

[DOI] 10.12016/j.issn.2096-1456.202550260

· 综述 ·

聚多巴胺在口腔疾病治疗中的研究进展

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【摘要】 由于口腔环境湿润, 龋病、牙周病等口腔疾病的治疗常面临生物膜清除难、药物滞留短、组织修复效率低等挑战。聚多巴胺(polydopamine, PDA)作为仿生物材料, 具有模拟贻贝黏附、智能响应释药等多机制协同特性。PDA黏附性源于其表面的邻苯二酚和氨基官能团, 可在湿润环境中保持较强的黏附性, 其智能响应性涵盖光热、pH、酶等多机制, 能在特定条件下实现药物的可控释放。PDA还兼具抗菌、抗炎、促进成骨细胞黏附与分化等功能, 在口腔疾病治疗中具有重要应用价值。在口腔硬组织疾病治疗方面, 对于龋病, PDA通过模拟羟基磷灰石晶体生长诱导釉质再矿化, 整合Ca²⁺促进牙本质胶原矿化, 同时发挥抗菌作用抑制致龋菌; 在颌骨缺损修复中, PDA通过表面涂层功能化修饰骨植入材料, 促进骨髓间充质干细胞黏附分化, 激活成骨相关信号通路, 并协同促进血管化, 改善骨-材料界面整合。在口腔软组织及联合病变治疗中, 对于牙周炎, PDA通过抗菌、抗炎及抑制破骨细胞活化, 减轻牙槽骨吸收; 在义齿性口炎等黏膜病的治疗中, PDA的强湿黏附性延长药物滞留, 光热效应与生成活性氧可协同实现广谱抗菌及促愈合。本文综述PDA的合成机制、生物学功能, 着重阐述其在口腔疾病治疗中的应用进展, 为口腔疾病治疗提供新策略。

【关键词】 聚多巴胺; 口腔疾病; 智能响应; 光敏剂; 活性氧; 药物递送; 纳米材料; 多模态抗菌疗法

【中图分类号】 R78 **【文献标志码】** A **【文章编号】** 2096-1456(2026)03-0302-13

【引用著录格式】 鲁翔相, 江珍, 邢爱丽, 等. 聚多巴胺在口腔疾病治疗中的研究进展[J]. 口腔疾病防治, 2026, 34(3): 302-314. doi:10.12016/j.issn.2096-1456.202550260.

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【Abstract】 Due to the moist environment in the mouth, there are many challenges that arise, such as difficult biofilm removal, short drug retention time, and low tissue repair efficiency, while treating dental caries, periodontal disease, and other oral diseases. As a biomimetic biomaterial, polydopamine (PDA) possesses multifunctional properties, including mussel-inspired adhesion and stimuli-responsive drug release. PDA adhesion properties originate from its surface catechol and amino functional groups, which maintain strong wettability in aqueous environments. With smart responsiveness encompassing photothermal, pH, and enzymatic stimuli, PDA enables controlled drug release under specific conditions. Additionally, PDA exhibits antibacterial, anti-inflammatory, and osteoblast-promoting functions, thus demonstrating significant application potential in the treatment of oral diseases. In hard tissue therapies, specifically for dental caries, PDA promotes enamel remineralization by inducing hydroxyapatite crystal growth and enhances dentin collagen



微信公众号

【收稿日期】 2025-06-19; **【修回日期】** 2025-08-06

【基金项目】 吉林省科技发展计划项目(20210203090SF)

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mineralization through Ca^{2+} chelation while inhibiting cariogenic bacteria. In mandibular defect repair, functionalized PDA coatings on bone implants facilitate mesenchymal stem cell adhesion and differentiation, activate osteogenic signaling pathways, and synergistically promote vascularization to improve bone-implant integration. For soft tissue treatments, specifically for periodontitis, PDA alleviates alveolar bone resorption via antibacterial and anti-inflammatory effects coupled with osteoclast inhibition. In denture stomatitis management, PDA's strong wet adhesion prolongs drug retention, while its photothermal effect and reactive oxygen generation provide both broad-spectrum antibacterial activity and wound healing promotion. This review summarizes PDA's synthesis mechanisms and biological functions, with an emphasis on its therapeutic applications in oral diseases, providing innovative strategies for oral healthcare.

【Key words】 polydopamine; oral diseases; intelligent response; photosensitizers; reactive oxygen species; drug delivery; nanomaterials; multimodal antibacterial therapy

J Prev Treat Stomatol Dis, 2026, 34(3): 302-314.

【Competing interests】 The authors declare no competing interests.

This study was supported by the grants from Jilin Province Science and Technology Development Plan Item (No. 20210203090SF).

口腔作为颌面部的重要结构,在咀嚼及言语中起关键作用。世界卫生组织《全球口腔健康状况报告》数据显示,全球约35亿人患有的一种或多种未经治疗的口腔疾病,其中龋病、牙周病发病率位居前列,严重影响公众健康^[1]。

口腔疾病可按其所累及的组织结构分为软组织疾病、硬组织疾病及软硬组织联合病变。口腔软组织疾病是以口腔黏膜、牙周膜等非矿化组织损伤为核心的口腔疾病。在临床治疗中,口腔湿润环境的特殊性对现有治疗方法构成显著挑战^[2]:传统的黏膜或牙周局部涂抹药物因耐冲刷性差,易被唾液和龈沟液快速稀释,导致药物滞留短、生物利用度不足;咀嚼运动产生的机械刺激则会加剧创面敷料脱落,降低传统贴剂的治疗持续性。口腔硬组织疾病是一类以牙齿、颌骨等矿化组织损伤为核心的口腔疾病。主要包括颌骨缺损和牙体缺损等疾病。目前,传统自体骨移植或同种异体骨移植对于颌骨缺损的疗效存在诸多局限性^[3],例如骨修复初期会面临力学支撑不足的问题。此外,口腔的湿润环境进一步放大了传统牙体硬组织修复材料的局限,如常规树脂粘结剂在湿润界面下粘结强度骤降,进而形成微间隙,细菌侵入牙齿与修复体界面,从而导致牙体组织继发龋^[4]。

