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·综述·

牙龈卟啉单胞菌促进阿尔茨海默病的机制研究进展

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【摘要】 阿尔茨海默病(Alzheimer's disease，AD)是最常见的神经退行性疾病之一。牙龈卟啉单胞菌(*Porphyromonas gingivalis*，*P.gingivalis*)感染与AD密切相关。本文综述了*P. gingivalis*及其毒力因子在AD发生发展过程中的多重作用及其机制，旨在深入阐明两者之间的内在联系。*P. gingivalis*可通过多种途径与AD发生发展相关联。首先，*P. gingivalis*可以增加神经炎症、促进淀粉样蛋白和Tau蛋白沉积、破坏血脑屏障等途径参与AD病理进程。其次，*P. gingivalis*分泌的牙龈蛋白酶能增加血脑屏障通透性并进入脑内诱导病理损伤是其促进AD的重要机制。临床样本检测也支持*P. gingivalis*或其效应分子促进AD病理进展。因此，*P. gingivalis*可能是AD的一个环境易感因素或可调控的风险因素。目前*P. gingivalis*在AD中的确切作用机制和*P. gingivalis*与其他可能影响AD的因素之间的关联研究不明确。本文深入分析*P. gingivalis*促进AD的分子机制，为研制*P. gingivalis*相关的AD新型防治策略提供参考。

【关键词】 牙龈卟啉单胞菌；　阿尔茨海默病；　牙龈蛋白酶；　血脑屏障；　牙周炎；　神经退行性疾病；　淀粉样β蛋白

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Research progress on the potential mechanisms of Porphyromonas gingivalis in promoting Alzheimer's disease

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【Abstract】 Alzheimer's disease (AD), a common neurodegenerative disease, has been linked to periodontitis, especially Porphyromonas gingivalis (*P. gingivalis*) infection. This review summarizes the potential mechanisms and pathways through which *P. gingivalis* and its virulence factors are involved in AD pathogenesis, aiming to provide the scientific basis for the development of novel prevention and treatment strategies for AD. *P. gingivalis* can promote AD by exacerbating neuroinflammation, facilitating amyloid beta and Tau deposition, and disrupting the blood-brain barrier. Gingipains, secreted by *P. gingivalis*, serve as core effector molecules by increasing the blood-brain barrier permeability. The association between *P. gingivalis* and its effectors and AD pathology has been validated by metagenomic analysis and sample detection, indicating that *P. gingivalis* may be an environmental susceptibility factor or modifiable risk factor for AD. However, the precise mechanisms by which *P. gingivalis* influences AD, and its interactions with other potential AD-related factors, remain unclear. Moreover, further research needs to be conducted on the therapeutic potential

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of *P. gingvalis* intervention in improving AD.

【Key words】 *Porphyromonas gingivalis*; Alzheimer's disease; gingipains; blood-brain barrier; periodontitis; neurodegenerative diseases; amyloid beta-protein

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阿尔茨海默病(Alzheimer disease,AD)是一种最常见的神经退行性疾病,主要表现为渐进性的认知功能障碍[1]。全球范围内AD的患病率呈上升趋势,给社会和家庭都带来沉重负担,严重影响老年人的生活质量[2]。AD的主要病理特征有脑内β淀粉样蛋白(Amyoid β,Aβ)沉积[3]、Tau蛋白过度磷酸化和神经纤维缠结(neurofibrillary tangles,NFT)[3]、神经元丧失和脑组织萎缩[4]。目前,AD的发病机制尚未完全阐明,有效的治疗和预防手段也非常有限。

牙周病作为一种高发的慢性炎症性疾病,其发病机制与AD存在一定的相似性。越来越多的流行病学研究显示,牙周病可以增加AD的发生风险,两者之间可能存在一定的病因联系[5-6]。牙龈卟啉单胞菌(*Porphyromonas gingivalis*,*P. gingivalis*)是牙周病的主要致病菌之一[7],其对AD发生发展具有重要促进作用,但其作用机制尚不明确。*P. gingivalis*作为一种革兰氏阴性厌氧菌,具有多种毒力因子[8]。研究表明,*P. gingivalis*及其毒力因子可以直接参与AD的关键物质如Aβ的生成、Tau蛋白的异常磷酸化以及神经炎症反应的启动。此外,*P. gingivalis*诱导的牙周炎作为慢性炎症,也可以加速AD病情。因此,深入探究*P. gingivalis*与AD的关系,寻找其作用靶点和可能的干预策略,对于疾病的防治具有重要意义。

