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·基础研究·

基于网络药理学和转录组学探讨姜黄素对口腔鳞状细胞癌细胞生物学行为的影响及机制

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【摘要】 目的　探讨姜黄素对口腔鳞状细胞癌（OSCC）细胞生物学行为的影响及其可能的分子机制，为姜黄素在OSCC防治中的应用提供实验依据。**方法**　本研究中的所有动物实验通过单位实验动物福利伦理委员会批准，并严格遵循相关动物伦理规范。基于TCMSP、SwissTargetPrediction、DrugBank及GeneCards数据库筛选姜黄素与OSCC的潜在靶点，构建蛋白互作网络并进行基因本体（GO）及京都基因与基因组百科全书（KEGG）富集分析。采用CAL-27及SCC-9细胞进行划痕及克隆形成实验检测姜黄素对细胞迁移与增殖能力的影响。结合RNA测序分析差异表达基因，并通过实时荧光定量PCR及Western blot分别验证姜黄素对细胞关键分子mRNA与蛋白表达的变化。同时建立CAL-27细胞BALB/c裸鼠移植瘤模型，采用免疫组化检测姜黄素处理对移植瘤组织中相关蛋白表达的影响。**结果**　共筛选出178个交集靶点，主要富集于PI3K/AKT信号通路及脂质代谢相关通路。姜黄素处理后，CAL-27及SCC-9细胞迁移及克隆形成能力降低。转录组分析筛选出828个差异表达基因，主要涉及脂质代谢及PI3K/AKT相关通路。实时荧光定量PCR结果显示PIK3CA、CCND1、BCL2及FASN表达下调，Western blot结果显示p-AKT及FASN蛋白表达降低。体内实验显示，姜黄素抑制移植瘤生长，并降低肿瘤组织中Ki-67、BCL2及p-AKT表达。**结论**　姜黄素可能通过调控PI3K/AKT信号通路及脂质代谢相关基因表达，抑制OSCC细胞迁移与增殖能力。

【关键词】 姜黄素；　口腔鳞状细胞癌；　PI3K/AKT信号通路；　脂质代谢；　CAL-27细胞；　细胞增殖；　细胞迁移；　转录组分析
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Influence and mechanism of curcumin on the biological behavior of oral squamous cell carcinoma cells based on network pharmacology and transcriptomics

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【Abstract】 Objective　To investigate the effects of curcumin on the biological behavior of oral squamous cell carcinoma (OSCC) cells and its potential molecular mechanisms, as well as to provide experimental evidence for the application of curcumin in the prevention and treatment of OSCC. **Methods**　All animal experiments in this study were approved by the Institutional Animal Welfare and Ethics Committee and strictly adhered to relevant animal ethics guidelines. Potential intersecting targets of curcumin and OSCC were screened using TCMSP, SwissTargetPrediction, Drug-

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Bank, and GeneCards databases, followed by construction of a protein - protein interaction network and gene ontology (GO) /Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses. Scratch and clone formation experiments were conducted using CAL-27 and SCC-9 cells to detect the effect of curcumin on cell migration and proliferation ability. Combining RNA sequencing analysis of differentially expressed genes, and verifying the changes in mRNA and protein expression of key cellular molecules by curcumin through real-time fluorescence quantitative PCR and Western blot, respectively. Simultaneously establish a CAL-27 xenograft BALB/c nude mouse transplant tumor model and use immunohistochemistry to detect the effect of curcumin treatment on the expression of related proteins in the transplant tumor tissue. **Results**　A total of 178 intersecting targets were identified, mainly enriched in the PI3K/AKT signaling pathway and lipid metabolism-related pathways. Curcumin significantly inhibited migration and colony formation of CAL-27 and SCC-9 cells *in vitro*. Transcriptomic analysis identified 828 differentially expressed genes enriched in lipid metabolism and PI3K/AKT pathways. Real-time fluorescence quantitative PCR showed downregulation of PIK3CA, CCND1, BCL2, and FASN, while western blot demonstrated decreased expression of p-AKT and FASN. *In vivo*, curcumin markedly suppressed tumor growth and reduced the expression of Ki-67, BCL2, and p-AKT in tumor tissues. **Conclusion**　Curcumin may inhibit the migration and proliferation of OSCC cells by regulating the PI3K/AKT signaling pathway and the expression of lipid metabolism-related genes.

【Key words】 curcumin;　oral squamous cell carcinoma;　PI3K/AKT signaling pathway;　lipid metabolism;　CAL-27 cells;　cell proliferation;　cell migration;　transcriptome analysis

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口腔鳞状细胞癌(oral squamous cell carcinoma，OSCC)是口腔最常见的恶性肿瘤类型，占口腔恶性肿瘤的90%以上[1-2]。尽管近年来手术、放疗及综合治疗水平不断提高，但OSCC总体预后仍不理想，5年生存率约为50%[3-4]。肿瘤侵袭、复发及耐药仍是影响患者生存及预后的重要因素，其分子机制尚未完全明确[5-7]。

姜黄素(curcumin)是来源于姜黄的一种天然多酚类化合物，具有抗炎及抗肿瘤等生物学活性[8]。既往研究显示，姜黄素可影响核因子κB(nuclear factor kappa-B，NF-κB)、转录激活因子3(signal transducers and activators of transcription 3，STAT3)等信号通路，在多种肿瘤中发挥抑制作用[9-11]。然而，其在OSCC中的作用机制尚需进一步研究。近年来，姜黄素在OSCC中的抗肿瘤作用逐渐受到关注。研究表明，其可抑制OSCC细胞增殖、迁移和侵袭，并诱导凋亡，相关机制涉及NF-κB、表皮生长因子受体(pidermal growth factor receptor，EGFR)及其下游蛋白激酶B(protein kinase B，AKT)、丝裂原活化蛋白激酶(mitogen-activated protein kinase，MAPK)、STAT3等多条信号通路，同时可能参与肿瘤免疫及氧化应激调控[12-15]。然而，现有研究多集中于单一通路或表型观察，对其是否通过信号转导与代谢重编程的协同作用参与OSCC进展，仍缺乏系统性认识。

磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase，PI3K)/AKT信号通路是OSCC中最关键的异常激活网络之一，广泛参与细胞增殖、凋亡、侵袭及耐药等过程，并与肿瘤微环境调控密切相关，已成为重要的潜在治疗靶点[16-17]。同时，脂质代谢重编程在OSCC中普遍存在，涉及脂肪酸合成及胆固醇代谢等过程，可为肿瘤细胞提供能量及结构基础，并促进肿瘤进展[18-20]。脂肪酸合成酶(fatty acid synthase，FASN)等脂质代谢相关酶在多种鳞状细胞癌中表达升高，并与肿瘤进展相关[21-23]。值得注意的是，脂质代谢异常与PI3K/AKT/哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin，mTOR)信号轴之间存在密切的功能耦联[19, 24-25]。

本研究旨在通过网络药理学预测、转录组学分析及体内外实验验证，系统探讨姜黄素对OSCC细胞生物学行为的影响及其分子机制，并为姜黄素在OSCC防治中的应用提供实验依据。

1　材料和方法

1.1　试剂与仪器

姜黄素(C7090，纯度≥98%，北京索莱宝科技有限公司，中国)以二甲基亚砜(dimethyl sulfoxide，DMSO)溶解配制为储备液，-20 ℃避光保存，使用前以培养基稀释至所需工作浓度。人OSCC细胞系CAL-27、SCC-9由上海交通大学医学院附属第九

