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·基础研究·

白色念珠菌促进口腔白斑恶性进展的临床队列与动物模型初步研究

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【摘要】 目的 探究白色念珠菌与口腔白斑病（oral leukoplakia，OLK）发展的相关性，为完善OLK恶性转化的致病机制提供依据。**方法** 利用公共数据库（NCBI BioProject，PRJNA788378；GEO，GSE227919）获得口腔相关微生物组学数据，采用生物信息学方法评估白色念珠菌感染与OLK的相关性。获得单位医学伦理委员会批准，收集OLK临床队列样本构建组织芯片，进行苏木精-伊红（hematoxylin and eosin，H&E）染色和过碘酸-Schiff（periodic acid-Schiff，PAS）染色，分析白色念珠菌检出率与临床病理特征之间的关系。获得单位实验动物伦理委员会批准，建立4-硝基喹啉-1-氧化物（4-nitroquinoline-1-oxide，4NQO）饮水联合白色念珠菌口腔接种的小鼠模型（4NQO+白色念珠菌组），以4NQO饮水并给予PBS处理作为对照组（4NQO+PBS组），比较两组上皮异常增生程度，评估白色念珠菌感染对病变进展的影响（本研究将高级别衍进定义为病变由轻/中度上皮异常增生向重度异常增生/原位癌乃至浸润性鳞状细胞癌发展的过程）。**结果** 生物信息学分析显示，与健康对照组相比，口腔潜在恶性疾患（oral potentially malignant disorders，OPMDs）及OLK组织中白色念珠菌检出率显著升高。临床样本染色结果发现白色念珠菌可在OLK病灶中定植，相对于白色念珠菌阴性患者，阳性患者为更高级别衍进状态。动物实验表明，与4NQO+PBS组相比，4NQO+白色念珠菌组小鼠口腔上皮异常增生程度显著加重，恶性转化率更高，提示白色念珠菌可促进OLK向高级别衍进。**结论** 白色念珠菌在口腔白斑癌变衍进过程中呈升高趋势，可加重OLK上皮异常增生程度，促进其向高级别病变转化，提示白色念珠菌在OLK高级别衍进过程中发挥重要促进作用。

【关键词】 白色念珠菌；口腔微生物；口腔白斑病；口腔潜在恶性疾患；上皮异常增生；口腔鳞状细胞癌；生物信息学分析；临床队列研究；动物模型
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***Candida albicans* promotes malignant progression of oral leukoplakia: a preliminary study based on clinical cohort and animal models**

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【Abstract】 Objective To explore the correlation between *Candida albicans* and the development of oral leukoplakia (OLK), and to provide a basis for improving the pathogenic mechanism of the malignant transformation of OLK. **Methods** Oral microbiome data were obtained from public databases (NCBI BioProject, PRJNA788378; GEO, GSE227919), and bioinformatic methods were employed to evaluate the correlation between *Candida albicans* infection

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and OLK. Approval was obtained from the institutional Medical Ethics Committee. A tissue microarray was constructed using samples collected from an OLK clinical cohort. Hematoxylin and eosin (H&E) staining and periodic acid-Schiff (PAS) staining were performed to analyze the relationship between the *Candida albicans* detection rate and clinicopathological features. Approval was obtained from the institutional Animal Ethics Committee. A mouse model was established by combining 4-nitroquinoline-1-oxide (4NQO) in drinking water with oral inoculation of *Candida albicans* (4NQO + *Candida albicans* group), while mice treated with 4NQO in drinking water and PBS served as the control group (4NQO + PBS group). The degree of epithelial dysplasia was compared between the two groups to assess the impact of *Candida albicans* infection on lesion progression (defined in this study as the progression from mild/moderate epithelial dysplasia to severe dysplasia/carcinoma in situ or invasive squamous cell carcinoma). **Results** Bioinformatic analysis revealed that the detection rate of *Candida albicans* in OPMDs and OLK tissues was significantly higher than that in the healthy control group. Staining results of clinical samples demonstrated that *Candida albicans* colonized OLK lesions; compared with *Candida albicans*-negative patients, positive patients exhibited a state of high-grade progression. Animal experiments indicated that, compared with the 4NQO + PBS group, the degree of oral epithelial dysplasia in the 4NQO + *Candida albicans* group was significantly exacerbated, and the malignant transformation rate was higher, suggesting that *Candida albicans* promotes the high-grade progression of OLK. **Conclusion** *Candida albicans* exhibits a increasing trend during the malignant progression of the OLK. It aggravates the degree of epithelial dysplasia in OLK and promotes its transformation into high-grade lesions, suggesting that *Candida albicans* plays a crucial promoting role in the high-grade progression of OLK.

