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·牙周医学专栏　综述·

牙周炎与人群衰老相关研究进展

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【摘要】 近年来，越来越多研究探索牙周炎对人群衰老的影响。已有流行病学证据显示，牙周炎与人群死亡率相关，亦有研究显示牙周炎可加速衰老的生物学过程。然而，目前关于牙周炎加速人群衰老的确切作用机制尚不明确。因此，本文对相关研究成果进行综述，发现牙周炎可能通过以下机制加速衰老：1）牙周炎产生的炎症介质溢出到血液，促进“炎症老化”，通过激活活化B细胞的核因子κ-轻链增强子（nuclear factor kappa-light-chain-enhancer of activated B cell，NF-κB）信号通路及衰老相关分泌表型（senescence associated secretory phenotype，SASP）加速衰老；2）牙周致病菌可通过以下3种途径促进衰老过程：①牙周致病菌本身及细菌产物借助血液循环推动“炎症老化”，且导致血液中重要衰老标志物沉寂信息调节因子1（silent information regulator 1，SIRT1）和哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）异常变化，诱发线粒体功能障碍，进而加速衰老；②牙龈卟啉单胞菌过度激活蛋白激酶B（protein kinase B，Akt）/叉头盒O1（forkhead box O1，FoxO1）通路直接促进树突状细胞（dendritic cells，DCs）衰老，损害宿主对病原体的反应能力，引起免疫衰老，同时诱导DCs产生外泌体传递和放大旁分泌免疫衰老；③牙周致病菌在肠道中异位定植导致肠道菌群失衡，间接加速衰老进程。

【关键词】 牙周炎；　衰老；　人群死亡率；　炎症老化；　牙周致病菌；　免疫衰老；　树突状细胞；　衰老相关分泌表型；　肠道菌群失衡
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Research progress on the association between periodontitis and the aging population

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【Abstract】 Recently, there has been a growing focus on investigating the influence of periodontitis on the aging population. There is epidemiological evidence that indicates periodontitis is associated with mortality, and it has been shown to accelerate the biological processes of aging. However, the precise mechanism by which periodontitis accelerates the process of the aging population remains to be elucidated. This paper reviews relevant research results and finds that periodontitis may be associated with accelerated aging and increased mortality through the following mechanisms: 1) the inflammatory mediators produced by periodontitis are released into the bloodstream and promote “inflammageing”, which accelerates aging through activation of the NF-κB signaling pathway and the senescence-associated secretory phenotype; 2) periodontal pathogens can promote the aging process in the following three ways: ① periodontal pathogens and bacterial products promote “inflammageing” through blood circulation, and they lead to abnormal changes in SIRT1

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and mTOR, important aging markers in the blood, which induces mitochondrial dysfunction and accelerates aging; ② porphyromonas gingivalis overactivates the Akt/FoxO1 pathway to directly promote the aging of dendritic cells and produce exosomes that transmit and amplify paracrine immunosenescence; and ③ periodontal pathogens are ectopically colonized in the intestinal tract and lead to gut dysbiosis, thus indirectly accelerating the aging process.

【Key words】 periodontitis; aging; population mortality; inflammageing; periodontal pathogen; immunosenescence; dendritic cells; senescence associated secretory phenotype; gut dysbiosis

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全球约有11亿人患有严重的牙周病，已成为全球健康领域的沉重威胁[1]。越来越多研究表明，牙周炎不仅是口腔健康问题，而且促进全身系统性疾病，是糖尿病、高血压等的独立风险因素[2]。这些全身系统性疾病与人群衰老密切相关，可导致健康状态恶化、生活质量下降以及人群死亡风险升高[3-5]。而牙周炎是否会直接加速生物衰老过程、影响人群死亡率也逐渐成为大家关注的研究热点。

研究表明，牙周炎可通过炎症反应引发或促进全身慢性疾病的发展，如心血管疾病、糖尿病等[6-9]。此外，牙周致病菌也通过不同途径与全身性疾病的发生发展相关[10-12]。这些过程可能对个体的生理功能和健康状况产生负面影响，进而加速人群衰老。因此，本文就牙周炎是否会加速人群衰老及其相关机制进行综述，以期为延缓生物衰老过程、降低一般人群死亡风险、提高患者生活质量提供参考。

