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·综述·

基于纳米材料的抗菌光动力治疗在口腔感染性疾病中的应用进展

曲昌兴，　刘钧
口腔疾病防治全国重点实验室 国家口腔医学中心 国家口腔疾病临床医学研究中心 四川大学华西口腔医院正畸科，四川 成都(610041)

【摘要】 抗菌光动力治疗是光敏剂在光照下产生活性氧，从而降低致病菌活性的治疗方法。近年来，该疗法逐步应用于口腔感染性疾病的治疗。单一光敏剂在组织和生物膜的穿透性较差，生物利用度低，研究者通过引入纳米材料改进光敏剂，增强抗菌光动力治疗的疗效。聚合物的优势在于可以通过调整其结构实现可控释放光敏剂，但它的稳定性难以保持；金属及金属氧化物本身具有较强的抗菌性能，但其潜在毒性需要深入评估；金属有机框架的灵活设计结构使其具备多功能性，但也存在稳定性和毒性问题。碳、硅纳米材料具有良好的抗菌性和生物相容性，但较高的制备成本限制了其广泛应用。壳聚糖、氧化石墨烯等具备抗菌效果的纳米材料具有更加广阔的应用前景，可以与光敏剂形成多模态协同抗菌平台，增强抗菌效果，消除感染。未来的研究可以增加其他功能材料，如抗炎材料、免疫调节材料等构建综合治疗纳米平台。

【关键词】 抗菌光动力治疗；　光敏剂；　活性氧；　纳米材料；　壳聚糖；　氧化石墨烯；　龋病；　牙周炎；　牙髓根尖周疾病；　口腔感染性疾病；　多模态抗菌疗法
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Application on the advancements in nanomaterial-based antimicrobial photodynamic therapy in oral infectious diseases

QU Changxing, LIU Jun.　State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases & The Department of Orthodontics, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China
Corresponding author: LIU Ju, Email: junliu@scu.edu.cn, Tel: 86-28-85502207

【Abstract】 Antimicrobial photodynamic therapy uses photosensitizers to produce reactive oxygen species under light exposure to inhibit pathogenic bacteria. Although its application in the management of oral infectious diseases has increased over recent years, it is limited by inadequate tissue and biofilm penetration and suboptimal bioavailability exhibited by individual photosensitizers. These challenges can potentially be surmounted through the integration of nanomaterials, such as polymers, metals and metal oxides, metal - organic frameworks, and carbon and silicon nanomaterials. Polymers allow the controlled release of photosensitizers through structural adjustments but have low stability, while metals and metal oxides possess strong antibacterial properties but can be potentially toxic. Meanwhile, metal - organic frameworks have flexible structures and multifunctionality but have low stability and potential toxicity. Moreover, carbon and silicon nanomaterials, despite exhibiting excellent antibacterial properties and biocompatibility, have limited application due to high production costs. Materials with inherent antibacterial properties, such as chitosan and graphene oxide, have broader application prospects, as they can form multimodal antibacterial platforms with photosensitizers, enhancing the antibacterial effects and eliminating infections. Future research could incorporate other functional materials,

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【作者简介】曲昌兴，硕士研究生，Email: qcx1152527420@163.com
【通信作者】刘钧，教授，博士，Email: junliu@scu.edu.cn，Tel: 86-28-85502207

such as anti-inflammatory agents and immunomodulatory materials, to construct comprehensive therapeutic nanoplatforms for the treatment of oral infectious diseases.

