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· 综述 ·

牙龈卟啉单胞菌与白色念珠菌交互作用在口腔疾病中的研究进展

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【摘要】 人类口腔微生物群中包含真菌、细菌、古细菌和病毒等700多种微生物,其中真菌和细菌之间的交互作用及其对宿主免疫系统的影响是目前口腔疾病研究领域的热点。牙龈卟啉单胞菌(*Porphyromonas gingivalis*, *P.g*)是慢性牙周炎的主要致病菌,白色念珠菌(*Candida albicans*, *C.a*)是一种常见的机会致病菌,*P.g*和*C.a*与多种口腔疾病相关。文献回顾表明,*P.g*和*C.a*协同增加生物膜量,二者相互黏附促进混合生物膜形成,同时*C.a*可利用致密菌丝以及代谢活动消耗氧气,为*P.g*提供低氧微环境,提升了*P.g*的活力和毒力;*C.a*和*P.g*还能够通过血红素竞争机制增强毒力并利用胞外多糖维护*P.g*的正常形态;此外,*P.g*和*C.a*还能够协同入侵宿主并进行免疫逃逸,导致宿主的慢性感染状态。基于*P.g*和*C.a*的密切交互作用,已有不少相关防治策略的研究,如各种复合材料以及天然植物的开发,然而此类药物多局限于表型且针对性较差,尚且缺乏特异性药物及其机制研究。本综述旨在回顾*P.g*和*C.a*交互作用在口腔疾病中的最新进展,强调研发针对*P.g*和*C.a*共同感染的治疗策略的重要性,为相关疾病的防治提供新思路。

【关键词】 牙龈卟啉单胞菌; 白色念珠菌; 细菌; 真菌; 交互作用; 牙周炎; 种植体周围炎; 口腔黏膜炎; 免疫应答; 免疫逃逸

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Research progress on the microbial interaction between *Porphyromonas gingivalis* and *Candida albicans* in oral diseases WANG Yuwei, ZOU Ling. State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases & Department of Cariology and Endodontics, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China

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【Abstract】 The human oral microbiota includes over 700 microorganisms such as fungi, bacteria, archaeobacteria, and viruses. The interaction between fungi and bacteria, as well as their impact on the host immune system, is currently a popular topic in the field of oral disease research. *Porphyromonas gingivalis* (*P.g*) is the key pathogenic bacterium of chronic periodontitis, while *Candida albicans* (*C.a*) is a common opportunistic pathogen. *P.g* and *C.a* are associated with various oral diseases. A review of the literature suggests that *P.g* and *C.a* synergistically increase the amount of biofilm. They adhere to each other, promoting the formation of mixed biofilms. At the same time, *C.a* can utilize its dense hyphae and metabolic activities to consume oxygen, providing a low-oxygen microenvironment for *P.g*, thereby enhancing its vitality and virulence. *C.a* and *P.g* can also enhance their virulence through heme competition mechanisms and maintain the normal morphology of *P.g* by extracellular polysaccharides. In addition, *P.g* and *C.a* can synergistically invade the host and escape from the host's immune system, ultimately leading to a state of chronic infection in the host. Based

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on the interactions of *P.g* and *C.a*, numerous studies on prevention and treatment strategies have been conducted, including those of various composite materials and natural plants. However, such drugs are mostly limited to phenotypes and suffer from poor selectivity, thus resulting in a lack of specific drugs and research on their mechanisms. This review aims to explore the latest advances in the bacterial-fungal interactions, highlighting the roles of *P.g* and *C.a* in oral diseases, emphasizing the importance of developing treatment strategies for co-infection of *P.g* and *C.a*, and providing new ideas for the prevention and treatment of related diseases.

