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· 综述 ·

抗菌肽在牙周组织再生中的作用机制及应用进展

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【摘要】 牙周炎可导致牙周支持组织进行性破坏, 传统抗感染治疗难以兼顾感染控制与组织再生。随着抗菌药物耐药问题加剧, 开发兼具抗感染与促再生功能的新型生物活性分子成为研究热点。抗菌肽(AMPs)因其多靶点抗菌机制及免疫调节特性, 在牙周组织再生领域受到关注。现有研究表明, 抗菌肽不仅可抑制牙周致病菌及生物膜形成, 还可通过调节巨噬细胞极化、抑制炎症因子释放, 并激活 Wnt/ β -catenin、MAPK/ERK 等信号通路, 促进牙周膜干细胞及骨髓基质干细胞的成骨分化, 同时通过诱导血管内皮生长因子(VEGF)表达增强血管生成, 从而构建有利于牙周组织再生的免疫微环境。尽管抗菌肽在牙周组织再生中表现出良好前景, 但其体内稳定性、剂量安全性及长期作用机制仍有待进一步阐明。未来研究应聚焦于抗菌肽调控牙周免疫微环境及成血管-成骨耦合再生的分子机制, 并结合结构优化、智能递送体系及人工智能辅助设计策略, 加速新型抗菌肽的开发与临床转化。

【关键词】 牙周炎; 抗菌肽; 抗菌; 牙周组织再生; 免疫调节; 血管生成; 骨再生; 成血管-成骨耦合; 临床转化

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【Abstract】 Periodontitis leads to progressive destruction of periodontal supporting tissues, and conventional anti-infective therapies often fail to simultaneously achieve infection control and tissue regeneration. Due to the increasing threat of antibiotic resistance, the development of novel bioactive molecules with both anti-infective and pro-regenerative properties has become a focus of research. Antimicrobial peptides (AMPs), characterized by multi-target antimicrobial mechanisms and immunomodulatory functions, have attracted considerable attention in periodontal tissue regeneration. Current evidence indicates that AMPs not only inhibit periodontal pathogens and biofilm formation, but they also regulate macrophage polarization, suppress inflammatory cytokine release, and activate signaling pathways, such as Wnt/ β -catenin and MAPK/ERK. These effects promote osteogenic differentiation of periodontal ligament stem cells and bone marrow mesenchymal stem cells, while enhancing angiogenesis through VEGF induction, thereby establishing a favorable immune microenvironment for periodontal regeneration. Despite these promising findings, the in vivo stability, dosage safety, and long-term mechanisms of AMPs remain to be fully elucidated. Future studies should focus



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on clarifying the molecular mechanisms by which AMPs regulate the periodontal immune microenvironment and angiogenesis – osteogenesis coupled regeneration. In addition, integrating structural optimization, advanced delivery systems, and artificial intelligence-assisted peptide discovery may accelerate the development and clinical translation of novel antimicrobial peptides.

【Key words】 periodontitis; antimicrobial peptides; antibacterial; periodontal tissue regeneration; immunomodulation; angiogenesis; bone regeneration; angiogenesis-osteogenesis coupling; clinical translation

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近年来,随着人口老龄化进程加快和缺失牙修复方式的改变,慢性牙周炎的发病率逐年攀升,给患者的生活质量和医疗系统带来严峻挑战^[1-4]。上述疾病常伴有硬、软组织的破坏,传统治疗手段多以控制炎症、抑制感染为主,虽能缓解症状,却难以实现组织的完全修复和功能重建,为恢复牙周支持组织的结构与生理功能,牙周组织再生理念逐渐形成,并通过生物材料、活性因子及干细胞等策略推动再生治疗的发展^[5]。目前,再生治疗已取得一定进展,但其疗效仍高度依赖局部微环境状态,特别是感染控制、免疫反应平衡以及血管生成与成骨过程的协同调控^[6]。

当前牙周组织再生面临的核心科学问题在于^[7-9]:持续存在的牙周致病菌及生物膜增加再生失败风险;炎症反应失衡和破骨活性增强破坏再生环境;同时,多重耐药菌株的出现削弱了传统抗感染治疗效果。因此,如何在有效控制感染的同时调节免疫微环境并促进组织重建,成为牙周再生医学亟需解决的关键问题。

在此背景下,抗菌肽(antimicrobial peptides, AMPs)作为天然免疫系统的重要组成部分,因其广谱抗菌、抗真菌和抗病毒活性以及良好的抗耐药性而受到关注^[10-11]。抗菌肽是一类天然存在的小分子多肽,可直接杀灭多种病原微生物^[12]。更重要的是,研究发现抗菌肽不仅具备抗菌活性,还可调节宿主免疫反应,参与炎症控制及组织修复过程^[13],并作为口腔先天免疫的重要因子,在维持牙周局部微生态稳态中发挥关键作用^[14]。

