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· 综述 ·

牙龈上皮细胞在牙周稳态维持中的作用及机制

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【摘要】 牙周稳态由牙龈上皮屏障、软组织细胞外基质、骨偶联系统以及牙周区域免疫之间复杂的交互作用共同塑造形成。牙龈上皮细胞主要由角质形成细胞和少数非角质形成细胞组成, 参与构成牙龈上皮屏障。上皮屏障具有抵抗病原体、外源物质和机械应力的基本功能。本文综述了牙龈上皮细胞在牙周稳态维持中的作用及其机制, 旨在深入阐明两者之间的内在联系。牙龈上皮细胞可通过多种途径参与维持牙周稳态: ① 牙龈上皮细胞可以通过自身增殖迁移、上皮-间充质转化和发生细胞凋亡, 产生中性粒细胞外诱捕网等途径来应对牙周炎症环境, 维持牙周稳态; ② 当牙龈上皮屏障遭到破坏后, 入侵的脂多糖无法通过局部反应清除, 牙龈上皮细胞也能够通过自身固有免疫反应来应对外界病原刺激入侵, 维持牙周稳态; ③ 牙龈上皮细胞与口腔微生物及免疫细胞的相互作用也是牙周稳态维持的重要途径。因此, 牙龈上皮细胞是牙周稳态维持过程中不可或缺的存在。但牙龈上皮细胞在牙周稳态维持中的重要作用及相关机制仍未阐述, 这为牙周稳态医学研究提供更多新的研究思路。

【关键词】 牙龈上皮细胞; 牙周稳态; 上皮屏障; 上皮间充质转化; 细胞凋亡; 免疫反应; 口腔微生物; 免疫细胞

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【Abstract】 Periodontal homeostasis is regulated by the complex interplay between the gingival epithelial barrier, the extracellular matrix of soft tissues, the bone coupling system, and immune responses within the periodontal region. Gingival epithelial cells are primarily composed of keratinocytes and a small proportion of non-keratinocytes, and they are integral to the formation of the gingival epithelial barrier. This epithelial barrier plays a fundamental role in defending against pathogens, exogenous substances, and mechanical stress. This study aims to explore the intrinsic connections between gingival epithelial cells and periodontal homeostasis. Research has shown that gingival epithelial cells participate in maintaining periodontal homeostasis through multiple pathways: ① gingival epithelial cells respond to the inflammatory environment by undergoing proliferation, migration, epithelial - mesenchymal transition, and forming apoptosis-

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mediated neutrophil extracellular traps; ② when gingival inflammation damages the epithelial barrier, lipopolysaccharides cannot be easily removed, and gingival epithelial cells play a defensive role by activating innate immune responses; ③ the interactions of gingival epithelial cells with oral microbiota and immune cells are essential for maintaining periodontal homeostasis. Thus, gingival epithelial cells are closely associated with periodontal homeostasis. However, the crucial role and mechanisms of gingival epithelial cells in the maintenance of periodontal homeostasis are not clear, which provides novel insights for the research of periodontal homeostatic medicine.

【Key words】 gingival epithelial cells; periodontal homeostasis; epithelium barrier; epithelial-mesenchymal transition; apoptosis; immune responses; oral microorganisms; immune cell

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稳态医学的概念于2022年被提出,其聚焦于疾病根源,探索分子、细胞、器官、系统等多层次的稳态平衡及调控策略。在生理条件下,牙龈上皮受丰富的菌群和食物持续刺激,与牙周局部的龈上下菌群、软组织细胞外基质以及骨偶联系统共同构成一个复杂的调控网络,共同维持着牙周稳态^[1-2]。作为牙周支持组织的重要组成部分,牙龈上皮细胞不仅参与构成口腔与外界环境之间的屏障,还在修复牙周组织损伤和调节局部免疫反应中发挥关键作用^[3-4]。近年来,研究表明牙龈上皮细胞通过细胞增殖迁移^[5-6]、上皮间充质转化(epithelial-mesenchymal transition, EMT)^[7-8]以及细胞凋亡^[9]等多种机制参与牙周炎的发生与发展,同时,在面临病原微生物和损伤刺激时,牙龈上皮细胞通过固有免疫反应进行防御,牙龈上皮与口腔微生物及免疫细胞的相互作用,对维持牙周稳态均具有重要意义^[10]。本文概述了牙龈上皮细胞在牙周稳态维持中的重要作用及机制的研究进展,以为牙周稳态医学研究提供更多新的研究思路。

