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·综述·

根管封闭剂抗菌修饰的研究进展

马金溢， 李博磊， 程磊
口腔疾病防治全国重点实验室 国家口腔疾病临床医学研究中心 四川大学华西口腔医院牙体牙髓病科，四川 成都（610041）

【摘要】 牙髓根尖周病是主要由细菌及其代谢产物引起的常见感染性疾病，通过根管治疗术去除根管内感染物质是目前最常用的治疗方法，然而根管内微生物的持续存在对根管治疗的成功率有着不利影响。现有观点认为，根管封闭剂能封闭核心充填材料无法充填的部分区域，通过其抗菌性对微生物产生抑制作用，降低再感染风险，提升根管治疗成功率。多种策略通过机械锁结或化学结合等各异的机制对根管封闭剂进行抗菌修饰，包括抗生素修饰、季铵化合物修饰、纳米颗粒修饰等，以求增强其抗菌性能。总体而言，抗菌修饰策略日益增多，在改良封闭剂抗菌性方面的效果毋庸置疑。季铵化合物和纳米颗粒修饰后的根管封闭剂在抗生物膜活性方面显示出一定优势，具备潜在的临床前景。然而，修饰后的材料是否具有长期抗菌效果，以及其在体内是否能发挥与体外相似的作用和其生物相容性等问题，还亟待解决。在未来，如何制备具有多维度理想性能的根管封闭剂还需要更长远而深入的探索。

【关键词】 根管封闭剂； 抗菌； 抗生素； 季铵化合物； 甲基丙烯酸十二烷基二甲铵； 甲基丙烯酸十六烷基二甲铵； 纳米颗粒； 壳聚糖纳米颗粒； 银纳米颗粒； 氧化锌纳米颗粒

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Research progress on antimicrobial materials modified root canal sealers

MA Jinyi, LI Bolei, CHENG Lei. State Key Laboratory of Oral Diseases& National Clinical Research Center for Oral Diseases& Department of Conservative Dentistry and Endodontics, West China Hospital of Stomatology , Sichuan University, Chengdu 610041, China
Corresponding author: CHENG Lei, Email: chengleidentist@163.com, Tel: 86-28-85501439

【Abstract】 Endodontic and periapical lesions are prevalent infectious diseases primarily caused by bacteria and their metabolic byproducts. The most widely used treatment method today is root canal therapy, which aims to remove infectious substances from the root canal. Root canal sealers can fill areas that core filling materials cannot reach, effectively reducing the risk of reinfection through their antimicrobial properties thus improving the success rate of root canal treatment. Various strategies have been employed to enhance the antimicrobial efficacy of root canal sealers through different mechanisms such as mechanical interlocking or chemical bonding. These strategies include antibiotic modification, quaternary ammonium compounds modification, nanoparticle modification, and others. Overall, antimicrobial modification strategies are increasingly diverse, and their effectiveness in enhancing the antimicrobial properties of sealers is beyond doubt. Root canal sealers modified with quaternary ammonium compounds and nanoparticles have shown certain advantages in antibiofilm activity and have potential clinical prospects. However, whether these modified materials have long-term antimicrobial effects, whether they can perform similarly in vivo as they do in vitro, and their biocompatibility are issues that still need to be addressed. In the future, the preparation of root canal sealers with ideal multidimensional properties will require further long-term and in-depth exploration.

【Key words】 root canal sealer; antimicrobial; antibiotics; quaternary ammonium compounds; dimethylami-

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【作者简介】马金溢，博士研究生，Email：majinyi001107@163.com
【通信作者】程磊，教授，博士，Email：chengleidentist@163.com，Tel：86-28-85501439

nododecyl methacrylate; dimethylaminohexadecyl methacrylate; nanoparticle; chitosan nanoparticle; silver nanoparticle; zinc oxide nanoparticle
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牙髓根尖周病是口腔最常见的疾病之一，其主要致病因素被认为是微生物及其代谢产物，常于根管壁上的生物膜群落中被发现[1-2]。牙髓病微生物大多都具有形成生物膜的能力，存活在生物膜中的细菌通常对宿主防御系统和抗菌药物具有抵抗力，在感染期间保护它们免受药物的不良影响[3]。因此，当牙髓炎症发生时，宿主防御或全身抗生素治疗均无法有效抑制感染[4]。