人民医院馈赠。

DMEM高糖培养基(11965092,Gibco公司,美国);胎牛血清(FBS,10099141C,A3206163CP,Gibco公司,美国);青链霉素双抗溶液(15140122,Gibco公司,美国);TRIzol总RNA提取试剂(15596026,Invitrogen公司,美国);SYBR Green实时荧光定量PCR试剂盒(SR1110,北京索莱宝科技有限公司,中国);Ki-67抗体(9449T,Cell Signaling Technology公司,美国);B细胞淋巴瘤因子-2(B-cell lymphoma 2,Bcl-2)抗体(15071T,Cell Signaling Technology公司,美国);p-AKT抗体(4060T,Cell Signaling Technology公司,美国);AKT抗体(9272S,Cell Signaling Technology公司,美国);FASN抗体(3180T,Cell Signaling Technology公司,美国);GAPDH抗体(2118T,Cell Signaling Technology公司,美国);实时荧光定量PCR所用引物由上海铂尚生物技术有限公司(中国)合成。4 ℃低温冰箱(REVCO,Thermo Scientific,美国);-20℃低温冰箱(BCD-223WDPT,海尔,中国);-80℃低温冰箱(ULTS1368,Thermo Scientific,美国);电热温水槽(Ni-1,长安科仪,中国);摇床(TS-8,其林贝尔,中国);烘箱(101-2BS,力辰,中国);电子天平(H0503,德科,中国);漩涡振荡器(XH-D,左乐,中国);高速离心机(PICO-17,Thermo Scientific,美国);低速台式离心机(TD5A-WS,湘仪,中国);超纯水仪(Milli-Q,Millipore,美国);电泳仪(ESP600,天能,中国);半干转移电泳槽(VE-386,天能,中国);PCR仪(Veriti96,ABI,美国);实时荧光定量PCR仪(Lightcycler 480 II,Roche,瑞士);生物安全柜(1300 series A2,Thermo Scientific,美国);细胞培养箱(HERAcell 150i1型,Thermo Scientific,美国),手动移液器(Research plus,Eppendorf,德国);麻醉机(SA428,塞昂斯,中国)。

1.2　姜黄素相关靶点与疾病基因的获取

姜黄素的化学结构信息(PubChem CID:969516)来源于PubChem数据库。通过中药系统药理学数据库与分析平台(Traditional Chinese Medicine Systems Pharmacology Database,TCMSP,https://tcmsp-e.com/)、SwissTargetPrediction(https://www.swisstargetprediction.ch/)及DrugBank数据库(https://go.drugbank.com/)检索姜黄素潜在作用靶点信息。将各数据库结果合并后去除重复项,并通过UniProt数据库进行基因名称标准化处理,物种限定为Homo sapiens,获得姜黄素相关靶点集合。以“oral squamous cell carcinoma”及“oral cancer”为关键词,在GeneCards、DisGeNET、OMIM及Therapeutic Target Database(TTD)数据库中检索OSCC相关基因,整合去重后同样进行标准化处理,获得OSCC相关基因集合。

1.3　交集靶点筛选与蛋白互作网络构建与分析

采用R语言绘制Venn图,对姜黄素相关靶点与OSCC相关基因进行交集筛选,获得潜在共同作用靶点。将交集基因导入STRING数据库(https://string-db.org/)构建蛋白-蛋白相互作用(protein-protein interaction,PPI)网络,物种限定为Homo sapiens,最低相互作用置信度评分设定为0.4以上。将PPI网络结果导出后导入Cytoscape 3.10.1软件进行网络可视化与拓扑特征分析,并采用CytoHubba插件对网络节点进行排序,依据degree值筛选连接度较高的核心靶基因,用于后续网络构建与机制验证。

1.4　交集靶点基因本体与京都基因及基因组百科全书富集分析

将交集基因分别上传至DAVID数据库(https://david.ncifcrf.gov/)及Metascape数据库(https://metascape.org/)进行功能富集分析。基因本体(gene ontology,GO)分析涵盖生物学过程(biological process,BP)、细胞组分(cellular component,CC)和分子功能(molecular function,MF)3个方面。京都基因与基因组百科全书(Kyoto Encyclopedia of Genes and Genomes,KEGG)分析用于识别交集靶点显著富集的信号通路与代谢通路。采用R语言clusterProfiler及ggplot2软件包对富集结果进行整理与可视化展示(包括气泡图、柱状图等),以$P<0.05$作为差异具有统计学意义的判定标准。采用Benjamini-Hochberg方法对P值进行多重检验校正,得到FDR值,以FDR<0.05作为显著富集通路筛选标准。

1.5　细胞培养与姜黄素药物处理方案

人OSCC细胞系CAL-27及SCC-9采用含10%胎牛血清及1%青链霉素的DMEM培养基,在37 ℃、5% CO_2恒温培养箱中培养。姜黄素以DMSO溶解制备储备液,使用前以培养基稀释至不同工作浓度。本研究根据预实验结果设置姜黄素处理浓度为0、1、5、10 μmol/L,每组3孔。各处理组DMSO终浓度控制在0.1%以下,对照组加入等

体积DMSO。

1.6　划痕实验观察姜黄素对口腔鳞癌细胞迁移能力的影响

将CAL-27及SCC-9细胞按约5×10^{5}个/孔的密度接种于6孔板，待细胞融合度达到90%以上时，使用无菌200 μL枪头在单层细胞表面垂直划痕形成均一伤口。用PBS轻轻洗涤以去除游离细胞后，加入含不同浓度姜黄素的低血清培养基继续培养，每组3孔。分别于0、12、24 h在相同视野位置采集图像记录划痕愈合情况。为保证观察视野一致，在0 h拍照后标记培养皿底部参考点，并在后续时间点于相同标记位置进行图像采集。图像采集采用倒置显微镜在×100放大倍数下完成。

1.7　克隆形成实验检测姜黄素对口腔鳞癌细胞克隆形成与增殖能力的影响

将CAL-27细胞及SCC-9细胞以800个/孔接种于6孔板，贴壁后加入不同浓度姜黄素（0、1、5、10 μmol/L）进行持续培养7~14 d，每组3孔，其间根据细胞生长情况每2~3 d更换含药培养基。培养结束后用固定液固定细胞并采用结晶紫染色，清水洗涤后晾干，统计50个以上细胞组成的克隆数，评价姜黄素对细胞长期增殖及克隆形成能力的影响。

1.8　RNA提取与转录组测序分析差异表达基因

采用TRIzol法提取细胞总RNA，经浓度与完整性检测合格后构建测序文库，并在Illumina Nova-Seq平台进行高通量测序。测序数据经标准流程质控与比对后，采用DESeq2软件进行差异表达基因分析，筛选阈值设定为$|\log_2FC|>1$且$P<0.05$。通过主成分分析、火山图及热图对样本分群及差异基因表达模式进行展示，并在差异基因基础上开展KEGG通路富集分析，筛选与PI3K/AKT信号通路及脂质代谢相关的显著富集通路，用于后续机制解释与实验验证。

1.9　实时荧光定量PCR检测关键基因mRNA表达水平

将CAL-27细胞及SCC-9细胞接种于6孔板，待细胞贴壁后给予姜黄素（0、1、10 μmol/L）处理24 h，每组3孔。采用TRIzol法提取总RNA，逆转录合成cDNA，使用SYBR Green法进行实时荧光定量PCR，以GAPDH为内参基因，采用$2^{-\Delta\Delta Ct}$法计算相对表达量。引物序列见表1。

表1　实时荧光定量PCR引物序列

Table 1　Primer sequences for real-time fluorescent quantitative PCR

Gene	Forward primer(5′→3′)	Reverse primer(5′→3′)
BCL2	TGTGCTTTGCATTCTTGGACGAG	ATTTCCTGCATCTCATGCCAAGG
MMP13	ACTGAGAGGCTCCGAGAAATG	GAACCCCGCATCTTGGCTT
FASN	AACCGGCTCTCCTTCTTCTT	TTGGGCTTCAGCAGGACATT
CCND1	TATTGCGCTGCTACCGTTGA	CCAATAGCAGCAAACAATGTGAAA
PIK3CA	CATGCATTGTTTTGCACCCC	ATGGAAGACGGGAGATTCACAT
GAPDH	AACTTTGGCATTGTGGAAGG	GGATGCAGGGATGATGTTCT

BCL2: B-cell lymphoma 2; MMP13: matrix metalloprotease 13; FASN: fatty acid synthase; CCND1: cyclin D1; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; GAPDH: glyceraldehyde-3-phosphate dehydrogenase

