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血小板与牙周炎相关性的研究进展

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【摘要】 血小板是血液循环中的小细胞碎片,除了与止血和血栓形成密切相关外,还参与了免疫炎症反应,在炎症中发挥着重要作用。牙周炎是由牙周致病菌感染引起的慢性炎症性疾病,造成了局部和全身的炎症反应,与许多全身疾病的发展有关。近年来,许多以动物和人体为对象的研究从血液、牙龈和龈沟液3个方面证明了牙周炎与血小板的相关性,并且发现活化的血小板在牙周炎的发生发展中起着十分重要的作用,可能的机制是牙龈卟啉单胞菌(*Porphyromonas gingivalis*, *P.g*)和炎症介质S100A8/A9引起血小板的聚集和活化,活化后的血小板与白细胞结合形成血小板-白细胞聚合物并迁移到牙周组织中,产生促炎因子,参与牙周组织的免疫炎症反应,促进牙周炎的发生和发展。研究还表明,牙周基础治疗可降低血小板活化程度,使血小板-白细胞聚合物的形成减少,这可能降低牙周炎患者患心血管疾病(cardiovascular disease, CVD)的风险;并且血小板活化抑制药物能够抑制牙周炎症和促进牙周组织修复。此外,*P.g*诱导的血小板上CD40L的表达还可能是牙周炎与心血管疾病之间的重要介质。因此,血小板作为参与牙周炎发生发展的重要炎症细胞,有望成为一个新的、潜在的治疗靶点。本文主要对牙周炎与血小板相关性的最新研究进展进行综述。

【关键词】 牙周炎; 血小板; 血小板指数; 血小板活化; 血小板-白细胞聚合物; 炎症; 牙周致病菌; 心血管疾病

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【Abstract】 Platelets, small cell fragments in the blood that prevent bleeding, are closely associated with hemostasis and thrombosis and play an important role in the inflammatory response. Periodontitis is a chronic inflammatory disease caused by periodontopathogenic bacteria, resulting in local and systemic inflammatory responses that are associated with many systemic diseases. In recent years, several animal and human studies have demonstrated the correlation between periodontitis and platelets from three aspects: gingiva, and gingival crevicular fluid, and found that activated platelets play a very important role in the development and progression of periodontitis. *Porphyromonas gingivalis* and inflammatory mediators S100A8/A9 activate platelets, which then combine with leukocytes to form platelet-leukocyte aggregates. These aggregates can migrate into periodontal tissue, producing proinflammatory cytokines, thereby promoting the development and progression of periodontitis. Available studies also suggest that initial periodontal therapy reduces platelet activation and platelet-leukocyte aggregate formation, which may reduce the risk of cardiovascular diseases (CVDs) in patients with periodontitis. Additionally, studies found that antiplatelet drugs can inhibit periodontal inflammation and promote periodontal tissue repair and that *P. gingivalis*-induced expression of CD40L on platelets may be an important mediator between periodontitis and CVD. These reports suggest that platelets can serve as novel therapeutic targets for the

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treatment of periodontitis. This review aims to discuss the current literature on the correlation and interaction mechanisms between periodontitis and platelets.

【Key words】 periodontitis; platelets; platelet indices; platelet activation; platelet-leukocyte aggregates; inflammation; periodontopathogenic bacteria; cardiovascular disease

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血小板是外周血中第二常见的细胞类型,是由源自骨髓和肺的巨核细胞制造的大小和密度不一的无核血细胞^[1]。大量证据表明,血小板也是炎症细胞,在免疫识别、炎症损伤的过程中,血小板的作用不可忽视^[2]。血小板不仅可以直接与中性粒细胞、内皮细胞等相互作用,还可以通过分泌免疫介质间接调节其他炎症细胞^[3]。牙周炎是由菌斑微生物引起的慢性炎症性疾病,在牙周炎的发生和发展过程中,炎症细胞和细胞因子在宿主反应中发挥重要作用。牙周炎除了会引起局部炎症反应外,还会造成广泛的全身影响^[4]。牙周组织炎症导致牙周袋形成和上皮内溃疡,这会引发细菌入血而造成一过性菌血症和全身性炎症,全身性炎症使血小板计数增加并促进血小板活化^[5]。血小板活化后释放促炎介质并暴露促炎受体,从而促进血小板与白细胞结合^[6]。血小板的这一功能使其成为炎症反应的重要参与者。此外,血小板活化与心血管疾病(cardiovascular disease, CVD)的发展有关^[7],因此牙周炎可能通过促进血小板活化而与CVD之间具有相关性。本文对牙周炎与血小板的相关关系及相互作用机制进行综述,以期为后续的相关研究提供参考依据。

