

牙龈卟啉单胞菌与非口腔疾病关系的研究进展*

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【摘要】 牙龈卟啉单胞菌是常见的牙周致病菌。近来,大量证据表明牙龈卟啉单胞菌不仅是口腔中常见致病菌,而且与非口腔疾病密切相关,包括炎症性肠炎、癌症、心血管疾病、阿尔茨海默病、类风湿关节炎、糖尿病、早产及非酒精性肝炎等。本文就近年来关于牙周致病菌牙龈卟啉单胞菌与非口腔疾病关系的研究进展进行综述,有助于判别牙龈卟啉单胞菌是否可作为这些非口腔疾病的辅助诊断标记和潜在治疗靶标,进而有利于开发相关疾病的治疗策略。

【关键词】 牙龈卟啉单胞菌 非口腔疾病 相关性

Developments in Research on the Relationship Between *Porphyromonas gingivalis* and Non-Oral Diseases ZHANG Ke-ke, SUN Yan, PAN Yi-huai[△]. School and Hospital of Stomatology, Wenzhou Medical University, Wenzhou 325000, China

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【Abstract】 *Porphyromonas gingivalis* (*P. gingivalis*) is a common periodontal pathogen. Recently, there has been increasing evidence suggesting that *P. gingivalis* is not only a common pathogen in the oral cavity, but is also closely associated with non-oral diseases, including inflammatory bowel disease, cancer, cardiovascular diseases, Alzheimer's disease, rheumatoid arthritis, diabetes mellitus, premature birth and non-alcoholic hepatitis, etc. Herein, we reviewed the developments in recent years in research on the relationship between *P. gingivalis*, a periodontal pathogen, and non-oral diseases, which will help determine whether *P. gingivalis* could be used as an auxiliary diagnostic biomarker or a potential therapeutic target for these non-oral diseases, thus contributing to the development of treatment strategies for the relevant diseases.

【Key words】 *Porphyromonas gingivalis* Non-oral diseases Correlation

近年来,流行病学调查、临床样本检测,体外实验及动物实验等研究结果均表明,“红色复合体”成员牙龈卟啉单胞菌(*Porphyromonas gingivalis*, *P. gingivalis*)不仅与牙周炎、口腔鳞状细胞癌密切相关,与炎症性肠炎、癌症、心血管疾病、阿尔茨海默病、类风湿关节炎、糖尿病、早产及非酒精性肝炎等非口腔疾病也密切相关。本文就牙周致病菌牙龈卟啉单胞菌与非口腔疾病关系的研究进展进行综述。

1 牙龈卟啉单胞菌与炎症性肠炎

有流行病学研究表明,与非炎症性肠病患者相比,炎症性肠病患者更容易患牙周炎,临床附着和牙周袋深度丧失的部位比例更高^[1]。牙龈卟啉单胞菌提取物可诱导CD4⁺T细胞凋亡,通过TLR4通路上调辅助性T细胞17(Th helper cell 17, Th17)相关转录因子ROR γ t的表达,增加促炎因子白介素(IL)-17及IL-6的产生;下调调节性T细胞(T regulatory, Treg)相关转录因子Foxp3的表达,降低抗炎因子TGF- β 及IL-10的产生^[2]。研究发现牙龈卟啉单胞菌的肽酰基精氨酸脱亚氨酶可能通过诱导原始CD4⁺T细胞转

化为促炎性Th17细胞,并抑制抗炎性Treg的产生,参与诱导溃疡性肠炎^[3]。关于小鼠结肠炎模型的实验研究表明口服牙龈卟啉单胞菌可显著增加结肠炎的严重程度,牙龈卟啉单胞菌的毒力因子牙龈蛋白酶在此过程中发挥了重要作用,牙龈卟啉单胞菌可通过直接与易感宿主的肠上皮屏障相互作用而加剧胃肠道炎症^[4]。而在直肠内植入牙龈卟啉单胞菌,炎症性肠炎疾病活动指数评分、结肠上皮损失和炎性细胞浸润加剧,肿瘤坏死因子(TNF)- α 和IL-6在结肠中高表达,证实牙龈卟啉单胞菌在炎症性肠炎恶化中发挥重要作用^[5]。近期研究表明牙龈卟啉单胞菌还可通过改变肠道微生物群和通过产生IL-9的CD4⁺T细胞破坏上皮屏障功能间接引起肠道炎症^[6]。