1.10　Western blot检测PI3K/AKT通路及脂质代谢相关蛋白表达

实验分组同1.9，每组3孔。弃去培养基后，使用预冷PBS洗涤细胞2次，加入RIPA裂解液（含蛋白酶抑制剂及磷酸酶抑制剂）于冰上裂解30 min，12 000×g、4 ℃离心15 min，收集上清提取总蛋白。采用BCA法测定蛋白浓度后，各组取等量蛋白进行SDS-PAGE电泳分离，并转膜至PVDF膜。以5%脱脂奶粉或BSA室温封闭1 h后，分别加入相应一抗工作液（1∶1 000）4 ℃孵育过夜。次日TBST洗膜后，加入相应HRP标记二抗工作液（1∶3 000）室温孵育1 h。洗膜后采用ECL化学发光试剂显色，并使用凝胶成像系统采集图像。

1.11　裸鼠移植瘤模型实验评估姜黄素体内抑瘤作用

本研究中的所有动物实验在佑曙生命科技（上海）有限公司动物实验室完成，所有实验均获得其实验动物福利伦理委员会批准（批准编号：YS-m202512002），并严格遵循相关动物伦理规范，按照ARRIVE指南2.0（https://arriveguidelines.org）实施报告，动物实验方案按伦理委员会批准的方案执行（未进行注册）。选用6周龄BALB/c裸鼠共

12只(体质量18~22 g),饲养于SPF级动物房内(温度22~25 ℃,相对湿度50%~60%,12 h光/暗循环,自由摄食和饮水,每日监测动物体重、活动状态),实验前适应性饲养1周。实验动物纳入标准:年龄和体质量相近、健康状态良好的雄性BALB/c裸鼠;排除标准:实验过程中出现明显健康异常、移植瘤未成功建立或非实验因素导致死亡的小鼠。实验动物样本量根据既往研究经验及前期预实验结果确定,以保证不同处理组间肿瘤生长差异具有足够的统计学效能,最终每组纳入6只裸鼠。本实验不设盲。

常规培养CAL-27细胞,收集后调整细胞悬液浓度至1×10^{6}个/100 μL。裸鼠经1%戊巴比妥钠腹腔麻醉后,于侧腹部皮下接种细胞悬液建立移植瘤模型。接种后观察成瘤情况,当肿瘤直径≥3 mm视为建模成功。

将成瘤裸鼠用随机数字法分为对照组和姜黄素处理组(n=6),分别给予等体积生理盐水或姜黄素(30 mg/kg)灌胃处理,每日1次,连续14 d。实验结束后采用二氧化碳吸入法对动物实施安乐死,确保动物在无痛苦、无挣扎的情况下失去意识,待动物呼吸停止、瞳孔反射消失后,继续维持二氧化碳暴露不少于5 min,以确保死亡。安乐死后剥离肿瘤组织并称重、拍照,使用游标卡尺测量肿瘤长径(L)和短径(W),按公式V =(L × W^2)/2计算肿瘤体积。用于评估姜黄素对肿瘤生长的抑制作用。

1.12　免疫组化检测移植瘤组织中Ki-67、BCL2及p-AKT蛋白表达

实验分组同1.11,每组6个样本。裸鼠移植瘤组织取材后置于4%多聚甲醛中固定,常规脱水、石蜡包埋并切片,切片厚度约4 μm。石蜡切片经二甲苯脱蜡、梯度乙醇复水后,采用枸橼酸盐缓冲液进行抗原修复。随后以3%过氧化氢室温孵育以封闭内源性过氧化物酶活性,并用山羊血清进行封闭。封闭后分别加入Ki-67(1∶800)、p-AKT(1∶100)及BCL2(1∶400)一抗,4 ℃孵育过夜。次日PBS洗涤后,加入相应二抗室温孵育,采用DAB显色,苏木精复染后脱水、透明并封片。在光学显微镜下观察并采集图像。根据染色强度及阳性细胞比例对免疫组化结果进行半定量分析,用于评价姜黄素对肿瘤组织增殖相关蛋白、PI3K/AKT通路及凋亡相关蛋白表达的影响。

1.13　统计学分析

所有体外实验均独立重复3次,n值代表独立实验次数或每组小鼠数量,数据以均数±标准差表示。采用GraphPad Prism 9.0软件(GraphPad Software,美国)进行统计分析。首先对数据进行正态性检验(Shapiro - Wilk检验)及方差齐性检验(Levene检验)。对于符合正态分布且方差齐的数据,两组间比较采用双尾独立样本t检验,多组间比较采用单因素方差分析(one-way ANOVA);当差异具有统计学意义时,进一步采用Tukey事后检验进行组间两两比较。检验水准α=0.05。

2　结　果

2.1　网络药理学筛选姜黄素抗OSCC潜在靶点

通过TCMSP、SwissTargetPrediction及DrugBank数据库共筛得姜黄素相关靶点130个。通过GeneCards、DisGeNET、OMIM及TTD数据库检索获得OSCC相关基因4 864个。将两者进行交集分析,共获得178个潜在作用靶点(图1a)。

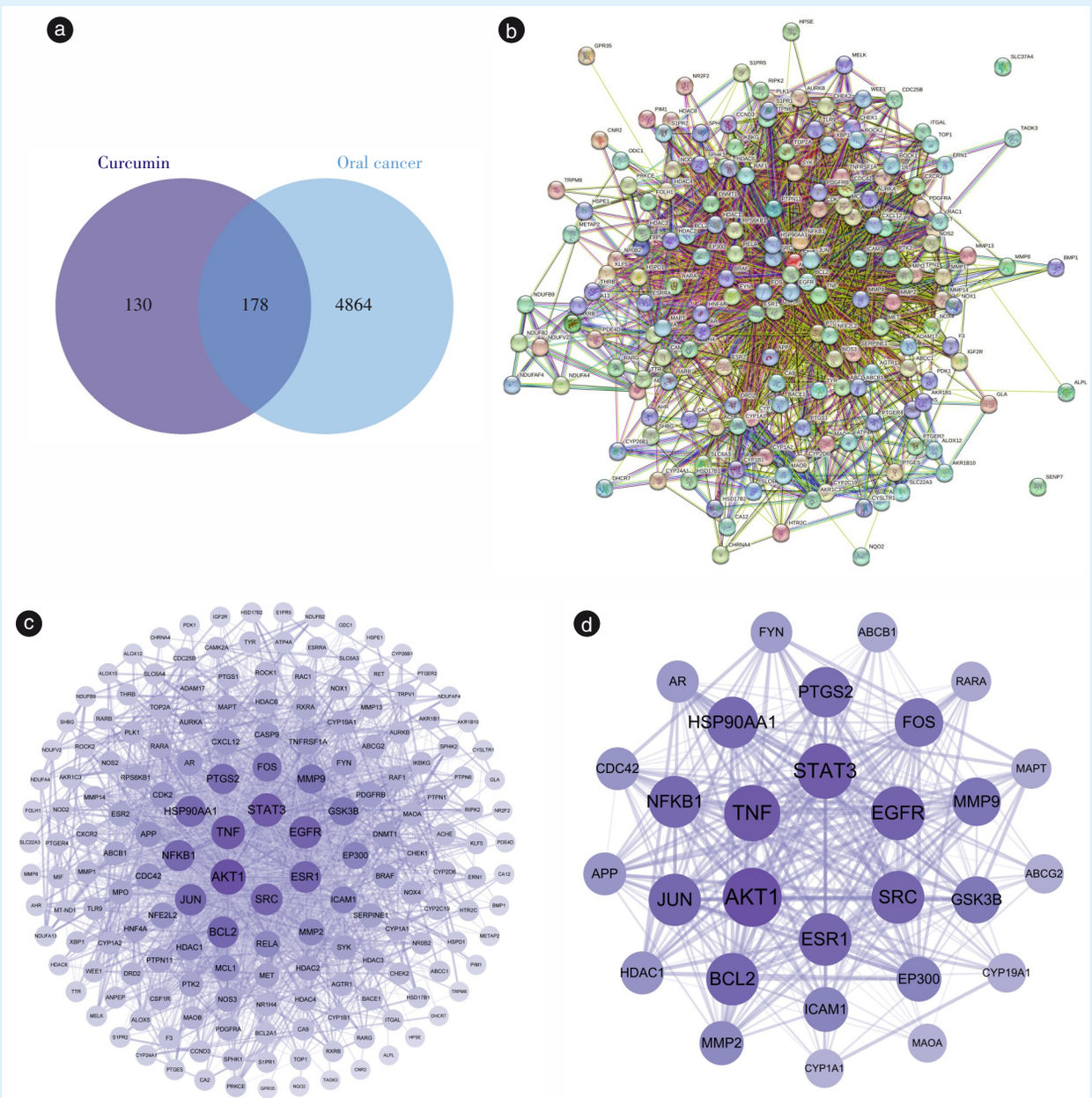
将交集基因导入STRING数据库构建蛋白-蛋白相互作用网络,置信度设定为0.4以上,构建得到包含146个节点、2 398条边的PPI网络(图1b)。经Cytoscape软件拓扑分析,筛选degree值较高的核心基因,包括AKT1、TNF、STAT3、JUN、NFKB1及BCL2等(图1c & 1d)。上述基因在网络中连接度较高。