1 血小板与牙周炎具有相关性的证据

1.1 动物研究

在过去的研究中,很多学者通过建立实验性牙周炎的小鼠模型对血小板与牙周炎的相关性进行探索,发现并证明了血小板与牙周炎的发生发展有一定的相关性。Zhang等^[8]建立了小鼠实验性牙周炎模型,收集龈沟液(gingival crevicular fluid, GCF)和牙龈组织进行免疫细胞化学染色和免疫组化分析,发现牙周炎初始阶段GCF和牙龈组织中仅有少量血小板存在,随着实验时间延长血小板

的浸润增多,这表明血小板可能参与了小鼠实验性牙周炎的发生发展。Silva等^[9]利用二磷酸腺苷对牙周炎大鼠血液中血小板的聚集程度进行检测,发现牙周炎大鼠中血小板聚集程度较高。Zhan等^[10]采集牙周炎小鼠的血液,检测血小板活化程度及血小板-白细胞聚合物的形成,结果表明牙周炎诱导血小板活化和血小板-白细胞聚合物的形成,并且牙周炎随着血小板-白细胞聚合物数量的增多而加重,因此血小板在牙周炎的炎症和组织损伤中起着至关重要的作用,是牙周组织的炎症介质。

1.2 人体对象研究

Papapanagiotou等^[11]比较了健康人和牙周炎患者全血中sP-selectin和血小板膜糖蛋白IIb/IIIa复合物(conformation of the glycoprotein IIb - IIIa complex, PAC-1)的水平,发现牙周炎患者血浆sP-selectin水平和血小板结合PAC-1的比例显著升高,从而证明了牙周炎与血小板的活化相关。Zhan等^[12]对广泛性侵袭性牙周炎(generalized aggressive periodontitis, GAgP)患者和健康人牙龈组织标本进行检测,发现健康牙龈组织中仅存在散在、孤立的小血小板,而炎症较重的牙龈组织中,血小板浸润范围和程度明显大于健康牙龈组织及轻度炎症的牙龈组织,这一研究结果表明在牙龈组织中,炎性浸润的范围和程度与血小板浸润程度呈正相关。Zhang等^[13]对20例牙周炎患者和10例健康人的GCF进行研究,发现牙周炎患者GCF中可见大量血小板-中性粒细胞聚集;并利用体外实验观察血小板与牙周病原体牙龈卟啉单胞菌(*Porphyromonas gingivalis*, P.g)和具核梭杆菌(*Fusobacterium nucleatum*, F.n)的相互作用,发现血小板可招募和吞噬牙周病原体,并且促进中性粒细胞胞外陷阱(neutrophil extracellular traps, NETs)的形成,该研究