【Key words】 *Porphyromonas gingivalis*; *Candida albicans*; bacterial; fungal; interaction; periodontitis; peri-implantitis; oral mucositis; immune response; immune escape

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真菌与细菌的交互作用广泛存在于各种生态系统,已被证明与烧伤伤口感染、义齿口炎、肺纤维化以及侵入性医疗器械感染等疾病有关^[1]。二者密切的交互作用涉及物理关联,如混合生物膜的形成,以及基因表达的调控和对宿主环境的影响,是许多生态系统功能和稳态变化的驱动因素。因此针对真菌与细菌交互作用的研究对人类健康和疾病治疗新策略的探索至关重要。

人类口腔微生物群包含真菌、细菌、古细菌和病毒等700多种微生物,其中真菌和细菌可通过形成生物膜定植于宿主。牙龈卟啉单胞菌(*Porphyromonas gingivalis*, *P.g*)不仅是慢性牙周炎的主要致病细菌,还可以通过影响宿主免疫促进自身病理状态的发展^[2-3]。白色念珠菌(*Candida albicans*, *C.a*)是一种常见于人体黏膜表面的机会致病菌,可引起反复的黏膜感染或危及生命的弥散性感染^[4]。二者与多种口腔疾病相关,在慢性牙周炎患者龈下生物膜以及牙周袋中能够共检出*C.a*和*P.g*^[5]。相比于健康人群,*C.a*在牙周炎患者中的检出率明显更高,且在严重牙周炎中的检出率高于一般程度牙周炎(47% vs. 17%)^[6-7]。另有研究表明*C.a*和*P.g*可能在牙周炎的活跃期起作用,二者共检出率与牙周袋≥6 mm伴探诊出血显著相关^[8];种植体周围炎也能够同时检出*C.a*和*P.g*,且体外种植体模型证实*C.a*促进了*P.g*生物膜的生长^[9]。本文就*P.g*和*C.a*的交互作用作一综述,以期对相关口腔疾病的防治提供新思路 and 策略。

1 *P.g*和*C.a*协同作用增加口腔生物膜量及其机制

1.1 *P.g*和*C.a*相互黏附促进口腔生物膜形成

生物膜是由附着于生物或非生物表面的微生物及其分泌的基质共同形成的聚集物,可增强微

生物之间的信息交流,为微生物提供保护并降低对抗生素的敏感性^[10]。微生物互相黏附是生物膜形成的首要条件^[11]。研究表明*P.g*和*C.a*能够利用其表面相关分子或酶的作用促进黏附,进而促进混合生物膜的形成、成熟。

凝集素样序列(agglutinin-like sequence, Als)是在*C.a*菌丝细胞壁上特异性表达的蛋白家族^[12],*C.a*可通过Als3与*P.g*的内侵袭素家族蛋白(invasion of listeria junction, InlJ)紧密结合。Sztukowska等^[13]发现Als3表达缺失的*C.a*与*P.g*的结合减弱,缺失InlJ亦可消除*P.g*对*C.a*的黏附。另有研究发现虽然Als1的缺失不影响*P.g*的黏附,但相比于只缺失Als3, Als1和Als3同时缺失时*P.g*对菌丝的黏附量更低,因此Als1可能部分接管了Als3的功能^[14]。Als3还可与*P.g*的牙龈素结合。牙龈素包括精氨酸特异性牙龈素(arginine-specific gingipains A/arginine-specific gingipains B, RgpA/RgpB)以及赖氨酸特异性牙龈素(lysine-specific gingipain, Kgp),对*P.g*的生存以及毒力至关重要^[15],能在多物种生物膜中起桥接作用,比如RgpA能够和*C.a*的Als3结合,有利于*C.a*和*P.g*的黏附^[16]。

*C.a*的一种细胞壁甘露糖蛋白(65 kDa manno-protein, MP65)与*P.g*接触时表达亦有上升^[16]。MP65结构中的RGD序列直接负责该蛋白的黏附特性,在与*P.g*的接触过程中MP65能够以与Als3相似的亲和力与RgpA结合,进而促进混合生物膜的形成^[16]。

烯醇化酶(alpha-enolase, ENO1)是*C.a*的一种多功能蛋白酶类^[17],能够稳定生物膜结构^[18]。ENO1可与牙龈素结合,与RgpA-Als3复合物相比, ENO1和RgpA的亲和力显著更强。此外, ENO1也容易被*P.g*产生的肽基精氨酸脱亚胺酶(porphy-

romonas peptidylarginine deiminase, PPAD) 瓜氨酸化^[19]。PPAD在脱亚胺化或瓜氨酸化的过程中将蛋白质分子中带正电荷的精氨酸残基转化为中性瓜氨酸残基^[20],这种翻译后修饰可以改变蛋白质分子的电荷,从而影响其结构、功能以及与其他分子相互作用的能力。部分真菌蛋白能够首先被牙龈素加工,使其C端精氨酸残基更容易被PPAD瓜氨酸化^[19],有利于二者相互黏附。有研究表明缺乏PPAD的*P.g*与真菌生物膜的黏附能力显著降低,这种现象可能与PPAD修饰RgpA有关^[21]。