2.2　富集分析结果

为明确交集靶点的功能分布,对178个潜在作用基因进行GO及KEGG富集分析。GO分析显示,这些基因在生物过程方面主要富集于氧化应激反应、脂质代谢过程及凋亡信号调控等相关过程(图2a)。在细胞组分方面,主要定位于膜筏结构、细胞质蛋白复合体及质膜区域(图2b)。KEGG通路分析结果显示,交集基因显著富集于多条肿瘤相关信号通路,其中PI3K/AKT信号通路、NF-κB信号通路及MAPK信号通路等均为显著富集通路(FDR <0.05)(图2c-2d)。

2.3　姜黄素抑制OSCC相关细胞迁移及克隆形成能力

基于网络药理学及通路富集分析结果,为进一步验证姜黄素对OSCC细胞生物学行为的影响,采用划痕实验和克隆形成实验进行体外功能评价。划痕实验结果显示,与对照组相比,姜黄素处理CAL-27细胞迁移能力明显降低,且随药物浓度

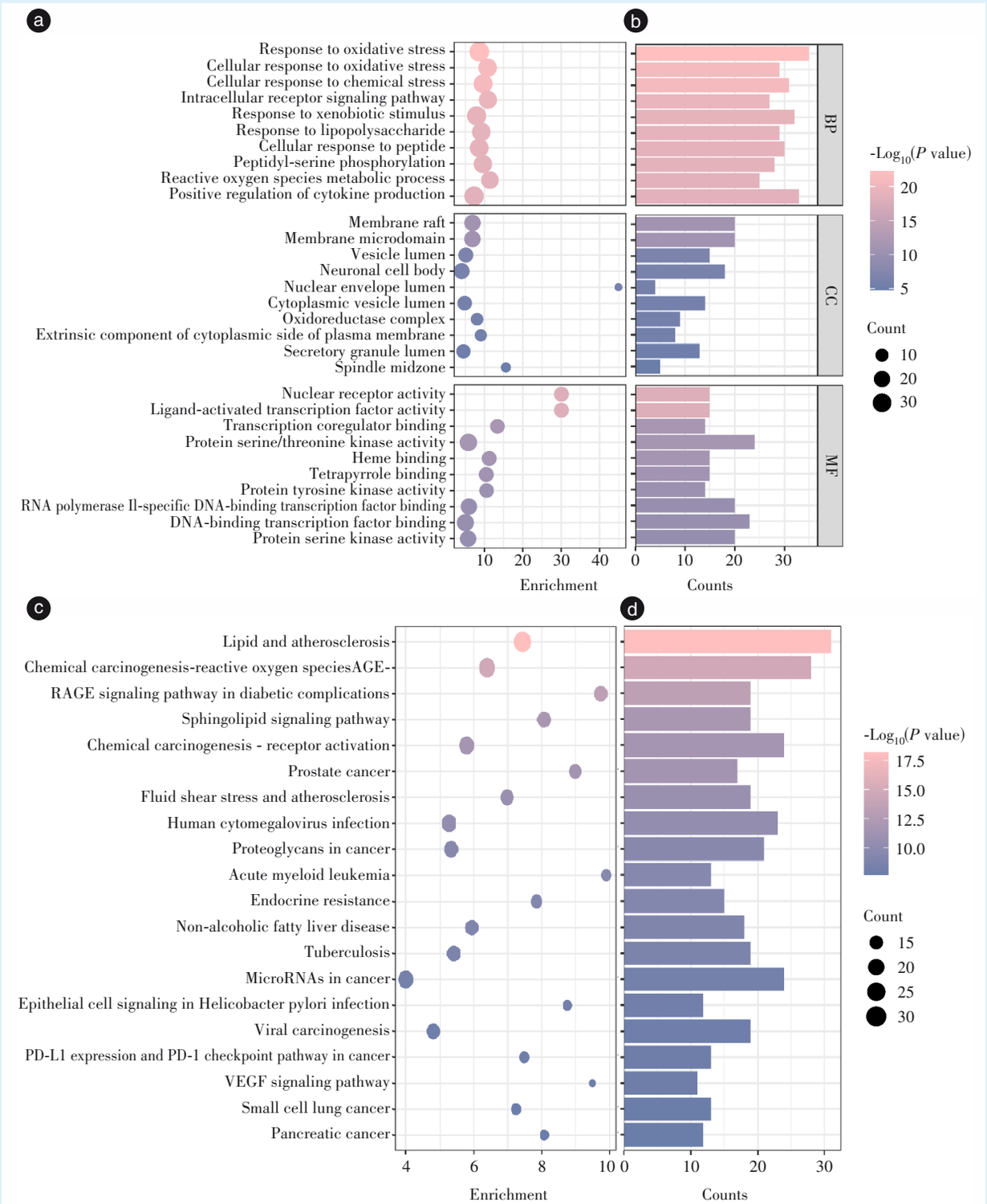


a: Venn diagram illustrating the overlap among 130 curcumin-associated targets and 4 864 oral squamous cell carcinoma (OSCC)-related targets; 178 shared genes were identified for further analysis; b: protein-protein interaction (PPI) network of the 178 overlapping targets generated using the STRING database with a confidence score threshold of > 0.4, comprising 146 nodes and 2 398 edges; c: cytoscape-based visualization of a simplified PPI network after topological filtering, highlighting nodes with higher degree values selected for subsequent hub gene analysis; d: Hub genes identified by topological analysis using the CytoHubba plugin. The node size represents the degree value, and darker colors indicate higher connectivity. Core hub genes, such as AKT1, TNF, STAT3, EGFR, SRC, HSP90AA1, JUN, and NFKB1, were identified as key mediators of curcumin's anti-OSCC effect

Figure 1　Screening and identification of potential therapeutic targets of curcumin against oral squamous cell carcinoma