本文概述和总结了*P. gingivalis*促进AD发生发展的可能机制,旨在进一步推动两者关系和发病机制的研究。笔者从病理相似性、*P. gingivalis*在AD中的检测结果以及动物模型实验结果3个方面进行综述和展望,为早期预防和治疗AD提供新的策略。

1　*P.gingivalis*与阿尔茨海默病的相关性研究

大量的人群队列研究显示,牙周病患者发生AD和轻度认知功能障碍的风险更高。同时,在AD患者样本中也检测到了*P. gingivalis*和关键毒力因子。通过流行病学调查发现牙周炎与认知功能衰退和痴呆症的发生密切相关。Iwasaki等[9]在一项为期5年的队列研究中发现,基线时牙周炎症状越重的患者,未来发生轻度认知功能障碍(mild cognitive impairment,MCI)的风险越大。Choi等[10]进行了一项为期10年的回顾性队列研究,通过分析来自韩国的数据库中的约25万人数据,发现慢性牙周炎患者比非牙周炎患者患痴呆和AD的风险更高。Ma等[11]进行了一项持续10年的队列研究,在调整糖尿病、心血管疾病等混杂因素后对得到的数据进行分析,结果显示患有痴呆症的人群患牙周病的风险均显著增加,且这种关联不受其他潜在影响因素的影响。Luo等[12]在一项队列研究中通过分析约6 000人样本得出,脱失牙数≥8颗的人群相比保留牙数较多者,发生MCI或AD的风险增加,提示牙周病与认知衰退高度相关。Demmer等[13]对8 000位参与者进行了基线牙周检查,并跟踪评估其痴呆和MCI的结果,通过18.4年的随访得出牙周疾病严重程度与痴呆的发生呈轻微相关,这一关联在年龄较年轻的参与者中表现更为明显。

Sung等[14]使用国家健康和营养调查数据库分析了4 663例20至59岁参与者的牙周状况和认知功能。结果显示,牙周炎患者在认知功能测试中表现出较低水平,经过多项因素调整后,发现牙周炎与认知功能下降显著相关,中重度牙周炎比轻度牙周炎患者发生痴呆的可能性高。Tsuneishi等[15]对近4万例日本老年人纵向数据进行整合分析,得出在牙齿数量较少和缺失牙位较多的人群中,认知功能障碍更为常见,提示缺牙情况可能加速认知衰退。

Leblhuber等[16]对20例认知障碍患者进行认知测试、常规实验室检查和脑磁共振断层扫描以确定诊断后,再检查样本的口腔微生物组成,研究发现在AD患者中存在特定的口腔致病菌,如牙龈卟啉单胞菌,并且这些病原菌与较低的认知测评分

数相关，由此推断牙周致病菌与认知障碍有关。此外，一项关注女性人群的纵向研究也显示，牙周炎可促进认知功能下降，且这一影响在女性中更为明显[17]。

Poole等[18]首次在临床阶段的AD患者脑组织中检测到*P. gingivalis*脂多糖，表明其可通过血脑屏障进入大脑参与病理过程。随后Dominy等[19]在AD患者的脑脊液和皮质组织中也检测到*P. gingivalis*和特异性毒力因子牙龈蛋白酶。Siddiqui等[20]通过高通量测序检出AD患者脑组织中激增的牙周致病菌DNA，提示其感染与大脑病变相关。2022年，Cirstea等[21]发现相比正常对照组，AD患者的口腔和肠道菌群中*P. gingivalis*的丰度显著增加。这些都为*P. gingivalis*参与疾病发生机制提供了大量证据。陈玉英等[22]比较AD患者人群与非神经系统性疾病患者的龈沟液中*P. gingivalis*、齿密垢螺旋体（*Treponema alveolaris*）以及炎症因子水平，结果发现AD患者的口腔微生物含量与炎症因子水平显著高于非神经系统性疾病患者，这与Cirstea[21]等的研究结果一致。