1　牙周炎加速生物衰老，影响人群死亡率

1.1　牙周炎加速衰老及影响人群死亡率的直接流行病学证据

近年来，已有流行病学研究开始探讨牙周炎与衰老及人群死亡率的关系。流行病学证据表明，牙周炎与特定原因死亡率和全因死亡率相关[13]。在一项为期17年的随访研究中，对60岁以上患有牙周炎的患者进行评估，发现牙周炎与所有个体，特别是男性的全因死亡率相关[14]。此外，另一项超过50年的纵向队列研究发现牙周炎的严重程度与全因死亡率呈正相关[15]。与此同时，采取治疗牙周炎的措施与降低死亡率相关[16-17]。定期洗牙作为预防及治疗牙周炎必不可缺的一部分，有一项回顾性队列研究显示，常规定期洗牙的中风患者死亡率更低[16]。另外，良好的口腔卫生习惯（如刷牙和使用牙线）亦有助于缓解牙周炎，维护牙周健康[18]，一项中位随访时间为18.8年的研究表明，良好口腔卫生习惯与心血管死亡风险显著降低相关[17]。

在流行病学研究中对衰老进行客观量化一直是一项挑战，其中一个可用于评估衰老的指标是表型年龄加速。表型年龄反映的是个体的生物学年龄而非实际年龄，表型年龄加速反映了表型年龄与实际年龄之间的差异，可用于衡量加速衰老。一项长达31年的前瞻性队列研究通过对这一指标的分析表明，在美国中老年人样本中，牙周炎会加剧生物衰老对死亡率的影响[19]。该研究发现表型年龄加速指标最高四分位数的中/重度牙周炎患者的全因死亡率、心血管疾病死亡率和癌症死亡率分别比最低四分位数的患者高144.6%、150.8%和131.7%。

除表型年龄加速这一指标外，还常使用衰老标志物客观评估衰老的生物学过程。端粒长度作为重要衰老标志物之一，可用来衡量细胞年龄和生物学老化状态，在牙周炎相关研究中也展现了其重要性。Song等[20]发现，在1999年至2002年的美国国家健康与营养调查（National Health and Nutrition Examination Survey，NHANES）数据中，中重度牙周炎患者端粒缩短概率比轻度或无牙周炎患者高47%。同样，Nguyen等[21]通过对2001年至2002年的NHANES数据分析表明，牙周炎对整个生命周期中端粒长度的减少有显著影响。另有研究发现，牙周炎的严重程度与检测到的端粒长度呈负相关[22]。

1.2　牙周炎影响咀嚼功能从而间接加速衰老及影响人群死亡率

牙周炎是全球成年人牙齿脱落的主要原因，有研究表明，缺失牙齿的数量越多，全因死亡率及与癌症、心血管疾病相关的死亡率就越高[23-26]。同时，一项为期10年的随访研究发现，牙齿数量与总预期寿命有关[27]。牙齿脱落致使咀嚼功能不足、整体生活质量下降都会有损整体健康、加重虚弱状态[28]。严重牙周炎导致的牙齿松动、脱落可影响个体的咀嚼功能，进而影响食物摄入和消化吸收，降低机体的营养吸收能力[29-30]。有研究发现，咀嚼能力受损以及饮食质量下降与加速衰老相关，导致更高的死亡风险[31]。同时，另一项研究亦发现咀嚼能力下降是中年人群死亡率增加的重要危险因素[32]。

2　牙周炎加速衰老的机制研究

2.1　牙周炎促进“炎症老化”加速衰老

衰老常伴随着“炎症老化”，“炎症老化”描述了随着年龄增长而发展的慢性、低水平全身性炎症，反过来其也为与年龄相关的疾病以及衰老奠定基础[33]。有研究证明全身性慢性炎症会促进细胞及机体衰老，且与老年人的死亡率之间存在显著关系[34-35]。一项包含3 047例患者的前瞻性队列研究表示，牙周炎和全身性炎症是独立且相互作用的死亡危险因素，且同时患有牙周炎和全身炎症的个体死亡率明显更高[36]。