近年来,随着糖尿病发病率的增加,伤口愈合缓慢、易感染等问题成为了口腔疾病治疗后的并发症之一。为了解决这些问题,具有多重生物学功能的新型材料在抑制感染、调控炎症及促进组织再生等方面展现出显著潜力^[5]。受贻贝黏附机制启发,聚多巴胺(polydopamine, PDA)凭借表面的

邻苯二酚、氨基官能团,几乎能黏附于任何材料表面。同时,PDA涂层改善了传统材料表面缺乏活性官能团和高疏水性的问题,促进细胞的黏附与生长^[6],为解决口腔湿润环境下的治疗难题提供了关键突破点。其次,PDA作为天然黑色素的仿生合成材料,其衍生物因能提升生物材料的抗菌、抗炎及促进组织再生等性能而日益受到关注。本综述通过简述PDA基生物材料的合成,并基于PDA的生物学功能,详细阐述其在口腔软硬组织疾病中的相关应用,为进一步材料创新研究提供依据。

1 PDA的合成

PDA由多巴胺(dopamine, DA)在碱性环境中的氧化自聚合反应合成。该过程以DA分子结构中的酚羟基质子解离为起点,后被氧化成多巴醌。多巴醌通过直接引发共价聚合反应或发生分子内环化反应两种方式,生成5,6-二羟基吲哚^[7]。这两种方式,共同驱动了PDA结构的形成。

PDA合成方法多样。主要包括溶液氧化法、电聚合法和酶氧化法等(图1,表1)。溶液氧化法操作简便、成本低廉,适用于可摘修复体的体外预制涂层^[8]。通过碱性溶液中DA的自聚合可在修复体表面形成PDA膜,赋予其抗菌性和细胞相容性。但是,体外合成PDA涂层转移至口腔后,需应对口腔进食过程中pH或温度等环境变化,这可能导致聚合稳定性下降,需优化涂层封闭性以避免唾液杂质附着。电聚合法能通过电极精准调控PDA沉积速率与厚度,尤其适合种植体、正畸托槽等金属修复体的表面改性^[9]。PDA在电极表面快

速成膜^[10],可满足椅旁即时应用,均匀的纳米结构修饰涂层可以有效模仿天然骨组织的形态,促进成骨细胞在种植体骨界面的增殖和分化,从而增强种植体与骨组织的结合力^[11],但其成本高限制了其广泛应用。酶氧化法通过体外酶催化反应合成PDA,相较于溶液氧化法,该方法可以在更广泛的pH值范围快速反应生成PDA^[12]。并且,温和的反应条件及环保特性使产物对于机体也更加友好。体外合成的PDA可被制备成涂层或载药微粒,用于牙周袋内抗菌药物的缓释,或辅助龋齿充填后的再矿化治疗。但目前,关于口腔中唾液蛋白酶对PDA的降解作用,尚缺乏相关研究数据,因此需通过体外预处理来维持其稳定性。

特性,从而衍生出智能响应性、药物递送、抗菌、抗炎及成骨等多重功能。本文从以下六大核心功能展开,系统阐述PDA的生物学功能。

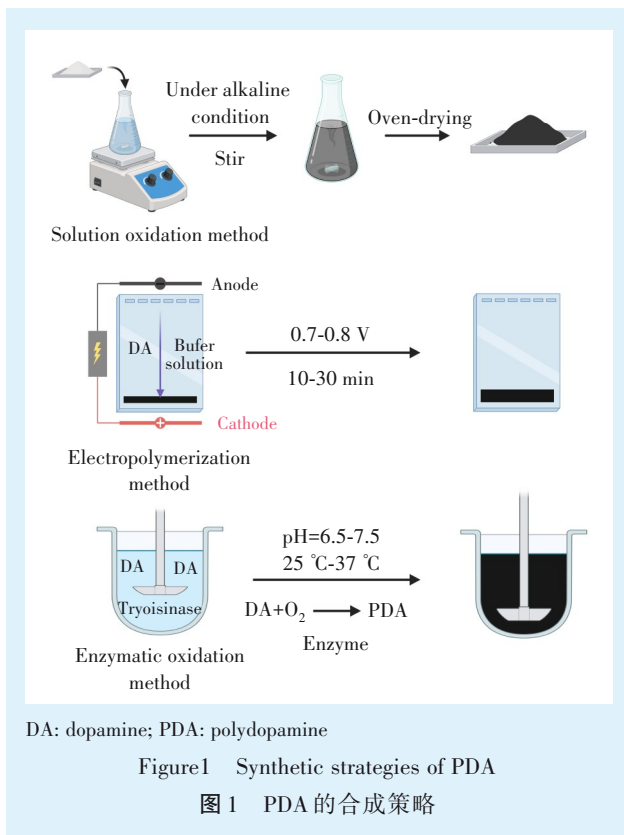
2.1 黏附性

PDA的黏附性能源自对海洋贻贝足丝蛋白的仿生设计,其作用机制核心在于模拟足丝蛋白中邻苯二酚基团与氨基的协同作用^[13]。DA自氧化聚合形成PDA后,其表面富集大量的邻苯二酚基团,可与材料表面的亲核基团发生迈克尔加成反应或席夫碱反应,形成共价键,从而增强黏附效果^[14-15]。口腔环境中因富含唾液、且食物对于口腔组织的机械摩擦,导致药物难以在靶区长期滞留,进而出现药物作用时间短、药物浓度难以维持等问题^[16]。Sadat等^[17]基于PDA的黏附性制备了多层黏膜黏附水凝胶,用于舌下黏膜局部给药。该水凝胶通过共价键与物理相互作用的双重机制,与黏膜的黏附强度达75.3 g。其次,在模拟口腔环境中,含PDA的水凝胶展现出优异的长期稳定性:其溶胀度最低且达到溶胀平衡的时间最长,减少了因唾液水合导致的结构松散,其6 h侵蚀率仅为33%(即体质量仅减少33%),远低于其他制剂;同时,PDA的黏附特性使制剂对黏膜的黏附持续时间超过16 h。这些数据表明,PDA能通过降低溶胀度、减少侵蚀率,在唾液环境中维持长期黏附稳定,为优化口腔局部给药策略提供了创新方案。