1 牙龈上皮细胞在牙周炎症环境中面临的挑战

1.1 生理机械性刺激导致牙龈上皮机会性感染

咀嚼或刷牙过程中产生的牙龈摩擦可导致生理机械性损伤,进而破坏上皮间紧密连接,最终由于机械应力的作用导致上皮结构的破裂^[11-13]。并且,食物团块与牙刷对口腔牙龈施加的间歇性压力,将龈沟或牙周袋内的内容物,包括龈沟液及其细菌,压向牙周袋上皮,活细菌在短时间内大量穿透破裂的紧密连接或小伤口,深入上皮下组织,甚至达到小静脉,之后转移到血液循环中,从而引

发一过性菌血症^[14]。牙龈起源的短暂性菌血症是牙龈发炎的特征^[15]。

1.2 口腔病原体及毒力因子入侵导致牙龈上皮屏障功能障碍

局部环境因素的改变可以导致牙龈上皮屏障功能障碍^[16]。口腔病原体及其毒力因子,如脂多糖(lipopolysaccharide, LPS)是导致局部牙龈上皮破坏的重要威胁^[17]。作为牙周病主要致病菌,牙龈卟啉单胞菌(*Porphyromonas gingivalis*, *P. gingivalis*)是牙周组织从健康向疾病转变的关键致病菌^[18]。研究发现,在*P. gingivalis*产生的大量毒力因子中,菌毛FimA以及牙龈蛋白酶K(gingipain R, Rgp)、牙龈蛋白酶P(gingipain K, Kgp)等可通过不同受体附着并侵袭牙龈上皮细胞^[19]。*P. gingivalis*中的牙龈蛋白酶还可以特异性地降解各种连接黏附分子,导致牙龈上皮对LPS、肽聚糖和牙龈蛋白酶的通透性增加^[20]。研究发现,伴放线菌团聚杆菌通过降低间隙连接相关蛋白的表达,抑制细胞间通讯;伴放线菌团聚杆菌外膜蛋白还能够特异性降解间隙连接蛋白,从而进一步减少细胞间相互作用^[21]。

2 牙龈上皮细胞应对牙周炎环境发生的反应

2.1 牙龈上皮细胞在牙周炎环境中的增殖和迁移

牙周袋是龈沟的病理性加深,是牙周炎最重要的病理改变之一。牙周袋形成后,机体为了修复局部组织破坏产生的缺损,会发生再上皮化过程,牙龈上皮细胞的增殖和迁移是保护牙周组织抵御各种感染的必要条件^[22-23]。牙龈上皮的增殖和迁移被证明和多种炎症因子相关。Stanton等^[24]采用将牙龈上皮组织暴露于LPS的方式来形成牙

周炎模型,发现组织样本中上皮细胞的增殖相关分子Ki67表达上调,这表明它们参与了细胞的再上皮化过程。Watanabe等^[25]将人牙龈上皮细胞在不同浓度的富血小板生长因子(Plasma rich in growth factor, PRGF)中处理48 h后发现,PRGF可以诱导牙龈上皮细胞白细胞介素-1(interleukin-1 β , IL-1 β)合成以促进其增殖和迁移,在进一步发生的组织伤口修复及再上皮化过程中起着重要的作用。Gürsoy等^[26]将人牙龈上皮细胞在不同浓度的人中性粒细胞防御素-1(human neutrophil defensin-1, HNP-1)培养20 h后发现,低浓度的HNP-1可以诱导牙龈上皮细胞的增殖和迁移,促进创口处组织愈合。