牙周炎产生的炎症介质从牙周组织溢出到血液[37]。牙周病变组织中储存了与牙周炎相关的促炎介质，这些炎症因子也可进入血液循环，增强机体的全身炎症状态[38]。研究证据表明，与健康对照组相比，严重牙周炎患者血清中白细胞介素-1（Interleukin-1，IL-1）、白细胞介素-6（Interleukin-1，IL-6）、C反应蛋白（C-reactive protein，CRP）和纤维蛋白原等促炎介质水平升高[39-43]。除临床研究外，在动物模型上进行的研究也支持牙周炎会引起全身性炎症的观点。在结扎诱导牙周炎大鼠模型中，血清中炎症标志物（IL-1、IL-6）的增加反映牙周炎诱发了全身炎症[44]。相反，有效的牙周治疗可降低全身性炎症水平，在非手术性牙周治疗后，牙周炎患者血清内炎症标志物（IL1、IL-8和CRP等）水平下降[45-48]。作为衰老的标志物之一，全身性慢性炎症可能通过B细胞的核因子κ-轻链增强子（nuclear factor kappa-light-chain-enhancer of activated B cell，NF-κB）信号通路及衰老相关分泌表型（senescence associated secretory phenotype，SASP）加速衰老。肿瘤坏死因子-α（tumor necrosis factor-α，TNF α）可通过独立激活NF-κB信号通路，上调血管内皮细胞中与衰老相关的癌胚抗原相关黏附分子1表达[49]。CRP也可显著激活NF-κB信号通路，引起细胞损伤[50]。此外，IL33（IL1家族成员）/ST2信号亦通过激活该通路促进SASP表达[51]。而IL-6，IL-8均属于SASP。关于SASP，它在牙周炎促进免疫衰老机制中有重要意义。SASP一旦通过p38丝裂原活化蛋白激酶（p38 mitogen-activated protein kinase，p38 MAPK）信号的启动，它就会长期存在。此外，SASP还能以自分泌的方式稳定表达细胞的衰老表型，并诱导邻近的健康细胞衰老，这种现象被称为旁分泌衰老或旁观者效应。

2.2　牙周致病菌加速衰老过程

牙周炎起源于特定的牙周致病菌，主要包括革兰氏阴性厌氧菌，如牙龈卟啉单胞菌和伴放线聚集杆菌等[37]。这些牙周致病菌在加速衰老过程中也扮演了重要角色。

2.2.1　牙周致病菌借助血液循环加速衰老过程

牙龈上皮屏障破裂会使细菌及其产物进入血液循环，导致菌血症，特别是严重牙周炎患者更易感[52]。这些细菌包括牙龈卟啉单胞菌和放线菌属等[53]。这些细菌进入血液后可播种到血管内皮及其他器官，激活全身内皮细胞或其他细胞类型，并在这些远端部位产生炎症介质，进而激活宿主的全身炎症反应加速衰老。

除菌血症外，牙周致病菌会产生富含毒力因子的细菌外膜囊泡（outer membrane vesicles，OMV）和次级代谢物（如丁酸）进入血液，通过细菌产物参与衰老进程。当OMV进入血液循环后，各种毒力因子（如脂多糖、蛋白水解酶等）可通过OMV从口腔输送到其他远端器官，激活和推动全身性炎症的发生发展[54]。此外，牙周病状态下牙周致病菌产生的次级代谢物丁酸会持续存在于牙龈组织中并逐渐进入血液，有研究为探究牙周病状态下牙龈组织中的丁酸是否会对大鼠的血液衰老过程产生影响，设计了一项实验[55]。这项实验将丁酸直接注入到年轻大鼠的牙龈部位，用以模拟牙周病状态下牙龈组织中丁酸的存在情况。实验的研究结果显示，经丁酸直接注射的年轻大鼠的血液中许多衰老标志物水平朝中年大鼠所观察到的水平移动，其中重要衰老标志物如沉寂信息调节因

子1（silent information regulator 1，SIRT1）和哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）在衰老过程中发挥重要作用。SIRT1通过缺氧诱导因子-1α（hypoxia inducible factor-1α，HIF-1α）和过氧化物酶体增殖激活受体-γ辅激活因子-1α（peroxisome proliferators-activated receptor γ coactivator lalpha，PGC-1α）激活线粒体生物发生，而在衰老过程中，SIRT1的减少使线粒体生物发生受损，导致线粒体功能障碍，从而加速衰老[56]。此外，mTOR通过PI3K-AKT-mTORC1轴参与线粒体生物发生，在衰老过程中mTOR异常激活使该信号通路失调，亦导致线粒体功能障碍，进而加速衰老[57]。