图1　姜黄素抗口腔鳞状细胞癌潜在作用靶点的筛选与分析

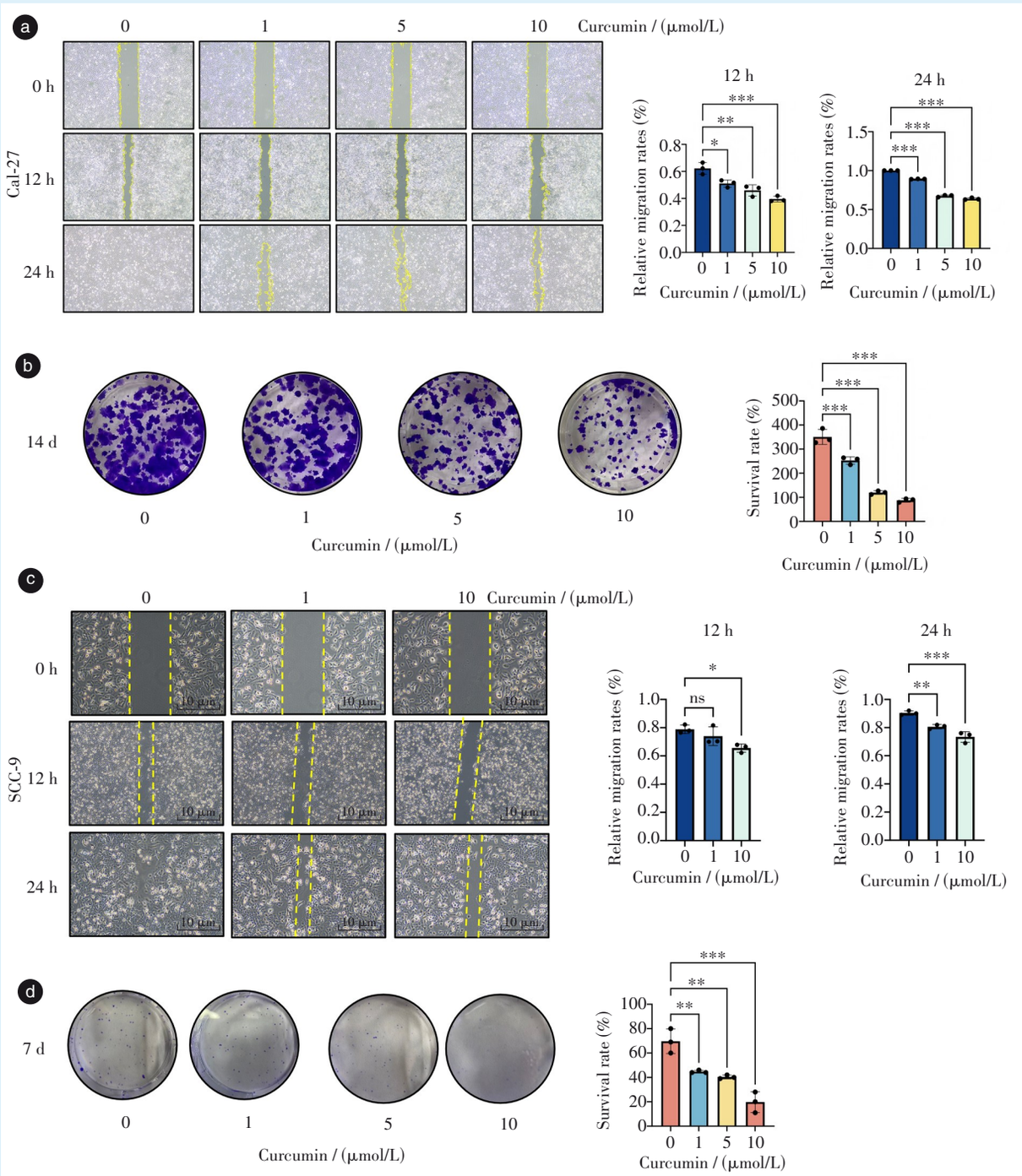
增加,划痕愈合速度逐渐减慢(图3a);克隆形成实验结果显示,姜黄素处理后CAL-27细胞克隆数量减少,克隆体积缩小(图3b)。在SCC-9细胞验证中,划痕实验同样表明姜黄素可显著降低细胞迁移能力,且划痕愈合速度随药物浓度升高逐渐减慢(图3c);克隆形成实验亦显示姜黄素处理后SCC-9细胞克隆数量减少(图3d)。



a: GO and BP enrichment bubble chart. The results show that the intersection targets are mainly enriched in biological processes such as oxidative stress response, lipid metabolism process, and apoptosis signal regulation; b: CC enrichment bar chart. The results show that the related target proteins are mainly located in cell structures such as membrane rafts, cytoplasmic protein complexes, and plasma membrane regions; c: KEGG pathway enrichment bubble chart. The results show that the intersection targets are significantly enriched in multiple lipid metabolism-related pathways; d: KEGG pathway enrichment significance ranking bar chart. The results show that lipid metabolism pathways have a relatively high enrichment degree. KEGG: Kyoto Encyclopedia of Genes and Genomes. GO: gene ontology; BP: biological process; CC: cellular component

Figure 2　GO and KEGG enrichment analyses of curcumin-oral squamous cell carcinomatargets

图2　姜黄素－口腔鳞状细胞癌交集靶点的GO及KEGG富集分析



a: representative images and statistical chart of the CAL-27 cell scratch assay. Compared with the control group, the cell migration distance in the curcumin treatment groups (0, 1, 5, and 10 μmol/L) was reduced, and it was positively correlated with the drug concentration; b: representative images and statistical chart of the colony formation assay. The number of CAL-27 cell colonies decreased after 14 days of treatment with different concentrations of curcumin, and this reduction was dependent on the increase in drug concentration; c: representative images and and statistical chart of the SCC-9 cell scratch assay. Compared with the control group, the cell migration distance in the curcumin treatment groups was reduced, and it was positively correlated with the drug concentration; d: representative images and statistical chart of the cloning formation experiment. After 7 days of treatment with different concentrations of curcumin, the number of SCC-9 cell clones decreased, and this decrease was dependent on the increase in drug concentration. All experiments above: representative images from three independent samples and statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test, n=3 biologically independent samples, ns: $P > 0.05$, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Figure 3　Curcumin inhibits migration and proliferation of CAL-27 cells and SCC-9 cells

图3　姜黄素对CAL-27及SCC-9细胞迁移及克隆形成能力的影响

2.4　转录组分析揭示姜黄素诱导的基因表达改变

为系统分析姜黄素对OSCC细胞基因表达的影响，对姜黄素处理组与对照组CAL-27细胞进行RNA测序分析。主成分分析结果显示，姜黄素处理组（1 μmol/L和10 μmol/L）与对照组在PC1和PC2维度上明显分离，组内重复性良好（图4a）。

差异表达分析共筛选出显著差异基因828个，其中上调基因726个，下调基因102个（图4b）。

进一步对差异表达基因进行GO富集分析，结果显示其主要富集于脂质代谢过程、类固醇代谢过程、胆固醇生物合成、细胞间信号传导及解剖结构形成等相关生物过程（图4c）。

KEGG通路分析显示，差异表达基因显著富集于PI3K/AKT信号通路、细胞因子—受体相互作用、MAPK信号通路、JAK-STAT信号通路及多条脂质代谢相关通路，包括类固醇生物合成和花生四烯酸代谢等（图4d）。

2.5　姜黄素对关键基因表达的影响

基于网络药理学及转录组分析结果，选取与PI3K/AKT信号通路及脂质代谢相关的关键基因PIK3CA、CCND1、BCL2和FASN，采用实时荧光定量PCR进行mRNA表达验证。结果显示，与对照组相比，姜黄素处理后CAL-27细胞及SCC-9细胞中PIK3CA、CCND1及BCL2的mRNA表达水平降低，FASN亦呈下降趋势（图5）。不同浓度组间变化幅度不完全一致，部分指标在中等浓度下变化更为明显。上述结果与转录组分析趋势基本一致。

2.6　姜黄素对PI3K/AKT通路及脂质代谢相关蛋白的影响

为在蛋白水平进一步验证姜黄素对PI3K/AKT信号通路及脂质代谢的调控作用，采用Western blot检测CAL-27及SCC-9细胞中AKT、p-AKT及FASN的表达变化。结果显示，与对照组相比，姜黄素处理后p-AKT蛋白表达水平明显降低，且在高浓度组中下降更为显著，而总AKT蛋白表达变化不明显。此外，FASN蛋白表达在姜黄素处理后亦呈下降趋势（图6）。

2.7　姜黄素抑制裸鼠移植瘤生长

为评价姜黄素在体内对OSCC生长的影响，本研究建立了CAL-27细胞裸鼠皮下移植瘤模型。肿瘤形成后，对照组给予等体积生理盐水处理，姜黄素处理组给予相应剂量姜黄素干预（图7a）。实验结果显示，实验结束时对照组肿瘤体积较大，而姜黄素处理组肿瘤体积明显减小（图7b）。进一步统计分析显示，姜黄素处理组肿瘤体积及肿瘤重量均低于对照组，差异具有统计学意义（图7c）。上述结果表明，姜黄素能够在体内抑制OSCC的生长。