2.2 牙龈上皮的EMT及其在组织修复中的作用

2.2.1 牙周炎中牙龈上皮可以发生EMT EMT是上皮细胞在完全或部分丧失其原始表型后获得间充质表型的过程。根据生物学背景的不同,EMT分为3型:1型EMT发生在胚胎期,被认为是原肠胚形成和器官发育的不可或缺的机制^[27]。在成年期,2型和3型EMT分别被归类为导致器官纤维化和癌症转移的病理过程,牙周炎被认为属于2型EMT^[28-29]。研究表明,EMT和牙周炎有共同的危险因素和驱动因素,包括革兰氏阴性菌、炎症细胞因子、吸烟、氧化应激和糖尿病等^[30-32]。此外,EMT特征性变化,关键上皮标志物(如E-钙黏蛋白)的下调以及转录因子和间充质相关蛋白(包括Snail1、波形蛋白和N-钙黏蛋白)的上调,也发生在牙周炎中^[33-34]。

Klucnavská等^[35]对牙周病患者及牙周健康患者唾液样本进行检测,发现牙周炎患者样本中纤连蛋白、基质金属蛋白酶2(matrix metalloproteinase-2, MMP-2)和基质金属蛋白酶9(matrix metalloproteinase-9, MMP-9)等表达增加;Wadie等^[36]进行了一项包含36名参与者的牙龈样本的病例对照研究,发现牙周炎的严重程度与转录生长因子 β -1(transforming growth factor-beta 1, TGF- β 1)和波形蛋白等EMT标志物的表达成正相关。Bostanci等^[37]将10种体外生物膜侵入人牙龈上皮,结果表明,牙周炎患者的牙周袋中肉芽组织数量显著增加,且这一组织纤维化过程与上皮完整性的丧失与2型EMT的特征一致。

2.2.2 牙龈上皮细胞中的EMT过程可促进伤口组织修复 2型EMT对瘢痕组织形成和组织修复至关重要。在发生EMT的牙龈上皮细胞中,上皮细

胞相关基因表达被下调,如细胞角蛋白表达的下调有助于细胞骨架的重构,有利于伤口愈合^[38];而间充质特性相关基因被上调,如MMPs表达上调可以通过降解细胞外基质成分,促进细胞迁移,有利于组织修复^[39]。Kadeh等^[40]研究表明,通过EMT,牙龈上皮细胞转化为间充质细胞,合成细胞外基质成分,并通过收缩作用加速创口的愈合,在伤口愈合的重塑和成熟阶段发挥着关键作用。Saliem等^[41]从牙周炎患者和牙周健康患者中收集牙龈组织样本,发现与牙周健康患者相比,牙周炎患者牙龈上皮细胞中Snail1表达显著上调。这一结果提示EMT过程在创口愈合中的关键作用。综上所述,在长期炎症状态下,牙龈上皮可以发生EMT过程,促进组织伤口修复。

2.3 牙龈上皮细胞发生细胞凋亡及中性粒细胞外诱捕网(neutrophil extracellular traps, NETs)形成

2.3.1 牙龈上皮细胞存在细胞凋亡过程 关于牙周炎中牙龈上皮存在细胞凋亡的研究早有报道。Umesh等^[42]将临床健康牙龈组织暴露于慢性低浓度细菌刺激下,检测发现上皮中与凋亡相关的胱天蛋白酶3(Caspase-3)基因、DNA损伤基因和B淋巴细胞瘤-2基因(B-cell lymphoma-2, Bcl-2)普遍表达。Bostanci等^[37]通过对龈下生物膜刺激下的牙龈上皮细胞进行蛋白质组学分析,发现多种牙周病原体,如*P. gingivalis*、普雷沃氏菌和具核梭杆菌等,能够诱发细胞凋亡。细胞凋亡过程在刺激后24 h内显著活跃,Caspase-3和胱天蛋白酶8(Caspase-8)的表达水平明显表达上调。与此同时,牙龈上皮中同样存在抗凋亡机制。Huang等^[43]通过在牙周炎小鼠应用IL-22或敲除IL-22基因,发现IL-22能够有效抑制上皮细胞的凋亡。此外,牙龈上皮中的抑凋亡机制也得到了进一步的研究。有研究表明,IL-8可降低伴放线放线杆菌诱导的原代牙龈上皮细胞中caspase-3及Bcl-2的表达,从而展现出抗上皮细胞凋亡的作用^[44]。然而,这种调节作用并不足以完全抵抗细胞凋亡。