综上所述，牙周致病菌，如牙龈卟啉单胞菌等，诱导的牙周慢性炎症同时伴随患者认知功能的改变，提示牙龈卟啉单胞菌等牙周致病菌感染可能加重AD的病理进程。

2　*P.gingivalis*促进阿尔兹海默病的机制研究

越来越多的动物实验也证实了*P. gingivalis*可加速AD模型小鼠的病理损伤，在动物模型中证实了*P. gingivalis*促进AD的作用。目前研究提示*P. gingivalis*主要通过促进神经炎症反应、增加Aβ生成、影响Tau蛋白磷酸化以及破坏血脑屏障等途径发挥作用（图1）。

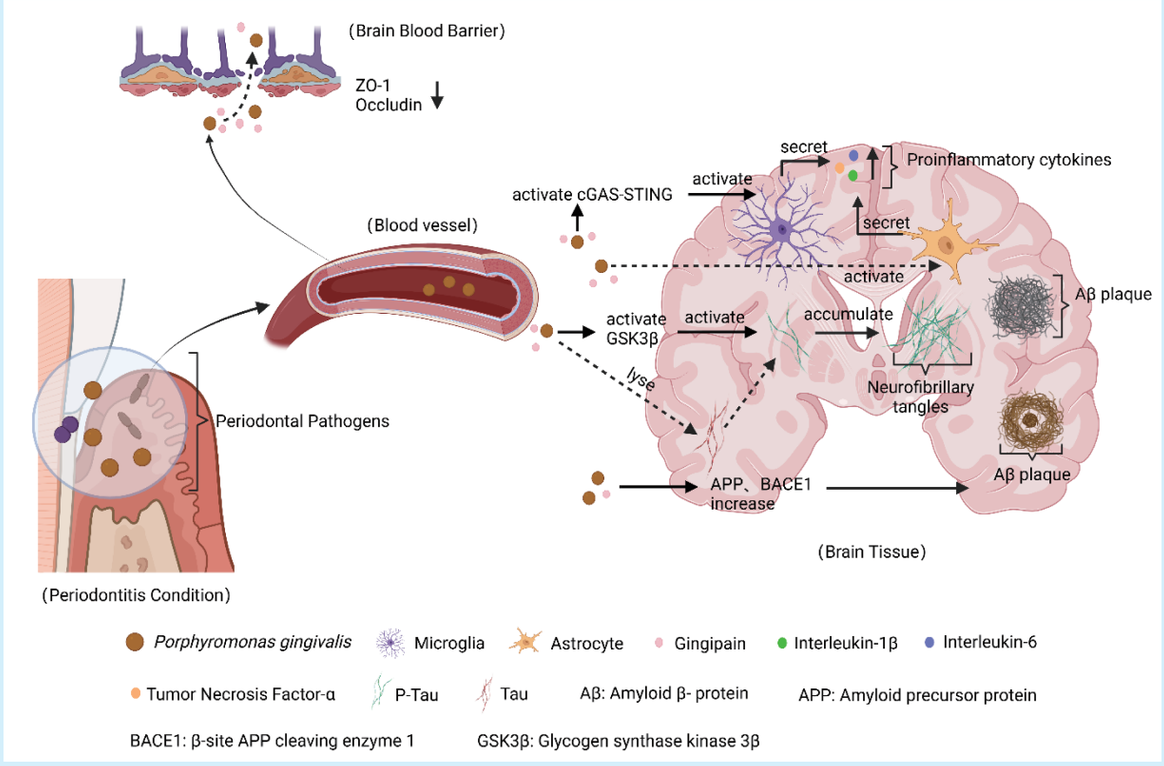

Figure 1　Association between *Porphyromonas gingivalis* and the pathogenesis of Alzheimer's disease

图1　牙龈卟啉单胞菌与阿尔茨海默症病理机制关系

2.1　*P. gingivalis*感染加重神经炎症

*P. gingivalis*可以激活先天性免疫cGAS-STING通路，促进小胶质细胞分泌炎症因子产生神经炎症反应[23-24]。*P. gingivalis*与小胶质细胞的相互作用，可促进AD的进展[25]。*P. gingivalis*的毒力因子，包括牙龈蛋白酶和脂多糖（Lipopolysaccharide，LPS）可引起多种促炎因子的释放，影响小胶质细胞介导的神经炎症[26]。*P. gingivalis*分泌的牙龈蛋