表明血小板迁移到龈沟,可直接或协助中性粒细胞发挥抗菌作用。综上,不论是动物研究还是人体对象研究都从血液、牙龈、龈沟液3个方面证明了血小板与牙周炎的相关性。

血小板指数(platelet indices, PI)是血小板活化的主要指标,包括血小板计数,平均血小板体积(mean platelet volume, MPV),血小板压积(platelet-crit, PCT)和血小板分布宽度(platelet distribution width, PDW)。MPV是衡量血小板活性的重要指标,在多种慢性炎症性疾病中可作为炎症、疾病活动性和抗炎治疗效果的标志^[14]。Ustaoglu等^[15]对57例慢性牙周炎患者的血液进行分析检查发现,与健康对照组相比,牙周炎患者中MPV和PCT水平更高。另一项研究表明,MPV和PCT水平可能是牙周炎严重程度的预测指标,因其发现与中度牙周炎患者和健康个体相比,重度牙周炎患者的MPV和PCT水平显著升高^[16]。但其他研究有不同的结论,研究发现临床牙周参数与MPV、PCT水平呈负相关,并且牙周炎患者的MPV水平低于健康对照组,而积极牙周治疗(active periodontal treatment, APT)后MPV水平上升并接近健康对照组^[17-18],这一相反的研究结果可能是因为血小板大小与全身炎症程度有关,在重度炎症性疾病中,大量高度反应性的大血小板迁移至炎症部位并被大量消耗,从而使MPV下降^[19]。虽然上述研究证明血小板指数与牙周炎具有相关性,但它们之间的具体关系仍需进一步明确。

血小板与淋巴细胞比率(platelet-to-lymphocyte ratio, PLR)与牙周炎有关,被认为是一种新兴的炎症生物标志物,可以阐明牙周炎与全身性疾病之间的联系,并可作为牙周炎预后和分级的参考指标^[20]。Acharya等^[21]对慢性牙周炎患者牙周基础治疗前后的PLR水平和临床牙周参数进行检测发现,治疗后的PLR水平和临床牙周参数显著降低。但Lu等^[22]发现,血小板指数和PLR在GAgP患者和健康对照组之间没有显著差异,也与牙周临床参数没有相关性,这一不同的结果可能是因为相比血小板的绝对数量,血小板的活化和功能在GAgP患者的免疫炎症反应中发挥更重要的作用。因此,尚需更多的研究来明确PLR与牙周炎之间的关系。

2 血小板参与牙周炎发生发展的可能机制

通过对国内外研究进行回顾分析,发现牙周

致病菌 *P.g* 和炎症介质 S100A8/A9 可引起血小板的聚集和活化,活化后的血小板通过与白细胞结合形成血小板-白细胞聚合物来参与牙周炎的发生和发展。

2.1 血小板的聚集和活化

P.g 是一种能够诱导口腔微生物菌群失调的关键病原体^[23],它被认为是牙周炎发生和发展的致病因素。*P.g* 表达广泛的毒力因子,其中一个主要的毒力因子是牙龈素(gingipains)^[24]。牙龈素能够裂解血小板表面的蛋白酶活化受体(protease activated receptors, PARs)^[25],这些受体的激活引起信号传导,诱导血小板聚集。并且 *P.g* 可以通过口腔治疗或常规口腔卫生维护过程进入血液循环,可引起包括血小板在内的多种血细胞的功能反应。表面形成细胞突起和延伸,这是被激活、扩散的血小板的特征^[26]。这种形状的改变取决于血小板肌动蛋白细胞骨架的快速组装和重排^[26]。肌动蛋白细胞骨架由球状单体亚基(g-肌动蛋白)组成,g-肌动蛋白在细胞膜上迅速组装成丝状聚合物(f-肌动蛋白)^[26],这些富含f-肌动蛋白的细胞延伸的形成是由Rho GTPases的低分子量蛋白质调控的。并且,丝状伪足是最早形成的血小板突起,其在血小板中的形成是由小GTPase Cdc42特异性催化的^[27]。因此Cdc42在血小板的活化中至关重要。Senini等^[28]研究发现了 *P.g* 的脂多糖(lipopolysaccharide, LPS)能够激活血小板Cdc42并刺激血小板肌动蛋白组装和扩散,导致血小板形状的改变,这是血栓形成的关键步骤。LPS是 *P.g* 的另一个主要毒力因子^[29]。Whitaker等^[30]研究表明,牙周致病菌福赛坦纳菌(*Tannerella forsythia*, Tf)也可以促进血小板的聚集,但其并未阐明具体机制。