2 牙龈卟啉单胞菌与癌症

2.1 牙龈卟啉单胞菌与结直肠癌

早期研究表明大肠癌患者的粪便中富含卟啉单胞菌^[7]。牙龈卟啉单胞菌与肿瘤共有分子亚型相关,后者与结直肠癌密切相关^[8]。体外实验表明牙龈假单胞菌可通过激活结直肠癌细胞的丝裂原活化蛋白激酶/细胞外调节蛋白激酶(mitogen-activated protein kinase/ extracellular signal-regulated kinase, MAPK/ERK)信号通路侵入结直肠

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癌细胞并促进其增殖,且在此过程中,牙龈假单胞菌的牙龈蛋白酶发挥了重要作用^[9]。牙龈卟啉单胞菌可上调结肠癌细胞中程序性细胞死亡因子配体1(programmed death-ligand-1, PD-L1),在此过程中细菌的肽聚糖发挥重要作用^[10]。此外,PD-L1的上调依赖于核苷酸结合寡聚化结构域1(nucleotide-binding oligomerization domain 1, NOD1)和核苷酸结合寡聚化结构域2(nucleotide-binding oligomerization domain 2, NOD2),并涉及受体相互作用丝氨酸/苏氨酸蛋白激酶2(receptor-interacting serine/threonine-protein kinase 2, RIPK2)和MAPK信号通路的激活。最新研究将大肠癌患者与大肠腺瘤患者或健康受试者进行比较,发现大肠癌患者的粪便和组织样本中牙龈卟啉单胞菌含量较高^[11]。牙龈假单胞菌与结直肠癌的不良预后相关,小鼠实验证实牙龈卟啉单胞菌在肿瘤组织中定植并富集,导致免疫微环境中NLRP3炎症小体的激活,最终促进结直肠癌的进展^[11]。

2.2 牙龈卟啉单胞菌与胰腺癌

2013年一项探索血液中口腔细菌抗体与胰腺癌风险之间关系的前瞻性研究结果显示,牙龈卟啉单胞菌抗体水平较高的个体比抗体水平较低的个体患胰腺癌的风险高出两倍^[12]。另一项前瞻性研究比较了361例胰腺癌患者和371例对照个体的口腔微生物组成,发现牙龈卟啉单胞菌和伴放线放线杆菌(*Aggregatibacter actinomycetemcomitans*, *A. actinomycetemcomitans*)的检出与胰腺癌高风险相关,表明牙龈卟啉单胞菌可能在胰腺癌病因中起作用^[13]。GNANASEKARAN等^[14]利用体外细胞实验异种移植模型表明,牙龈卟啉单胞菌在胰腺癌细胞内存活并促进胰腺癌细胞增殖。此外,牙龈卟啉单胞菌的脂多糖可诱导小鼠高表达胰腺癌相关的胰岛再生源蛋白(regenerating islet-derived 3 G, Reg3G)及其编码基因^[15]。在另一个小鼠模型中,口腔暴露于牙龈卟啉单胞菌可加速胰腺导管腺癌的发展;转化生长因子- β (transforming growth factor- β , TGF- β)信号通路可能参与牙龈卟啉单胞菌的促癌作用^[16]。此外,动物实验表明:在暴露于牙龈卟啉单胞菌后,原位和皮下胰腺癌小鼠模型中的肿瘤发展加快,胰腺癌呈现出中性粒细胞为主的促炎性肿瘤微环境;牙龈卟啉单胞菌可通过提高中性粒细胞趋化因子和中性粒细胞弹性蛋白酶的分泌促进胰腺癌进展^[17]。