2.2 智能响应性

2.2.1 光响应性

PDA的光响应性主要表现为光热效应和光触发化学反应两大机制,在口腔疾病治疗中可基于这两大机制精准调控实现智能释药。口腔局部治疗中,近红外激光可促使PDA分子链中醌式结构与芳香环构成的共轭体系吸收光子能量,驱动电子从基态跃迁至激发态;激发态的电子通过非辐射跃迁释放能量,最终使光能以热能形式转换^[18]。同时,PDA表面的半醌自由基在近红外激光作用下发生电子转移,引发自由基链式反应,继而改变PDA的氧化还原电位,使其电子



2 PDA的生物学功能

作为模拟贻贝足丝蛋白的仿生聚合物,PDA的生物学功能源于其仿生化学结构与多维度响应

表1 PDA合成方式的特点及适合口腔应用的场景

Table 1 Characteristics of PDA synthetic methods and suitable oral application scenarios

Synthetic methods	Advantages	Limitations	Oral application scenarios
Solution oxidation method	Simple preparation, low cost	Uneven synthesis thickness	Removable restorations, temporary crowns
Electropolymerization method	Uniform and controllable thickness	High cost, complex operation	Bone implants, metal brackets
Enzymatic oxidation method	Good biocompatibility	Poor stability, slow reaction rate	Drug carriers, tissue engineering scaffolds

PDA: polydopamine

云分布及共轭结构发生改变,促使PDA从还原态转变为氧化态。两大机制协同作用:光热效应直接抑制口腔相关致病菌的活性^[19],并且PDA涂层的光热效应对巨噬细胞极化的调节具有显著影响^[20];光触发化学反应则促使PDA载药体系构象重排,通过破坏药物与载体间的氢键或疏水作用,实现药物的可控释放^[21]。Xiu等^[22]构建了一种多功能复合微球,经PDA表面修饰并负载盐酸米诺环素,使微球具备长期滞留牙周袋内的能力。在红外激光照射下,可触发材料光热效应,有效抑制牙周致病菌活性,并实现米诺环素在牙周袋内的精准释放。

2.2.2 pH 响应性 口腔微环境的pH动态变化使PDA构象变化为pH响应释药提供了天然触发条件^[23]。例如,龋病发生时,变异链球菌可通过代谢碳水化合物生成有机酸,导致牙表面pH降至酸性范围^[24];口腔癌细胞导致的局部组织代谢失调及继发感染,也会使组织微环境呈弱酸性^[25-26]。该条件下,PDA表面的氨基发生质子化,进而导致分子间作用力减弱、载体结构破坏,从而实现药物的靶向释放。这种酸性环境触发释药的特性,可减少健康组织的药物暴露,降低药物的副作用^[27]。Shi等^[28]利用PDA前体物质作为功能单体和交联剂,通过在Fe₃O₄纳米颗粒上负载阿霉素并进行分子印记,开发了多功能纳米平台。在肿瘤酸性微环境中,该平台基于PDA层的顺序降解,实现了阿霉素的精准释放,体外实验显示药物释放率接近100%,为口腔癌的局部智能给药提供了依据。

2.2.3 其他响应性 除光、pH响应外,PDA可响应超声、酶、电等多模态刺激。Li等^[29]开发了负载阿霉素的PDA基超声响应微胶囊,利用高强度聚焦超声引发的空化效应触发内部结构破裂,实现药物释放;Wen等^[30]在PDA-聚乙烯亚胺体系中引入脲键,构建脲酶响应性微胶囊(递送阿维菌素),在生理pH范围内,pH升高增强脲酶活性,药物累积释放量达42.03%;Xie等^[31]通过电化学沉积在钛表面制备PDA/聚吡咯电响应微胶囊,通过电刺激脉冲调控药物释放。

2.3 药物递送

PDA表面的官能团和亲水性赋予其优异的细胞亲和力^[32],通过合理的药物负载策略,可以构建形态与结构各异的PDA基体内药物递送体系^[33-34]。目前,典型负载策略主要包括以下三类^[35]。

2.3.1 物理吸附策略 借助PDA修饰纳米颗粒的

表面吸附力,将药物物理吸附于颗粒表面,是PDA基递药系统的经典负载方式。

2.3.2 化学键合策略 通过共价键合将药物嵌入PDA基质,或构建分子印迹结构,形成药物-PDA共轭物,实现药物与载体的稳定结合。

2.3.3 纳米封装策略 将药物封装于PDA空心纳米颗粒内部,或装载于金属-有机框架的介孔结构中,利用PDA层作为“门控组件”,结合光、pH、酶等刺激响应性调控药物释放。

上述研究通过整合能够引发载体结构或化学性质改变的刺激信号、响应机制与药物递送策略,借助激光照射等外部干预信号及酸性环境等病变微环境特征,实现了药物精准释放,拓展了PDA在口腔疾病多模态智能响应治疗领域的应用场景,为跨学科治疗奠定基础。