【Key words】 *Candida albicans*; oral microbiome; oral leukoplakia; oral potentially malignant disorders; epithelial dysplasia; oral squamous cell carcinoma; bioinformatics analysis; clinical cohort study; animal model

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口腔潜在恶性疾患(oral potentially malignant disorders,OPMDs)是一类具有较高癌变风险的口腔黏膜疾病,其共同特征是可在一定条件下发展为口腔鳞状细胞癌(oral squamous cell carcinoma,OSCC)。随着全球OSCC发病率逐年上升,OPMDs的早期识别与干预已成为预防OSCC的重要环节。口腔白斑病(oral leukoplakia,OLK)是最常见的OPMDs类型之一,临床表现为口腔黏膜上不可刮除的白色斑块,常见于舌部、口角、牙龈等部位[1-3]。OLK病因尚不明确,与多种因素相关[4]。近年来,口腔微生态失衡被认为是其发生与发展的重要因素之一[5-6],越来越多临床研究表明,白色念珠菌在OLK患者中可被检出[7],提示其与OLK的发生与恶变过程相关,但其是否为明确的促进因素尚待进一步阐明。

白色念珠菌(*Candida albicans*)是一种常见的条件致病菌,通常栖息在颊黏膜、舌背、咽喉等部位[8-9]。在免疫功能正常或菌群平衡的状态下,通常作为共生菌存在[10]。但在免疫抑制、使用抗菌药物、黏膜屏障受损等可能导致口腔微生态失衡的条件下[11],白色念珠菌会转变为致病形态,导致多种疾病的发生[12-14]。白色念珠菌转变为致病形态的重要特征是由酵母型转变为菌丝型,菌丝型白色念珠菌常与组织侵袭和致病能力增强密切相关[15-16]。

尽管现有研究表明白色念珠菌可能参与OLK的病理进程,但临床证据多基于小样本研究,且缺乏体内实验的验证。因此,尚无法确认其在OLK高级别衍进中是发挥促进作用,或仅为伴随现象;本研究将高级别衍进定义为病变由轻/中度上皮异常增生向重度异常增生/原位癌乃至浸润性鳞状细胞癌发展的过程[17-18]。此外,现有的动物模型大多采用单一的诱导方式,难以模拟体内复杂的感染环境真实再现其病理作用[19]。为此,本研究综合利用生物信息学分析、临床样本组织学检测及动物模型实验,探讨白色念珠菌在OLK高级别衍进中的作用机制,旨在为临床预防与靶向干预提供科学依据。

1　材料和方法

1.1　主要试剂和仪器

苏木素染色液（C0107，碧云天，中国）；伊红染色液（C0109，碧云天，中国）；过碘酸-Schiff（periodic acid-Schiff，PAS）染色试剂盒（G1281，索莱宝，中国）；4%多聚甲醛固定液（BL539A，Biosharp，中国）；C57BL/6背景的野生型（6~8周龄）小鼠（合格证编号：B202508040861）；异氟烷（R510-22-10，瑞沃德，中国）；白色念珠菌（sc5314，四川大学华西口腔医院馈赠）；4-硝基喹啉-1-氧化物（4-nitroquinoline-1-oxide，4NQO）（N8141，sigma，美国）；PBS缓冲液（G4202，塞维尔生物，中国）；石蜡切片机（RM2235，Leica，美国）；高分辨率切片扫描仪（APERIO VERSA 8，Leica，美国）；恒温培养箱（GHP-9270，上海一恒，中国）；恒温摇床（ZHWY-1038，ZHCHENG，中国）。