【Key words】 antimicrobial photodynamic therapy; photosensitizer; reactive oxygenr; nanomaterials; chitosan; graphene oxide; caries; periodontitis; endodontic disease; oral infectious diseases; multimodal antimicrobial therapy

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抗菌治疗是口腔感染性疾病治疗的核心环节，但传统的抗菌治疗方法如应用抗生素存在耐药性、机械除菌存在速度较慢、灭菌不彻底等问题。近年来，光动力治疗（photodynamic therapy，PDT）被引入抗菌治疗中，被称为抗菌光动力治疗（antimicrobial photodynamic therapy，aPDT），它的工作原理是在特定波长光的照射下，光敏剂从基态转变为激发态，与环境中的分子相互作用产生羟基自由基、超氧阴离子、单线态氧等活性氧（reactive oxygen species，ROS），这些ROS通过与生物分子反应发挥抗菌作用。aPDT可克服传统抗菌方法缺陷，有望应用于口腔感染性疾病的临床治疗。研究者围绕光敏剂构建了一系列纳米治疗平台，这些纳米材料的加入提高了光敏剂的生物利用度，增加其在生物膜的穿透性和产生ROS效率，进一步提高了aPDT在口腔感染性疾病中的疗效。

1　aPDT的原理与特性

aPDT是一种利用光、光敏剂和周围分子产生ROS以清除病原微生物的治疗手段，其清除病原微生物的机制较为明确[1-2]。光敏剂穿透感染的部位到达致病性生物膜，当暴露于特定波长时，光敏剂从低能量的单线态基态转变为单线态激发态。此时，一部分会回到基态，产生荧光和热量；另一部分则会变成具有更大能量的三重激发态。三重激发态可通过以下两种机制与周围分子相互作用，产生ROS。Ⅰ型光化学反应：通过与相邻分子交换电子或氢原子产生羟基自由基，超氧阴离子和过氧化氢；Ⅱ型光化学反应：直接将能量转移到基态分子氧，产生单线态氧。这些ROS氧化损伤微生物的多种生物分子，例如脂质、蛋白质和核酸等，破坏其结构和功能，降低致病性生物膜的活性。

在临床应用中，aPDT的光源可以分为激光、发光二极管（light-emitting diode，LED）和气体放电灯等。其中LED由于其产热低、组织损伤小、低成本、低能耗和便携性等优点，应用更为广泛[3-4]。对于光敏剂，吩噻嗪类阳离子如甲苯胺蓝（toluidine blue，TBO）和亚甲基蓝（methylene blue，MB）较为常用，易与细菌结合且生物安全性较好。其他光敏剂如吲哚菁绿（indocyanine green，ICG）、二氢卟吩e6（chlorin e6，Ce6）、孟加拉红（rose-bengal，RB）、姜黄素和酞菁等也表现出良好的抗菌性能。对于光的工作波长，目前大多数集中在紫外-可见光区域内[2]。近红外光（near infrared，NIR）相比于短波长光的组织穿透性更好，因此使用其激发的光敏剂是目前研究的热点之一。

2　与aPDT相关的纳米材料

纳米材料是指大小在纳米量级（1～100 nm）的材料[5]。对于aPDT，根据光敏剂特性设计纳米系统以克服水溶性差、组织穿透能力弱等治疗缺陷。这些纳米材料可作为载体负载光敏剂，或本身发挥光敏剂作用，它们具备以下几个特性[6-7]：①控制光敏剂的释放，减小细胞毒性；②提高光敏剂的水溶性和生物利用度，减少分解；③与病原微生物特异性结合；④增加细菌或生物膜穿透性；⑤增加组织穿透性。根据它们的化学成分，可以分为有机纳米材料和无机纳米材料。

2.1　有机纳米颗粒

有机纳米材料是由聚合物或脂质组成的固体纳米材料，包括聚合物胶束、脂质体等，其颗粒粒径可达1 000 nm[8]。该材料有良好的生物安全性、生物利用度、水溶性和较高的包封效率。

2.1.1　聚合物胶束　聚合物胶束是由疏水聚合物（如聚乳酸）与亲水聚合物（如聚乙二醇）组成的两亲性嵌段共聚物，在水中自组装形成胶束，处于可逆的动态过程。这种动态性保证聚合物胶束在目