2.3.2 牙龈上皮细胞与NETs形成 NETs是一种由中性粒细胞释放的网状纤维结构,被认为是机体固有免疫的关键组成部分^[45]。现有研究表明,NETs不仅通过溶解基底膜影响上皮结构,而且能够通过杀死上皮细胞引起上皮溃疡的形成。Kim等^[46]发现NETs在牙周炎小鼠的牙龈组织中广泛存在,显著促进上皮细胞的裂解和坏死,提示炎症反应的加重。此外,有研究发现,NETs形成相关基

因的缺陷显著增加了个体患牙周炎的风险。Brenchley等^[47]发现先天性中性粒细胞减少症患者由于中性粒细胞弹性蛋白酶基因突变,表现出更高的严重牙周炎发生率。进一步的研究还表明,NETs的形成失调可增加牙周疾病的发生风险,尤其是在迟发性牙周炎中,多形核中性粒细胞的高反应性会导致过量NETs的产生^[48],这不仅加重上皮损伤,甚至还可能加剧牙周炎症的发展。

2.4 牙龈上皮细胞在牙周炎中的免疫反应

2.4.1 牙龈上皮细胞调控免疫调节因子的产生

研究表明,牙龈上皮细胞可作为关键细胞产生抗菌因子和趋化因子,这些因子不仅能够招募中性粒细胞,还能调控其他白细胞亚群的活性,进而介导炎症反应的发生^[49]。目前,已知与牙周炎相关的促炎细胞因子包括IL-1、IL-6和肿瘤坏死因子(tumor necrosis factor, TNF)家族成员。Bui等^[50]通过将人牙龈上皮细胞暴露于具核梭杆菌6 h,核苷酸结合寡聚化结构域样受体蛋白3(NOD-like receptor protein 3, NLRP3)炎症小体被激活,并促进IL-1 β 等促炎因子的释放。Tada等^[51]将人牙龈上皮细胞暴露于*P. gingivalis* 24 h后,评估了IL-33(IL-1家族成员)的表达,结果发现牙龈蛋白酶的表达显著增强了牙龈上皮细胞中IL-33的水平。Huang等^[43]通过转录组测序,比较了牙龈上皮细胞对口腔共生菌和机会致病菌的反应,发现牙龈上皮细胞在受到牙周致病菌刺激后,TNF- α 等促炎因子的表达显著增加。此外,研究还表明,TNF可能会增加牙周炎的易感性,而其他含有高水平TNF的全身系统性疾病(如糖尿病)也会显著提高个体对牙周炎的易感性^[52]。

2.4.2 牙龈上皮细胞自身产生抗菌肽发挥直接抗菌作用

抗菌肽是一类小型内源性聚阳离子分子,是先天性免疫系统的关键组成部分,广泛存在于多种组织中。LL-37和防御素是抗菌肽家族的重要成员,它们能够在牙龈上皮细胞中表达,并具有直接的抗菌活性^[53]。LL-37具有典型的 α 螺旋结构。其抗菌活性主要通过和细菌表面带负电的分子相互作用,以及破坏细胞膜实现^[54]。研究表明,LL-37对多种致病菌,如*P. gingivalis*、放线菌及链球菌等,表现出具有显著的抗菌作用^[55]。此外,LL-37还能够通过与脂多糖结合,激活脂多糖结合蛋白或受体,从而抑制脂多糖诱导的炎性细胞因子的产生,这一机制被认为有助于防止先天免疫系统过度反应,维持局部组织的免疫稳态^[56]。

另一种来自于牙龈上皮细胞的抗菌肽 β -防御素(β -defensins)具有显著的抗菌和抗病毒活性^[57-58]。在牙周健康的个体中, β -defensins-1和 β -defensin-2主要在牙龈上皮的颗粒层和棘层中表达。研究表明, β -defensins-2不仅具有直接的抗菌活性,还能通过促进上皮细胞的迁移和分化,参与牙周组织的修复和愈合过程^[59]。在外界刺激下,多种信号通路能够上调 β -defensins-2和 β -defensins-3的表达。尤其是在牙周炎患者的牙龈组织中,细菌及其代谢产物通过TLR受体依赖性或非依赖性途径调控 β -defensins的表达,从而增强局部免疫反应^[60]。