炎症介质也可诱导血小板活化。有研究表明牙周感染会导致血浆S100A8/A9水平升高^[31]。胞外S100A8/A9能够结合靶细胞上的受体,包括CD36^[32]、晚期糖基化终末产物受体(receptor for advanced glycation end, RAGE)^[33]和Toll样受体4(Toll-like receptor 4, TLR4)。血小板表面表达CD36^[32]和RAGE^[33],这两种信号都与血小板活化直接相关。Zhan等^[12]体外验证发现rhS100A9或rhS100A8/A9可诱导健康人及GAgP患者全血血小板活化并且来自GAgP患者的血小板对rhS100A9或rhS100A8/A9的激活具有更高的敏感性。

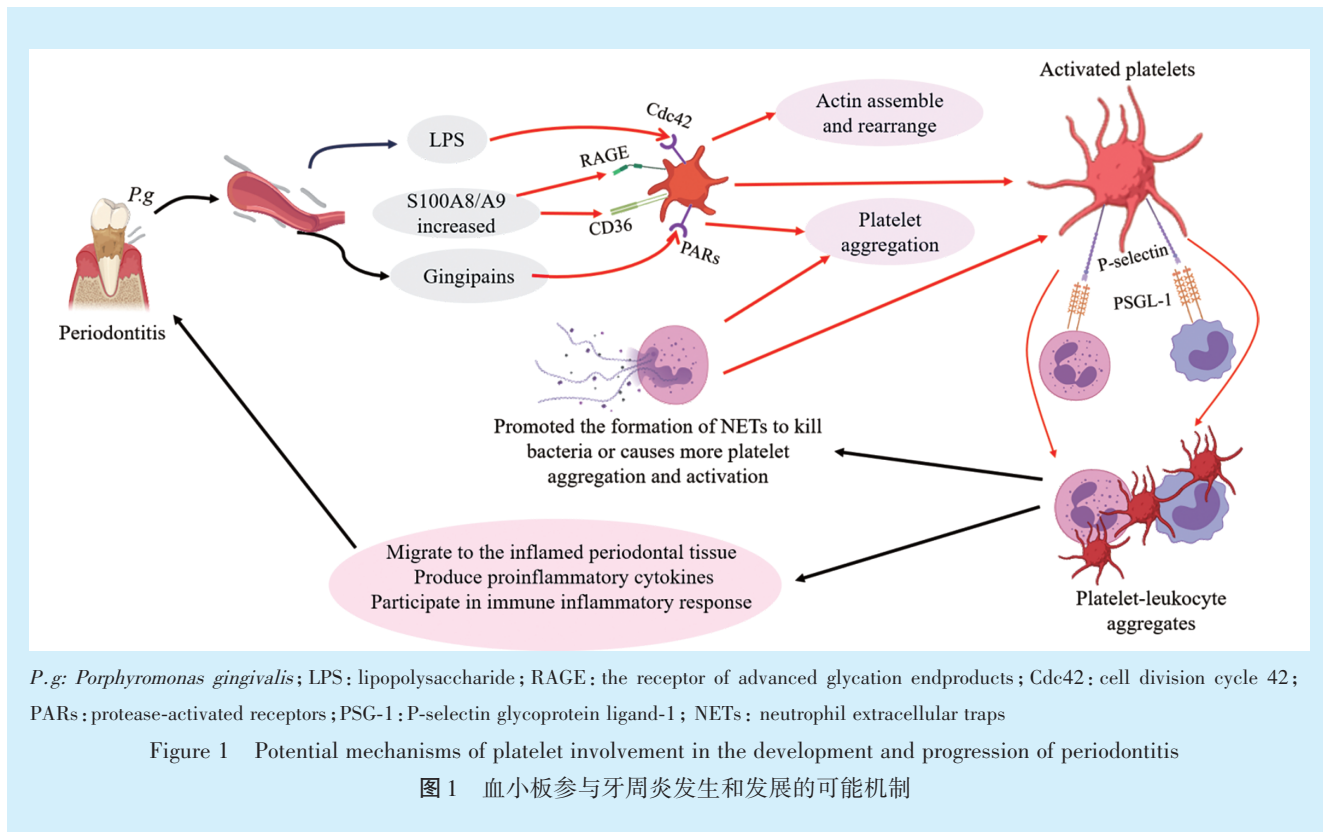
以上研究表明, *P.g* 和炎症介质 S100A8/A9 分别通过牙龈素、LPS 和 CD36、RAGE 受体来引起血