1.2　研究方法

1.2.1　白色念珠菌与OLK相关性的生物信息学分析　本研究首先基于NCBI BioProject数据库公开获取的微生物组学数据（PRJNA788378，https：//www.ncbi.nlm.nih.gov/bioproject/ term=PRJNA788378），对不同组别的颊黏膜、牙菌斑和唾液样本进行分析。所用数据包括健康对照组（HC，n=30）、OPMDs组（n=32）和OSCC组（n=29）3组受试者的颊黏膜拭子、牙菌斑拭子和唾液样本的微生物组数据[20]。首先提取数据中念珠菌属相关分类单元的比较结果，计算各组间的丰度差异值。计算公式为：效应量Δ = 实验组（OPMDs组或OSCC组）平均丰度−对照组（HC组或前一阶段疾病组）平均丰度，以量化疾病进展中的微生物变化，并绘制森林图呈现结果（Y轴为样本类型与疾病分组组合，X轴为Δ值，垂直零点线作为无差异基准）。为在以OLK为代表的OPMDs亚型中进一步验证上述丰度变化趋势，本研究从GEO数据库中纳入了另一个注释明确的口腔微生物组学数据（GSE227919，https：//www.ncbi.nlm.nih.gov/bioproject/ term=GSE227919），该队列同样包含HC组、OLK组和OSCC组3类样本，同样提取其中白色念珠菌相关丰度数据，按上述方法提取并计算白色念珠菌在HC组、OLK组与OSCC组之间的丰度差异值，并绘制森林图进行展示。

1.2.2　OLK临床队列与组织学检测　本研究已通过四川大学华西口腔医院医学伦理委员会的审批（批件号：WCHSIRB-D-2023-052-R1）。本研究共收集四川大学华西口腔医院口腔黏膜病科确诊的41例OLK患者的石蜡包埋组织标本。同时，纳入了16例取自全身健康及口腔健康志愿者的正常口腔黏膜组织作为健康对照组（HC组），所有标本均由两名病理专家复核苏木精-伊红（Hematoxylin and eosin，H&E）染色切片。在复核确认的代表性病灶区域切取组织样本，交由上海芯超生物科技有限公司制备组织芯片。为检测组织中白色念珠菌的存在，对组织芯片切片进行了过碘酸-Schiff（periodic acid-Schiff，PAS）染色。具体操作如下：经二甲苯脱蜡后，使用自来水冲洗2~3 min，再用蒸馏水浸洗两次；将切片室温置于氧化剂中8 min，使用自来水冲洗2~3 min，再用蒸馏水浸洗两次；放入Schiff染色液，置于室温阴暗处，浸洗15 min；自来水冲洗10 min；苏木素染色液30 s；酸性分化液4 s；流水反蓝10 min；中性树脂封片并晾干。在此基础上，从白色念珠菌阳性组和阴性组中各随机抽取8例样本，依据2017年WHO口腔黏膜病变诊断标准[21]，进行上皮异常增生程度半定量评分：无异常增生为0分，轻度为1分，中度为2分，中度至重度为3分，重度异常增生/原位癌为4分，浸润性癌为5分。

1.2.3　动物模型构建与评估　本研究经四川大学实验动物伦理委员会审查批准（审批号：WCHSIRB-D-2024-590）。实验在四川大学华西口腔医学院实验动物中心屏障环境SPF级别动物房完成，动物尸体按照动物研究伦理准则处理。选用6~8周龄雌性SPF级小鼠，于标准SPF环境［温度（24±2）℃，12 h光/暗周期］中自由摄食饮水。动物随机分为两组：4NQO+PBS组（n=10）与4NQO+白色念珠菌组（n=10）。模型构建方法如下：所有小鼠均通过饮水持续给予4NQO（浓度为50 μg/mL）16周[22-24]。自第17周起，4NQO+白色念珠菌组小鼠每隔1 d使用沾有白色念珠菌（浓度为10^7 CFU/mL）的刷子对小鼠舌部刷伤，持续至第22周，以建立局部感染[25]；4NQO+PBS组小鼠每隔1 d使用PBS浸润的刷子对小鼠舌部刷伤，同样持续至第22周。实验进行至第23周时，所有小鼠均采用颈椎脱位法处死，确认死亡后迅速切取舌组织样本进行后续病理学评估。组织处理与染色：舌组织经4%多聚甲醛固定24 h，常规脱水及石蜡包埋，切取4 μm连续切片，于65 ℃下烤片2 h。H&E染色流程：切片经二甲苯脱蜡与酒精梯度脱水（梯度为100%、95%、90%、85%、80%、75%）后，使用4%多聚甲醛