标部位释放光敏剂。目前研究者致力于开发刺激响应型的聚合物胶束，例如对酸碱度或酶的响应，增加该材料的靶向性[9]。

2.1.2　聚合物颗粒　聚合物颗粒通过单体或聚合物与表面活性剂结合而获得，包括天然聚合物如明胶、壳聚糖和合成聚合物如聚乳酸、聚甲基丙烯酸甲酯等。该种材料表面改性灵活，可防止光敏剂在生物环境中降解，有良好的生物相容性和稳定性，限制光敏剂的暗毒性，在aPDT中应用较为广泛。

2.1.3　脂质体　脂质体由一个或多个同心脂质双分子层组成，脂双层内部和脂双层之间为亲水相[10]。这种独特结构允许亲水性光敏剂装载在内部，疏水性光敏剂装载在脂质双分子层。常规脂质体的半衰期较短，为了解决这个问题常用聚乙二醇修饰脂质体，使半衰期显著增加。

2.2　无机纳米材料

无机纳米材料是另一类广泛应用的纳米技术材料，其颗粒粒径通常小于100 nm[11]，主要包括金属纳米颗粒、金属氧化物纳米颗粒、二氧化硅纳米颗粒、碳量子点等。

2.2.1　金属纳米颗粒　金属纳米颗粒由原子团构成，粒径大小为10～100 nm，具有很高的表面-体积比，容易与细菌生物膜相互作用，产生杀菌效果[12]。常用的金属纳米颗粒包括金和银纳米颗粒。金纳米颗粒形状易操控[13]，可根据需要设计成纳米簇、纳米球、纳米棒和纳米花等。此外在光照射下会出现局部表面等离子体共振现象[14]，光敏剂激发速率增加，产生更多的ROS。在金纳米颗粒合成过程中，会在其表面诱导一个负电荷，光敏剂可通过静电吸附在表面。纳米银本身具有一定的抗菌活性，通过直接接触破坏细胞膜和释放银离子导致蛋白质失活，长期用于靶向抗菌[15]。纳米银负载光敏剂可发挥协同作用，增强抗菌效果。

2.2.2　金属氧化物纳米颗粒　金属氧化物纳米颗粒包括氧化锌、氧化钛和氧化铁等。氧化锌和氧化钛是具有生物相容性和独特的光学特性的半导体材料，其本身可在紫外光的作用下将电子转移到氧中形成ROS，可作为一种高效的光敏剂参与aPDT[16]。此外，氧化锌本身也可发挥抑菌剂的作用，与aPDT协同抗菌。

2.2.3　二氧化硅纳米颗粒　介孔二氧化硅颗粒（mesoporous silica nanoparticles，MSN）粒径大小为2~50 nm，具备可调节的孔结构，多样的形态和较大表面积，相比于其他二氧化硅材料有更高的负载能力，可以作为光敏剂的良好载体。其表面容易被酶、抗体等配体修饰[17]。

2.2.4　碳量子点　碳量子点是基于碳纳米材料的纳米粒子，以石墨烯量子点为代表。石墨烯量子点具备光稳定性和抗光降解性，较小的直径（＜10 nm）和较大的表面积，在水中溶解性好，表面容易被修饰，其本身可作为光敏剂，产生大量ROS，也可装载其他光敏剂进行aPDT[18-19]。

2.2.5　上转换纳米颗粒　上转换纳米颗粒通过在陶瓷纳米材料中加入镧系元素、过渡金属或镧系元素，实现反斯托克斯效应，即吸收波长较长的光，发射出波长较短的光[13]。它可以使原本由可见光激活的光敏剂改变为被近红外光激活，提高激活光的穿透组织能力，常被用于治疗局部深度感染[20-21]。