白酶可通过激活蛋白酶激活受体2(protease-activated receptor 2,PAR 2)诱导小胶质细胞的迁移和炎症反应[27]。

Liu等[28]对12月龄的雄性小鼠进行连续3周的*P. gingivalis*腹膜内注射,发现在小鼠的海马内IL-1β(interleukin-1β)、IL-6(interleukin-6)等促炎细胞因子表达增加。Ilievski等[29]证实年轻小鼠通过22周*P. gingivalis*口服感染可以显著增加IL-1β、IL-6和TNF-α(tumor necrosis factor-α)等促炎细胞因子在脑组织中的表达。Ding等[30]也发现*P. gingivalis*诱导的牙周感染可引起中年小鼠的脑组织中促炎因子的释放。这表明牙周感染可通过全身炎症反应导致脑内炎症。此外,在AD转基因小鼠中建立的实验性牙周炎模型中,脑组织中的TNF-α和IL-1β水平也显著上调[31-32],提示两种疾病之间可能形成恶性循环。

2.2　*P. gingivalis*感染促进Aβ生成

牙周感染会增加脑组织Aβ的生成。Dominy等[19]发现通过对小鼠实施口服*P. gingivalis* 6周干预,可加速小鼠海马组织Aβ的积累;抑制*P. gingivalis*分泌的牙龈蛋白酶,有助于降低Aβ表达。该结果表明长期*P. gingivalis*感染可直接促进脑内Aβ生成和聚集。同时Su等[33]通过对小鼠实施24周的口服*P. gingivalis*感染,与对照组相比,*P. gingivalis*感染后的小鼠海马内出现Aβ沉积。苏心怡等[34]连续4周和12周对大鼠静脉注射*P. gingivalis*,以此构建外周感染模型,检测结果显示,*P. gingivalis*外周感染可以促进海马组织中β淀粉样蛋白的表达。此外,有研究发现通过丹酚酸B的抗炎治疗可以部分逆转*P. gingivalis*诱导的Aβ生成增加[28]。这表明除了*P. gingivalis*毒力因子的直接作用外,由其引起的炎症状态也可能间接促使Aβ表达上调。*P. gingivalis*诱导形成实验性牙周炎的小鼠中,研究发现牙周炎小鼠中淀粉样蛋白前体蛋白(Amyloid precursor protein,APP)在牙龈和大脑皮层中的表达增加,同时β-分解酶1(β-site APP cleaving enzyme 1,BACE1)的表达也增加,提示*P. gingivalis*诱导的Aβ增加可能与APP的加工异常有关[35]。

2.3　*P. gingivalis*感染引起Tau蛋白异常磷酸化

磷酸化和聚合的Tau蛋白是AD另一关键病理特征[36]。研究发现*P. gingivalis*可通过多途径改变磷酸化Tau的生成。①牙龈蛋白酶可直接作用于Tau蛋白产生裂解,促进磷酸化Tau聚集[19,37];②*P. gingivalis*感染也可激活Tau蛋白异常磷酸化的关键激酶GSK3β(glycogen synthase kinase 3β)[38];③*P. gingivalis*诱导的神经炎症状态变化也可导致Tau蛋白失衡[39-40]。因此,*P. gingivalis*可通过直接和间接影响途径促进Tau蛋白的病理性聚合。