小板的聚集和活化。

2.2 血小板-白细胞聚合物的形成和作用

免疫炎症反应需要白细胞通过血管内皮系统滚转、黏附和迁移到炎症组织中,从而参与宿主防御。血小板-白细胞聚合物的形成可促进上述过程^[34]。当血小板被激活时,它们在表面表达CD62P(又称P-Selectin)和PAC-1^[35]。PAC-1会与多种黏附蛋白特异性结合,加速血小板-纤维蛋白原-血小板的聚集引起血小板血栓^[36]。CD62P与中性粒细胞和单核细胞上的P-选择素糖蛋白配体1(P-selectin glycoprotein ligand 1,PSGL-1)受体结合,形成血小板-白细胞聚合物(图1),这是血小板

活化和白细胞招募到炎症部位的关键步骤^[37]。Chen等^[38]研究了人全血中血小板和中性粒细胞对*P.g*的反应,发现*P.g*促进了血小板的活化并形成血小板-中性粒细胞聚合物,进一步导致了NETs的释放,NETs一方面会引发更多的血小板聚集和活化,另一方面会参与杀菌作用。研究还表明,血小板-白细胞聚合物的形成比未形成的细胞产生更多的促炎因子,并能迁移到牙周组织中参与免疫炎症反应,造成结缔组织破坏和骨吸收,并且牙周炎的进展随着血小板-白细胞聚合物数量的增加而加快^[12]。因此,上述研究表明血小板-白细胞聚合物可能参与了牙周炎的发生和发展。



3 牙周基础治疗可降低血小板的活化程度

研究表明,牙周炎的成功治疗伴随着全身炎症标志物如C反应蛋白(C-reaction protein,CRP)的下降^[39]。Arvanitidis等^[40]对25例牙周炎患者进行牙周干预,发现牙周状况的改善伴随着血小板反应性的显著降低,这表现为CD62P(在活化后的血小板和内皮细胞表面表达,介导白细胞与这些活化细胞的黏附)表达降低,血小板-白细胞聚合物的形成减少。Laky等^[41]研究表明牙周基础治疗可最大限度地减少牙周炎患者血小板活化的程

度,这可能减少牙周病患者患其他相关疾病的风险;还分析了血小板的RNA含量,发现未经牙周治疗的牙周炎患者的血小板RNA含量高于治疗组(血小板RNA含量越高,未成熟血小板的反应性越强)。Zhan等^[17]对59例GAgP患者进行积极牙周治疗,3个月后复查探诊深度(probing depth,PD)、附着丧失(attachment loss,AL)和出血指数(bleeding index,BI)并检测血小板指数的变化,发现牙周治疗后MPV显著升高并且MPV的升高与BI的降低具有统计学意义。上述研究表明,牙周治疗可

降低血小板的反应性及血小板的活化程度,并且使血小板-白细胞聚合物的形成减少,但具体机制仍需进一步研究。

4 血小板活化抑制药物对实验性牙周炎的影响

既往研究已证明了血小板与牙周炎的相关性,并且对其机制进行了阐明,发现血小板活化在牙周炎的发生发展中起着十分重要的作用,因此,血小板活化抑制药物有可能通过减弱血小板活性从而对牙周炎产生积极的作用。

两项研究^[10,42]对实验性牙周炎的小鼠分别使用血小板活化抑制药(阿司匹林或氯吡格雷)治疗后发现,小鼠釉牙骨质界(cemento enamel junction, CEJ)与牙槽嵴顶距离显著缩短,并且可显著减少血小板-白细胞聚合物的形成。这表明血小板活化抑制药物(阿司匹林,氯吡格雷)能够降低血小板活化的水平,减轻牙周炎症。可能的机制包括氯吡格雷这种噻吩吡啶类抗血小板药物能够降低炎症标志物(如p-selectin、CD40受体、组织因子)的表达,并改善内皮细胞功能^[43];而阿司匹林作为一种非甾体类抗炎药可以抑制炎症反应^[44]。此外,还有一项研究表明阿司匹林与氯吡格雷联合应用能够减弱牙周致病菌 *T.f* 对血小板的聚集作用^[30]。但关于血小板活化抑制药物对牙周炎作用机制的研究尚有不足,且相关研究较少,因此今后仍需进一步的临床和实验室研究来了解抗血小板药物在抑制牙周炎症和促进牙周组织修复中的作用。