3 牙龈上皮细胞与微生物的相互作用

当前,口腔微生物群与牙龈上皮细胞的相互作用研究主要聚焦于牙龈上皮屏障功能。牙龈上皮细胞中的角质形成细胞通过跨膜复合物相互连接,维持上皮屏障的完整性。Nonaka等^[61]发现紧密连接蛋白的表达水平与*P. gingivalis*侵袭呈负相关,表明牙龈上皮细胞间紧密连接在抵御外界病原体入侵中的关键作用;此外,研究表明*P. gingivalis*分泌的牙龈蛋白酶可诱导宿主基质金属蛋白酶的表达,促进胶原降解,同时可通过调控N-钙粘蛋白、VE-钙粘蛋白及 β -整合素的表达,削弱细胞间及细胞-细胞外基质的黏附性,从而加速牙龈上皮细胞的脱落^[62]。

口腔共生菌与牙龈上皮的相互作用亦在维持牙周稳态中发挥重要作用。Shang等^[58]利用人类牙龈模型与源自唾液的多菌种生物膜共培养,发现健康牙龈在保持组织完整性的同时,可以维持多样且稳定的微生物群落;Helliwell等^[63]通过48 h的体外实验研究发现,血链球菌分泌的胞外膜囊泡(extracellular membrane vesicles, EMVs)可以保护牙龈上皮细胞免受牙周致病菌*P. gingivalis*的侵袭,防止牙龈上皮细胞死亡和脱落,维持口腔稳态。

4 牙龈上皮细胞与免疫细胞的相互作用

中性粒细胞为健康牙龈中占比最高的固有免疫细胞,主要通过防御病原体、调节炎症反应和与适应性免疫相互作用来维持牙周稳态。在牙龈健康状态下,中性粒细胞可以在趋化因子的引导下从血液迁移至龈沟液,形成抵御微生物入侵的屏障,维持牙龈上皮屏障的组织完整性^[64-65]。Silva

等^[66]发现,当长期微生物或机械刺激下导致牙周组织炎症状态时,牙龈上皮细胞会上调CXCL1、CXCL2和CXCL8等趋化因子的表达,促进中性粒细胞募集,表现出增强的炎症反应;Williams等^[49]通过对口腔黏膜上皮单细胞测序分析发现,牙龈上皮细胞可以与基质细胞通过分泌趋化因子(如CXCL8)协同促进中性粒细胞黏附与迁移,以维持局部稳态。