根管治疗可以通过三维立体地清除根管内感染废物及使用根管充填材料封闭根管系统，达到消除炎症、促进组织愈合的目的[5-6]。尽管根管治疗过程中的根管冲洗和根管消毒可以显著降低感染根管内微生物数量，但由于根管系统本身的解剖复杂性及微生物耐药，分布于根尖分歧、侧根管、峡部、隐窝和牙本质小管等根充材料难以抵达的复杂解剖区域的感染难以被清除[7-8]。文献指出，现阶段想要完全消灭根管系统中的微生物是不可能的，微生物的持续存在是根管治疗失败或再感染的主要原因[9-10]。所以，如何有效地持续抑制根管内微生物成为了根管治疗中需要攻克的一项挑战。

根管充填作为根管治疗的重要环节，对根管封闭和防止细菌再感染起着关键作用[11-12]。为了达到更佳疗效，一类具有一定流动性与抗菌性能，能适应根管系统复杂形态并对根管内微生物产生抑制作用的材料被应用于根管充填中，即根管封闭剂[13-14]。根管封闭剂，也叫根充糊剂，理想的根管封闭剂应具有良好的物理性能（包括封闭性、流动性、机械强度等）、抗菌性能及生物相容性[15]。在过去的研究中发现，绝大多数根管封闭剂都可以对根管内微生物产生一定的抑制作用[16]。然而，大多数根管封闭剂仅具有较为短期的抗菌活性，且其抗菌效果随时间减弱[17]。在根管充填中倘若能使用具有长期抗菌活性的根管封闭剂，对微生物产生持续的抑制作用，那么患牙再感染的风险就会降低，这利于提高根管治疗成功率，改善预后。近年来，多种策略已被用于修饰根管封闭剂，如季铵化合物、纳米颗粒、抗生素等，以求在保持其物理性能及生物相容性的前提下优化其抗菌性能及抗菌时效。综上，本文将就近年来根管封闭剂各类抗菌修饰策略的研究进展进行综述。

1 抗生素

抗生素作为最为经典的抗菌药物，学者们曾尝试将其加入封闭剂中，以增强封闭剂的抗菌活性。一项研究将阿莫西林制备为微球形式，用10%质量分数的阿莫西林微球与树脂类实验封闭剂相混合，发现封闭剂的抗菌活性在96 h内显著增强，且其理化性质或生物相容性未受影响[18]。有学者认为，使用纳米载体可以提高药物在特定区域的化学稳定性及生物利用度，还可能减少药物潜在的不良反应[19-20]。一项研究将甲硝唑制备为液体纳米胶囊，将其与硅酸钙基封闭剂粉剂进行混合，发现虽然封闭剂的抗压强度下降，但其抗菌活性在固化长达9个月后仍保持在一定水平[21]，这为使用抗生素修饰封闭剂提供了新的思路。但局部应用抗生素可能会导致根管菌群产生耐药性，在封闭剂中添加抗生素引发了人们对耐药性的普遍担忧[22-23]。

2 季铵化合物（quaternary ammonium compounds，QACs）

自1994年季铵盐型抗菌单体甲基丙烯酰氧十二烷基嗅吡啶首次被Imazato等合成问世后，甲基丙烯酸十二烷基二甲铵（dimethylaminododecyl methacrylate，DMADDM）和甲基丙烯酸十六烷基二甲铵（dimethylaminohexadecyl methacrylate，DMAHDM）等QACs相继问世。与抗生素不同，QACs不容易引发细菌的耐药性[24]，因此部分学者将目光投向了QACs。现有观点认为，QACs的抗菌性能主要通过杀伤细胞、影响生物被膜的形成、干扰黏附实现，并可能与氧化应激诱发细菌凋亡有关[25-26]。其

中,杀伤细胞的假说最为学者们认可,可能的机制是QACs的长链烷基尾端与细菌接触后和其细胞膜发生结合,破坏细胞膜完整性而引起细菌溶解,即对口腔细菌具有“接触性杀灭”作用[27-28]。但这一假说仍缺乏直接证据支持,QACs与细菌结合后通过何种分子途径诱导细菌死亡还有待研究。