鉴于抗菌肽兼具抗感染与再生调控功能,其在牙周组织再生中的作用机制及应用模式有必要进行系统梳理。因此,本文将围绕抗菌肽的结构与分类、作用机制及其在牙周组织再生中的应用进展进行综述,并探讨当前存在的挑战与未来研究方向,以期为其在牙周再生医学中的进一步发展提供理论依据。

1 抗菌肽的分类

1.1 结构分类

抗菌肽根据其分子结构可分为以下5类:① α 螺旋型抗菌肽,螺旋结构可以由氨基酸之间的氢键来稳定,形成亲水和疏水的两亲螺旋,主要通过插入细菌细胞膜形成孔道,导致细菌内容物泄漏^[15];② β 折叠型抗菌肽,通常由二硫键稳定。该结构是两亲性的,疏水残基和极性残基交替定位,便于细菌膜上的脂质双层结合,破坏膜的完整性,且具有抗降解的稳定性;③环状肽,是通过两个残基之间的共价键形成闭环结构,如主肽键、酯键、硫醚键或其他化学稳定的键。这种结构安排增强了它们的稳定性,使它们比线性肽更能抵抗蛋白水解降解。更适合用于高挑战的口腔环境;④伸展型抗菌肽,这些肽不形成常规的二级结构,主要是通过干扰DNA复制和蛋白质合成,具有灵活性和功能性^[16];⑤混合 α 螺旋和 β 折叠型抗菌肽, α -螺旋和 β -折叠类抗菌肽结合了 α -螺旋的柔韧性和 β -折叠的稳定性。结构中常通过形成二硫键来稳定,增强它们的抗菌活性和特异性,且能减少耐药性^[11]。

1.2 来源分类

动物来源抗菌肽:动物(如哺乳动物、昆虫和两栖动物等)能产生多种抗菌肽。例如,人类皮肤分泌的防御素就是一类重要的抗菌肽^[17]。

植物来源抗菌肽:一些植物合成的抗菌肽能够对抗细菌、真菌和病毒。例如,植物源抗菌肽对病原微生物具有抑制作用^[18]。

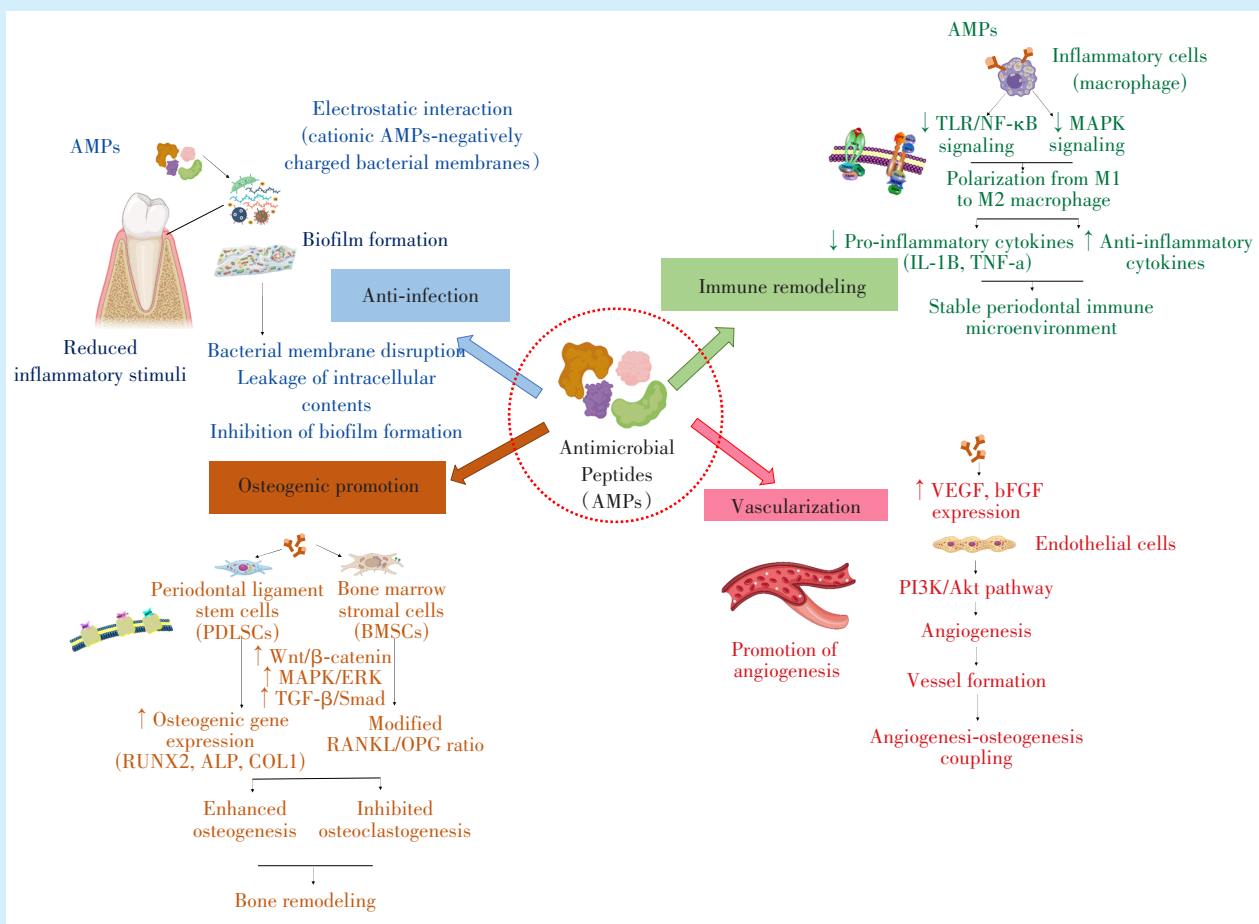
微生物来源抗菌肽:细菌、真菌和其他微生物也能合成抗菌肽,例如由细菌产生的细菌素就属于微生物来源的抗菌肽^[19]。