2.2.2　牙龈卟啉单胞菌通过影响树突状细胞促进免疫衰老加速全身衰老　在衰老过程中，先天性免疫和适应性免疫功能衰退被称为“免疫衰老”[58]。它影响免疫系统的各个部分，涉及免疫细胞、淋巴器官以及循环免疫因子等一系列变化[59]。有研究发现，免疫系统受损引起的免疫衰老会有力驱动实体器官衰老，促进全身性衰老[60]。

牙龈卟啉单胞菌作为牙周病的关键病原体，可以影响连接先天性免疫和适应性免疫的抗原呈递细胞——树突状细胞（dendritic cells，DCs），在牙周炎促进免疫衰老中发挥重要作用。Elsayed等[61]针对暴露于牙龈卟啉单胞菌的DCs进行研究，有如下发现：暴露于牙龈卟啉单胞菌的环境下，年轻小鼠的DCs（young dendritic cells，yDCs）发生衰老，且不论是老年或年轻小鼠的DCs的成熟功能都会受损。此外，牙龈卟啉单胞菌诱导产生的DC外泌体（exosomes of DCs cocultured with *P. gingivalis*，PgDCexo）可放大受体yDCs的旁分泌免疫衰老作用。牙龈卟啉单胞菌直接入侵DCs导致其发生免疫衰老的机制为过度激活蛋白激酶B（protein kinase B，Akt）/叉头盒O1（forkhead box O1，FoxO1）通路[62]。牙龈卟啉单胞菌的致病作用与菌毛等毒力因子密切相关[63]。其表面的菌毛可靶向DCs的受体树突状细胞特异性细胞间黏附分子-3结合非整合素因子（DC specific intercellular adhesion molecule-3-grabbing nonintegrin，DC-SIGN），激活Akt/FoxO1通路。当Akt被激活时，它定位于细胞核，磷酸化和失活细胞核上的FoxO1。FoxO1磷酸化后易位至细胞质，在细胞质发生多泛素化，随后降解蛋白酶体，从而抑制细胞凋亡[62]。牙龈卟啉单胞菌还可诱导抗凋亡的B淋巴细胞瘤-2基因（B-cell lymphoma-2，Bcl2）表达增加和促凋亡蛋白与Bcl-2相互作用的细胞死亡介导因子（Bcl-2 interacting mediator of cell death，Bim）和与Bcl-2相关的X蛋白（Bcl-2 associated X protein，Bax）的减少，与激活的Akt/FoxO1通路一同抑制DCs的凋亡。DCs对细胞凋亡抵抗力的增加是DCs衰老的重要功能标志，衰老的DCs表现出I型干扰素（interferon，IFN）反应减弱，并且外源性抗原呈递给$CD8^+$ T细胞的效率低下，损害宿主对病原体的反应能力，引起免疫衰老[64-65]。

此外，牙龈卟啉单胞菌诱导的DC外泌体（PgDCexo）是传递和放大旁分泌免疫衰老的有效机制[61]。Elsayed等[61]对与牙龈卟啉单胞菌共培养、诱导产生的PgDCexo进行了纯化、定量和表征，发现PgDCexo的数量是对照组的2倍，而PgDCexo富含与衰老相关的微RNA（microRNA，miRNA），这些miRNA会通过负调控细胞凋亡和自噬功能来破坏免疫稳态；PgDCexo富集了牙龈卟啉单胞菌纤毛黏附蛋白Mfa1和炎症相关因子，且从功能上讲，PgDCexo很容易通过旁分泌途径被受体yDCs内吞，致使其过早丧失成熟和抗原递呈的功能，促进衰老诱导。有研究将PgDCexo注射到牙龈内，以评估对免疫衰老的影响，结果发现PgDCexo促进年轻小鼠牙龈组织和引流淋巴结中衰老相关的β-半乳糖苷酶（senescence-associated β-galactosidase，SA-β-Gal）、细胞周期蛋白依赖的激酶抑制剂2A（cyclin-dependent kinase inhibitor 2A，CDKN2A/p16）、细胞周期蛋白依赖的激酶抑制剂1A（cyclin-dependent kinase inhibitor 1A，CDKN1A/p21）表达的增加以及$CD28^-$、$CD57^+$标志的衰老，$CD4^+$ T细胞和SASP的增加[66]。这项研究中PgDCexo导致衰老的$CD4^+$ T细胞增加，表明其影响了年轻小鼠T细胞的抗衰老性，这证明PgDCexo是在旁观者正常细胞中传递和放大旁分泌衰老的有效机制。还有研究发现，牙龈卟啉单胞菌诱导产生的外泌体能够穿透小鼠的血脑屏障[67]。上述研究结果表明，牙龈卟啉单胞菌感染会诱导DCs的衰老，并增加致病性外泌体的释放，从而将病原体相关分子和SASP带到远处的旁观者细胞。