2.4　*P. gingivalis*破坏血脑屏障完整性

维持血脑屏障完整性对保护中枢神经系统免疫特异性至关重要[41]。进入大脑的牙周病原体和/或其毒力因子会促进AD患者的血脑屏障破坏,这可能是该疾病的早期特征[42]。有研究发现,*P. gingivalis*可显著增加血脑屏障通透性,损害屏障完整性从而导致脑内病理损伤加重[43]。具体机制可能涉及紧密连接蛋白如ZO-1和Occludin的下调[40,44],或毛细血管细胞膜转运蛋白表达变化等[45]。Furutama等[46]通过4周的结扎方式建立小鼠牙周炎模型后,发现海马中的紧密连接蛋白Caludin-5表达降低,从而导致血脑屏障的通透性增加。Xue等[47]采用12个月的结扎方式形成慢性牙周炎模型后,发现肠道屏障的紧密连接蛋白Claudin-1、Occludin和ZO-1的表达降低,以及血脑屏障中Claudin-5、Occludin和ZO-1的表达减少。*P. gingivalis*感染后也可以通过激活组织蛋白酶B/核因子-κB(nuclear factor kappa-B,NF-κB)通路,上调脑内皮细胞的糖基化末端产物受体(receptor for advanced glycation end products,RAGE)表达,介导Aβ的脑内流[48]。Rokad等[49]通过口服*P. gingivalis*感染转基因小鼠12周,发现转基因小鼠海马微血管结构内羟基和氧化蛋白增加,提示氧化应激水平增高,从而可能导致相关的紧密连接蛋白发生降解影响,从而损害其血脑屏障的功能完整性。这为*P. gingivalis*和毒力因子进入脑组织提供了通路(图2)。

综上所述,*P. gingivalis*感染通过不同途径加速了AD发生和发展。*P. gingivalis*感染可以激活先天免疫cGAS-STING通路,促进了小胶质细胞分泌炎症因子,引发神经炎症反应。这些炎症反应不仅加剧了AD病理进程中的神经炎症,还可能通过影响神经元和细胞间的交流进一步损害脑功能。*P. gingivalis*的毒力因子如牙龈蛋白酶增加了Aβ的生成及聚集,并通过多种机制促进Tau蛋白的异常磷酸化,包括直接作用于Tau蛋白产生裂解和激活Tau蛋白磷酸化的关键激酶。这些变化共同推动了AD的关键病理特征,即神经纤维缠结的形成。此外,*P. gingivalis*通过破坏血脑屏障的完整

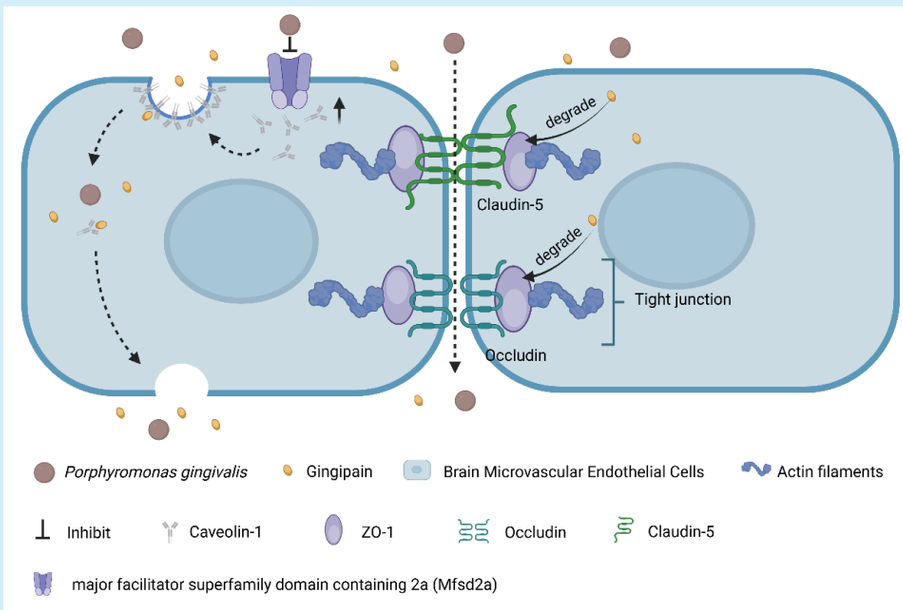

Figure 2　Entry pathways of *Porphyromonas gingivalis* into the brain
图2　牙龈卟啉单胞菌的入脑途径

性，增加了脑组织对病原体和炎症因子的通透性，进一步加剧了AD的病理损伤。

3　*P. gingivalis* 牙龈蛋白酶增加血脑屏障通透性的机制研究

牙龈蛋白酶是*P. gingivalis*分泌的一种半胱氨酸蛋白酶，主要包含赖氨酸特异性牙龈蛋白酶（lysine-gingipain，Kgp）和精氨酸特异性牙龈蛋白酶（arginine-gingipain，Rgp）两大类[19, 45]。这些蛋白酶通过识别位点特异性水解宿主细胞蛋白，在*P. gingivalis*的致病性中发挥核心作用，参与组织侵袭、免疫逃避、营养摄取等多种生理过程[7]。研究者通过全基因组分析和定向突变验证发现，Kgp和Rgp对脑部病变影响尤为关键。