2.3 牙龈卟啉单胞菌与食管癌

早期研究发现牙龈卟啉单胞菌感染可能是食管鳞状细胞癌的高危因素,食管鳞状细胞癌组织中牙龈卟啉单胞菌的含量明显高于癌旁组织、正常食管组织^[18]。食管鳞状细胞癌患者血清中的牙龈假单胞菌免疫球蛋白IgG

和IgA的平均表达水平显著高于其对照组^[19]。此外,牙龈卟啉单胞菌IgG或IgA在血清中的高表达与食管鳞癌患者的预后较差相关,特别是对于0~II期或淋巴结转移阴性的患者,且IgG和IgA高表达的食管鳞癌患者预后最差^[19]。与正常人相比,食管鳞状细胞癌患者的唾液中卟啉单胞菌显著富集。体外研究表明,牙龈卟啉单胞菌促进了食管鳞状细胞癌细胞的增殖和迁移,可通过NF- κ B信号通路进行调节^[20]。此外,细胞实验证实牙龈卟啉单胞菌通过miR-194/GRHL3/PTEN/Akt信号轴促进食管鳞状细胞癌的增殖和迁移^[21]。研究发现牙龈卟啉单胞菌的存在与食管癌晚期临床分期和不良预后相关。在小鼠模型中,还发现其与食管癌发病率升高以及异种移植肿瘤生长增加有关;牙龈卟啉单胞菌增加了IL-6的产生,并促进了上皮-间质转化和髓源性抑制细胞的募集^[22]。一项分析了312例食管癌食管切除术患者临床病理数据的临床研究发现,牙龈卟啉单胞菌阳性患者5年生存率较低,且与多种临床病理因素和病理肿瘤、淋巴结、转移分期有关;其中85例接收新辅助化疗的患者,其牙龈卟啉单胞菌感染率与较低的新辅助化疗应答率和5年生存率相关;且牙龈卟啉单胞菌感染可导致食管鳞状细胞癌的凋亡抗性并促进癌细胞存活;细胞实验和动物实验证明该凋亡抗性与牙龈卟啉单胞菌的菌毛和癌细胞的信号传导转录激活因子3(signal transducer and activator of transcription, STAT3)密切相关^[23]。牙龈卟啉单胞菌感染与食管鳞癌组织中自噬调控蛋白Beclin1表达呈负相关,牙龈卟啉单胞菌感染和Beclin1低表达与食管鳞状细胞癌患者的分化状态、肿瘤浸润深度、淋巴结转移、临床分期和预后相关^[24];此外,体外实验证实牙龈假单胞菌感染和Beclin1的下调增强了食管鳞状细胞癌细胞的增殖、迁移和抗凋亡能力^[24]。

2.4 牙龈卟啉单胞菌与肺癌

牙周病与肺癌相关,但因果关系仍然存疑^[25]。近期研究表明牙周致病菌牙龈卟啉单胞菌与肺癌相关。由于食管与气管密切相邻,一项基于牙龈卟啉单胞菌可能通过口腔或血液定植于肺癌细胞并促进肺癌恶性发展的研究假设的临床试验^[26]发现,牙龈卟啉单胞菌在肺癌组织中检出显著高于癌旁肺组织;牙龈卟啉单胞菌感染与肺癌患者吸烟史、饮酒史、淋巴结转移率和临床分期密切相关;此外,牙龈卟啉单胞菌感染患者的生存率和中位生存时间显著缩短,研究团队推测长期吸烟和饮酒会导致不良的口腔环境,增加牙龈卟啉单胞菌感染的风险,从而促进肺癌的恶性进展。