5 血小板可能是牙周炎与心血管疾病之间的重要联系

炎症在动脉粥样硬化的发病机制中起着重要作用,牙周炎被认为与CVD的发展有关。Assinger等^[45]收集26例牙周炎患者和19例健康人的全血,研究牙周病原菌伴放线聚集杆菌(*Actinobacillus actinomycetemcomitans, A.a*)和 *P.g* 对CD40L表达的影响,发现 *P.g* 通过Toll样受体2(toll-like receptor 2, TLR2)和TLR-4诱导人血小板上CD40L的表达,而CD40L及其受体CD40是血管系统炎症通路的重要组成部分^[46]。血小板释放的CD40L诱导内皮细胞的炎症反应,它启动活性氧的形成,抑制一氧化氮的生成,释放趋化因子,以及增加多种黏附受体和组织因子的表达^[47]。此外,最近的研究结果表明,CD40L可能是斑块不稳定性的一个重要预测因子^[48],并且CD40L已被确定为急性冠脉综合征

(acute coronary syndrome, ACS)和卒中的预测因子^[49]。因此,牙周致病菌诱导血小板上CD40L的表达可能是牙周炎与CVD之间的介质。

血管内血栓的形成也是动脉粥样硬化的一个诱因,Chen等^[50]用 *P.g* 预处理人全血,然后用PFA-100在高剪切条件下测量血小板血栓的形成,发现 *P.g* 可以通过启动信号通路来激活血小板,从而增强血小板血栓形成潜能。Lee等^[51]使用单细胞RNA测序分析比较了11例健康受试者和10例牙周炎患者的血小板转录谱,发现在牙周炎患者中凝血相关的基因转录水平上调。以上结果提示,牙周炎促进了血栓的形成和动脉粥样硬化的进展。

Androsz-Kowalska等^[52]对伴或不伴冠心病的慢性牙周炎患者进行牙周和血液学的检查,发现PD和临床附着水平(clinical attachment level, CAL)与MPV之间存在微弱正相关,这表明PD和CAL与冠心病患者的MPV之间具有相关性。

牙周炎可导致血小板-白细胞聚合物的形成,其在心血管疾病中也得到了广泛的研究。有症状冠心病患者的血小板-白细胞聚合物水平高于健康人^[53]。与健康受试者相比,ACS患者中含有单核细胞的血小板-白细胞聚合物增加^[54]。同样,与非心源性胸痛组相比,ACS或慢性冠脉综合征(chronic coronary syndrome, CCS)患者的血小板-单核细胞聚集水平更高。因此,血小板-白细胞聚合物有可能是牙周炎与CVD之间的介质,但潜在的病理生理学机制仍需进一步研究。

以上研究从血小板CD40L表达、牙周炎促进血小板血栓形成、牙周参数与冠心病患者MPV相关性以及血小板-白细胞聚合物这4个方面,证明了血小板是牙周炎与CVD之间的重要联系。

6 小结

大量的动物和临床研究从血液、牙龈、龈沟液3个方面证明了血小板与牙周炎密切相关。牙周致病菌 *P.g* 及其毒力因子,炎症因子S100A8/A9引起血小板活化并与白细胞结合形成血小板-白细胞聚合物,血小板-白细胞聚合物会参与牙周结缔组织破坏和骨破坏,并与CVD的发生密切相关。牙周基础治疗和抗血小板活化药物治疗后可使血小板-白细胞聚合物形成减少。因此,血小板可能是一个新的、有效的治疗靶点,这不仅有利于牙周炎的治疗,还可能降低CVD的风险。但仍需要大量的分子、微生物、动物和临床研究来解释血小板在

牙周炎和CVD中的具体作用和机制,为临床牙周炎的治疗及CVD的预防提供更具体的指导。

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