumulation may alter T-cell receptor (TCR) signaling, leading to T-cell exhaustion and impaired anti-tumor immunity, thereby facilitating immune evasion by OSCC cells [48].Understanding DAG's dual role provides critical insights into lipid metabolism-targeted therapies.Strategies aimed at modulating DAG levels or selectively inhibiting DAG-PKC signaling in OSCC could potentially suppress tumor progression while preserving DAG's protective function in OLP. Future studies should focus on dissecting the molecular interactions of DAG with key oncogenic pathways and investigating therapeutic interventions such as PKC inhibitors or metabolic modulators to exploit DAG's biphasic nature for precision medicine approaches in OLP and OSCC management.

This study presents a novel application of MR, providing strong evidence for the causal relationship between lipid metabolism (particularly DAG/TAG) and OSCC. However, further research is needed to determine whether these lipid changes are specific to OSCC or common across different cancer types. In addition to cancer-specific metabolic alterations, lipid metabolism in OSCC is influenced by external factors such as the immune system and diet. Lipid metabolites, particularly DAG, regulate immune cell function and contribute to the inflammatory tumor microenvironment [49]. Dysregulation of the lipid profile in OSCC may shift the immune response from anti-tumor immunity to pro-tumor immunity, thereby promoting cancer progression. Changes in lipid metabolism also affect macrophage polarization, with tumor-associated macrophages (TAMs) adopting a pro-tumor phenotype [50]. Furthermore, dietary factors, especially high-fat and omega-3/-6 fatty acids, influence lipid metabolism [51–52]. A comprehensive analysis of dietary effects and their interaction with lipid metabolism can offer insights into potential nutritional interventions for OSCC patients.

In addition, this study employed differential gene expression analysis to identify several key genes (hub genes) related to lipid metabolism and explored their expression changes and potential biological significance in OLP and OSCC. Lipid metabolism plays a crucial role in tumor initiation, progression, and immune evasion, and genes closely associated with lipid metabolism exhibit differentiated functions across various cancer types, suggesting their potential involvement in tumor transformation processes.First, SLC27A6, a fatty acid transporter, was found to be downregulated in OLP and

upregulated in OSCC in this study. The downregulation of SLC27A6 may reduce fatty acid uptake, thereby inhibiting the production of pro-inflammatory metabolites [53]. This change could be closely related to the transition of OLP to OSCC. Previous studies have shown that SLC27A6 is associated with several cancers, with a dual role in tumors such as breast cancer, papillary thyroid cancer, and esophageal squamous cell carcinoma. In breast cancer, SLC27A6 promotes tumor growth and the maintenance of lipid metabolism, while its low expression in non-cancer cells inhibits cell proliferation and lipid absorption [54]. This dual effect suggests that the function of SLC27A6 in different tissues may depend on the specific tumor microenvironment and its metabolic state. In this study, SLC27A6 was downregulated in OLP and upregulated in OSCC, indicating that SLC27A6's role in the tumor microenvironment may change according to the cell type and pathological state. Thus, SLC27A6 may serve as an important marker for the transformation of OLP to OSCC and is a promising candidate for targeted therapy.Additionally, members of the fatty acid-binding protein (FABP) family play an important role in lipid metabolism. FABP4, in particular, is involved in regulating inflammation in macrophages and the accumulation of cholesteryl esters, and has been shown to play a significant role in obesity, metabolic syndrome, and cancer progression [55]. Increased expression of FABP4 is associated with the development of various malignancies, including breast cancer, ovarian cancer, and liver cancer. FABP3 has shown enhanced expression in the progression of gastric cancer, and studies have indicated that it promotes tumor invasion in non-small cell lung cancer [56–57]. Although FABP3 is considered a tumor suppressor in breast cancer, its role in other cancer types may promote tumor progression by regulating lipid metabolism and cell migration. The oxidized phospholipid component 1-palmitoyl-2-glutaroyl-sn-glycero-3-phosphocholine (PGPC) can increase FABP3 expression via the CD36 receptor, inducing ferroptosis in endothelial cells, leading to endothelial dysfunction. Inhibition of FABP3 or ferroptosis can restore endothelial dysfunction induced by PGPC [58]. CD36, expressed in various cell types, has been shown to promote metastasis. In primary tumor biopsies, CD36 expression was significantly higher in malignant lymph nodes compared to pathological-negative groups. In ovarian cancer, CD36 facilitates the metastasis of tumor cells. In gastric cancer, palmitic acid (PA) induces upregulation of CD36 on cancer cells, activating downstream pro-tumor signaling pathways. PA has also been found to promote CD36-mediated metastasis in head and neck squamous cell carcinoma (HNSCC) [59].In this study, the expression changes of FABP3 and FABP4 in OSCC were closely related to the tumor's invasiveness and metastatic potential, suggesting that these genes may participate in the regulation of the tumor microenvironment and influence tumor cell proliferation and migration.