人工合成抗菌肽:通过化学合成或基因工程手段制备的人造抗菌肽,常用于研究和治疗。这些肽常常通过优化自然抗菌肽的结构而增强其效力或特异性^[20-21]。

2 抗菌肽的作用机制

抗菌肽有着多变的作用机制并且能够跟不同的分子靶标相互反应,从而大大减少了微生物耐

药性的产生可能,以下介绍了抗菌肽的不同作用机制(图1)。



TLR2/TLR4: Toll-like receptor 2/4; NF- κ B: nuclear factor kappa-B; Wnt/ β -catenin: Wnt/ β -catenin signaling pathway; MAPK/ERK: mitogen-activated protein kinase/extracellular signal-regulated kinase signaling pathway; RANKL/OPG ratio: ratio of receptor activator of nuclear factor- κ B ligand to osteoprotegerin; FPRL1/VEGFR2: formyl peptide receptor like-1/vascular endothelial growth factor receptor 2; FGFR: fibroblast growth factor receptor; JAK2/STAT3: Janus kinase 2/signal transducer and activator of transcription 3 signaling pathway; VEGF: vascular endothelial growth factor; bFGF: basic fibroblast growth factor. AMPs: antimicrobial peptides; TLR: toll-like receptor; IL-1 β : interleukin-1 beta; TNF- α : tumor necrosis factor alpha; PDLSCs: periodontal ligament stem cells; BMSCs: bone marrow stromal cells; TGF- β : transforming growth factor beta; Smad: mothers against decapentaplegic homolog; RUNX2: runt-related transcription factor 2; ALP: alkaline phosphatase; COL1: collagen type i; PI3K: phosphoinositide 3-kinase; Akt: protein kinase b

Figure 1 The mechanism of antimicrobial peptides in promoting periodontal tissue regeneration

图1 抗菌肽促牙周组织再生的作用机制

2.1 直接抗菌作用

关于抗菌肽是如何直接发挥作用的,其中最为熟知的机制就是其膜破坏作用,主要原因是抗菌肽通常带正电荷,而细菌表面带负电荷,两者间会产生表面电荷差。抗菌肽能够通过穿透并破坏细菌细胞膜,导致细胞内成分泄漏,从而杀死细菌^[22-23]。抗菌肽的膜溶解机制有几种不同的形式。

环孔模型:以抗菌肽 magainin II (PDB: 2MAG) 为代表,具体过程表现为多肽诱导脂质双分子层弯曲,形成由肽分子和脂质头基团排列的孔隙,这也可以发生在一个较不结构化的形式,称为无序环孔孔隙模型^[24]。

桶洞模型:以抗菌肽 polyphemusin I (PM1) (PDB: 1X7K) 为代表,多肽聚集在膜表面,并以肽

脂复合物的形式在双分子层上转运,形成短暂的不规则孔隙^[25]。在以抗菌肽 dermeidin (PDB: 2YMK)为代表的桶壁模型中,多肽垂直插入膜中并寡聚形成由多肽自身排列的跨膜孔^[26]。

地毯模型:以抗菌肽 aurein 1.2(PDB: 1VM5)为代表的毯样模型,多肽在膜表面积聚覆盖,当达到阈值浓度时,以类似洗涤剂的方式破坏双分子层^[27]。细菌膜双分子层完整性的破坏可能发生在阳离子 AMP 与阴离子膜分子相互作用后,这是通过革兰氏阴性细菌膜中阳离子肽和阴离子组分之间的静电相互作用来协调的。这些相互作用导致膜的不稳定,造成破坏作用,最终导致细胞内容物泄漏。