*P.g*和*C.a*还可能通过静电作用相互黏附。在生物膜形成过程中,位于*C.a*菌丝表面的葡聚糖、甘露聚糖,以及位于更深层的几丁质,可通过疏水或静电相互作用使得其结构变得更易于与细菌黏附^[22]。

1.2 *C.a*为*P.g*提供低氧微环境

*P.g*作为严格厌氧菌常定植于龈下,无法在有氧环境中生存。而*C.a*可通过菌丝形态的转换或代谢活动建立低氧微环境促进*P.g*的生存和生长,有利于混合生物膜的形成。

在定植感染期间,*C.a*黏附在宿主表面并在酵母和菌丝形态之间转换形态。菌丝形态促进有密集菌丝网络的生物膜形成,增强真菌对抗菌剂或环境变化的抵抗力,同时有利于氧气的消耗;另外,*C.a*在生物膜内还能通过抗氧化或代谢产物创造低氧微环境支持*P.g*的生长^[23]。Karkowska-Kuleta等^[19]发现在大气氧浓度下,当*P.g*与*C.a*共同孵育时,*P.g*生存能力比在单种生物膜中明显更强。de Jongh等^[14]表明,在有氧条件下,*P.g*只能在有活性*C.a*存在的情况下存活,而在添加了线粒体呼吸抑制剂后,*C.a*大部分氧气消耗被阻断,*P.g*的存活率也随之下降,进一步证实了*C.a*的氧气消耗对*P.g*生存的重要性。这种由*C.a*建立的缺氧环境还增强了*P.g*的生存能力,相比于浮游菌形式,*P.g*在厌氧生物膜中表现出更高的黏附性,活力增强,牙龈素的表达也明显上调,有利于对宿主的侵袭^[14]。此外,*C.a*还能通过分泌天冬氨酸蛋白酶(aspartic protease, SAP)为*P.g*提供保护,SAP对生物膜结构的形成、成熟至关重要,可作用于*P.g*表面蛋白或其他分子,对*P.g*起到稳定作用,同时MP65也被观察到明显上调,可通过促进混合生物膜的生长或调节宿主免疫反应增强*P.g*对外界刺激的抵抗能力^[16]。

综上,*C.a*能通过对氧气的消耗建立有利于*P.g*

生长的低氧微环境,在此环境下*P.g*的活力和毒力都有显著提升。

2 *C.a*和*P.g*通过血红素竞争机制增强毒力

血红素是*P.g*和*C.a*的重要铁元素来源。Guo等^[24]在不同血红素浓度下建立了*C.a*和*P.g*双菌种生物膜,结果表明在低血红素条件下*P.g*的活力和凝集红细胞的能力增强。

基因水平分析表明,*P.g*上调血红蛋白酶基因(hemoglobin protease, hum)(如hmuY和hmuR)、血红蛋白摄取序列A基因(hemoglobin uptake sequence A, husA)及与Toll样受体基因(Toll-like receptor, tlr)相关的基因表达,在和*C.a*竞争关系中处于优势^[24]。HmuY能与血红素结合并负责血红素的转移,HmuR可吸收HmuY转移到细菌中的血红素^[25]。以上基因的上调表明*P.g*在竞争血红素过程中提高了血红素的利用效率。此外,与另外两条血红素利用途径有关的HusA和Toll样受体(toll-like receptors, TLR)相关基因也显著上调^[23]。*P.g*对血红素的利用能够提高细胞毒素的产生,如丁酸盐、丙酸盐和琥珀酸盐,增强其毒力^[26]。血红素竞争状态下*P.g*牙龈素的表达也显著增加,牙龈素参与红细胞的分解和血红蛋白的水解^[26]。在混合生物膜中Kgp、RgpA以及RgpB的mRNA表达量均高于单物种生物膜,提示共培养后*P.g*黏附和水解活性显著增强^[24]。牙龈素不仅参与血红素的利用过程,还是*P.g*重要的毒力因子,一方面可利用其水解特性降解宿主细胞外基质和黏附分子^[15],另一方面可作用于宿主表皮生长因子受体,进一步激活磷脂酰肌醇3激酶-蛋白激酶B信号通路,显著促进炎症和骨吸收^[27]。此外,牙龈素还可降解宿主免疫相关分子从而逃脱血清的杀灭,抵抗宿主的免疫攻击^[24]。胞外多糖(exopolysaccharides, EPS)的量也可通过血红素竞争机制提高。EPS的包封作用能够帮助EPS更有效地抵抗外界压力^[28]。当血红素有限时,相比单菌种生物膜,混合生物膜中可观察到大量的EPS,有利于*P.g*的存活,避免因外界压力而导致的异常“拉长”的细菌形态,而当血红素丰富时上述差异消失^[24]。