维持血脑屏障通透性稳态对保护中枢神经系统至关重要。大量研究表明*P. gingivalis*牙龈蛋白酶可通过多途径导致血脑屏障通透性增加。Nonaka等[44]发现Kgp可显著降解细胞间连接蛋白ZO-1和Occludin的表达，损伤脑毛细血管内皮细胞联结；此外，Rgp还可上调胞吞作用相关蛋白Caveolin-1来增加胞饮作用促进血脑屏障开放[45]。除直接作用外，牙龈蛋白酶还可通过促炎和促凋亡途径间接损害血脑屏障[50]。这些变化最终导致屏障通透性增加，毒力分子和炎症因子大量涌入脑实质组织。病理学和分子生物学检测直接证实了*P. gingivalis*牙龈蛋白酶可进入中枢神经系统。通过对AD患者脑脊液和皮层脑组织检测发现*P. gingivalis*和Kgp的阳性表达[19]；而AD和老年痴呆的大鼠模型样本中Kgp的存在也得到验证，并且还发现Rgp可以与神经元细胞共定位[51]。这些结果说明经血液循环和（或）神经传导途径，牙龈蛋白酶可越过血脑屏障进入脑内参与病理生理过程。

牙龈蛋白酶进入脑内后可直接扰乱Aβ和Tau蛋白的代谢过程。通过模拟酶解和定点突变分析发现，Kgp和Rgp可高效催化Aβ单体产生积累；同时其还可直接作用于Tau蛋白产生有害的异常截短片段和诱导错误聚合[19]。这种直接作用机制可急性触发AD病理表型。Haditsch等[52]用*P. gingivalis*感染神经元细胞，感染72 h的结果显示，磷酸化的Tau蛋白水平增加，此时神经元内的*P. gingivalis*不能被培养，但仍然可以稳定表达牙龈蛋白酶（包括Kgp和Rgp），提示这可能是牙龈蛋白酶对Tau蛋白作用的结果。由此可以推断，牙龈蛋白酶可能通过调控神经炎症和调节细胞信号通路间接影响Aβ和Tau的过程[29, 53]。

4　*P. gingivalis* 的其他毒力因子促进阿尔茨海病的机制研究

除了牙龈蛋白酶，*P. gingivalis*的毒力因子还包括LPS和外膜囊泡（outer membrane vesicle，OMV）。研究发现两种毒力因子对AD的病理过程也具有一定的促进作用。Wu等[54]连续5周对小鼠进

行腹膜内注射*P. gingivalis*-LPS，发现全身暴露于*P. gingivalis*-LPS的中年小鼠，在海马体区可发现Aβ沉积增多。Gong等[40]连续8周给小鼠口服*P. gingivalis*-OMVs，发现*P. gingivalis*-OMVs的处理提高了IL-1β和NLRP3炎症小体的表达，同时引起Tau蛋白Thr231位点上的磷酸化表达增加。Yoshida等[37]连续12周给小鼠腹腔注射*P. gingivalis*-OMVs，结果显示大脑中磷酸化Tau蛋白含量和活化的小胶质细胞增加。

5　总结与展望

越来越多的证据表明*P. gingivalis*感染与AD之间密切相关。针对牙周病原体的治疗可减轻全身炎症负担，且部分研究显示这可对认知功能产生积极影响[55-56]。通过牙周根面刮治后患者IL-6水平显著下降，记忆力改善[57-58]。在AD前临床阶段患者中，接受牙周治疗可显著减缓病变脑区萎缩[59]。针对*P. gingivalis*特异性感染，一些新兴小分子抑制剂通过抑制*P. gingivalis*毒力因子，减轻牙周和全身炎症，并显示出一定的认知保护作用[60-63]。从基础研究角度而言，还应进一步深入探究*P. gingivalis*核心毒力分子的精确作用机制，这可以为联合治疗策略的设计和药物靶点筛选提供依据。

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