当抗菌肽在膜表面达到一定浓度时,便可通过类似洗涤剂的机制引发膜破裂,并最终导致膜的胶束化^[28]。尽管该类膜溶解机制对病原体具有显著杀伤力,但由于抗菌肽本身具两亲性,常常也可与哺乳动物细胞膜发生非特异性作用,导致宿主细胞毒性^[29]。这种“协同损伤效应”是制约抗菌肽临床转化应用的主要障碍之一。

2.2 免疫调节作用

抗菌肽不仅具有直接抗菌活性,还在宿主免疫调控中发挥重要作用。研究表明,抗菌肽可通过激活先天免疫信号通路、调控免疫细胞趋化及极化状态,对炎症反应进行精细调节。在感染早期,抗菌肽有助于增强宿主对病原体的免疫清除能力;而在炎症消退与组织修复阶段,其又可抑制过度炎症反应,降低促炎细胞因子水平,从而减少慢性炎症对组织造成的损伤。这种具有时间依赖性的免疫调节特性,使抗菌肽在口腔感染控制及术后组织修复过程中具有重要意义,并为后续再生微环境的构建奠定基础^[30-31]。

2.2.1 激活天然免疫与 Toll 样受体通路 抗菌肽是连接先天免疫与适应性免疫的重要桥梁。它们可以作为模式识别受体(pattern recognition receptors, PRRs)的激动剂,识别微生物相关分子模式(pathogen-associated molecular patterns, PAMPs),激活宿主细胞表面的 Toll 样受体(Toll-like receptors, TLR)家族,尤其是 TLR2 与 TLR4^[32]。这一激活过程能迅速引发下游 NF- κ B、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)等信号级联,诱导促炎细胞因子如 IL-1 β 、IL-6、TNF- α 的大量分泌,从而增强免疫系统对病原体的反应能力^[33]。

2.2.2 趋化免疫细胞,调控炎症定向反应 部分抗菌肽具有趋化功能,如 LL-37 可激活甲酰肽受体样 1(formyl peptide receptor-like 1, FPRL1)受体,吸引中性粒细胞和单核/巨噬细胞向感染区域迁移; hBD-2 与 hBD-3 则通过 C-C 趋化因子受体 6(C-C chemokine receptor 6, CCR6)调节记忆 T 细胞与树突状细胞的趋化。这种定向调控促进免疫细胞聚集于病灶区域,实现快速而精准的免疫应答^[34]。此外一些抗菌肽还可以调节巨噬细胞的极化从而影响后续的免疫反应,如人 β 防御素 3(human beta defensin 3, hBD3)可以促进 M2 型巨噬细胞的激活从而缓解牙龈卟啉单胞菌诱导的炎症^[24]。

2.2.3 抗炎与修复阶段的双向调节 抗菌肽具有炎症“双向调控”能力^[30]。在急性期,抗菌肽增强免疫清除能力;而在修复期则通过抑制 NF- κ B 持续活化、降低 IL-6 与 TNF- α 表达,促进巨噬细胞向 M2 表型极化,协助组织修复与抗瘢痕形成。这种时间与效应依赖性的动态调节,使抗菌肽在慢性炎症性口腔疾病中具备重要治疗潜力^[35]。

2.3 促血管生成

新生血管形成是组织再生过程中必不可少的部分,而抗菌肽不仅可以直接抗菌抗炎参与再生过程,还可以影响血管形成过程中细胞迁移功能和相关细胞因子的表达等,从而进一步证明了抗菌肽在牙周组织再生中的重要性。

2.3.1 诱导内皮细胞增殖与管腔形成 抗菌肽,尤其是 LL-37,可通过激活 FPRL1 与血管内皮生长因子受体 2(vascular endothelial growth factor receptor 2, VEGFR2)通路,促进内皮细胞如人脐静脉内皮细胞(human umbilical vein endothelial cells, HUVEC)的增殖、迁移与体外管腔样结构的形成。LL-37 还能上调基质金属蛋白酶-1(matrix metalloproteinase-1, MMP-1)与 MMP-9 的表达,分解基质障碍物,为内皮细胞提供穿行路径,加速新生毛细血管的构建过程^[36]。Takahashi 等^[37]研究发现 hBD3 可以激活 FGFR/JAK2/STAT3 信号通路,促进成纤维细胞和血管内皮细胞迁移与成管。

2.3.2 调控促血管因子表达 抗菌肽在巨噬细胞、成纤维细胞等免疫或基质细胞中,能诱导关键促血管因子的表达,包括 VEGF、bFGF 与 IL-8 等^[38]。如 LL-37 可刺激巨噬细胞分泌 IL-8,从而增强血管生成信号,为再生组织提供持续氧供与营养支持^[36]。