表1总结了aPDT相关纳米材料在口腔感染性疾病中的应用情况。

3　基于纳米材料的aPDT在口腔感染性疾病中的应用

3.1　aPDT与龋病

Gholibegloo等[34]探究肌肽和羟基磷灰石修饰的氧化石墨烯负载吲哚菁绿在抑制变异链球菌中的效果。在纳米系统中，氧化石墨烯作为载体增加吲哚菁绿的水溶性和稳定性，同时其本身发挥抗菌活性；肌肽的修饰增加了抗菌性能；羟基磷灰石的多孔隙使得整个材料的负载率提高。研究结果显示该光敏剂纳米系统有效抑制游离的变异链球菌活性、生物膜的形成以及致龋基因表达。Li等[27]设计一种海藻酸钠水凝胶膜，在其中加入合成的高效光敏剂氯氧化铋和抑菌剂氧化亚铜纳米颗粒。在绿色光照射下，产生ROS实现局部牙齿美白、抑菌和生物膜去除的效果。

生物膜会限制抗菌药物的扩散，使病变部位无法保持有效的药物浓度[39-40]。如何使光敏剂及抗菌药物穿越生物膜是目前aPDT治疗龋病的难题。Balhaddad等[28]设计了磁场响应的光敏剂纳米平台，通过微乳液法将甲苯胺蓝和超顺磁性氧化铁纳米颗粒组装在一起。在外界磁场的作用下，光敏剂穿透生物膜屏障，无论是对变异链球菌菌斑还是混合菌斑，该光敏剂纳米平台的抗菌效果都明显好于单纯甲苯胺蓝。

表1　抗菌光动力治疗在口腔感染性疾病中的应用总结

Table 1　Nanomaterials used in antimicrobial photodynamic therapy for the treatment of oral infectious diseases

Nanomaterial		Photosensitizer	Disease	Microorganisms	Advantage in aPDT	Effects (compared to the sole photosensitizer)	References
Polymer	α-Cyclodextrin	RB	Caries	*S. mutans*	Controlled release and targeted binding	Promoting bacterial uptake: nanoparticles evident within the intracellular cytosol under microscopic examination	Alexandrino et al[22]
	Polyethylene glycol micelles	IR780 and Ce6	Caries	*S. mutans*		Facilitating photosensitizer release: maximum release rate observed under acidic conditions	Yu et al[23]; Liu et al[24]
	Chitosan	RB	Endodontic disease	*E. faecalis*		Enhancing stability: singlet oxygen release time increased by 3 min	Shrestha et al[25]
	Self-assembling peptides	Ce6	Periodontitis	*P. gingivalis*		Promoting bacterial uptake rate: increased by > 50%	Li et al[26]
Metal and metal oxide nanoparticles	Bismuth oxychloride and cuprous oxide	Bismuth oxychloride	Caries	*S. aureus*, *E. coli*, and *S. mutans*	Exhibiting inherent therapeutic properties	Self-antibacterial effect rate: increased by > 50%; teeth whitening: significant change in surface color	Li et al[27]
	Iron oxide	TBO	Caries	*S. mutans*		Self-antibacterial effect rate: increased by approximately 1.5×	Balhaddad et al[28]
	Titanium dioxide and hydroxyapatite	Titanium dioxide	Caries	*S. mutans*		Facilitating mineralization: increase in calcium:phosphorus ratio (1.67:1.59)	Wang et al[29]
	Cerium dioxide	Ce6	Periodontitis	*P. gingivalis*, *F. nucleatum*, and *S. gordonii*		Anti - inflammatory effect: promoting macrophage M2 polarization	Sun et al[30]
	Gold nanoparticles	MB and TBO	Oral candidiasis	*C. albicans*		Self - antibacterial effect: increased by approximately 0.2×	Sherwani et al[31]
Metal-organic frameworks	ZIF-8	Ce6	Caries	*S. mutans*	Multifunctionality (oxygen storage, photosensitizer, antibacterial properties, etc.)	Oxygen storage: increase in oxygen and reactive oxygen species; self-antibacterial effect: increased by approximately 0.5 absorbance units	Wang[32]
	CuTCPP	CuTCPP	Periodontitis	*P. gingivalis*, *F. nucleatum*, and *S. aureus*		Photosensitizer: generation of singlet oxygen under light exposure; self-antibacterial effect rate: increased by > 99% (planktonic)	Li et al[33]
Carbon nanomaterials	Graphene oxide	ICG, graphene oxide, and curcumin	Caries, periodontitis, and endodontic disease	*S. mutans*, *P. gingivalis*, and *E. faecalis*	Exhibiting inherent antibacterial properties and enhancing stability	Enhancing stability: degradation reduced by 41%; self-antibacterial effect rate: increased significantly (planktonic and biofilm)	Gholibeglooetal[34]; Pourhajibagher et al[35]; Ghorbanzadeh et al[36]
Silicon nanomaterials	Silane and mesoporous silica nanoparticles	Ce6	Periodontitis	*P. gingivalis*, *F. nucleatum*, and *S. gordonii*	Enhancing biocompatibility and stability	Enhancing stability: photosensitizer release observed even after several days of static conditions; enhancing cell compatibility: increased number of viable fibroblasts	Sun et al[37]; Qi et al[38]
Upconversion nanoparticles	$NaYF_4$: Yb^{3+}	Titanium dioxide and Ce6	Periodontitis	*P. gingivalis* and *F. nucleatum*	Enhancing light penetration	Excitation light shifting from red to near-infrared, increasing tissue penetration by 0.5 cm	Qi et al[21]; Zhang et al[20]