综上,血红素竞争机制可提高*P.g*的毒力,还能促进EPS的产生,帮助微生物抵抗外界压力。值得一提的是,虽然牙周炎初期血红素缺乏导致*P.g*处于优势地位,*C.a*相对劣势,但*P.g*增强的毒力将加速炎症发展,形成营养丰富环境,促进*C.a*生长,一定程度上解释了牙周炎患者的龈下*C.a*高检出率。

3 *P.g* 和 *C.a* 协同作用影响宿主反应

3.1 *C.a* 和 *P.g* 协同侵袭宿主

C.a 的细胞壁成分有助于 *P.g* 识别和入侵宿主。TLR 是多种细胞均可表达的模式识别受体, *P.g* 在入侵宿主的过程中通过激活 TLR 诱导宿主细胞的固有免疫应答, 被 *P.g* 激活的 TLR 向脂筏转运, *P.g* 再利用脂筏进一步入侵宿主^[29]。

研究表明, 脂筏被 *C.a* 和 *P.g* 联合激活时比单独被 *P.g* 激活更有效, 经热杀灭的 *C.a* 及其细胞壁成分预处理的 *P.g* 比未经处理的 *P.g* 更容易侵入宿主细胞, 一方面 *C.a* 成分可诱导活性氧的产生, 活性氧进一步诱导 TLR 向脂筏运输^[30]; 另一方面, *C.a* 细胞壁由多种物质组成^[31], 可被多种人类宿主受体识别, 如 Dectin-1^[32], 经 *C.a* 活化的 Dectin-1 定位于人牙龈上皮细胞和成纤维细胞的脂筏微结构域, 用于信号传递和吞噬功能的激活^[33], 促进 *P.g* 对宿主的入侵。此外, 还有一种由网格蛋白介导的内吞作用^[34]。 *P.g* 可通过网格蛋白侵入上皮细胞^[35], *C.a* 能够招募网格蛋白^[36], 因此 *C.a* 预处理促进 *P.g* 对网格蛋白的募集和对宿主细胞的侵袭^[30]。 *C.a* 的侵入性菌丝还能帮助 *P.g* 插入上皮细胞并在血液中传播。在此过程中 *P.g* 黏附于 *C.a*, 吞噬细胞被 *C.a* 吸引^[37] 并可能借此进一步与 *P.g* 密切接触, 将其携带至血液中, 引起全身疾病的发展^[38-39]。 *P.g* 也能够增强 *C.a* 的侵袭性和致病性。 *P.g* 通过其蛋白酶与 *C.a* 相互作用, 使 *C.a* 的细胞壁修饰酶 Bgl2 和 Phr1 的表达量增加, 这些酶促使 *C.a* 向侵袭性更强的菌丝形态的转换, 调控其他毒力因子的表达以及促进生物膜的形成^[16, 40]。然而, Truong 等^[41] 的研究发现当 *P.g* 作用于 *C.a* 后, *C.a* 细胞壁蛋白以及多种代谢相关的酶的表达被下调, 这可能是因为该研究使用的是热杀灭的而非有活性的 *P.g*。