2.3.3 稳定新生血管与促进成熟 抗菌肽不仅促

进血管形成,也通过调节细胞间黏附分子-1(inter-cellular adhesion molecule-1, ICAM-1)与血管细胞黏附分子-1(vascular cell adhesion molecule-1, VCAM-1)等黏附分子表达,增强内皮细胞与基底膜的结合稳定性,防止新生毛细血管的早期回缩^[39]。这一机制对于维持牙龈与牙周组织再生中的血管网络完整性具有重要意义。

2.4 促骨生成与基质形成

除了以上作用外,抗菌肽还能激活 BMP/Runx2 等成骨信号通路,促进成骨细胞黏附、分化与矿化能力。

2.4.1 激活成骨信号通路 多种抗菌肽如 GL13K、LL-37 等,可激活 Wnt/ β -catenin 或 MAPK/ERK 等经典成骨信号通路,诱导成骨转录因子 RUNX2 的表达,提升碱性磷酸酶(alkaline phosphatase, ALP)、I 型胶原(type I collagen, COL1)、骨钙素(osteocalcin, OCN)等骨形成相关基因的转录水平,从而促进牙周膜干细胞或成骨前体细胞向成熟成骨细胞转化^[40]。

2.4.2 抑制破骨活性,调控骨重塑 抗菌肽可抑制炎症因子介导的破骨细胞分化,通过调节 RANKL/OPG 比值,抑制破骨细胞形成与骨吸收,从而维持骨重建的动态平衡^[41-42]。在慢性炎性破骨环境(如牙周炎)中,抗菌肽具有重要的骨保护功能。

2.4.3 与支架材料协同提升骨修复效果 抗菌肽可负载于生物支架或骨替代材料聚乳酸-羟基乙酸共聚物上,如[poly(lactic-co-glycolic acid), PLGA]、羟基磷灰石(hydroxyapatite, HA)、胶原等,提高局部成骨效率。

如 LL-37 修饰的 PLGA 支架在动物骨缺损模型中表现出显著的新骨形成量,且无明显炎症反应。这一策略已成为骨组织工程中实现“抗菌+成骨”一体化的重要方向^[43-44]。

2.4.4 促进“成血管-成骨耦合”协同再生 部分抗菌肽(如 LL-37)兼具促血管与成骨作用,能同步激活 VEGF 与 BMP 通路,协同调节血管-骨再生网络^[45-47]。这种“成血管-成骨耦合”机制在骨移植、牙槽骨重建等临床应用中具有巨大潜力。

2.5 多功能生物活性抗菌肽的结构—功能—应用整合

多功能生物活性抗菌肽的作用并非简单功能叠加,而是由其分子结构特征、作用靶点及递送方式共同决定。从结构—功能整合的角度,牙周组

织再生相关抗菌肽可按功能组合模式分为抗菌—免疫调节型、抗菌—成骨/再生促进型以及自组装或材料复合型。

抗菌—免疫调节型抗菌肽通常具有两亲性结构,既可靶向细菌膜结构,又能与宿主免疫受体相互作用,从而在清除病原体的同时调控炎症反应。例如,LL-37 可介导免疫细胞趋化并调节炎症信号通路^[28],hBD3 则可促进巨噬细胞向修复相关的 M2 表型极化,在抑制炎症的同时改善再生微环境^[24-26]。这类多功能性主要源于天然抗菌肽在宿主防御中的生理适应。

抗菌—成骨/再生促进型抗菌肽多由人工设计或序列优化获得,通过调控二级结构和电荷分布,在保留抗菌活性的同时增强对宿主细胞行为的调节能力。例如,GL13K 在抑制牙周致病菌及菌斑生物膜形成的同时,可促进成骨相关细胞分化,体现了人工设计抗菌肽的靶向多功能优势^[40]。

自组装与材料复合型抗菌肽可在局部微环境中形成稳定的三维结构,实现持续抗菌并为细胞黏附和组织再生提供支撑。通过与可降解高分子或无机材料复合,可进一步提高其局部滞留性和功能稳定性,实现抗感染与再生过程的协同调控。

总体来看,多功能抗菌肽的研究正由功能罗列向“结构—功能—应用”协同设计转变。未来,结合炎症微环境响应释放或多靶点协同调控策略,有望进一步提升抗菌肽在牙周组织再生中的精准应用潜力。

2.6 牙周组织再生相关代表性抗菌肽

在牙周解剖系统中,龈沟和牙周袋等微环境易形成复杂生物膜结构,持续感染可诱发免疫失衡及骨吸收增强。抗菌肽在牙周组织中不仅通过直接杀灭致病菌抑制生物膜形成,还可调节局部免疫微环境并参与组织再生过程^[48-49]。