3 牙龈卟啉单胞菌与心血管疾病

已有研究表明慢性牙周炎与心血管疾病发病率之间存在联系,但具体机制仍然不明确。动物实验发现,动脉粥样斑块中存在大量的生物菌群,可来源于口腔、呼吸道、肠道以及皮肤等^[27]。近几年研究将牙龈卟啉单胞菌诱导加速动脉粥样硬化的可能机制归为炎症、内皮损伤、氧化应激以及分子模拟等^[28]。同时牙龈卟啉单胞菌可通过自身毒力因子如脂多糖、菌毛、热休克蛋白等结构和牙龈蛋白、外膜囊泡等分泌成分来加速该疾病的进程^[29]。牙龈卟啉单胞菌可影响多种细胞的生理活动和转化,包括内皮细胞、血管平滑肌细胞、巨噬细胞、T细胞和树突状细胞来,从而促进动脉粥样硬化的发展^[30]。同时,在小鼠实验中发现,昼夜节律紊乱也可以促进牙龈卟啉单胞菌诱导的动脉粥样硬化进展^[31]。近来,一项研究指出牙龈卟啉单胞菌可通过粒体功能障碍相关机制促进冠状动脉粥样硬化的进程^[32-33]。

4 牙龈卟啉单胞菌与阿尔茨海默病

许多大样本的研究表明牙周炎增加了罹患阿尔茨海默病的风险^[34-36]。牙龈卟啉单胞菌可通过独特而复杂的机制持续存在于宿主组织中,如改变炎症信号通路、互补系统、细胞周期、细胞凋亡以及和各种宿主受体的相互作用^[37]。动物实验表明,牙龈卟啉单胞菌还可以影响血脑屏障的通透性,促进细菌以及含有赖氨酸-牙龈素(lysine-gingipain, KGP)的外膜囊泡进入大脑,并通过阻止免疫细胞进入大脑而影响局部的炎症反应,导致不溶性淀粉样蛋白清除障碍^[38]。牙龈卟啉单胞菌毒素侵入诱导多能干细胞来源的成熟神经元也表现出类似阿尔茨海默病的神经病理征象^[39]。研究已在人类阿尔茨海默病患者脑脊液和血清中检测到牙龈卟啉单胞菌DNA和抗体^[40]。动物模型、细胞系培养、解剖病理都支持了脑部牙龈卟啉单胞菌感染在阿尔茨海默病发病中起作用的假说^[41]。目前对于人体内牙龈卟啉单胞菌诱导的阿尔茨海默病发病机制尚不明确,但有研究报道了在小鼠脑内,牙龈卟啉单胞菌可激活小胶质细胞,增加TNF- α 、IL-1 β 、IL-6的表达,诱导M1小胶质细胞的分化成熟^[42]。M1小胶质细胞释放的促炎细胞因子可加重阿尔茨海默病,导致突触功能障碍、神经元死亡和神经发生抑制^[43]。牙龈卟啉单胞菌毒力因子赖氨酸-牙龈素靶向的小分子抑制剂COR388有效降低了牙龈卟啉单胞菌感染野生型小鼠脑内细菌量、减少了阿尔茨海默病相关疾病的炎症因子,预防了海马区Gad67⁺中间神经元的丢失^[44-45]。

5 牙龈卟啉单胞菌与糖尿病

LÖE于1993年首次描述了糖尿病患者牙周炎风险增加,并发现牙周炎是糖尿病的并发症之一。在牙龈卟啉单胞菌参与糖尿病发病相关机制中,胰岛素抵抗是最重要的。牙龈卟啉单胞菌主要通过诱导内毒素血症、改变肠道微生物群和在受损的区域适应性免疫增加全身炎症,特别是脂肪组织,最终导致胰岛素抵抗^[46-48]。据报道,炎症和炎症标志物(如C-反应蛋白CRP和IL-6)水平的升高也可诱导胰岛素抵抗^[29]。因此,牙龈卟啉单胞菌引起的全身促炎性小细胞因子水平升高可能促进胰岛素抵抗。另一项研究表明,牙龈卟啉单胞菌通过其支链氨基酸的生物合成加剧了小鼠高脂饮食诱导的胰岛素抵抗^[49]。此外,牙龈卟啉单胞菌外膜囊泡中含有牙龈素,并通过其转移至小鼠肝脏,导致胰岛素敏感性减弱和肝糖原合成抑制^[50]。除胰岛素抵抗外,牙龈卟啉单胞菌对糖尿病的促进作用可能存在其他潜在机制。牙龈卟啉单胞菌的脂多糖具有刺激胰腺 β 细胞分泌胰岛素的能力,并对牙周炎患者糖尿病前期 β 细胞代偿的进展具有重要意义。口服牙龈卟啉单胞菌诱导了小鼠牙龈卟啉单胞菌和牙龈蛋白向胰腺的移位,导致胰岛结构和 β 细胞凋亡的显著变化,这可能与糖尿病前期的发展有关。牙龈卟啉单胞菌可能减弱了由HepG2细胞中的胰岛素调节的转录因子FOXO1的磷酸化和转位,从而增加肝脏糖异生,并导致血糖升高^[51]。