综上, *C.a* 和 *P.g* 能够互相促进侵袭性, 加重宿主的感染性疾病。

3.2 *C.a* 和 *P.g* 协同降低宿主炎症因子水平

P.g 和 *C.a* 协同降低宿主炎症因子水平, 牙龈素在这一过程发挥重要作用(*C.a* 促进 *P.g* 产生牙龈素)。 *P.g* 的多种成分可作用于 TLR, 尤其是 TLR2 和 TLR4, 随后激活 MyD88 依赖性和非依赖性信号通路, 进一步激活下游通路, 诱导炎症因子产生^[42-43]。白介素-1 β (interleukin-1 β , IL-1 β) 是触发和延续炎症的关键, 牙周炎患者龈沟液中 IL-1 β 的浓度相较于健康人群明显更高^[44]。在微生物作用下巨噬细胞以自分泌的方式介导继发性炎症因子 IL-6 和 IL-8 的释放^[45]。与单菌种相比, *P.g* 和 *C.a* 的

双菌种生物膜与巨噬细胞相互作用时产生更多 IL-1 β , 巨噬细胞还分泌外泌体保护 IL-1 β , 然而这种早期快速的 IL-1 β 保护释放机制之后是较慢、低水平且非保护性的 IL-1 β 的释放^[46]。此外, IL-1 β 还能够被活跃的牙龈素降解, 导致含量进一步减少^[47]。IL-8 的次级炎症因子反应进一步证实了牙龈素的关键调节作用。 *P.g* 和 *C.a* 分别与巨噬细胞接触时促进 IL-8 的产生, 而在双菌种生物膜中 IL-8 浓度极低^[46]。这可能是因为 IL-8 极易被牙龈素分解^[48], 因此 IL-8 的快速降解可以解释为混合生物膜中牙龈素的活性增加^[46], 从而影响宿主免疫反应。

P.g 还会促进巨噬细胞产生肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α), 但在 *P.g* 和 *C.a* 双菌种生物膜中 TNF- α 明显降低。TNF- α 是 RgpA、RgpB 和 Kgp 的底物, 且具有不同的蛋白水解动力学, 双菌种生物膜中 TNF- α 的水平下降可能是因为牙龈素的表达增加促进了 TNF- α 的降解^[24]; 同时, 牙龈素和 *C.a* 表面 Als3 的作用提高牙龈素催化结构域的活性, 进一步导致炎症因子的降解^[46]。

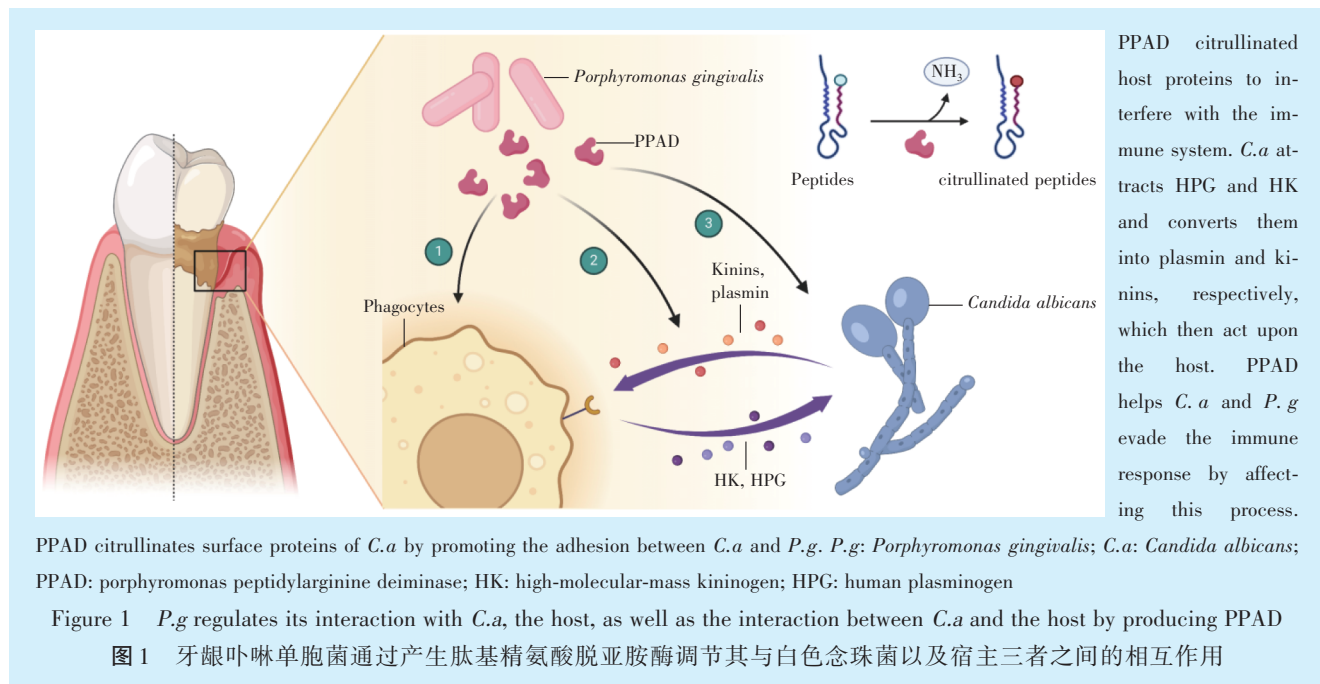
综上, *C.a* 和 *P.g* 将导致慢性感染, 当免疫减弱时容易使感染加重, 其中牙龈素发挥了重要作用, 这在一定程度上解释了为何 *C.a* 与 *P.g* 活菌能够协同降低宿主炎症因子水平, 但却促进 *P.g* 细菌成分(非活菌)诱导的炎症因子的产生^[49]。