在人源抗菌肽中, β -防御素和 cathelicidin 类抗菌肽是目前研究最为深入的代表。人 β 防御素 3(human beta-defensin 3, hBD3)可抑制 *P. gingivalis*-LPS 诱导的炎症反应,调节巨噬细胞极化,并促进成骨相关基因表达,从而改善炎症性骨破坏^[50-53]。LL-37 作为人类唯一的 cathelicidin 类抗菌肽,除具有广谱抗菌活性外,还可通过调控 NF- κ B、MAPK 等信号通路减轻炎症反应,并促进牙周膜细胞迁移、血管生成及成骨分化,在牙周组织再生微环境中发挥协同调控作用^[54-56]。

此外, GL13K 作为人源抗菌肽衍生肽, 可在抑制牙周致病菌的同时调节炎症相关信号, 并通过影响 RANKL/OPG 平衡促进成骨分化, 在炎症相关骨丧失模型中展现出再生潜力^[57]。Esculentin-1a (1-21)NH₂ 衍生肽则通过激活 PI3K/AKT 通路促进血管生成, 为牙周组织再生所需的成血管-成骨耦合提供支持^[58]。CATH-2 衍生肽被证实可抑制 NF-

κB 和 NLRP3 炎症小体活化, 降低促炎因子表达, 并在炎症微环境中保护成骨相关细胞功能, 从而为再生过程创造有利条件^[59]。

这些机制使得抗菌肽成为牙周疾病预防和治疗中的潜在靶点。表 1 中列出了牙周组织再生相关代表性抗菌肽的分子特征与功能介绍。

表 1 牙周组织再生相关代表性抗菌肽的分子特征与功能概述

Table 1 Molecular characteristics and functional overview of representative antimicrobial peptides involved in periodontal tissue regeneration

Antimicrobial peptide	Source	Structural features	Major target microorganisms	Immunomodulatory and regenerative functions	Main applications
LL-37 ^[54]	Human cathelicidin	α-helical	Gram-positive bacteria, Gram-negative bacteria, fungi	Suppresses NF-κB activation, induces M2 macrophage polarization, promotes angiogenesis and osteogenic differentiation via MAPK/ERK and Wnt/β-catenin pathways	Periodontal regeneration, periodontal defect repair
hBD3 ^[50-53]	Human β-defensin	β-sheet (disulfide-bond stabilized)	Gram-positive and Gram-negative bacteria	Modulates macrophage polarization, attenuates inflammatory cytokine release, enhances osteogenic gene expression and periodontal tissue regeneration	Periodontitis treatment, local periodontal delivery systems
GL13K ^[57]	Human parotid secretory protein-derived peptide	α-helical, cationic peptide	Periodontal pathogens (e.g., <i>P. gingivalis</i>)	Regulates RANKL/OPG balance, suppresses inflammatory signaling, promotes osteogenic differentiation and inhibits inflammation-induced bone resorption	Periodontal bone regeneration strategies
Esculentin-1a (1-21) NH ₂ ^[58]	Frog-derived AMP derivative	Amphipathic α-helical	Gram-positive and Gram-negative bacteria	Activates PI3K/AKT signaling, promotes angiogenesis and tissue repair, supports vascular-bone coupling during regeneration	Periodontal tissue engineering and regenerative microenvironment modulation
CATH-2 (derivative) ^[59]	Avian cathelicidin-derived peptide	α-helical	Gram-negative bacteria	Inhibits NF-κB and NLRP3 inflammasome activation, reduces pro-inflammatory cytokine expression, preserves osteogenic cell function in inflammatory conditions	Immunomodulation-assisted periodontal regeneration

AMP: antimicrobial peptide. MAPK/ERK: mitogen-activated protein kinase/extracellular signal-regulated kinase. Wnt/β-catenin: wingless-related integration site/β-catenin. hBD3: human beta-defensin 3. RANKL/OPG: receptor activator of nuclear factor-κB ligand/osteoprotegerin. PI3K/AKT: phosphoinositide 3-kinase/protein kinase B. NF-κB: nuclear factor-κB. NLRP3: NOD-like receptor family pyrin domain containing 3

3 抗菌肽在牙周组织再生中的作用

3.1 调控牙周免疫微环境: 抗感染与免疫重塑协同机制

牙周炎相关组织破坏的本质是感染驱动的免疫失衡与骨吸收异常。因此, 牙周组织再生的前提不仅是清除病原菌, 更在于重建稳定的免疫微环境。近年来研究表明, 抗菌肽在牙周组织再生中的作用呈现出“抗感染—免疫调控—促再生”协同模式^[60-61]。