6 牙龈卟啉单胞菌与类风湿性关节炎

牙龈卟啉假单胞菌与类风湿性关节炎密切相关。有研究发现类风湿性关节炎与龈沟液中的牙周病原菌如牙龈卟啉假单胞菌有关,监测龈沟液的细菌组成可能有助于及早发现类风湿性关节炎^[52]。ARVIKAR等^[53]通过检测类风湿性关节炎患者的牙周状况,口腔液(唾液和龈沟液)、血清和关节炎症特征以及牙龈卟啉假单胞菌的生物标记,发现尽管有常规的牙科护理,类风湿性关节炎患者的口腔液中常有炎症,但口腔液中的炎症特征与血清和关节中的炎症特征不同。无论牙周状况如何,口腔液中的中性粒细胞炎症特征表明,牙龈组织是类风湿性关节炎患者关节外炎症的常见部位^[53]。研究表明类风湿性关节炎的治疗抵抗与牙周病原菌感染有关,牙龈卟啉假单胞菌等感染会干扰类风湿性关节炎的治疗^[54]。类风湿性关节炎高危人群唾液微生物组成的特征变化,表明口腔微生态失调发生在类风湿性关节炎的“临床前”阶段,与类风湿性关节炎高风险相关,并与全身自身免疫特征有关^[55]。

类风湿性关节炎的发展是通过丧失对瓜氨酸蛋白的免疫耐受性来促进的, 抗瓜氨酸化蛋白抗体(anti-citrullinated protein antibodies, ACPAs)的量可预测当前和未来的疾病发生^[56]。牙龈卟啉假单胞菌可能导致蛋白质的局部瓜氨酸化, 潜在地触发抗瓜氨酸化蛋白抗体的产生。CHENG等^[57]的研究结果证明, 抗环瓜氨酸肽阳性的高危人群存在牙周菌群失调和牙龈卟啉假单胞菌丰度增加的现象, 说明牙龈卟啉假单胞菌在类风湿性关节炎的发病过程中起着重要的作用。通过研究牙周治疗前后牙周炎队列中, 抗瓜氨酸化蛋白抗体血清应答与抗细菌血清抗体和牙周炎菌斑微生物群的关系, 发现牙龈卟啉假单胞菌携带者可能与针对牙龈卟啉假单胞菌的IgG抗体和抗瓜氨酸化蛋白抗体有关, 证明了牙龈卟啉假单胞菌和抗瓜氨酸化蛋白抗体存在的相关性^[58]。牙龈卟啉单胞菌感染产生的细菌瓜氨酸表位是抗瓜氨酸化蛋白抗体生产中缺失的一环^[59]。尽管牙龈卟啉单胞菌的肽酰基精氨酸脱亚氨酶(*P. gingivalis* peptidylarginine deiminase, PPAD)能瓜氨酸化牙龈卟啉单胞菌的内源蛋白组, 但这些瓜氨酸化蛋白并不能代表早期类风湿性关节炎患者自身免疫反应的主要靶点, 且该酶的活性在炎症性关节炎病理驱动中的作用有限^[60]。而在早期类风湿性关节炎中, 针对瓜氨酸化牙龈卟啉单胞菌感表位的抗体增加, 并可由牙龈组织B细胞产生^[61]。