以往研究表明,DMADDM是具有优良抗菌性能的季铵化合物[29-30]。一项研究发现,DMADDM与甲基丙烯酸酯基根管封闭剂EndoREZ的主要成分均具有双键结构,在一定条件下理论上可以发生化学反应,形成交联结构,发挥长效抗菌作用[31]。此研究将DMADDM加入EndoREZ中,直接接触试验(direct contact test,DCT)结果显示含有DMADDM的封闭剂对多种细菌的抑制作用明显,并可以降低多菌种生物膜中粪肠球菌的占比;但当DMADDM的质量分数达到5%时,封闭剂的封闭性、溶解度及生物相容性会受到显著影响[31]。另外一项研究同样将DMADDM用于修饰EndoREZ,研究者将DMADDM与EndoREZ混合搅拌后进行光固化,以促进二者形成交联结构[32]。研究者发现修饰后的封闭剂能有效减少根尖周病变体积和炎症程度,特别是在粪肠球菌再感染情况下,2.5%质量分数的DMADDM组表现出更佳的疗效[32]。有学者将磁性纳米颗粒(magnetic nanoparticle,MNP)与DMADDM纳米颗粒用于修饰封闭剂,发现修饰后的封闭剂具有较好的生物膜抑制作用,并且在外部磁场作用下具有更优越的渗透性,其生物相容性及物理性能均未受到明显不良影响[33]。Fan等[34]也使用MNP和DMADDM对EndoREZ进行修饰,得到了类似的结论。

DMAHDM与DMADDM类似,同样被许多研究者用于修饰根管封闭剂。研究发现,联合应用DMAHDM和银纳米颗粒(sliver nanoparticle,NAg)与单独使用二者之一对封闭剂进行修饰相比,封闭剂的抗菌性能更强,且其物理性能无显著改变[35-36]。有学者在环氧树脂基封闭剂AH Plus中加入2.5%质量分数的DMAHDM和0.15%质量分数的NAg,以探究封闭剂的物理性能与抗菌性能,DCT结果显示封闭剂抗浮游细菌活性及时效均显著增强[35]。研究者将2-甲基戊酸银溶解于甲基丙烯酸叔丁基氨基乙酯[2-(tert-butylamino)ethyl methacrylate,TBAEMA]中,但由于DMAHDM及TBAEMA均不会与环氧树脂发生聚合,研究者认为DMAHDM及NAg均以机械锁结的方式停留在AH Plus中[35]。Baras等[36]以同样的方式制备了NAg,用5%质量分数的DMAHDM和0.15%质量分数的NAg修饰实验封闭剂。研究者认为,DMAHDM及溶解于TBAEMA的NAg均能与甲基丙烯酸酯基实验封闭剂发生聚合,通过形成化学键的方式将二者结合于树脂基质[36]。结果显示,修饰后的封闭剂对体外构筑的生物膜模型的抑制效应显著增强,生物膜产多糖能力下降且其菌落形成单位(colony-forming unit,CFU)减少了近6个数量级[36]。他们在另一项研究中向封闭剂中额外添加了不同质量分数的无定形磷酸钙纳米颗粒(nanoparticles of amorphous calcium phosphate,NACP),结论为加入DMAHDM、NAg和NACP不会对封闭剂的流动性和膜厚度产生不利影响,NACP还可使牙本质硬度增加[37]。在这项实验中,生物膜模型构筑于牙本质样本上,结果显示修饰后的封闭剂使生物膜CFU与对照组相比减少了近3个数量级[37]。

综上所述,DMADDM和DMAHDM在增强封闭剂抗菌性能方面均显示出显著成效,在一定浓度范围内可以保持封闭剂的理化性能和生物相容性。尽管这些研究的结果都令人可喜,但未来仍需更多相关的体内及长期研究,进一步评估修饰后封闭剂的临床应用可能性。

3 纳米颗粒(nanoparticle,NP)

纳米颗粒是1 ~ 100 nm尺度范围内的颗粒。除了上文提到的纳米颗粒外,包括壳聚糖纳米颗粒(chitosan nanoparticle,CS-NP)、氧化锌纳米颗粒(zinc oxide nanoparticle,ZnO-NP)等在内的多种纳米颗粒也被用于修饰牙科材料,聚焦于提高抗菌性能、增强机械性能及促进组织再生等方面[38-39]。纳米颗粒的抗菌性可能与其更高的比表面积和电荷密度能够增强材料与微生物细胞的相互作用有关,其致细菌死亡的可能机制为破坏细菌细胞膜完整性、生成活性氧及抑制细菌代谢等[40-41]。同时,纳米材料具有优良的抗生物膜作用,将其用于修饰根管封闭剂可以增强封闭剂对根管生物膜的抑制作用[42]。但纳米颗粒存在一定毒性及对物理性能的潜在不利影响,在应用时需要注意材料的生物相容性问题等,以实现有效的临床转化[43-44]。