一方面, 抗菌肽可直接破坏牙周致病菌细胞膜并抑制生物膜形成, 从源头减少炎症刺激。另

一方面, 其可调节巨噬细胞极化状态, 促进由促炎 M1 型向修复相关 M2 型转化。本课题组研究证实, hBD3 可通过调节巨噬细胞极化改善牙周炎进展, 并促进牙周组织再生^[50, 53]。在炎性微环境中, 抗菌肽还能抑制 IL-1β、TNF-α 等炎症因子表达^[62], 降低破骨信号激活程度, 从而为再生过程创造有利条件。

此外, 抗菌肽可通过 TLR 相关信号、NF-κB 通路及 MAPK 级联反应参与炎症信号调控, 体现出对牙周免疫微环境的双向调节特性^[12, 63]。这种“免疫重塑”功能是其区别于传统抗生素的重要优势。

3.2 作用于牙周膜干细胞与成骨相关细胞:促再生信号通路激活

牙周膜干细胞(periodontal ligament stem cells, PDLSCs)及骨髓基质干细胞(bone marrow stromal stem cells, BMSCs)是牙周组织再生的核心效应细胞。研究显示,抗菌肽不仅可改善炎症环境,还可直接调节干细胞行为。

LL-37被证实可促进牙龈成纤维细胞及牙周膜细胞(periodontal ligament cells, PDLs)迁移与增殖,并增强I型胶原及骨桥蛋白表达,促进牙周附着重建^[64-66]。同时,抗菌肽可诱导PDLs表达VEGF、bFGF等促血管因子,并激活TGF- β /Smad、PI3K/Akt等信号通路^[61],实现免疫调控与再生信号的协同。

在成骨分化层面,抗菌肽可激活Wnt/ β -catenin及MAPK/ERK通路,增强RUNX2、ALP及COL1表达,促进成骨分化并调节RANKL/OPG比值,从而抑制破骨细胞形成,维持骨重塑平衡^[50, 53]。这种“抑破骨—促成骨”的双向调控机制对于牙周炎背景下的骨再生尤为关键。

3.3 成血管-成骨耦合与再生微环境构建

牙周组织再生不仅涉及骨形成,还依赖于血管生成与基质重建。抗菌肽可通过诱导VEGF表达及激活相关信号通路,促进内皮细胞迁移与管腔形成,增强血管生成能力^[67]。血管网络的重建为再生组织提供氧供和营养支持,同时促进干细胞募集与分化。

因此,在牙周组织再生背景下,抗菌肽通过调节炎症细胞、干细胞及内皮细胞等多类细胞行为,实现感染控制、免疫平衡及成血管-成骨耦合再生的整合调控。其多功能特性为构建“抗炎抗菌+促再生”一体化治疗策略提供了理论基础^[68]。

4 现有局限和解决手段

4.1 生物相容性与安全性问题

部分抗菌肽在高浓度条件下可能对宿主细胞产生细胞毒性^[69],其原因在于抗菌肽除作用于病原体外,亦可能与哺乳动物细胞膜发生非特异性相互作用^[70]。为降低毒性并提高选择性,近年来研究逐渐转向靶向细菌胞内关键生物分子而非细胞膜的策略^[71]。目前已报道的胞内靶点主要包括膜形成与维护相关蛋白复合体、DNA/RNA与蛋白质合成通路以及分子伴侣系统等。典型例子包括:抑制脂多糖转运系统LptB₂FGC的宏环肽zos-

urabalpin(RG6006)^[72];靶向BamA抑制外膜蛋白折叠的darobactin^[73];以及通过结合心磷脂干扰细菌能量代谢的抗菌肽EcDBS1R4^[74]。此外,富脯氨酸抗菌肽可通过核糖体结合抑制蛋白翻译^[75],而部分抗菌肽(如P113、butorin II)还能干扰细菌核酸相分离过程^[76]。部分昆虫来源抗菌肽则通过抑制分子伴侣蛋白DnaK和GroEL的ATP酶活性发挥抗菌作用,且对宿主细胞毒性较低^[77-78]。

4.2 稳定性与递送系统优化

抗菌肽在体内易被蛋白酶降解,限制了其持续疗效^[11],因此递送系统优化成为提升其应用潜力的关键方向。当前常用策略包括表面固定化、纳米载体与水凝胶体系。

抗菌肽通过共价或物理方式固定于引导再生膜或生物陶瓷等材料表面,可在局部长期维持抗菌环境并降低系统毒性风险^[78]。纳米颗粒载体(如脂质体、聚合物或无机纳米粒)可提高抗菌肽的稳定性与局部富集能力,在抑制牙周致病菌和生物膜的同时促进成骨相关细胞功能^[79]。水凝胶体系则可作为抗菌肽的局部缓释平台,尤其适用于牙周袋、拔牙窝或骨缺损部位,并可通过刺激响应机制实现可控释放^[80]。此外,基于静电自组装的递送体系在提升抗菌肽稳定性和抗生物膜治疗方面亦展现出良好潜力^[81]。