固定切片10 min，苏木素染色液30 s，流水返蓝10 min，伊红复染30 s，随后使用中性树胶封片并晾干[26]。对于动物模型的上皮异常增生的评估，从各组中随机选取6只小鼠，随后采用了与临床队列一致的病理分级标准进行评分。

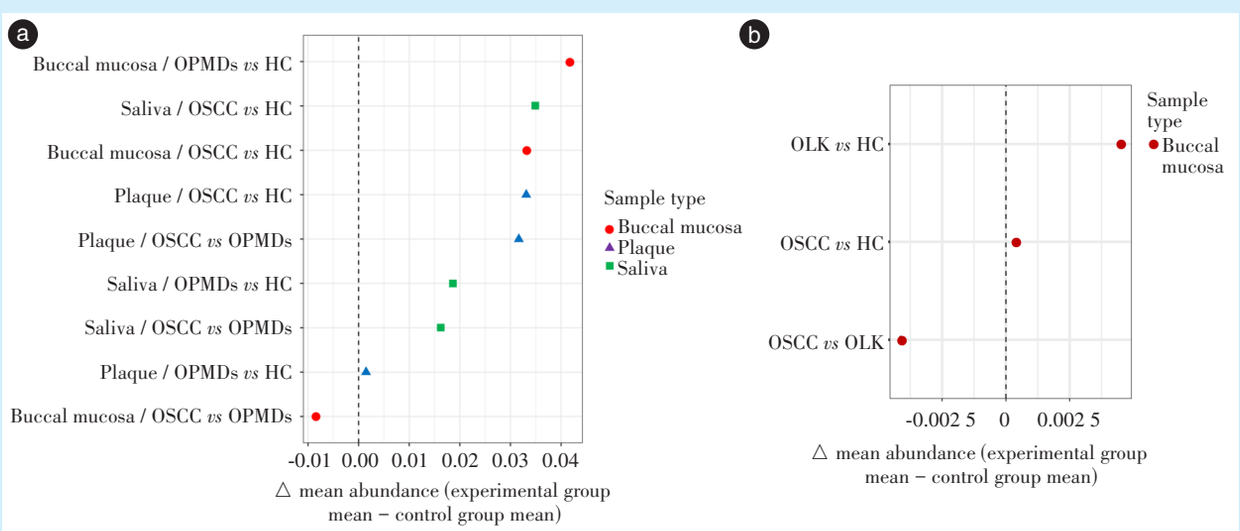
1.3　统计学分析

采用GraphPad Prism 9.0软件进行统计学分析。采用Shapiro-Wilk对计量资料进行正态性检验。符合正态分布的数据以均数±标准差表示，组间比较采用独立样本t检验；不符合正态分布的数据采用非参数Mann-Whitney U检验。计数资料用n(%)表述，组间比较采用卡方检验。$P < 0.05$为差异具有统计学意义。

2　结　果

2.1　白色念珠菌丰度随OLK进展逐级升高

通过微生物组学分析(PRJNA788378队列)，白色念珠菌丰度差值作为效应量绘制了分组差异森林图。结果显示，在颊黏膜、牙菌斑和唾液三类样本中，与HC组相比，OPMDs组的效应量均位于零点右侧，提示OPMDs组的白色念珠菌丰度更高。进一步将OSCC组与HC组对比时，在唾液和牙菌斑样本中，散点整体较前者进一步右移，表明随着病程由健康向OPMDs再向OSCC推进，白色念珠菌丰度呈逐级升高趋势。而在颊黏膜样本中，虽然OSCC组丰度亦高于HC组，但富集程度在OPMDs组最为显著，推测可能是由于OSCC患者颊黏膜表面常出现溃疡，为厌氧菌的生长提供条件，这些细菌可能会在生态位上与白色念珠菌产生竞争，导致其丰度略微下降，但仍远高于HC组(图1a)。在此基础上，进一步分析了GSE227919队列(包含HC、OLK与OSCC组)，结果同样证实了白色念珠菌在OLK组中的丰度显著升高，与整合队列中颊黏膜样本的总体趋势相符合(图1b)。