3.1 壳聚糖纳米颗粒(CS-NP)

有学者用不同质量分数(10%、20%、30%)的CS-NP对环氧树脂基封闭剂AH 26进行修饰,通过琼脂扩散试验发现封闭剂抗粪肠球菌活性得到了

增强，并且经不同浓度CS-NP修饰后的封闭剂具有比原封闭剂更低的细胞毒性[45]。还有学者将洗必泰和CS-NP用于修饰AH Plus等五种封闭剂，结果显示二者不论单独还是联合应用均能增强封闭剂抗粪肠球菌活性，且联合应用二者修饰后的封闭剂具有最佳的抗菌活性[46]。壳聚糖作为一种无毒且具有一定抗菌作用的天然多聚糖，将其用于修饰根管封闭剂在生物相容性方面较其他材料具有较大优势。然而上述两项研究均只测试了新鲜配置的封闭剂的抗菌性能，CS-NP能否改善封闭剂的长期抗菌活性还需要进一步研究。

3.2　银纳米颗粒（NAg）

此前已有大量研究将NAg用于修饰牙科材料，探索其对材料性能的影响[47-48]。最近有学者合成了银二氧化硅核壳纳米颗粒，并将10%质量分数的核壳纳米颗粒用于修饰实验封闭剂[49]。研究结果表明，封闭剂的流动性、膜厚度及生物相容性无明显变化，且修饰后的封闭剂固化24 h时对生物膜中的粪肠球菌存在抑制作用，这种抑制作用在9个月后仍存在[49]。NAg的主要可能的缺陷是细胞毒性，其细胞毒性具有浓度依赖性[50]，在将其用于修饰封闭剂时应进行多次测试以确定理想浓度，达到生物相容性与抗菌性的协调统一。

3.3　氧化锌纳米颗粒（ZnO-NP）

在诸多研究中，ZnO-NP被证明拥有不俗的抗菌性能[51-52]。有学者将针样的ZnO-NP用于修饰实验封闭剂，结果显示封闭剂在24h时的抗粪肠球菌活性增强，且材料的流动性、溶解度等物理性能未观察到显著的不利影响[53]。最近的一项研究用1%质量分数的ZnO-NP修饰硅酸钙基水门汀，同样发现材料在24h时抗粪肠球菌活性显著提高，且物理性质没有明显不良改变，还可减少促炎细胞因子产生[54]。ZnO-NP除了可以改善材料的抗菌性能外，还能减轻炎症反应[55]，这对于提高根管治疗疗效也具有一定裨益。