ADIPOQ is an important gene involved in the regulation of fat and carbohydrate metabolism. Its high expression in adipocytes makes it a key regulator of lipid metabolism. Moderate expression of ADIPOQ in renal epithelial cells, macrophages, and CD4 + T cells also suggests its potential role in immune responses [60]. PLIN1, a protein located on the surface of lipid droplets, plays a crucial role in regulating lipolysis and metabolism in adipocytes and is closely associated with various tumor types, including liposarcoma, breast cancer, and squamous cell carcinoma of the lung [61]. In OSCC, increased expression of SLC2A4 has been significantly associated with poor overall survival and relapse-free survival, potentially promoting metastasis via the TRIM24/DDX58 axis. SLC2A4 expression and function are also closely linked to type 2 diabetes, obesity, and aging [62]. Similarly, high expression of ACTA1 is associated with shortened survival in OSCC patients. Invasive nerves can upregulate ACTA1 expression in tumor cells, leading to epithelial-mesenchymal transition (EMT) and promoting tumor cell invasion and metastasis, resulting in a poorer prognosis [63]. In contrast, in adenocarcinomas, the expression of SLC2A4 alone is associated with better prognosis. Persistent upregulation of SLC2A4 expression is expected to suppress not only inflammation but also cancer progression [64].

In addition to the genes mentioned above, MYH7, FLNC, and GPD1 also show significant expression differences in OSCC. These genes may influence tumor cell invasiveness and metastatic potential through various mechanisms. The MYH7 gene, a key regulator of muscle contraction, may have a role in tumor invasiveness and metastasis, as its differential expression in HNSCC is associated with tumor aggression [65]. FLNC plays an important role in tumor invasion and metastasis, with its upregulation in tumor cells closely linked to the metastatic process [66]. GPD1 plays a vital role in lipid metabolism and the maintenance of cancer stem cell characteristics, especially in glycerophospholipid metabolism [67]. Furthermore, GPIHBP1, a gene associated with fat metabolism, plays an important role in immune evasion and metastasis of tumor cells. Inhibition of GPIHBP1 expression may help suppress cancer progression, particularly in advanced cancers like colorectal cancer [68]. In this study, the expression changes of ADIPOQ and PLIN1 in OSCC may reflect alterations in the metabolic state of tumor cells, providing new insights for the early diagnosis and treatment of cancer. The peroxisome proliferator-activated receptor (FABP4 plays a crucial role in regulating cellular metabolism, energy homeostasis, and immune responses throughout the body [69].

Enrichment analysis in this study revealed that lipid metabolism-related genes such as FABP3, FABP4, ADIPOQ, SLC27A6, and PLIN1 are all enriched in the PPAR signaling pathway. The PPAR signaling pathway not only plays a key role in tumor cell proliferation, differentiation, and apoptosis, but also promotes tumor growth and metastasis by influencing the metabolic activities of immune and stromal cells within the tumor microenvironment [70]. Studies suggest that activation of the PPAR pathway may regulate immune cell function and suppress inflammation, thereby altering the tumor microenvironment to promote tumor cell proliferation and metastasis. Therefore, regulation of PPAR pathway-related genes not only provides strong support for cancer diagnosis and prognosis but also offers potential targeted strategies for tumor treatment.Research indicates that activation of the PPAR pathway may regulate immune cell function, suppress inflammatory responses, and thus alter the tumor microenvironment, promoting tumor cell proliferation and metastasis. The PPAR signaling pathway plays a critical role in the progression of OLP to OSCC by regulating lipid metabolism, inflammation, and cell differentiation. In OLP, lipid metabolism dysregulation and chronic inflammation are key factors driving malignant transformation. PPARs, particularly PPAR-α and PPAR-γ, can modulate inflammation, immune cell infiltration, and cell proliferation within the tumor microenvironment [71]. This pathway influences fatty acid metabolism and immune cell polarization, shifting the environment toward a pro-tumor phenotype. Dysregulation of the PPAR signaling pathway may disrupt normal cell differentiation, thereby promoting malignant transformation [72]. Therefore, the regulation of PPAR pathway-related genes not only provides strong support for cancer diagnosis and prognosis but also offers potential targeted strategies for tumor therapy.