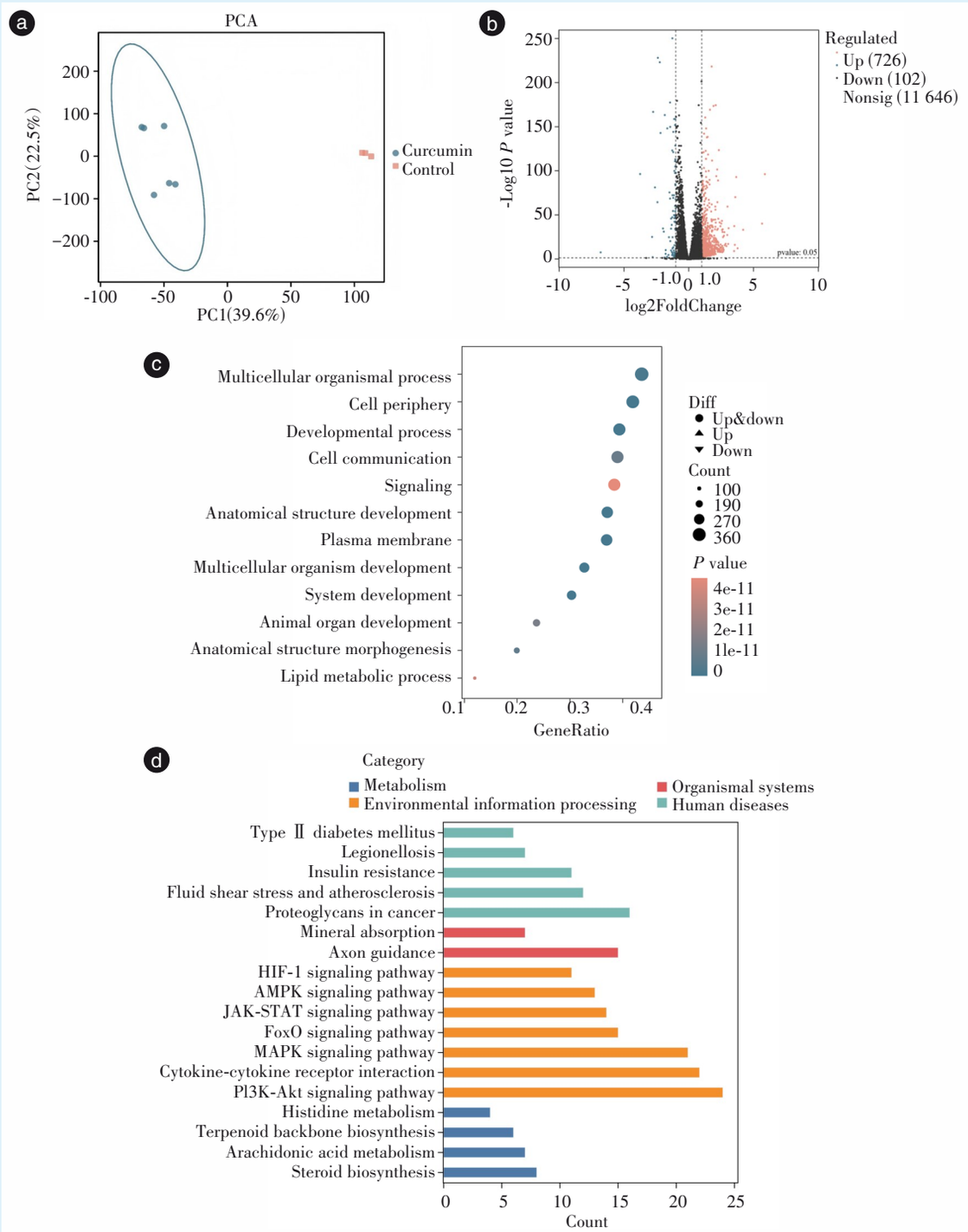
免疫组化结果显示，与对照组相比，姜黄素处理组肿瘤组织中Ki-67、BCL2及p-AKT表达均降低（图7d & 7e）。其中，Ki-67阳性细胞比例减少，提示肿瘤细胞增殖活性下降；BCL2及p-AKT表达降低，表明相关抗凋亡及PI3K/AKT信号通路活性受到抑制。

3　讨　论

OSCC是口腔颌面部最常见的恶性肿瘤类型，具有侵袭性强、复发率高及预后相对较差等特点[26-27]。近年来研究表明，信号通路异常激活及代谢重编程在OSCC发生发展过程中发挥重要作用[28]。

网络分析提示*AKT1*、*STAT3*、*EGFR*及*BCL2*等基因可能在姜黄素调控OSCC过程中发挥关键作用，且多参与PI3K/AKT信号通路及炎症相关过程。既往研究已证实，PI3K/AKT信号在口腔鳞癌组织中持续激活，与肿瘤细胞增殖及抗凋亡密切相关[29]。值得注意的是，上述富集通路并非孤立存在，而是可能通过共同的信号网络相互调控。其中，PI3K/AKT信号通路在多种肿瘤中被认为是连接细胞增殖、炎症反应及代谢重编程的关键枢纽。因此，本研究结果提示姜黄素可能通过以PI3K/AKT为核心的多通路协同调控网络发挥作用，而非仅作用于单一信号通路。近年来，多项研究从不同角度探讨了姜黄素在OSCC中的抗肿瘤作用。Schiavoni等[14]系统总结了姜黄素及其类似物在OSCC中的作用，其可调控NF-κB、STAT3、MAPK及PI3K/AKT等多条信号通路，从而抑制肿瘤进展；Fu等[30]的研究表明，姜黄素及其类似物可通过多靶点机制抑制OSCC细胞增殖并诱导细胞凋亡。然而，现有研究多集中于单一信号通路或特定分子机制，对多通路协同调控及代谢重编程的系统性研究仍较为有限。本研究在此基础上，结合网络药理学与转录组学分析，将PI3K/AKT信号通路与脂质代谢纳入统一研究框架，从多通路协同调控角度进一步探讨了姜黄素的作用机制。

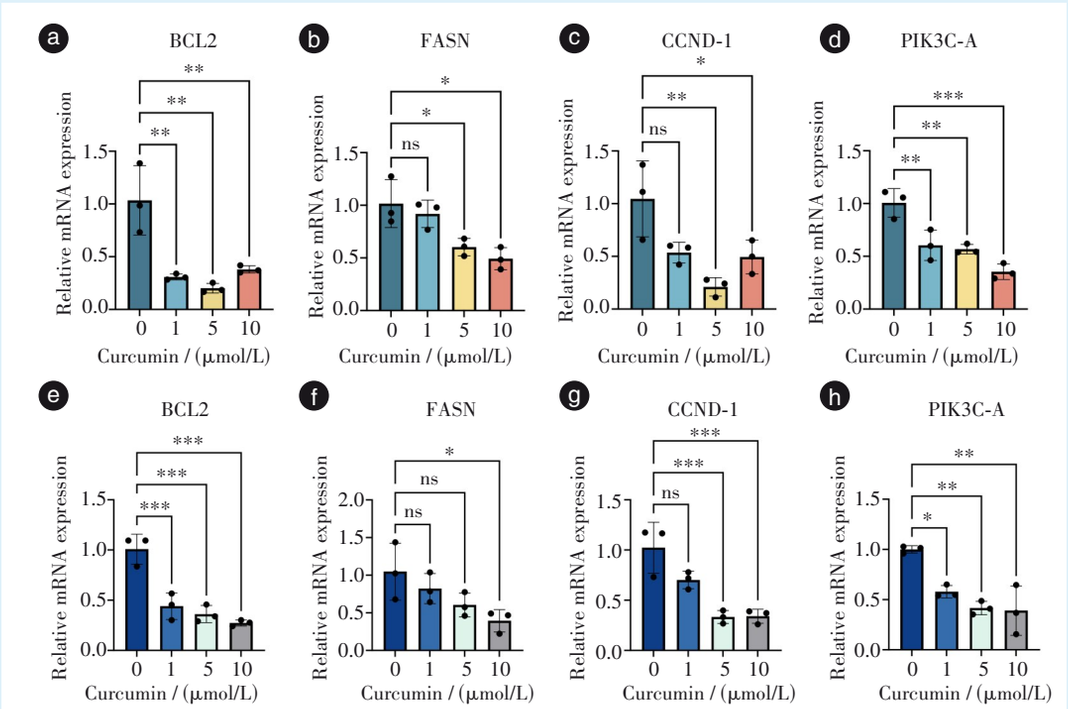
本研究发现姜黄素对CAL-27及SCC-9细胞迁移及克隆形成存在抑制作用，进一步支持其潜在抗肿瘤活性，该结果与既往关于姜黄素抑制肿瘤