Publicly available microbiome data were analyzed to calculate the effect size of *Candida albicans* abundance across healthy control (HC, n=30), oral potentially malignant disorders (OPMDs, n=32), and oral squamous cell carcinoma (OSCC, n=29) samples. The results were visualized across three sample types: buccal mucosa, dental plaque, and saliva. The effect size (Δ) was calculated using the following formula: Δ= mean abundance of experimental group(OPMDs or OSCC) − mean abundance of healthy control group (HC or the preceding disease stage). Meanwhile, a forest plot comparing *Candida albicans* abundance among HC, OLK, and OSCC samples was further generated to verify the consistency of this abundance trend within OPMDs subtypes, with OLK serving as a representative entity. OLK: oral leukoplakia; Note: the x-axis represents the difference in abundance. Scatter points located to the right of the vertical zero line indicate a positive effect, suggesting that the abundance of *Candida albicans* is significantly increased in the comparison group; conversely, points located to the left indicate decreased abundance

Figure 1　Forest plot of *Candida albicans* abundance in HC, OPMDs (OLK), and OSCC groups

图1　HC、OPMDs(OLK)、OSCC组白色念珠菌丰度差异的森林图

2.2　OLK临床队列组织中白色念珠菌检出率显著升高

为明确白色念珠菌检出例数在OLK病理进程中的作用，笔者构建了41例OLK患者的临床队列(表1)。PAS染色结果显示，OLK组织中的白色念珠菌检出率高于HC组(图2)。值得注意的是，部

分OLK组织中观察到菌丝样结构，提示其已发生侵袭性生长。白色念珠菌阳性患者的组织上皮异常增生程度更为明显，显示出向高级别衍进。上述结果提示，白色念珠菌在OLK中并非单纯的机会性定植，而是可能参与了其恶性进展过程。

表1　口腔白斑病患者的临床病理特征及白色念珠菌的病理检出率

Table 1　Clinical and pathological characteristics of patients with oral leukoplakia and pathological detection rate of *Candida albicans*

n=41

Items	Groups	Cases detected for *Candida albicans*(%)	χ^2	*P*
Gender	Male (*n*=28)	6(21.4)	0.420	0.517
	Female (*n*=13)	4(30.8)		
Age/yeras	≤40 (*n*=7)	1(14.3)	0.563	0.755
	41-60 (*n*=24)	6(25.0)		
	>60 (*n*=10)	3(30.0)		
Lesion site	Buccal mucosa (*n*=13)	3(23.1)	1.976	0.853
	Palate (*n*=6)	2(33.3)		
	Dorsal tongue (*n*=9)	1(11.1)		
	Ventral tongue (*n*=8)	2(25.0)		
	Gingiva (*n*=2)	1(50.0)		
	Lip (*n*=3)	1(33.3)		
Histopathological diagnosis	Mild epithelial dysplasia (*n*=11)	2(18.2)	4.123	0.532
	Mild-moderate epithelial dysplasia (*n*=10)	1(10.0)		
	Moderate-severe epithelial dysplasia (*n*=7)	3(42.9)		
	Severe epithelial dysplasia/carcinoma in situ (*n*=5)	1(20.0)		
	Squamous cell carcinoma (*n*=4)	2(50.0)		
	Others (erythroleukoplakia, verrucous leukoplakia, *n*=4)	1(25.0)		