To explore potential therapeutic strategies, we queried major drug databases such as DrugBank, DGIdb, and TCMSP to identify drugs associated with central genes. Among these, palmitic acid (PA), a saturated fatty acid found abundantly in vegetable oils, possesses various pharmacological activities, including antiviral, anti-inflammatory, and analgesic effects. PA has been shown to induce cell cycle arrest and promote apoptosis, and it can inhibit the proliferation of liver cancer cells. Research indicates that low concentrations of PA can induce lymphocyte proliferation, while high concentrations exhibit cytotoxicity [73]. FABP3, a fatty acid-binding protein, plays a significant role in lipid metabolism, affecting the uptake and utilization of fatty acids by cells. Silencing FABP3 improves the viability, Pdx1 gene expression, and insulin secretion function of cells cultured with PA for prolonged periods [74]. This suggests that inhibiting FABP3 may effectively alleviate lipotoxicity and improve pancreatic β-cell function. Thus, the interaction between FABP3 and palmitic acid may offer new insights for treating tumors associated with lipid metabolism disorders.Pyruvate dehydrogenase kinase (PDK), an important enzyme regulating mitochondrial metabolism, can enhance oxidative phosphorylation and promote tumor cell apoptosis when PDK4 is inhibited. Sodium dichloroacetate (DCA), a PDK inhibitor, reduces PDK activity, suppresses the phosphorylation of pyruvate dehydrogenase (PDH), and increases oxidative metabolism. Studies show that DCA enhances oxidative phosphorylation in tumor cells and promotes ROS accumulation, ultimately leading to tumor cell apoptosis [75]. Tumor microenvironment factors may modulate the efficacy of dichloroacetate. DCA-induced PDK inhibition results in a greater reduction in PDH phosphorylation in cells adapted to acidic environments. DCA also induces a decrease in glycolytic flux and an increase in oxidative phosphorylation [76]. Imatinib, a targeted therapy drug, has been shown to have significant effects in treating various types of cancer. Studies on OSCC cells demonstrate that imatinib effectively inhibits cell proliferation in a time- and concentration-dependent manner. Imatinib promotes apoptosis by enhancing the expression of p53, Bax, and PARP, while inhibiting Bcl-2 expression. It also suppresses OSCC cell migration and colony formation by inhibiting the PI3K/AKT/mTOR signaling pathway, highlighting its potential in OSCC treatment [77]. These findings suggest that imatinib not only serves as an anticancer drug but also significantly improves the clinical prognosis of OSCC patients by modulating apoptosis and signaling pathways.Ascorbic acid, a compound with strong antioxidant properties, has been found to exhibit anticancer effects by inducing oxidative stress and DNA demethylation. Studies suggest that ascorbic acid has significant adjuvant effects when used in platinum-based treatments for OSCC, alleviating the side effects and resistance associated with platinum-based drugs [78]. This finding highlights the potential of ascorbic acid as an adjunct in cancer therapy, especially in enhancing the efficacy of chemotherapy while reducing side effects and resistance. Metformin, an oral drug commonly used to treat type 2 diabetes, has garnered widespread attention for its potential in cancer treatment in recent years. Numerous studies show that metformin inhibits tumor initiation and progression through multiple mechanisms. GPD1, a key metabolic regulator in tumor cells, enhances the anticancer effects of metformin, particularly by improving mitochondrial function and synergistically inhibiting tumor cell proliferation [79]. Thus, the overexpression of GPD1 may serve as an important biomarker for metformin-based cancer therapy, offering new insights for clinical application.

In OLP treatment, oral standard doses of all-trans retinoic acid (ATRA) are an effective and safe option