2.4 抗菌作用

PDA作为天然多酚类高分子,凭借优异的纳米载体功能和表面修饰潜力,为构建高效抗菌体系提供理想平台。目前,其抗菌机制可归纳为以下三类:

2.4.1 接触灭菌 在酸性条件下,PDA因氨基质子化带正电荷,通过静电吸附作用与带负电荷的细菌表面结合,强化材料与细菌的接触效率^[36]。接触后PDA发挥抗菌作用的机制主要分为两类^[37-38]。①氧化损伤机制:PDA表面邻苯二酚基团通过氧化还原反应产生活性氧(reactive oxygen species, ROS),或螯合金属离子诱导细菌氧化损伤,干扰代谢功能;②膜破坏机制:通过化学修饰在PDA表面引入N-卤胺抗菌基团,该基团释放卤素原子,破坏细胞膜完整性并阻断生理代谢,最终导致细菌失活。相较于金属离子介导的接触灭菌,PDA良好的生物相容性,避免了潜在毒性风险。

2.4.2 促ROS生成 多重耐药细菌的出现导致疾病治疗难度显著增加,为控制此类细菌感染,亟需新的抗菌策略。其中,诱导高浓度ROS是已被广泛研究的重要抗菌方式之一,可用于治疗多重耐药菌感染^[39]。PDA表面的邻苯二酚基团具有氧化还原活性:一方面可淬灭自由基表现出抗氧化能力;另一方面,其可生成超氧阴离子和过氧化氢,从而破坏细菌细胞膜的脂质结构^[40]。值得注意的是,PDA的ROS生成与清除功能看似矛盾,实则通过氧化还原响应性实现环境依赖的功能切换,在感染早期通过ROS生成发挥抗菌作用,后期通过ROS清除介导抗炎效应,从而实现两者的协同作用。

2.4.3 光热灭菌 基于前文所述的光热效应,在近红外激光照射下,材料表面局部温度可突破热休克蛋白的温度阈值,诱导细菌蛋白变性^[41]。该热能不仅能够抑制细菌增殖,还可阻碍生物膜形成^[42]。基于此,Deng等^[43]开发了介孔PDA纳米颗粒(polydopamine nanoparticle system, PDA-NPs)介导的光热响应水凝胶。激光照射5 min后,材料表面温度升至47 °C,停止照射后快速降温,体现良好安全性。并且,激光组在光照后的菌落数量显著减少,为光热抗菌临床转化提供数据支撑。

2.5 抗炎作用

PDA的抗炎作用通过多维度机制实现,包括氧化应激调控、炎症信号通路抑制及协同促血管生成,形成从抑制过度炎症到促进损伤修复的良性循环。

2.5.1 氧化应激调控 炎症微环境中,机体免疫细胞会释放大量ROS,通过氧化脂质、蛋白质加剧组织损伤并放大炎症反应^[44]。PDA表面丰富的酚羟基可通过电子转移直接清除ROS,在炎症微环境中可中和过量自由基,减少氧化应激对组织细胞的损伤,直接缓解炎症反应^[45]。其次,Hu等^[46]利用PDA表面修饰血红蛋白从而提高氧气载体的稳定性并协同PDA抗氧化机制减少细胞氧化损伤,共同发挥抗炎作用。

2.5.2 信号通路 抑制核因子 κ B(nuclear factor κ B, NF- κ B)是调控炎症反应的核心通路。静息时,NF- κ B与抑制 κ B蛋白(inhibitor of κ B, I κ B)结合,滞留于细胞质中并呈失活状态。当受到口腔致病菌细胞壁成分脂多糖的刺激时,可通过Toll样受体4(toll-like receptor 4, TLR4)等细胞膜受体将信号传递至细胞内,激活I κ B激酶(I κ B kinase, I κ K)复合体;I κ K磷酸化I κ B使其被降解,释放的NF- κ B进入细胞核,结合靶基因启动子,启动促炎细胞因子的转录,引发炎症反应^[47]。Jin等^[48]发现,PDA可通过多环节抑制该通路:首先降低TLR4和髓样分化因子88(myeloid differentiation factor 88, MYD88)的表达,阻断上游信号启动;其次抑制I κ K- α / β 和I κ B- α 的磷酸化,阻止NF- κ B入核;最终减少了肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)和白细胞介素-6(interleukin-6, IL-6)等促炎因子的分泌。

2.5.3 促进血管生成 PDA通过促进血管生成及损伤部位血供重建,在炎症消退与组织修复再生中起关键作用^[49]。Cheng等^[50]发现,PDA涂层通过

调控表面功能基因影响血管内皮细胞行为,进而促进血管生成:例如,通过调节表面醌基与氨基平衡,可促进人脐静脉内皮细胞黏附、迁移及增殖,增强管腔形成能力,同时上调血管内皮生长因子、血管生成素-1等关键基因的表达,直接驱动血管新生;其次,ROS的清除可保护血管内皮细胞完整性,减少因血管通透性增加导致的炎症因子蓄积^[51],同时通过血流循环带走局部代谢废物,阻断炎症持续的物质基础,最终衔接炎症消退与组织愈合过程。