RB: rose-bengal; Ce6: chlorin e6; TBO: toluidine blue; MB: methylene blue; ZIF-8: zeolitic imidazolate framework-8; ICG: indocyanine green

致龋菌还会摄取食物中的碳水化合物产生有机酸，在生物膜内形成酸性微环境（pH：4.5 ~ 5.5）[41]。因此，设计pH响应型的纳米平台可增加光敏剂的靶向性，使aPDT的治疗更精准。Yu等[23]开发了酸性微环境诱导的聚乙二醇可脱壳纳米平台，当该平台穿透生物膜后在弱酸性条件下硼酸键解离，聚乙二醇外壳脱落，暴露细菌靶向硼酸配体。同时，酸性微环境导致乙撑双硬脂酰胺水解，所载环丙沙星和IR780释放发挥抗菌作用。

龋病的治疗不仅需要杀灭致龋菌，还需要考虑生物膜去除后牙体硬组织的修复[29]。Wang等[29]构建二氧化钛-羟基磷灰石纳米系统，该纳米

系统在可见光激活下，可抑制游离变异链球菌活性，抑制生物膜形成，增加脱矿部位钙磷比，促进再矿化。

3.2　aPDT与牙周炎

杀死致病菌或清除牙菌斑生物膜对于牙周炎的治疗至关重要，但目前机械清除的方法对于窄而深的牙周袋以及根分叉区域的效果较差。通过设计纳米平台，将aPDT应用到牙周炎的抗菌治疗中。Li等[33]设计了氧化铁原子层改性的二维卟啉金属-有机骨架材料光敏剂系统，将其掺入聚乙二醇基质中形成软膏以应用到牙周炎的aPDT治疗中。氧化铁的修饰增强了二维卟啉金属-有机骨架的能量转移和电荷转移，使光动力过程产生更多的ROS，对牙龈卟啉单胞菌等牙周炎致病菌杀菌效率达到99%。整个光敏剂系统还可释放铜离子和铁离子，协同抗菌和牙周组织修复。Sun等[42]将Ce6和香豆素6（coumarin 6，C6）共同负载到四氧化三铁-硅烷核壳结构中，形成磁场作用下靶向结合的多功能纳米颗粒。结果显示，基于该纳米系统的aPDT可显著抑制血链球菌、牙龈卟啉单胞菌和具核梭杆菌生物膜的活性，使菌落形成单位降低4～5个数量级。