for patients with severe chronic OLP [80]. Topical use of curcumin has been shown to alleviate pain and promote clinical healing in OLP patients, with numerous studies supporting its efficacy. Curcumin, a natural polyphenol, has been widely studied and proven to have various pharmacological activities, including antibacterial, anti-inflammatory, and anticancer effects [81–82]. Topical curcumin effectively alleviates pain and promotes healing in OLP patients, with several studies confirming its potential in oral disease treatment [83]. The translational significance of drug candidates that modulate lipid metabolism in the treatment of OLP and OSCC is significant, as these interventions offer potential therapeutic approaches for managing both conditions. ATRA is effective due to its ability to modulate lipid metabolism, particularly by affecting retinoid signaling pathways that influence cellular differentiation and immune responses [84]. This makes ATRA potentially a useful option for patients with chronic OLP, with the potential to reduce the progression of OSCC. Additionally, Curcumin exerts its anticancer effects by targeting cancer cells and modulating the tumor microenvironment, through mechanisms such as cell cycle arrest, promotion of apoptosis, ROS induction, endoplasmic reticulum stress, inhibition of epithelial-mesenchymal transition, and reduction of extracellular matrix degradation [85]. Furthermore, curcumin restores the activity of CD8 + cytotoxic T cells, further enhancing the immune system's anticancer ability [86]. In the TCMSP database, ADIPOQ is associated with several traditional Chinese medicine components, such as Polygonum cuspidatum root, Morus alba root bark, and Dioscorea opposita tuber, which show significant antitumor potential. Polygonum cuspidatum root contains resveratrol, which has strong antioxidant and anti-inflammatory properties and has been shown to have positive effects in oral diseases [87–88]. Morus alba root bark and Dioscorea opposita tuber also exhibit antioxidant effects and have demonstrated neuroprotective properties in diseases associated with high glucose-induced oxidative damage [89–90]. These traditional Chinese medicine components may provide new targeted therapeutic approaches for OSCC and OLP by modulating the tumor microenvironment. By targeting lipid metabolism through pharmacological and natural therapies, these interventions have the potential to slow down the transition from OLP to OSCC, alleviate symptoms, and improve the clinical outcomes for patients. Thus, lipid metabolism modulation represents an important avenue for the development of novel clinical treatments for OLP and OSCC, offering promising therapeutic strategies.

The translational significance of drug candidates that modulate lipid metabolism in the treatment of oral lichen planus (OLP) and oral squamous cell carcinoma (OSCC) is significant, as these interventions offer potential therapeutic approaches for managing both conditions. All-trans retinoic acid (ATRA), widely used in OLP treatment, is effective due to its ability to modulate lipid metabolism, particularly by affecting retinoid signaling pathways that influence cellular differentiation and immune responses. This makes ATRA a useful option for patients with severe chronic OLP, potentially reducing the progression to OSCC.

Conclusion

This study integrates Mendelian randomization analysis, differential gene expression, and drug prediction data to uncover the central role of lipid metabolism in the transformation of OLP to OSCC, offering new insights for early diagnosis and targeted therapy. The novelty of this study lies in its systematic analysis of the dynamic role of lipid metabolism in the OLP-OSCC transition, filling a critical gap in the "chronic inflammation-metabolic reprogramming-carcinogenesis" mechanism chain. The study reveals that DAG plays a protective role in OLP by modulating T cell function and epithelial barrier integrity, but in OSCC, it transforms into a carcinogenic factor. This dual role suggests that dynamic changes in DAG levels could serve as an early biomarker for cancer risk in OLP. Key genes, such as SLC27A6 and FABP4, regulate lipid metabolism reprogramming and influence the inflammatory microenvironment and immune evasion through dynamic expression. Additionally, drug prediction analysis identified candidate drugs, such as ATRA and curcumin, providing new directions for the clinical treatment of OLP and OSCC. Moving forward, our research group plans to focus on investigating the role of SLC27A6, FABP4, and PPAR signaling pathways in the OLP to OSCC transition. This will involve examining their mechanisms through tissue samples, cell experiments, and animal models, as well as evaluating the impact of the PARP pathway in lipid metabolism regulation. Simultaneously, we will screen and validate candidate drugs targeting these pathways, assessing their antitumor effects using molecular docking, in vitro, and in vivo experiments to clarify their mechanisms of action. Ultimately, these studies will reveal the key role of lipid metabolism in the development of OSCC and promote the clinical translation of precision therapies.

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Author contributions

MY and YL were responsible for the conception and design of the study. MY conducted the statistical analyses and drafted the initial manuscript. HS, TL, HL, and JZ provided critical revisions for important intellectual content. BD

performed English language revisions. All authors contributed to the article and approved the fnal version submitted for publication.

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Data availability
The datasets analyzed for this study are available in the following public resources: GWAS Catalog (https://www.ebi.ac.uk/gwas/), GEO database (https://www.ncbi.nlm.nih.gov/geo/), FINNGEN database (https://www.finngen.fi/en/access_results), TCGA database (https://www.cancer.gov/ccg/), Genecards database (https://www.genecards.org/), Venny platform (https://bioinfogp.cnb.csic.es/tools/venny/), DAVID database (https://david.ncifcrf.gov/), STRING database (https://string-db.org/), DrugBank (https://go.drugbank.com/), DGIdb (https://dgidb.org/) and TCMSP (https://old.tcmsp-e.com/index.php) databases.

Declarations

Ethics approval and consent to participate
This study utilized publicly accessible databases; therefore, ethical approval was not required as the research did not involve human participants or personal data.

Competing interests
The authors declare no competing interests.

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