2.2.3　牙周致病菌导致肠道菌群失调间接加速衰老过程　肠道微生物组成的变化以及它们产生和分泌的代谢物的变化（肠道菌群失调）构成了衰老的12个细胞和分子标志之一[68]。将年轻小鼠的肠道微生物移植至中年小鼠中，可观察到中年小鼠的血管衰老标志物水平显著逆转[69]。将老年小鼠

的肠道微生物移植至年轻小鼠中，在年轻小鼠的主动脉和肠道组织中都观察到端粒功能障碍，表明年轻小鼠血管和肠道均出现过早衰老，同时还观察到肠道氧化应激、炎症水平升高，这提示年轻小鼠的肠道微生物特征趋向老年化[70]。另一项研究中，SIRT6基因敲除小鼠（3周龄即出现早衰症状）发生肠道菌群失调，移植其肠道微生物至正常小鼠可诱发早衰，而将正常小鼠的肠道微生物移植至早衰小鼠则能改善菌群失调并延长寿命[71]。上述研究均显示肠道菌群失调与加速衰老密切相关。关于肠道菌群失调加速衰老的机制研究尚不明确，Munteanu等[72]认为肠道菌群失调可显著减少H_2S生成，进而抑制SIRT激活，损害线粒体功能，加速衰老进程。

据报道，慢性牙周炎患者肠道菌群的多样性降低，且在重度慢性和侵袭性牙周炎患者中观察到肠道菌群失调[73-74]。人每天产生大约1～1.5 L唾液，患有严重牙周炎的患者每天可能会通过唾液摄入10^{12}～10^{13}个口腔细菌[75]。口腔与肠道在解剖上具有连续性，有学者推测，胃酸度下降以及当牙周致病菌载量超过消化屏障杀菌阈值时，口腔微生物可到达肠道[76]。与此同时，有研究认为牙周致病菌经唾液途径通过口腔-肠道轴在肠道中异位定植，扰乱肠道微生物群的稳态，导致正常肠道微生物群失衡[77-79]。有研究将严重牙周炎患者的唾液微生物群灌胃至小鼠体内，发现牙周炎和肠道炎症的共同病原体牙龈卟啉单胞菌和梭杆菌在肠道中显著富集，且肠道产生低度炎症反应[80]。Arimatsu等[81]通过口服强饲法给予小鼠牙龈卟啉单胞菌，一定时间后在回肠和结肠中均检测到这种细菌，且在接种后不久诱导肠道菌群失调。此外，伴放线聚集杆菌（*Aggregatibacter actinomycetemcomitans*，*Aa*）也被报道可诱导肠道菌群失调[82-83]。另一项动物实验则证实非手术牙周治疗有助于患牙周炎小鼠的肠道微生物组恢复到健康状态[84]。同时，一项包含36例老年患者的横断面研究发现临床牙周炎与肠道菌群失调指标相关，牙周炎的存在会导致肠道菌群失调[85]。

目前牙周致病菌影响肠道菌群失调的具体机制仍不完全清楚。一项评估*Aa*对健康小鼠肠道菌群和免疫系统影响的研究显示，*Aa*的胃内接种减少了结肠固有层中髓系细胞（结肠巨噬细胞、中性粒细胞和单核细胞）的数量，并诱导了肠道菌群失调[82]。在固有层细胞群中，结肠巨噬细胞、中性粒细胞和单核细胞通过识别病原体和适当的免疫反应来维持肠道环境的稳态。而*Aa*可以杀死这些白细胞[86]，进而可能会损害肠道微生物群的免疫调节，增加肠道菌群失调的风险。此外有研究观察到牙龈卟啉单胞菌感染肠上皮细胞后存在自噬抑制[87]。在这项研究中，观察到牙龈卟啉单胞菌周围存在单膜液泡，基于这一特性，这种细菌可驻留在自噬囊泡内来逃避自噬降解，使其能够在宿主细胞内生存甚至繁殖以避免清除，从而使肠道中致病菌群的丰度增加。