a: Principal Component Analysis (PCA) results. The samples in the curcumin treatment groups (1 μmol/L and 10 μmol/L) were significantly separated from the control group in the PC1 and PC2 dimensions, suggesting significant differences in gene expression profiles under different treatment conditions; b: volcano plot of differentially expressed genes. Compared with the control group, a total of 828 differentially expressed genes were identified, including 726 up-regulated genes and 102 down-regulated genes ($|\log_2 FC|>1$, $P<0.05$); c: GO enrichment analysis results. The differentially expressed genes were mainly enriched in biological processes related to lipid metabolism, steroid metabolism, cholesterol biosynthesis, and multicellular development; d: KEGG pathway enrichment analysis results. The differentially expressed genes were mainly involved in the PI3K/AKT signaling pathway and multiple lipid metabolism-related pathways. KEGG: Kyoto Encyclopedia of Genes and Genomes; GO: gene ontology; PI3K: phosphoinositide 3-kinase; AKT: protein kinase B

Figure 4　Global transcriptomic profiling of CAL-27 cells following curcumin treatment

图4　姜黄素处理后CAL-27细胞转录组表达谱分析



a-d: relative mRNA expression levels of BCL2 (a), FASN (b), CCND1 (c), and PIK3CA (d) in CAL-27 cells after treatment with different concentrations of curcumin (n=3 biologically independent samples), statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test, *P < 0.05,**P < 0.01,*** P < 0.001). The expression levels of FASN and PIK3CA decreased significantly with the increase in curcumin concentration, while the changes in BCL2 and CCND1 were more obvious at medium concentrations; e-h: relative mRNA expression levels of BCL2 (e), FASN (f), CCND1 (g), and PIK3CA (h) in SCC-9 cells after treatment with different concentrations of curcumin (n=3 biologically independent samples), statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test, ns: P > 0.05, *P < 0.05, **P < 0.01, ***P < 0.001). The expression levels of BCL2, FASN, and PIK3CA decreased significantly with the increase in curcumin concentration, while the changes in CCND1 were more obvious at medium concentrations. BCL2: B-cell lymphoma 2 gene; FASN: fatty acid synthase; CCND1: cyclin D1; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

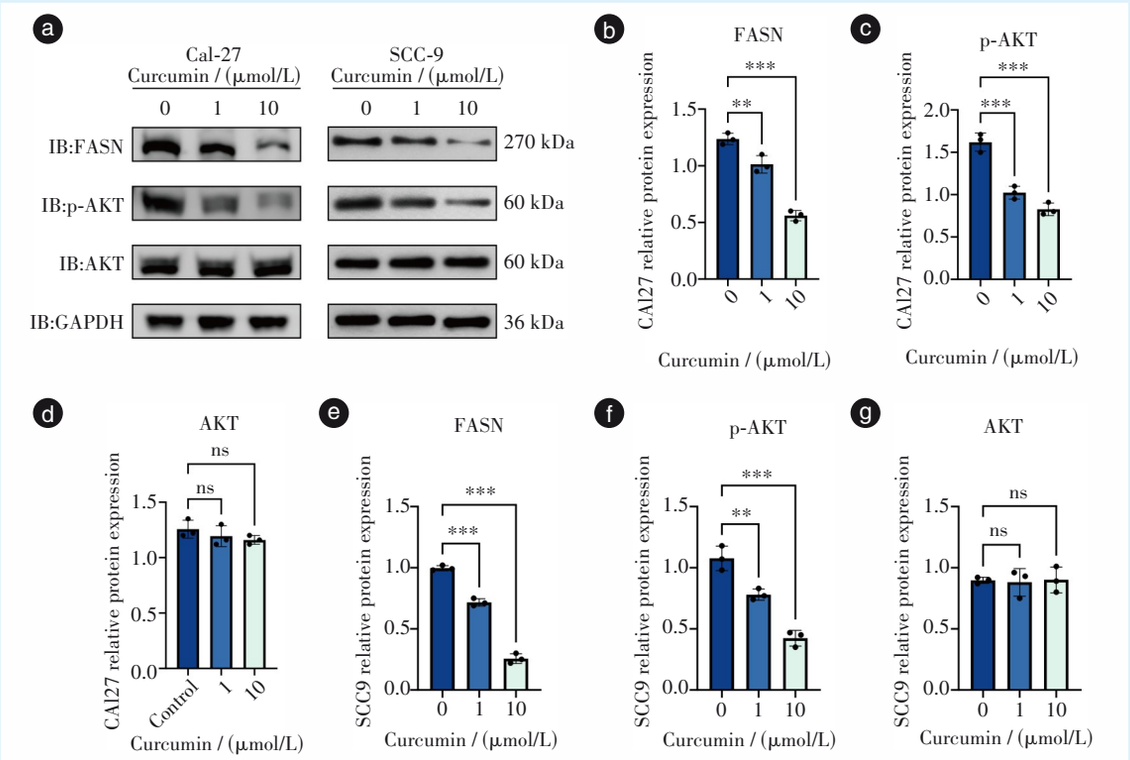
Figure 5　Changes in the expression of key genes in CAL-27 cells and SCC9 cells after curcumin treatment

图5　姜黄素处理后CAL-27细胞及SCC9细胞关键基因表达变化

细胞增殖及侵袭能力的报道一致[31-32]。转录组层面的变化进一步支持其在脂质代谢及PI3K/AKT相关通路中的调控作用。需要指出的是，本研究中不同指标对姜黄素的反应强度并不完全同步，部分基因在中等浓度时即出现较明显变化，而表型抑制效应在较高浓度下更为突出。该现象提示姜黄素对OSCC细胞的调控可能并非简单线性增强，而更可能体现出多靶点干预背景下分子事件早期发生、表型改变逐步累积的特点。其生物学意义在于，较低或中等浓度姜黄素可能已能触发部分关键信号及代谢过程重塑，而更高浓度则进一步放大对细胞迁移和克隆形成等恶性表型的抑制作用。

关键基因表达变化进一步从分子层面支持上述通路调控的可能性。FASN作为脂肪酸合成关键酶，在多种头颈部肿瘤中呈高表达，与肿瘤进展相关[30]。本研究结果显示，PIK3CA、BCL2及FASN等基因表达下调；Western blot结果进一步证实p-AKT及FASN蛋白表达降低；体内实验及免疫组化结果显示，姜黄素处理后肿瘤组织中Ki-67、p-AKT及BCL2表达均降低。上述结果从转录、蛋白及体内模型多层面支持姜黄素通过调控PI3K/AKT信号及脂质代谢相关过程参与OSCC的发生发展。

从临床角度看，OSCC目前仍以手术为核心治疗手段，并根据病理危险因素联合放疗、同步放化疗及近年来逐渐发展的免疫治疗，但总体生存获益仍有限，且传统治疗常伴随功能损伤、毒性反应及生活质量下降等问题[1, 33-34]。研究显示，围手术期免疫治疗已开始改善局部晚期头颈鳞癌的事件无进展生存，提示OSCC治疗正逐步向综合化和个



a: representative Western blot result from three independent repeats, the left panel shows the western blot protein banding patterns of AKT, p-AKT, FASN, and the internal reference in CAL-27 cells; the right panel shows the western blot protein banding patterns of AKT, p-AKT, FASN, and the internal reference in SCC-9 cells. b-g: quantitative results. n=3 biologically independent samples, statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test, ns: P>0.05, **P<0.01, ***P<0.001. In both groups of cells, for total AKT protein abundance, there were no significant differences between each treatment group and the control group, while the protein abundances of p-AKT and FASN gradually decreased with the increase of curcumin concentration. FASN: fatty acid synthase; AKT: protein kinase B.