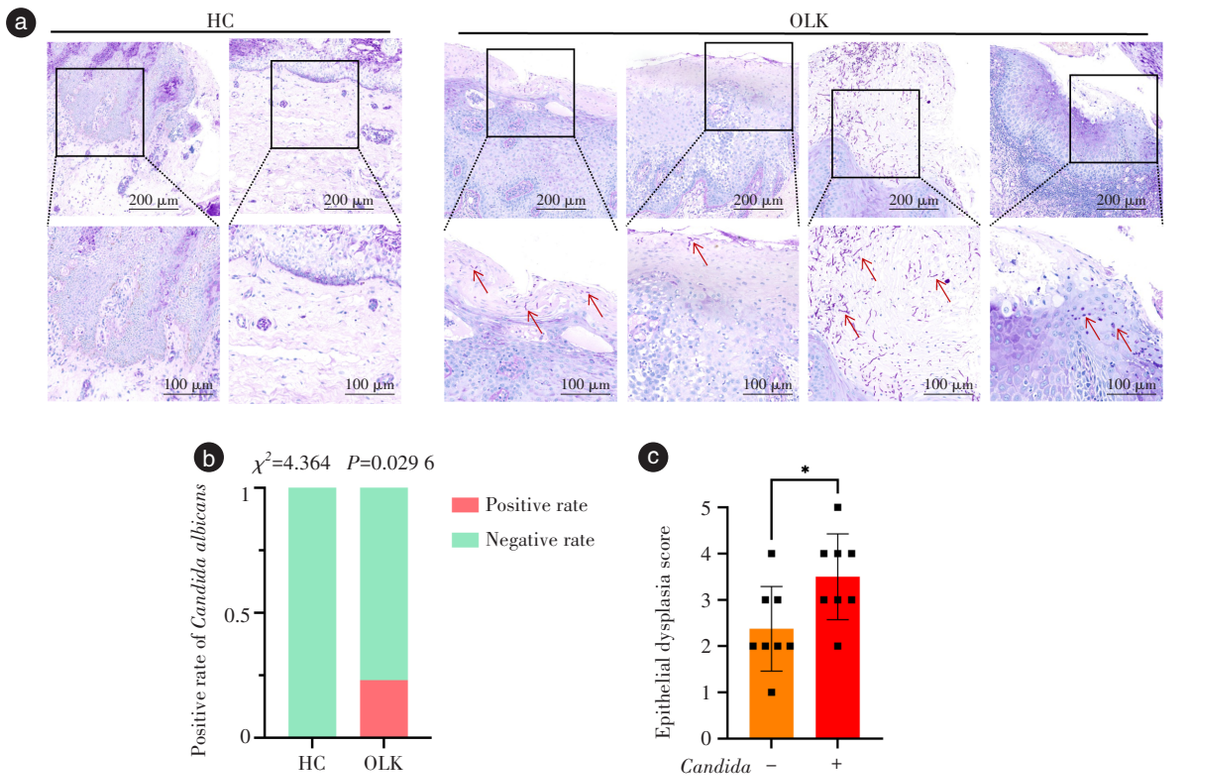
2.3　白色念珠菌促进4NQO诱导的OLK的高级别衍进

为验证白色念珠菌在OLK发生发展中的作用，本研究采用4NQO饮水法成功构建小鼠OLK模型，并在此基础上通过机械刷伤联合局部接种建立白色念珠菌感染模型（图3a）。大体观察显示，4NQO+白色念珠菌组小鼠舌部白色斑块面积增大，并伴有明显的舌体肿胀，其病变程度较4NQO+PBS组更为突出（图3b）。H&E染色结果显示，与4NQO+PBS组相比，4NQO+白色念珠菌组小鼠舌黏膜病变加重，表现为上皮不规则增厚、棘层细胞排列紊乱并伴随不规则突起，局部可见异常角化（图3c）。固有层内炎症细胞大量浸润，其范围与程度均显著高于4NQO+PBS组。对两组切片恶性病变程度进行组织学评分，结果显示4NQO+白色念珠菌组的恶性转化率明显更高（图3d）。综上所述，这些结果表明，白色念珠菌感染能够在4NQO诱导的损伤基础上，进一步加剧局部组织的病理损伤与炎症反应，促进上皮异常增生，并推动OLK向恶性转化。

3　讨　论

OLK是临床上常见的OPMDs，具有明确的恶性转化风险，能够在炎症与微环境刺激下逐步演变为OSCC[27-28]，但其具体衍进机制尚未阐明。近年来研究表明，OLK患者的口腔菌群结构与健康个体相比存在显著差异，表现为微生物群落失衡及致病菌的富集，这种失衡常伴随上皮的不典型增生与炎症[29-31]。白色念珠菌是临床上最常见的真菌病原体之一，在正常免疫及菌群平衡下以酵母型存在，而在黏膜屏障受损时可转变为致病的菌丝型[32]。尽管已有研究在OLK中检测到白色念珠菌，但由于临床样本量有限、动物模型构建方式单一等因素，尚且难以区分白色念珠菌在病变发展中是伴随现象还是驱动因素[6, 33-35]。因此，系统探讨白色念珠菌在OLK高级别衍进中的功能属性，对理解癌前病变的微生态学机制具有重要的意义[36-37]。