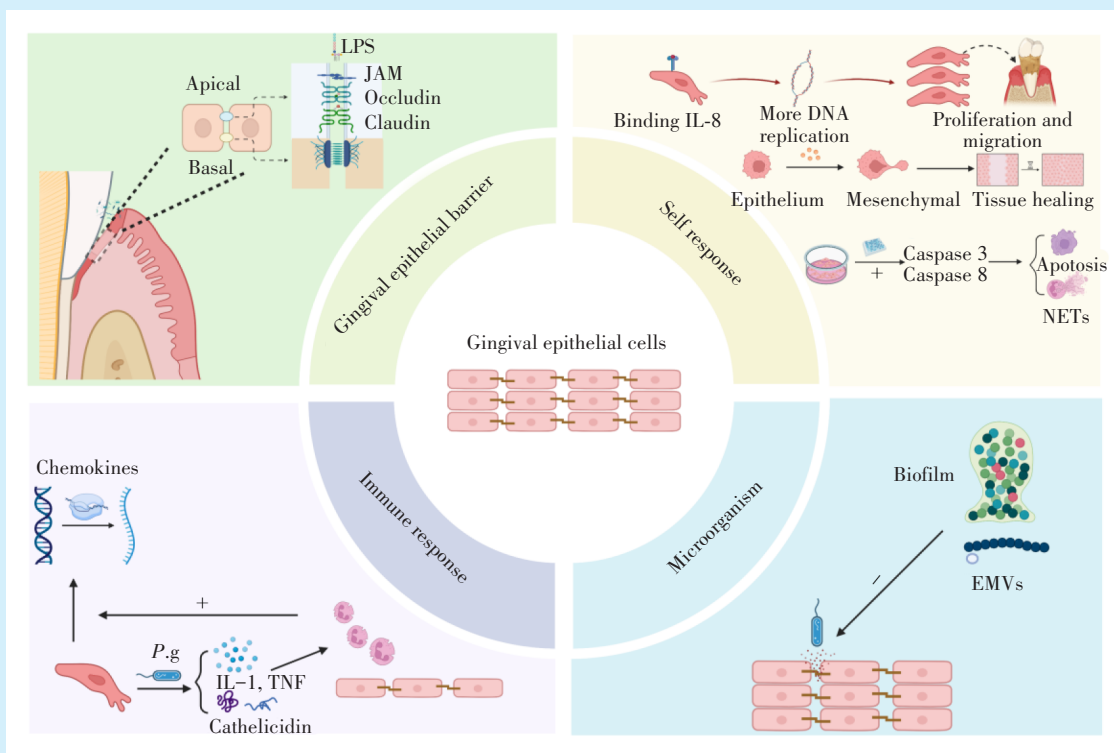
5 总结与展望

牙龈上皮细胞在牙周稳态维持中有重要作用,不仅作为物理屏障抵御外界病原,还通过调节免疫反应参与牙周炎的发生与发展。本文综述了牙龈上皮细胞在牙周炎中的作用机制,发现牙龈上皮通过多种途径应对牙周炎中的挑战。牙龈上皮细胞通过EMT、细胞增殖与迁移、细胞凋亡及NETs形成等方式,响应病原刺激,并调节局部免疫

反应。当牙龈上皮屏障受损时,牙龈上皮细胞还可通过固有免疫反应应对外界病原体,维持局部免疫稳态。牙龈上皮细胞与口腔微生物及免疫细胞的相互作用,同样是其参与维持牙周稳态维持的重要途径(图1)。

尽管目前的研究揭示了牙龈上皮细胞在牙周炎中的重要作用,但其具体机制仍不完全明确。首先,牙龈上皮细胞如何在长期的慢性牙周炎中维持免疫平衡尚需进一步研究。其次,牙龈上皮与牙周致病菌之间的相互作用以及细胞因子、抗菌肽在免疫反应中的协同作用仍需深入探索。此外,牙龈上皮在牙周组织修复过程中的作用,特别是在EMT和组织再生中的潜力,值得进一步关注。

未来的研究应结合现代分子生物学技术,如单细胞测序和基因编辑技术,深入探讨牙龈上皮在牙周稳态中的作用机制,尤其是在免疫调节和



Gingival epithelial cells can form a barrier with cell junctions such as JAM, preventing LPS invasion. Further, Gingival epithelial cells respond to the periodontal inflammatory environment through pathways such as proliferation and migration, EMT, apoptosis, and formation of NETs. Gingival epithelial cells can produce IL-1, TNF, cathelicidin, and chemokines to promote the production of neutrophils and initiate their innate immune responses to maintain periodontal homeostasis. Additionally, EMVs in the biofilm can protect gingival epithelial cells from the invasion of *P. gingivalis*. LPS: lipopolysaccharide; JAM: junctional adhesion molecule; IL8: Interleukin-8; NETs: neutrophil extracellular traps; *P. g*: *Porphyromonas gingivalis*; IL-1: interleukin-1; TNF: tumor necrosis factor; EMVs: extracellular membrane vesicles

Figure 1 Pathways and mechanisms of gingival epithelial cells in the maintenance of periodontal homeostasis

图1 牙龈上皮细胞在牙周稳态维持中作用途径及机制

组织修复中的具体功能。通过揭示牙龈上皮细胞在牙周稳态维持中的复杂作用,未来有望为牙周疾病的精准诊断和个性化治疗提供新的理论基础和临床策略。

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