3.3 *C.a* 和 *P.g* 协同进行免疫逃逸

P.g 毒力因子 PPAD 不仅有上文所述的促进黏附作用, 还能帮助 *C.a* 和 *P.g* 进行免疫逃逸。

一方面, PPAD 可直接瓜氨酸化宿主蛋白进行免疫逃逸。首先, 中性粒细胞暴露于 PPAD 时将降低参与吞噬作用的相关蛋白的水平; 此外, PPAD 可帮助微生物从中性粒细胞胞外陷阱中逃逸; PPAD 还能够瓜氨酸化溶菌酶衍生的阳离子抗菌肽 LP9, 从而限制其抗菌活性^[50]。另一方面, PPAD 同时修饰 *C.a* 和宿主蛋白, 从而影响其相互作用。 *P.g* 和 *C.a* 能够干扰人体凝血、纤维蛋白溶解和激肽系统, 这些系统负责维持人体的内稳态和凝血^[51-52]。 *C.a* 表面蛋白能够吸引这些系统的蛋白成分并进行处理, 如人纤溶酶原 (human plasminogen, HPG) 和高分子量激肽原 (high-molecular-mass kininogen, HK)^[53-54]。

HPG 被 *C.a* 激活成纤溶酶后参与纤维蛋白凝块的裂解、补体级联的调节以及基质金属蛋白酶的激活^[55-56]。PPAD 和牙龈素对 *C.a* 表面蛋白的修饰可以影响其与 HPG 的作用, 降低二者的结合水平, 从而影响宿主的免疫反应^[57] (图1)。



HK是具有血管活性的促炎介质激肽的前体,在炎症中起关键作用^[58]。*C.a*吸附HK并将其转化为激肽作用于宿主B2和B1受体,刺激炎症因子的产生^[59],同时将有营养物质的血浆转移到感染处,有利于微生物随血液传播。*C.a*的Als3和Eno1能与HK结合,且对PPAD的瓜氨酸化敏感^[60],然而这些修饰并不影响真菌与HK的结合水平,但PPAD对HK转化成的激肽的瓜氨酸化可影响其与B2受体的作用^[57]。激肽C端的正电荷能够补偿羧基的负电荷,进而作用于B2受体^[61],瓜氨酸化消除这种补偿作用后将导致激肽对B2受体的亲和力降

低,降低宿主炎症反应。

综上,PPAD能够通过瓜氨酸化微生物和宿主蛋白,改变其结构功能,影响*C.a*与宿主蛋白或宿主蛋白与宿主受体的结合,降低宿主的炎症反应从而进行免疫逃逸。

4 问题与展望

综上,*P.g*和*C.a*相互黏附形成生物膜,*C.a*为*P.g*提供厌氧微环境并提高其毒力;*C.a*和*P.g*还能协同入侵宿主并进行免疫逃逸,导致宿主的慢性感染(图2)。然而,二者交互作用还有待更深入的