部分光敏剂的激发光工作波长位于紫光或蓝光范围，组织穿透能力较弱，对于深牙周袋或根分叉区域的治疗效果不理想。通过应用上转换的策略，将激发光转换为穿透能力较强的近红外光。Qi等[21]构建上转换纳米颗粒和二氧化钛的核壳结构纳米系统，上转换纳米颗粒核心使二氧化钛原本的紫色激发光转变为近红外光，增加了组织穿透性，使致病菌生物膜的CFU降低3～4个量级。Zhang等[20]使用上转换纳米材料（NaYF4: Yb^{3+}, Er^{3+}）负载光敏剂Ce6，使激发光转变为近红外光，增强光照的组织穿透性。

Sun等[30]构建Ce6涂覆在二氧化铈表面的光敏剂纳米系统。二氧化铈发挥超氧化物歧化酶和过氧化物酶作用，清除aPDT杀灭细菌后剩余的ROS，减少组织氧化应激，调节巨噬细胞M1/M2比例，减少促炎因子表达，增加抗炎因子表达，达到抗炎效果。

基于纳米材料的aPDT也被用于种植体周围炎的治疗中。尹贻鑫[43]在钛表面涂覆氮化钛涂层，在可见光的激发下，涂层材料引发的aPDT对金黄色葡萄球菌和大肠埃希菌有明显的抑制作用，抑菌效率达到60%。

3.3　aPDT与牙髓根尖周疾病

研究者将aPDT应用到根管部位的抗菌治疗中。Ghorbanzadeh等[36]探究还原氧化石墨烯负载姜黄素在粪肠球菌的aPDT治疗中的效果。结果显示，光动力方法对粪肠球菌的生物膜最小抑菌浓度低于单独光敏剂和单独LED照射，细菌生物膜中4个致病相关基因表达水平显著降低。

根管内的成分，如牙髓组织、牙本质等会与光敏剂相互作用，导致进入细菌细胞内的光敏剂减少，aPDT抗菌效果降低。Shrestha等[25]探究当这些组织成分存在时壳聚糖偶联RB的纳米颗粒（CS-RBnp）的aPDT治疗效果，结果显示牙髓组织和牛血清蛋白在一定程度上抑制CSRBnp、亚甲基蓝和RB的抗菌活性，但是CSRBnp引导的aPDT在作用24 h后仍然可以完全杀灭细菌。

3.4　aPDT与口腔念珠菌病

目前口腔念珠菌病的治疗方法包括调节易感因素以及使用抗真菌药物。然而，白色念珠菌的生物膜生长方式容易出现耐药性和感染复发。Carmello等[44]探究阳离子纳米乳剂包封氯铝酞菁引导的aPDT治疗小鼠口腔念珠菌病的疗效，aPDT使白色念珠菌细胞活力降低1.4个数量级，降低其黏附和生物膜形成能力。Sherwani等[31]探究金纳米颗粒偶联亚甲基蓝和甲苯胺蓝对白色念珠菌的aPDT效果，该治疗显著抑制生物膜的生长，清除成熟的生物膜，在小鼠模型的舌体组织中白色念珠菌细胞和菌丝也显著减少。

4　小结与展望

aPDT具备低耐药性、广谱性、快速、高效等优点。纳米材料的加入和结合解决了光敏剂生物利用度低、靶向结合性差等问题。此外，对于本身具有抗菌效果的纳米材料，例如壳聚糖、氧化石墨烯和氧化亚铜等的加入帮助构建了以aPDT为核心的多模态抗菌疗法。aPDT通过物理吸附、离子释放、酶活性抑制、胞外多糖生成抑制等多种机制抑制微生物活性，对于典型致病菌表现出良好的抗菌性能，在龋病、牙周炎、牙髓根尖周炎和白色念珠菌病等口腔感染性疾病的治疗中展现广阔的应用前景。然而，目前研究主要以提高抗菌效果为导向设计纳米治疗平台。未来的研究可以在改善传统光敏剂缺陷的基础上，使用多种功能性材料，构建aPDT、气体治疗、抗氧化治疗、免疫调节、组织修复等综合性治疗平台。

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