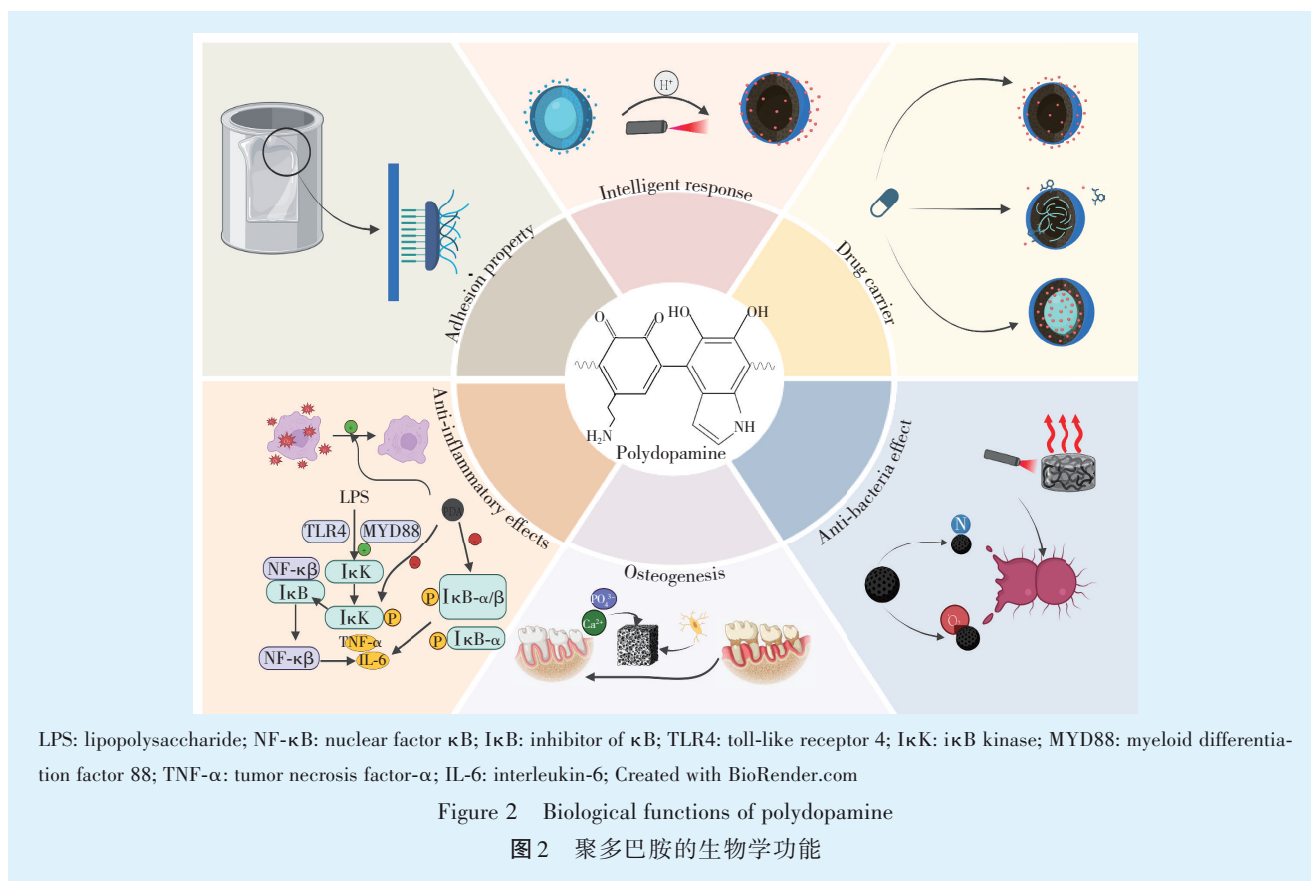
2.6 成骨作用

PDA通过仿生黏附与仿生矿化和促进成骨分化等机制,为成骨细胞行为调控与硬组织再生提供微环境支持。

2.6.1 仿生黏附 PDA的表面化学结构可模拟细胞外基质中胶原蛋白氧化产生的多酚类结构,促进细胞在材料表面的黏附^[52]。Gan等^[52] PDA修饰的透明质酸复合物引入到水凝胶支架中,该支架通过模拟天然细胞外基质,利用PDA的多酚模拟特性强化细胞黏附。其次,透明质酸分子链中的糖基序列与成软骨细胞表面受体的特异性结合,显著增强成软骨细胞与透明质酸的相互作用,进而促进细胞黏附及软骨分化。

2.6.2 仿生矿化 PDA表面可通过静电吸附Ca²⁺、PO₄³⁻等离子,诱导羟基磷灰石(hydroxyapatite, HA)晶体定向生长,加速矿化进程^[53]。Li等^[53]将PDA沉积于脱矿牙本质表面后,浸入钙磷过饱和溶液中。结果显示牙本质脱矿后仅需12 h即可完成再矿化,且再矿化牙本质的力学性能与耐酸性均优于普通矿化牙本质。

2.6.3 促进成骨分化 PDA因具备均匀成膜特性及优异的细胞亲和性,已被广泛应用于骨修复支架的表面改性研究。已有研究表明,PDA涂层可通过增加支架表面粗糙度,显著促进接种骨髓间充质干细胞的黏附与成骨分化过程。进一步的mRNA测序分析结果显示,PDA表面涂层能够通过激活钙信号通路、Wnt(wingless/integrated, Wnt)信号通路及转化生长因子- β (transforming growth factor- β , TGF- β)信号通路,上调骨标志物的表达水平并促进成骨相关基因的转录^[54]。另有实验证实,PDA涂层经近红外触发产生的温和热刺激可有效诱导巨噬细胞向M2表型极化,进而减轻受损骨组织的炎症反应^[55]。基于PDA多种生物学功能(图2),其在口腔医学中具有广泛的应用前景。