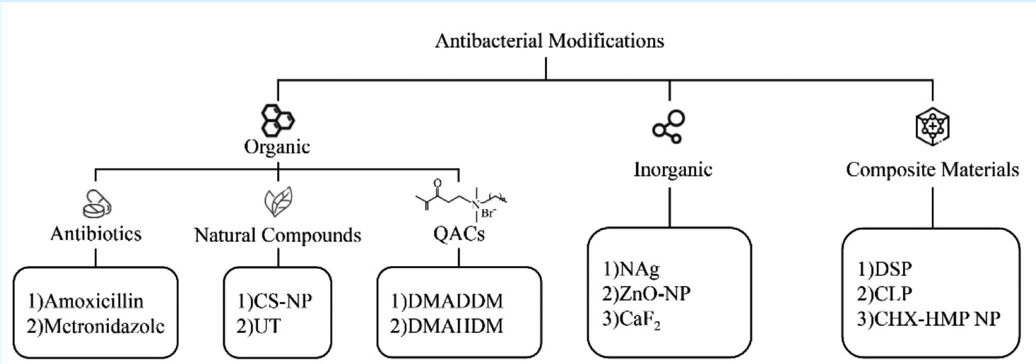
4　其　他

随着研究的深入及探索思路的拓展，用于修饰根管封闭剂的抗菌物质日益增多。一项研究将二氧化硅与盐酸奥替尼定（octenidine dihydrochloride）制备为药物-二氧化硅共组装颗粒（drug-silica coassembled particle，DSP），用于修饰AH Plus及硅酸钙基封闭剂EndoSequence BC Sealer，结果显示DSP显著降低了BC组的菌落总数，且这种作用在4周内持续存在[56]。还有一项研究将25%质量分数的含有氯化十六烷基吡啶（cetylpyridinium chloride，CPC）的聚甲基丙烯酸羟乙酯（2-hydroxyethyl methacrylate，HEMA）-三甲基丙烯酸酯（trimethylolpropane trimethacrylate，TMPT）颗粒（CPC - loaded polyHEMA/TMPT particle，CLP）加入树脂基封闭剂MetaSEAL Soft中，结果显示封闭剂在2周时的抗菌活性显著增强，且固化性能、封闭性能未发生不利影响[57]。有学者将氟化钙用于修饰三氧化矿物凝聚体（mineral trioxide aggregate，MTA），发现添加超过5%质量分数的氟化钙可以提高MTA对粪肠球菌、牙髓假单胞菌和牙龈假单胞菌的抗菌效果，但封闭剂的长期抗菌活性未进行测试[58]。Carvalho等[59]将2%和5%质量分数的氯己定-六偏磷酸钠纳米颗粒（chlorhexidine-hexametaphosphate nanoparticle，CHX-HMP NP）用于修饰AH Plus等三种封闭剂，DCT结果显示经2%CHX-HMP NP修饰后的三种封闭剂在30 d后较原封闭剂表现出更强的抗粪肠球菌活性。而经5%CHX-HMP NP修饰后，封闭剂在7~30 d后均表现出较修饰前更强的抗粪肠球菌活性[59]。还有学者将植物钩藤（uncaria tomentosa，UT）加入硅酸钙基封闭剂MTA Fillapex中，DCT结果表明用5%质量分数的钩藤修饰MTA Fillapex可以降低其细胞毒性，提高抗菌作用，而对材料的流动性、溶解度、凝固时间等物理性质的影响仍在ISO标准内[60]。总体而言，上述修饰策略在改良封闭剂抗菌性方面的效果毋庸置疑。然而，修饰后的材料是否具有长期抗菌效果，以及其在体内是否能发挥与体外相似的作用和其生物相容性如何等问题，还亟待解决。

5　总　结

许多研究者在对根管封闭剂进行抗菌修饰方面做出了多维度的探索。然而，不同的研究采用了大量不同的方法来评估新型材料，这使得要将材料性能直接进行对比是不可能的。不同的抗菌修饰策略通过各异的机制加入到根管封闭剂中，如季铵化合物由于其主要成分含有双键，理论上可与主要成分同样含有双键的甲基丙烯酸酯基封闭剂发生聚合，产生化学交联。然而，其余抗菌添加剂是否能与封闭剂发生化学结合尚不清楚，研究者们推测它们可能依赖机械锁结等物理作用停留于封闭剂中，发挥修饰作用。季铵化合物和纳米颗粒在抗生物膜活性方面显示出一定优势，具

备潜在的临床前景。但季铵化合物的作用机制尚未得到证实,纳米颗粒修饰需要优化其物理、化学和生物学特性。此外,还有许多策略被用于修饰封闭剂(图 1),均改善了封闭剂的抗菌性能,具备临床应用潜力。然而,在封闭剂中添加阿莫西林等传统抗生素引发了人们对根管菌群产生耐药性的担忧。需要引起重视的是,目前的大部分研究均为体外研究,还需要更多相关的体内研究以揭露新型根管封闭剂的真实性能;同时,不同策略的长期抗菌活性及其对封闭剂物理性能、生物相容性的影响也需要进一步测试,以评估其应用前景。在未来,如何制备兼具理想物理性能、抗菌性能及生物相容性的根管封闭剂还需要更长远且深入的探索与努力。



QACs: quaternary ammonium compounds; CS-NP: chitosan nanoparticle; UT: uncaria tomentosa; DMADDM: dimethylaminododecyl methacrylate; DMAHDM: dimethylaminohexadecyl methacrylate; NAg: sliver nanoparticle; ZnO-NP: zinc oxide nanoparticle; DSP: drug-silica coassembled particle; CLP: cetylpyridinium chloride-loaded polyHEMA/TMPT particle; CHX-HMPNP: chlorhexidine-hexametaphosphate nanoparticle

Figure 1　Antibacterial modification strategies for root canal sealers

图 1　根管封闭剂抗菌修饰策略

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