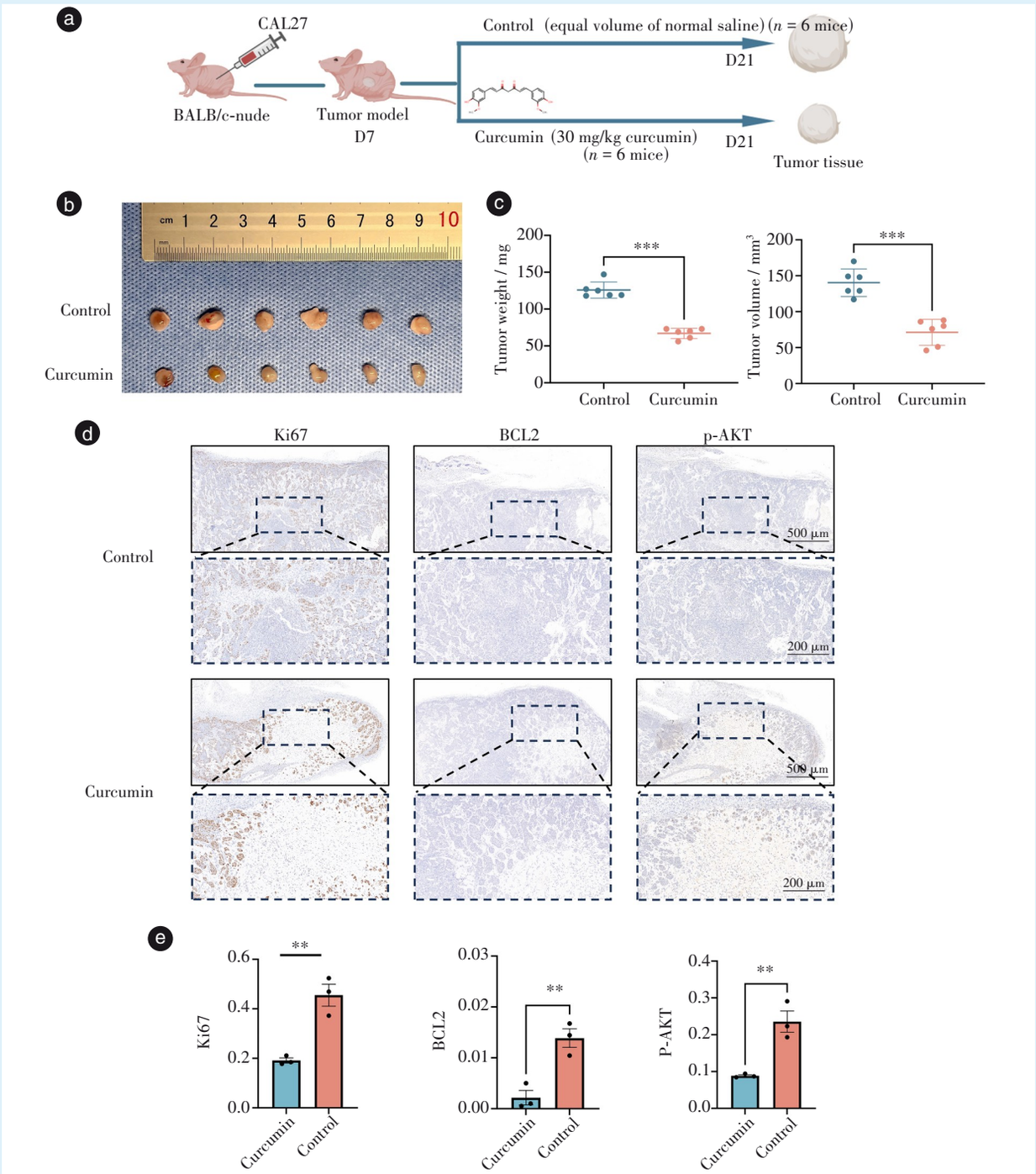
Figure 6　Effects of curcumin on the PI3K/AKT pathway and related protein expression in CAL-27 cells and SCC-9 cells

图6　姜黄素对CAL-27细胞及SCC-9细胞PI3K/AKT通路及相关蛋白表达的影响

体化方向发展[35-36]。基于此，姜黄素作为来源广泛、具有多靶点调控特征的天然化合物，具有作为辅助治疗药物的潜在可行性，尤其可能在增强肿瘤细胞对放化疗或免疫治疗敏感性、降低炎症反应及干预代谢重编程等方面发挥协同作用[37-38]。另一方面，其临床转化仍面临若干现实问题，包括口服生物利用度低、水溶性差、体内药代动力学不稳定以及有效体外浓度与体内可达浓度之间仍存在差距[39-40]。因此，姜黄素未来更合理的研究方向可能不是替代现有标准治疗，而是作为辅助干预成分，结合纳米递送系统、结构修饰或联合治疗策略，在提高肿瘤局部有效暴露的同时降低全身不良反应。

需要指出的是，本研究仍存在一定局限性。首先，本研究仅通过裸鼠皮下移植瘤模型初步验证了姜黄素的体内抑瘤效应，未涉及更为复杂的肿瘤微环境及免疫背景，其在免疫健全模型中的作用与机制仍有待深入探索。其次，本研究仅选用CAL-27与SCC-9两种口腔鳞癌细胞系，尚不能完全反映口腔鳞癌的肿瘤异质性，结论仍需在更多细胞模型及临床样本中进一步验证。此外，本研究主要从相关性层面揭示姜黄素可能通过PI3K/AKT通路及脂质代谢发挥作用，未通过基因敲低、过表达或通路回补等功能实验明确关键分子的因果调控关系。后续可采用通路激活剂或基因干预策略，进一步验证PI3K/AKT及脂质代谢关键分子在姜黄素抑制OSCC细胞增殖与迁移中的核心作用，为其机制提供更直接的实验证据。

综上所述，本研究结果表明，姜黄素可通过调控PI3K/AKT信号及脂质代谢相关过程，抑制OSCC细胞迁移及增殖能力。相关作用在转录水平、蛋白水平及体内模型中均得到验证。本研究为进一



a: schematic diagram of the subcutaneous tumor transplantation experiment in nude mice; b: representative images of tumor tissues from the control group and the curcumin treatment group showing that the tumor volume in the curcumin treatment group was significantly reduced; c: quantitative comparison of tumor weight and volume between the control group and the curcumin treatment group, showing that the tumor volume and weight in the curcumin treatment group were both lower than those in the control group; d: representative images of tumor tissue staining in the curcumin intervention group and the control group, showing that the expressions of Ki-67, BCL2, and p-AKT in the curcumin treatment group were all lower than those in the control group; scale bars: upper panel = 500 μm, lower panel = 200 μm. e: quantitative results showing that the expressions of Ki-67, BCL2, and p-AKT after curcumin treatment were lower than those in the control group. c&d: n=6 mice (biologically independent replicate), statistical analysis was performed using unpaired two-tailed Student's t-test, *P < 0.05, **P < 0.01, ***P < 0.001. AKT: protein kinase B; BCL2: B-cell lymphoma 2

Figure 7　Effects of curcumin on the growth of transplanted tumors in nude mice

图7　姜黄素对裸鼠移植瘤生长的影响

步阐明姜黄素在口腔鳞癌中的作用机制及其潜在应用提供了实验依据。

【Author contributions】 Liu JA and Xu B performed the experiments and wrote the article. Zhang L designed the study and reviewed the article. All authors read and approved the final manuscript as submitted.

【Ethics statement】 All animal procedures were carried out in compliance with the ARRIVE guidelines (https://arriveguidelines.org) and adhered to the guidelines for the care and use of laboratory animals issued by the China Animal Research Council. All animal experiments were approved by Youshu Life Technology (Shanghai) Co., Ltd (No.YS-m202512002).

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【Data availability statement】 The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author upon reasonable request.

【Generative AI statement】 The authors declared that generative AI was not used in the creation of this manuscript.

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