7 牙龈卟啉单胞菌与早产

早产是新生儿死亡的主要原因, 是孕妇不良妊娠结局之一^[62]。几项病例对照研究证实, 孕妇牙周炎可能会增加早产或低出生体重的风险^[63-64]。评估妇女妊娠期口腔微生物群落稳定性的研究显示, 与非孕妇相比, 孕妇的口腔微生物群发生了明显的变化^[65]。在妊娠的各个阶段, 孕妇体内的可培养微生物总量明显高于非孕妇^[66]。妊娠晚期的菌斑细菌群落更加多样化^[67-68]。与非孕妇相比, 孕妇的牙龈卟啉单胞菌和中间卟啉单胞菌的检出率显著增加^[69-70]。怀孕时期体内激素水平的差异, 口腔微生物群落的动态变化, 增加了牙龈炎和牙周炎等各种口腔疾病的易感性^[65, 68, 71]。在早产婴儿、足月婴儿的脐带血和母体牙菌斑中检测牙龈卟啉单胞菌发现, 该菌在早产组中数值显著增加^[72]。动物实验也证明牙龈卟啉单胞菌可诱导小鼠妊娠期肥胖, 改变妊娠小鼠肝脏和棕色脂肪组织中的基因表达, 并导致分娩的小鼠体质量过轻^[73]。牙龈卟啉单胞菌可以在人羊膜间充质细胞中诱导炎症反应, 从而导致早产^[74]。目前主要存在两种致病机制来解释口腔病原菌与不良妊娠之间的关系包括直接途径和间

接途径。直接途径, 牙周病原体的血源性传播可能导致胎儿-胎盘出现转移性感染, 引起局部炎症^[64, 75-77]; 间接途径, 促炎细胞因子在牙周组织局部产生, 然后通过血流到达胎盘或肝脏, 产生炎症细胞因子或急性期反应物并引发不良妊娠结局^[76, 78]。

8 牙龈卟啉单胞菌与非酒精性脂肪肝炎

在高脂饮食诱导的非酒精性脂肪性肝炎小鼠模型中, 牙龈牙源性感染牙龈卟啉单胞菌加剧了肝脏炎症和纤维化^[79]。且在肝脏中有牙龈卟啉单胞菌感染的非酒精性脂肪性肝炎患者显示出晚期纤维化评分^[79]。在小鼠模型中, 牙源性感染牙龈卟啉单胞菌可通过TGF- β 1激活肝星状细胞(肝纤维化中的关键效应细胞), 以及从肝星状细胞和肝细胞产生半乳糖凝集素3(Galectin-3)加重非酒精性脂肪肝的纤维化^[80]。而去除牙龈卟啉单胞菌的牙源性感染可抑制其诱导的非酒精性脂肪性肝炎进展^[81]。牙龈卟啉单胞菌在小鼠模型中可通过CD36-PPAR γ 途径加剧非酒精性脂肪肝的进展^[82]。此外, 研究还发现牙龈卟啉单胞菌可能通过增加血清支链氨基酸水平来加重高脂饮食喂养小鼠的非酒精性脂肪肝进展, 并且这种作用依赖牙龈卟啉单胞菌的支链氨基酸转运系统^[83]。

9 展望

目前大量研究表明牙龈卟啉单胞菌与非口腔疾病的密切相关, 但更为关键的是找出牙龈卟啉单胞菌与这些非口腔疾病的因果关系。理解这些逻辑问题将有助于判定牙龈卟啉单胞菌是否可作为这些非口腔疾病的辅助诊断标记和潜在治疗靶标。此外, 研究牙龈卟啉单胞菌与这些非口腔疾病作用的具体分子机制将有利于开发相关疾病的治疗策略。

* * *

利益冲突 所有作者均声明不存在利益冲突

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