3　总结与展望

综上，牙周炎对衰老及人群死亡率的影响已逐渐成为研究热点，现有的研究表明牙周炎主要与加速生物衰老过程有关，它通过牙周炎促进“炎症老化”进程以及牙周致病菌通过借助血液循环、影响树突状细胞促进免疫衰老以及肠道异位定植导致肠道菌群失衡来实现这些影响（图1）。

然而目前关于牙周炎引发和推进全身性炎症更深层次的分子机制仍待挖掘，了解其机制对于开发靶向治疗策略以减轻其对宿主衰老进展的影响至关重要。此外，目前关于牙周致病菌促进免疫衰老的研究较为局限，文中仅介绍了DCs在牙周炎促进免疫衰老中发挥的关键作用。在牙周炎发生发展的过程中，中性粒细胞是最早被募集到感染部位的免疫细胞之一，牙周炎的持续炎症状态可导致中性粒细胞活化异常和促炎介质持续释放，事实上，局部免疫中性粒细胞释放的炎症介质、免疫复合物和氧化应激在全身免疫中也发挥作用[88]，这提示中性粒细胞可能亦是将牙周炎与衰老联系起来的关键参与者。不仅如此，牙周免疫微环境还涉及多种宿主免疫细胞，包括巨噬细胞、T细胞、自然杀伤细胞和间充质干细胞等等，任何种类的局部细胞功能障碍或过度激活等都可能是牙周炎促进免疫衰老的机制之一。

牙周健康是全身健康的基石，深入研究牙周炎对衰老和死亡率的影响，有助于开发以牙周健康为重点的延缓衰老和促进健康长寿的新策略；进一步探索牙周病在加速衰老以及影响人群死亡率的潜在机制，为预防衰老和延长寿命提供新机遇和挑战。

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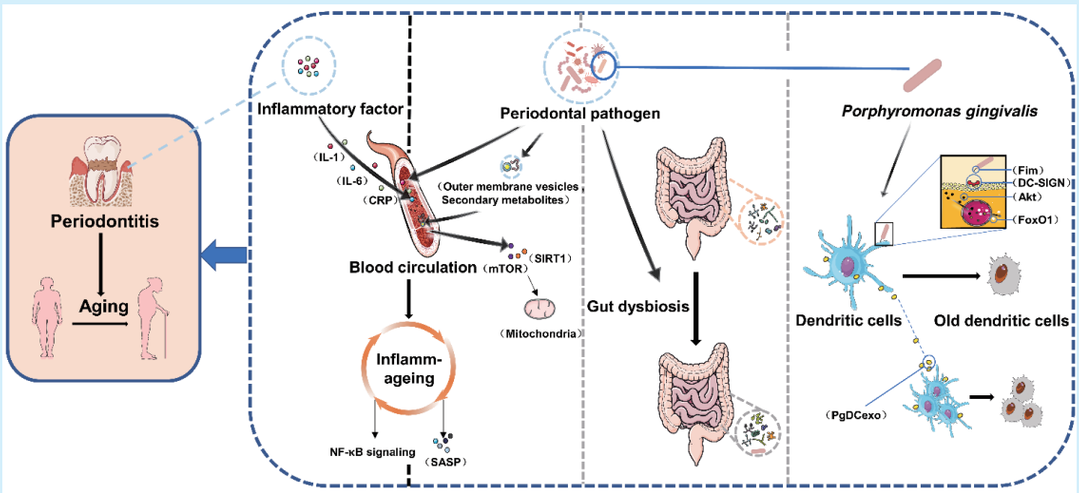

IL-1: interleukin-1; IL-6: interleukin-6; CRP: C-reactive protein; SIRT1: silent information regulator 1; mTOR: mammalian target of rapamycin; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cell ; SASP: senescence associated secretory phenotype; Fim: Fimbriae; DC-SIGN: DC specific intercellular adhesion molecule-3-grabbing nonintegrin; Akt: protein kinase B; FoxO1: forkhead box O1; PgDCexo: exosomes of DCs cocultured with *P. gingivalis*

Figure 1　Mechanisms associated with periodontitis accelerating aging in the population

图1　牙周炎加速人群衰老的相关机制

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