本研究通过微生物组学分析发现，白色念珠菌在OLK人群中丰度显著升高，且总体趋势随着病程由健康、OLK至OSCC逐级递增，该发现与既



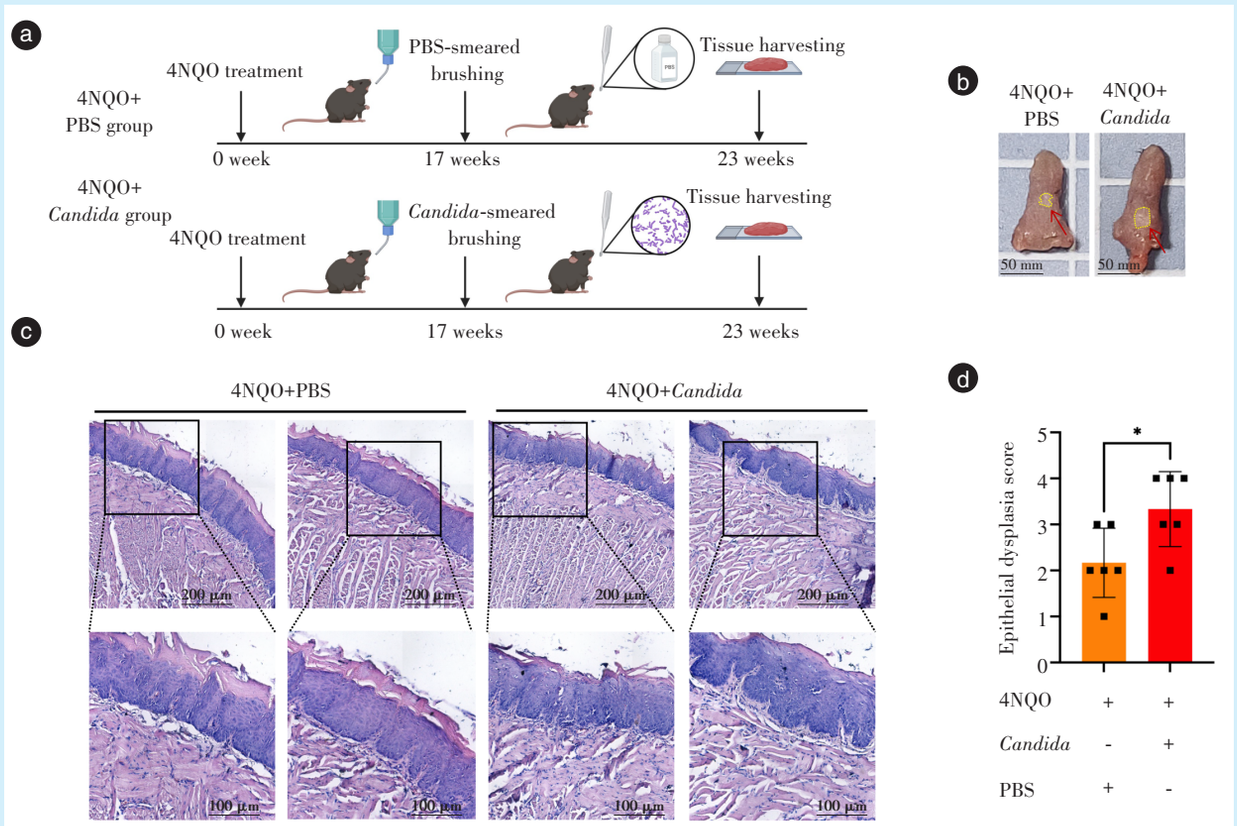
a: representative periodic acid-Schiff (PAS)-stained images of clinical tissues from healthy control (HC) and oral leukoplakia (OLK) patients. Periodic acid-Schiff-positive *Candida albicans* appear magenta(indicated by red arrows), with some cases showing hyphal invasive growth. Enlarged insets highlight fungal colonization at the epithelial surface and within the lamina propria. b: statistical comparison of *Candida albicans* detection rates, showing a significantly higher positive rate in the OLK group (n=41) than in the HC group (n=16). c: quantitative analysis of epithelial dysplasia scores showed that the *Candida*-positive group had significantly higher dysplasia scores than the *Candida*-negative group (P<0.05, n=8)

Figure 2　PAS staining analysis of tissues from the oral leukoplakia clinical cohort