3 PDA 在口腔疾病治疗中的应用

3.1 口腔硬组织疾病

口腔硬组织疾病包括牙体硬组织病变和颌骨硬组织病变。PDA 在两类疾病中均有应用,其中在颌骨修复中与骨修复材料的协同作用尤为突出,为硬组织再生提供了创新策略。

3.1.1 龋病 龋齿是一个全球性的口腔难题,致病机制为细菌产酸和感染而导致的牙体硬组织脱矿和牙本质小管暴露^[56]。其中以牙釉质龋和牙本质龋最为常见。

PDA 凭借抗菌活性与药物负载能力,在釉质龋预防中展现出独特优势。其表面官能团可模拟 HAp 晶体生长,抑制釉质脱矿并诱导釉质表面再矿化^[57-58]。Madhubala 等^[59]发现,PDA 包覆的生物源无定形磷酸钙对变形链球菌的抑菌率高达 72.6%,显著优于对照组;同时,PDA 通过离子吸附及 HAp 成核作用,提升釉质再矿化效率,修复后硬度接近天然矿化层。

当龋病进展至牙本质层时,细菌及其代谢产物侵入牙本质小管,刺激牙髓神经末梢,引发牙本质敏感等症状。牙本质由胶原蛋白基质和 HAp 组成,脱矿后其力学性能降低。PDA 邻苯二酚基团

可通过螯合 Ca^{2+} 提高局部钙浓度,增加 I 型胶原蛋白含量,加速无定形磷酸钙成核进而促进牙本质再矿化^[60-61]。Qu 等^[62]进一步发现,PDA 可降低胶原纤维与无定形磷酸钙的界面能,减少 HAp 成核的能量壁垒,实现胶原纤维内定向矿化。上述机制使修复后的牙本质结构与天然牙本质相似,为深龋修复提供了仿生矿化策略。

3.1.2 颌骨骨髓炎 颌骨骨髓炎是一种严重的骨感染性疾病,抗生素治疗通常难以治愈^[63]。临床上主要以骨组织破坏、死骨形成为特征,控制感染与阻断骨破坏是其核心治疗手段^[64]。PDA 通过抗菌-抗炎协同机制阻断感染进展。Sun 等^[65]研究表明,借助 PDA 的黏附性,将硫酸庆大霉素固定于涂层中,能够实现抗菌药物的负载与缓释,有效增强植入物的持续抗菌活性。此外,PDA 通过免疫调节诱导巨噬细胞向 M2 型极化,增强骨植入物的抗感染作用。Wu 等^[66]通过 PDA 外壳包裹负载地塞米松的二氧化硅纳米颗粒核心,并在外壳表面嵌入 Ag-NPs。该结构利用 Ag-NPs 的表面暴露特性实现 Ag^+ 的早期释放以发挥显著抑菌作用,而后期随着 PDA 外壳的降解或环境响应,地塞米松开始释放并促进成骨分化。该设计通过药物保护与抗菌

剂负载的时序释放调控实现协同作用,为骨髓炎治疗提供了抗菌与成骨的协同治疗方案。

3.1.3 颌骨缺损 颌骨缺损是口腔颌面硬组织修复的重要挑战,多由颌骨骨髓炎、创伤等引发。现有骨缺损修复材料难以实现骨-材料界面的理想整合与骨结合。而组织工程技术为骨缺损治疗提供了一种新方法^[67]。组织工程修复骨缺损的核心机制包括^[68-69]:促进成骨分化、抑制NF- κ B信号通路介导的破骨细胞分化、在炎症微环境中诱导M2型巨噬细胞极化及抗炎因子表达,以及促进骨缺损区域的快速血管化等。目前,常见的骨修复材料可分为金属材料 and 无机非金属材料。金属材料具备较强的耐腐蚀性和机械强度,但其惰性表面限制了成骨潜力,而PDA表面修饰可有效改善这一不足^[70]。Zhang等^[71]等多孔钛表面构建了PDA仿生涂层。PDA凭借丰富的氨基、酚羟基等官能团实现药物高效负载,其生物相容性及黏附性还能显著促进大鼠骨髓间充质干细胞的黏附与增殖:3 d时的细胞骨架染色结果显示,多孔钛表面的细胞密度显著高于其他组,且细胞形态发育良好,表明其为成骨分化提供了适宜微环境。

由于金属材料不能原位成型和非金属材料机械性能较差,故临床可用于长期植入的骨修复材料相当有限^[72]。HAp作为天然骨主要无机成分,具有良好生物相容性和机械性能,但单纯HAp无抗菌作用且细胞黏附性不足。而研究发现,PDA可通过化学修饰策略,可实现骨诱导因子重组人骨形态发生蛋白-2与HAp的稳定固载,从而提高了材料的钙沉积能力和成骨细胞在骨修复材料中的增殖活性,与HAp协同发挥骨修复作用^[73]。Huang等^[74]利用PDA表面儿茶酚基团与镁离子形成共价键,同时通过表面酚羟基还原银离子并固定银纳米颗粒,合成了以胶原蛋白和HAp为基底的复合膜材料,用于口腔颌面部骨缺损修复。HAp为材料提供良好机械性能,同时借助PDA的黏附特性实现金属离子的缓慢释放,改善了HAp骨修复材料的抗菌性能。

3.2 口腔软组织疾病

3.2.1 口腔黏膜病 口腔黏膜病是发生于口腔黏膜及相关软组织中一类疾病的统称^[75]。其中,口腔溃疡和口腔念珠菌病作为临床最常见的两大类型,一直是口腔医学领域的防治难点。

口腔溃疡是口腔黏膜病中最常见的疾病之一,目前主要的治疗目标为减轻疼痛和促进溃疡

愈合。由于口腔环境湿润的特点^[76],An等^[77]利用PDA的黏附性和生物相容性,开发了一种具有较强湿黏附力和较高韧性的水凝胶。该水凝胶可在口腔环境中稳定存在,且具有高细胞亲和性,能有效促进细胞黏附和增殖。此外,通过负载地塞米松利用水凝胶的缓释特性,促进口腔溃疡创面的愈合。