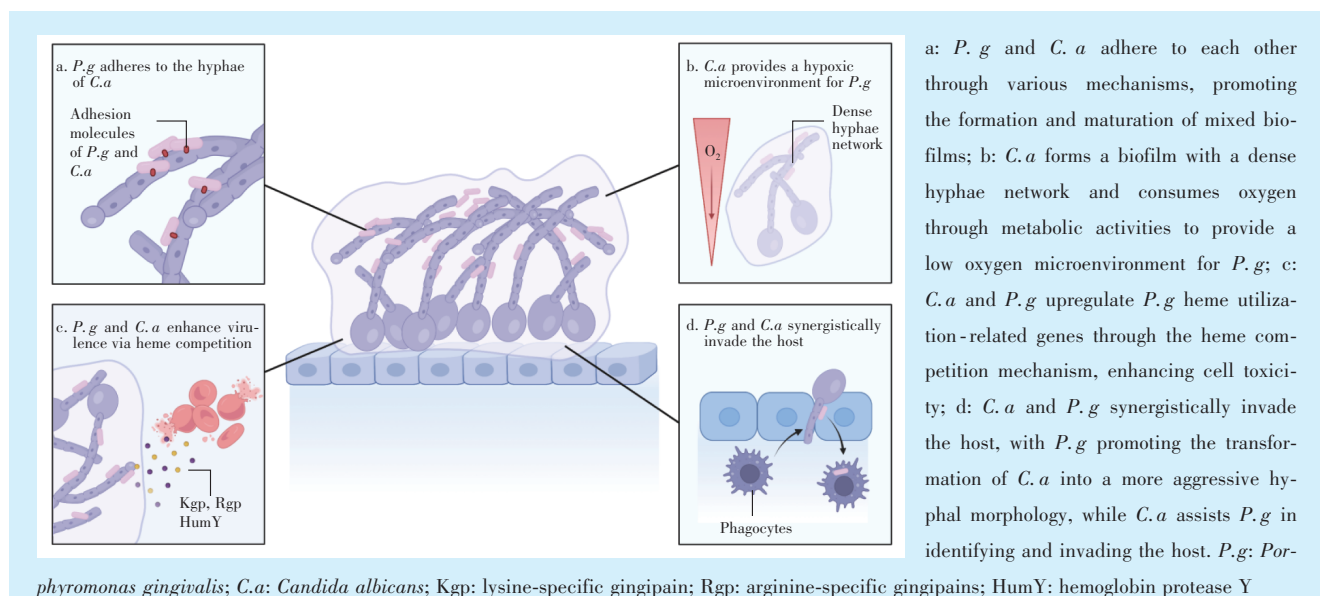


Figure 2 The microbial interaction between *P.g* and *C.a*

图2 牙龈卟啉单胞菌与白色念珠菌的交互作用

研究,尤其是二者相互作用之后作用于宿主的生物学功能、作用的分子靶点及相关机制。此外,目前缺乏动物实验和临床队列研究,*P.g*和*C.a*在体内是否能有和体外相同的作用还需论证;其次,*P.g*和*C.a*常在严重牙周炎部位被共同检出,牙周袋刮治后进行抗生素治疗是常见的治疗策略,因此二者对抗生素耐药性的研究亦是一个颇具临床意义的研究方向。

基于*P.g*和*C.a*的密切交互作用,针对二者的共同治疗策略引起了重视。不少研究开始发掘能够对二者同时起到抗菌作用的药物。有研究创新了具有抗菌效果的复合材料,如搭载抗生素的凝胶或基质,包括盐酸莫西沙星^[62]、甲硝唑^[63]和盐酸左氧氟沙星^[64]等,以及葡聚糖基纳米材料^[65]。此外,不少天然药物也被发掘出具有优越的抗菌性能,如黑种草^[66]和一些混合草药^[67]。然而以上药物多局限于表型,且并非*P.g*和*C.a*的特异性抗菌药物。Amer等^[68]的研究弥补了这一空缺,他们利用*P.g*和*C.a*表面特定蛋白酶研发了可控释放抗菌肽的前药策略,为相关疾病的治疗提供了新的可能性。综上,针对*P.g*和*C.a*的抗菌策略研究尚缺乏,尤其是药物作用于二者的靶点及相关机制还需进一步研究,以期研发出效果更好的特异性药物。

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