图2　口腔白斑病临床队列组织的PAS染色分析

往研究认为白色念珠菌主导的菌群失调与OSCC发生密切相关的观点相符[38-39]。进一步的临床队列组织学分析显示，OLK患者病灶中白色念珠菌的检出率显著高于HC组，部分样本中可以观察到典型的菌丝结构，表明其已经发生侵袭性生长，该发现与Wu等[40]的观点一致。此外，白色念珠菌阳性的OLK组织常伴随更严重的上皮异常增生和炎症浸润，支持了真菌感染可诱导持续性免疫激活并促进上皮增生的观点[41]。与既往单一层面的研究相比，本研究的特点整合了微生物组学、临床队列及动物模型的三重证据，系统阐述了白色念珠菌在从健康状态到OLK乃至OSCC的疾病谱系中的潜在作用。在动物实验中，4NQO诱导的小鼠OLK模型联合白色念珠菌感染，可显著增加舌黏膜的炎症反应，提示白色念珠菌在4NQO诱导的病变过程中具有协同促进作用。

结合近5年发表的高证据文献，推测白色念珠菌促进OLK高级别衍进的潜在机制可能涉及多维度的分子调控网络。首先，最新研究聚焦于由细胞延长程度蛋白1（extent of cell elongation 1，ECE1）基因编码的细胞溶素，这种肽毒素由白色念珠菌特异性分泌，不仅能破坏上皮细胞膜的完整性，更能激活上皮细胞表面的表皮生长因子受体（epidermal growth factor receptor，EGFR）及下游的丝裂原活化蛋白激酶/细胞外信号调节激酶（mitogen-activated protein kinase/extracellular signal-regulated kinase，MAPK/ERK）和p38信号通路，进而诱导上皮细胞释放大量的白细胞介素-1β（interleukin-1β，IL-1β）、白细胞介素-6（nterleukin-6，IL-6）等关键促炎因子[42]。其次，长期的白色念珠菌定植及其诱导的细胞因子级联反应可能会募集肿瘤相关巨噬细胞，从而构建特异性的促肿瘤炎症



a: schematic diagram of the experimental design. Mice were treated with 4-nitroquinoline-1-oxide (4NQO) in drinking water for 16 weeks, followed by normal water feeding and oral brushing with *Candida albicans* suspension. Tongue tissues were collected at week 23 for histological analysis. b: gross appearance of tongue tissues. The 4NQO+*Candida* group exhibited noticeably larger whitish plaque-like lesions compared to the PBS+*Candida* group, suggesting that *Candida* infection accelerates OLK progression (red arrows). c: representative H&E-stained images of tongue mucosa from the 4NQO+PBS(n=10)and 4NQO+*Candida* groups(n=10). The 4NQO+PBS group received 4NQO-containing drinking water to induce OLK and was administered PBS oral swabbing as a control, whereas the 4NQO+*Candida* group received *Candida albicans* suspension via oral swabbing on the basis of 4NQO-induced OLK. The 4NQO+*Candida* group showed irregular epithelial thickening and focal keratosis compared to the PBS group. d: quantitative analysis of epithelial dysplasia scores, assessed in 6 randomly selected mice per group. The 4NQO+*Candida* group showed significantly higher dysplasia scores than the 4NQO+PBS group (P<0.05, n=6)

Figure 3　Construction of a 4NQO combined *Candida albicans* infection mouse model of oral leukoplakia

图3　4NQO联合白色念珠菌感染诱导小鼠口腔白斑病的模型构建

微环境[25]。这种持续且失调的炎症微环境可能通过诱导DNA损伤或促进上皮-间充质转化，最终协同4NQO加速OLK向浸润性癌的高级别衍进[43-44]。

本研究仍存在一定局限性，虽然上述可能的机制分析提供了理论框架，但尚未在细胞及分子水平对相关关键靶点进行功能验证。未来可在现有临床与动物模型基础上，结合体外共培养实验及转录组学、蛋白质组学和空间转录组学等多组学技术，重点分析白色念珠菌感染相关炎症因子和关键信号通路的变化，更全面地揭示其在OLK高级别衍进中的确切分子机制。

综上所述，本研究通过临床队列和动物模型的分析数据直观展示了白色念珠菌感染促进OLK高级别衍进之间的关联，为从口腔微生物视角理解癌前病变的发生发展提供了新的依据。相关数据不仅巩固了真菌参与OLK病理进程的理论基础，也为未来基于菌群干预的早期防控策略提供了新的思路。

【Author contributions】 Cheng FB performed the experiments, and wrote the article. Zhang SY performed the experiments, and revised the article. Wang Y, Li J conceptualized the study and revised the article. All authors read and approved the final manuscript as submitted.

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