口腔念珠菌病,俗称“鹅口疮”,是由念珠菌属引起的机会性感染性疾病,在免疫功能受损、高龄及存在局部易感因素的个体中尤为常见^[78]。其发病机制与口腔菌群失调及局部微环境改变密切相关。在口腔临床中,长期佩戴义齿导致的黏膜创伤和炎症会损害上皮完整性,为真菌侵袭提供有利条件。义齿性口炎最常见的临床表现为针状充血和弥漫性充血^[79]。针对义齿性口炎的治疗需求,Liu等^[80]研发了一种双光响应型口腔黏附剂,其中PDA修饰的氧化锌具有光催化抗菌特性,而单宁酸作为湿润黏膜的锚定基团,通过氢键作用进一步增强材料的口腔黏附。材料通过激光照射产生光热效应及ROS,实现对包括白色念珠菌等病原微生物广谱抗菌,提升材料的抗炎及促愈合能力。

3.2.2 口腔癌 口腔癌是头颈部最常见的恶性肿瘤之一^[81],其中口腔鳞状细胞癌在口腔恶性疾病中最为常见^[82]。患有口腔癌的患者通常面临预后不良、生存率低以及严重的身体和心理方面的困扰^[83]。并且,现有治疗手段仍面临疗效有限、全身副作用大和复发率高等瓶颈^[84]。基于光热转换材料的新型微创治疗策略,通过材料的光热特性产生局部高温,选择性杀灭肿瘤细胞,最大限度减少化疗对正常组织的损伤,成为近年研究热点^[85]。

Chen等^[86]开发了负载姜黄素的可注射短纤维体系,通过注射实现肿瘤部位的药物原位递送。该材料经PDA修饰后具备光热效应,同时通过pH响应方式实现药物控释,协同杀伤口腔癌细胞。Yin等^[87]构建了表面PDA修饰的阿霉素负载纳米递药系统,其双重靶向机制包括:①利用纳米颗粒尺寸效应通过肿瘤组织高渗透和长滞留效应实现药物被动靶向积累;②PDA表面官能团与肿瘤细胞非特异性结合介导药物主动靶向积累,显著提高肿瘤部位药物浓度。此外,基于PDA的光热效应及肿瘤微环境的微酸性响应性,该系统可实现对光热治疗与化疗的协同作用,有效抑制肿瘤生长。

3.3 口腔软硬组织联合病变

3.3.1 牙周炎 牙周炎是最常见的口腔疾病之一,也是导致成年人牙齿脱落的主要原因。细菌感染与宿主免疫反应失衡是决定牙周炎发生发展的主要因素^[88]。牙菌斑作为牙周炎的始动因子,菌斑堆积和口腔微生物群落失衡是牙周炎进展的重要驱动因素^[89]。牙周炎常伴随牙周组织破坏,进而形成复杂的牙周袋,进一步加剧了菌斑的清理难度。Liu等^[90]通过介孔PDA负载亚精胺,构建了一种可注射水凝胶。该水凝胶可紧密贴合不规则的复杂牙周袋。在激光照射下,PDA的光热效应使牙周袋内致病菌及生物膜蛋白变性,显著降低牙周细菌数量,有效抑制牙槽骨的吸收。在宿主免疫应答中,巨噬细胞与牙周炎的进展密切相关。当牙周致病菌侵袭牙周组织后,可刺激宿主细胞释放炎症因子,进而诱导宿主启动免疫炎症应答;该应答可招募巨噬细胞浸润至病变部位,后者通过分泌相关细胞因子促进破骨细胞活化,这是牙槽骨吸收的核心驱动因素之一^[91]。Zhang等^[92]利用免疫代谢干预疗法,将槲皮素包封在介孔PDA中。该材料下调M1巨噬细胞标记物和诱导型一氧化氮合酶的表达,同时上调M2巨噬细胞标记物的表达,降低牙周组织中炎症因子IL-6、IL- β 的水平,从而减轻牙周炎症,减少牙槽骨丢失。

目前,牙科种植技术已广泛应用于牙列缺失/缺损的修复,其功能接近于天然牙且长期稳定性良好,显著提升了患者满意度与生活质量^[93]。但牙周炎引发的牙列缺损的患者往往伴随骨量不足、局部感染风险高等问题,常规种植体存在骨结合效率低、抗菌性能有限等局限,可能影响种植成功率。PDA涂层种植体凭借其独特优势为这类患者的种植修复提供了新思路。Ma等^[94]汇总的动物实验数据显示,在健康大鼠股骨髁模型中,PDA涂层种植体4周骨-种植体接触率(bone-implant contact, BIC)达 $58.2\% \pm 4.5\%$,显著高于对照组($32.7\% \pm 3.8\%$);在骨质疏松大鼠模型中,PDA涂层种植体4周BIC为 $45.6\% \pm 5.2\%$,显著优于空白对照组($28.9\% \pm 4.1\%$)。针对感染高发的牙周炎患者,兔下颌骨感染模型中,PDA-Ag复合涂层钛种植体6周后感染率仅8.3%(对照组58.3%),感染区骨丢失体积减少61%,BIC仍保持 $49.2\% \pm 4.7\%$ (对照组 $22.1\% \pm 3.5\%$),且表面生物膜厚度控制在 $5 \mu\text{m}$ 内(对照组 $>20 \mu\text{m}$)。这些结果表明,PDA涂层通过促骨结合、抗菌双重作用,在牙周炎相关牙列缺损