4.2.1 结构改性 为提高抗菌肽在体内的稳定性,研究者广泛采用D-氨基酸替换、肽环化及N端修饰等结构改性手段,以增强其抗蛋白酶降解能力并延长半衰期^[82-84]。例如,本课题组构建的D-hBD3在保持良好生物相容性的同时增强了抗菌活性,并可缓解小鼠实验性牙周炎进展,同时通过调节巨噬细胞极化改善免疫平衡^[85]。

此外,计算辅助设计(in silico)已成为AMP优化的重要工具,通过遗传算法、机器学习及语言模型对肽序列进行迭代优化,可显著提升抗菌活性与稳定性^[86]。相关研究已成功获得高效抗菌肽,如抗菌肽temporin-Ali的活性显著增强^[87],以及活性可媲美FDA批准抗生素的T2-9^[88]。同时,AMP杂交与自组装策略亦被用于构建兼具高稳定性和强抗菌活性的功能肽体系^[89-92]。

4.2.2 缓释与稳定性提升 在口腔复杂环境中,唾液冲刷、酶降解及机械应力会显著降低抗菌肽的局部有效浓度。通过与生物材料共价结合,可延长抗菌肽在局部的作用时间并维持材料表面的长期抗菌性能,适用于组织工程支架等材料^[93-96]。

微胶囊化递送(如PLGA微球或海藻酸盐体系)则可实现抗菌肽的持续释放,在抑制牙周致病菌和炎症反应的同时,与成骨或成纤维细胞保持良好相容性^[97-98]。总体而言,缓释策略有助于协调抗感染与组织再生过程,是推动抗菌肽临床应用的重要技术支撑。

4.3 临床转化挑战

尽管抗菌肽在抗感染和免疫调控方面具有显著优势,其临床转化仍受制于合成成本高、稳定性不足及潜在毒性等问题^[11]。鉴于牙周疾病解剖位置明确、适合局部干预,抗菌肽在牙周局部应用中较系统给药更具现实优势,可在降低全身毒性风险的同时提高治疗效率。

除抗菌作用外,抗菌肽还可通过调节炎症反应、免疫细胞行为及成骨/成纤维细胞功能,为组织再生创造有利微环境。然而,不当或长期使用抗菌肽可能诱导细菌耐受性,甚至影响宿主内源性免疫肽功能,如 mcr-1 介导的脂多糖修饰机制^[99-100]。因此,结构优化与递送系统联合设计被认为是推动抗菌肽安全转化的关键方向。

4.4 技术实现与产业化考量

在产业化层面,传统固相合成虽具可控性,但成本较高;相比之下,基于微生物发酵的生物合成策略在规模化生产中更具优势。 ϵ -poly-L-lysine 的成功工业化为抗菌肽的大规模制备与质量控制提供了可行路径^[47, 71]。

同时,计算辅助设计与实验验证相结合的迭代开发模式,显著提升了抗菌肽研发效率^[88]。随着针对肽类药物的监管框架逐步完善,抗菌肽在安全性评价、药代动力学及临床研究方面的规范化进程不断推进,为其在牙周组织再生及口腔疾病防治中的应用奠定了基础。

5 小结与展望

综上所述,抗菌肽在牙周组织再生中的作用已从单纯抗感染扩展至免疫调控与再生促进的多维协同模式。现有研究表明,人源抗菌肽如 LL-37 和 hBD3 在调节巨噬细胞极化、抑制炎症因子释放及激活 Wnt/ β -catenin、MAPK/ERK 等信号通路方面具有明确证据支持,在促进血管生成和成骨分化中表现出较为稳定的再生潜力。因此,兼具免疫调节与促成骨能力的抗菌肽,可能是目前最具临床转化前景的候选分子。

尽管如此,抗菌肽在牙周组织再生领域仍面

临若干关键科学问题:其在复杂牙周炎微环境中的长期稳定性与安全剂量范围尚未明确;不同结构类型抗菌肽的再生机制差异及其对干细胞命运调控的精细机制仍有待深入解析;此外,如何实现可控释放并避免潜在耐受或免疫副反应,仍是制约临床应用的技术瓶颈。

未来研究应聚焦于:①系统阐明抗菌肽调控牙周免疫微环境及成血管-成骨耦合再生的分子网络;②优化结构设计与智能递送体系以提升稳定性与选择性;③结合机器学习与人工智能算法开展抗菌肽序列预测与功能筛选,加速新型高选择性、低毒性抗菌肽的发掘与优化;④推进大动物模型及长期安全性研究,为临床转化奠定依据。总体而言,抗菌肽为构建“抗感染—免疫平衡—再生促进”一体化牙周治疗策略提供了新的生物学工具,但其机制精细化解析与可控应用策略仍是推动临床转化的关键方向。

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