修复中展现出良好应用前景。

3.3.2 种植体周围炎 虽然临床数据显示牙种植体的总体存活率较高,但种植体相关再治疗的有效性仍尚不明确。这也提示,仍需警惕种植体周围炎导致种植失败的潜在风险^[95]。由于缺乏天然牙周组织的保护,种植牙周围的菌斑积累可导致种植体周围炎并刺激周围软组织,造成邻近牙槽骨吸收^[96]。Wang等^[97]利用PDA涂层的光热效应,通过红外激光使氧化锆表面温度升高,有效抑制菌斑生成。此外,PDA涂层通过促进牙龈成纤维细胞的增殖与黏附,调节结缔组织形成,进而改善种植体与周围牙龈及结缔组织的功能性结合及长期稳定性。Liu等^[98]开发了基于沸石咪唑酸盐框-8(zeolitic imidazolate framework-8, ZIF8)搭载PDA和辛伐他汀的温敏水凝胶系统。该材料在生理温度下成胶,通过PDA的光热效应发挥抗菌作用,同时借助ZIF8的药物负载能力实现辛伐他汀的可控释放,诱导T淋巴细胞向调节性T细胞分化,减轻了种植体周围炎的感染与炎症反应,为其非手术治疗提供了新策略。

综上,PDA因其优异的湿黏附性、抗菌抗炎性能及作为生物活性分子载体的成骨诱导作用,尤其适用于口腔潮湿环境。目前,PDA在口腔疾病治疗与组织修复中的研究日益增多,近年PDA在口腔领域的应用进展总结见表2。

4 局限性和展望

尽管PDA在口腔疾病治疗中展现出优异的生物学特性,但其临床转化仍面临诸多挑战。首先,PDA的聚合机制和沉积过程中形成的关键中间体的结构仍存在争议^[99],制约了材料的创新设计与性能优化;其次,尽管PDA单体已被证实具有良好的生物相容性^[100],但其与金属、聚合物等材料复合后的长期生物相容性、可控降解行为及药物释放仍需系统性探究。并且,对于PDA的临床转化数据,目前主要依赖动物实验,尚缺乏人体临床试验证据。此外,PDA聚合后呈现的黑褐色特征,可能对前牙等口腔美学区域的修复效果产生不利影响,限制其在美观要求较高场景中的应用。

展望未来研究方向,可聚焦于以下创新领域:
①开发智能响应型PDA基递药系统,重点突破材料界面动态调控技术。例如,通过构建pH/光双响应涂层,实现对口腔微环境变化的精准应答;②基于PDA的黏附性与多官能团特性,设计抗菌-免疫

表2 PDA在口腔疾病中治疗的应用

Table 2 Applications of PDA in oral diseases treatment

Composite materials	Biological properties	Application scenarios
Oral hard tissue diseases		
PDA-coated amorphous calcium phosphate ^[59]	Promoting enamel remineralization, anti-bacterial effect	Dental enamel caries
PDA-functionalized collagen surface ^[62]	Promoting collagen mineralization	Dentin caries
Porous polyetheretherketone modified with PDA and gentamicin sulfate ^[65]	Promoting osteogenesis, antibacterial effect, immunoregulation	Osteomyelitis
Spatiotemporal drug release scaffold with PDA-functionalized mesoporous silica nanoparticles (core/shell) loaded with silver nanoparticles and dexamethasone ^[66]	Promoting osteogenesis, antibacterial effect	Osteomyelitis
Porous titanium modified with PDA (loaded with antimicrobial peptides and zinc ions) ^[71]	Antibacterial effect, promoting osteogenesis	Jaw bone defect
Bimetallic/PDA network-collagen-HAp membrane ^[65]	Antibacterial effect, promoting osteogenesis	Jaw bone defect
Oral soft tissue diseases		
Mussel-inspired Janus gelatin-PDA-nanoclay wet-adhesive high-toughness hydrogel ^[77]	Adhesive property	Oral ulcer
PDA-modified double-network wet-adhesive hydrogel ^[80]	Adhesive property, antibacterial and anti-inflammatory effects	Oral candidiasis
PDA-modified injectable polylactic acid/polycaprolactone staple fibers loaded with curcumin ^[86]	Photothermal effect, acid responsiveness	Oral cancer
PDA surface-modified hyperbranched polymer nanoparticles ^[87]	Photothermal effect, acid responsiveness	Oral cancer
Oral hard and soft tissue combined lesions		
Injectable thermosensitive photocrosslinkable hydrogel with spermidine-modified mesoporous PDA ^[90]	Antibacterial and anti-inflammatory effects	Periodontal disease
Quercetin-modified mesoporous PDA nanoparticles ^[92]	Anti-inflammatory effect	Periodontal disease
Polydopamine-coated zirconia implants ^[97]	Antibacterial effect, adhesive property	Peri-implantitis
Simvastatin-loaded ZIF8@PDA NPs thermosensitive injectable hydrogel ^[98]	Antibacterial and anti-inflammatory effects	Peri-implantitis

PDA: polydopamine; HAp: hydroxyapatite; ZIF8: zeolitic imidazolate framework-8; NPs: nanoparticles

调节-促修复一体化的多功能骨植入物,增强对慢性感染性骨缺损的治疗效果;③通过分子设计优化PDA聚合工艺,如引入浅色单体共聚或调控纳米结构改善光散射特性,缓解其颜色对美学区域应用的限制;④在解决上述问题后,未来可推动PDA基材料从动物实验向人体临床试验转化,系统验证其在人体环境中的生物学性能,加速其在口腔疾病治疗中的实际应用。

综上所述,PDA凭借其独特的化学结构、丰富的生物学特性及良好的生物相容性,已成为多学科领域的研究焦点。通过跨学科融合与创新,PDA基生物材料有望在疾病预防与临床诊治中占据重要地位,为口腔疾病治疗提供突破性思路与技术支撑。

【Author contributions】 Lu XX wrote the article. Jiang Z, Xing AL, Zhao B collected the references, revised the article. Sun B conceptualized and revised the article. All authors read and approved the final manuscript as submitted.

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