

静电纺丝纳米纤维在颌面部组织修复中的应用

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[摘要] 口腔疾病发病率较高, 其治疗常需要新材料的应用。静电纺丝纳米纤维 (ENF) 凭借其独特的结构特征和优异的生物学功能, 在口腔医学领域展现出广泛的应用价值, 尤其在颌面部组织修复和牙齿再生等方面发挥着重要作用。对此, 本文综述近年来 ENF 在口腔医学中的研究进展, 简要概括其制备过程和特点, 从口腔疾病中的临床应用进行分类阐述, 并总结其在口腔疾病治疗中所面临的挑战及发展前景, 旨在为口腔疾病的基础研究和临床应用提供参考。

[关键词] 静电纺丝; 纳米纤维; 口腔疾病; 组织工程; 药物输送

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Application of electrospun nanofibers in maxillofacial tissue repair

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[Abstract] The incidence of oral diseases is high, and its treatment often requires the application of new materials. Characterized by their unique structural properties and exceptional biological functions, electrospinning nanofibers (ENFs) have shown significant application potential in oral medicine, particularly in maxillofacial tissue repair and tooth regeneration. This work reviews the research progress of ENFs in stomatology, summarizing their preparation process and characteristics, categorizing and elaborates their clinical applications in oral diseases, and outlining their challenges and development prospects in the treatment of oral diseases. The findings provide reference for basic research and clinical application of ENFs against oral diseases.

[Key words] electrospinning; nanofiber; oral disease; tissue engineering; drug delivery

口腔疾病常常影响颌系统的功能和美观,

严重降低患者的生活质量, 其发生率较高, 约占全球人口的45%^[1]。大多数口腔疾病的治疗依赖于材料的应用, 如牙体缺损的充填材料、颌面缺损的组织修复材料、牙齿缺失的种植植入材料等。然而, 传统口腔材料以解决口腔疾病为基础, 仅有简单的结构和功能, 其性能未得到显著的改善, 如树脂充填材料仅考虑强度、硬度而抗菌性能稍显不足。近年来, 随着口腔纳米材料的高速发展, 不同制作工艺的纳米材料弥补了传统口腔疾病治

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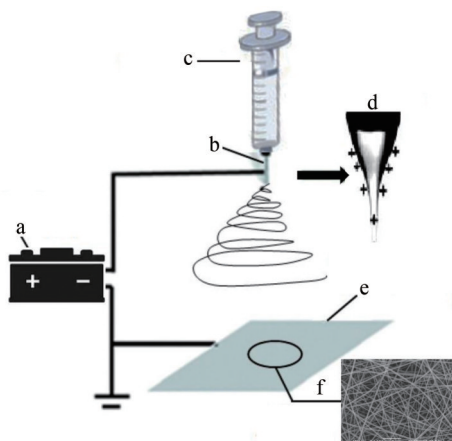
疗中的不足,改善了口腔疾病治疗观念^[2]。静电纺丝纳米纤维(electrospinning nanofibers, ENF)其直径与天然细胞外基质类似且具有比表面积大和孔隙率高等特性^[3-4],近几年被广泛应用于各类口腔疾病治疗的研究,成为口腔材料制备方向之一。

本文综述近年来ENF在口腔医学中的研究进展,对ENF在口腔疾病中的应用进行分类介绍,并总结ENF在口腔疾病治疗过程中面临的挑战及发展前景。

1 静电纺丝的原理及其特点

1.1 静电纺丝的构成及原理

静电纺丝技术主要由高压电源、注射泵、喷丝头和收集装置构成^[5-6],其通过电压驱动,使表面液滴改变形态,达到临界电压时,液滴在喷丝头末端形成Taylor锥,然后经过椎体喷射流出,在溶剂蒸发后,通过不断拉伸和搅动,最终固化沉积形成纳米纤维^[7-9](图1)。



a: 高压电源; b: 喷丝头; c: 注射器; d: 泰勒锥; e: 收集器; f: 纤维形态。

图 1 主要静电纺丝装置及结构

Fig 1 Main electrospinning devices and structures

1.2 静电纺丝纤维制品特点

传统ENF主要存在形式是聚合物纤维堆积紧密的膜结构,其特点是具有较高的孔隙率和比表面积^[10]。由于其致密的小孔阻碍细胞浸润和生长,现在有学者采用层状3D纳米纤维支架增加其孔径,能够促进细胞全方位的增殖并与周围的微环境充分融合,最终形成类似于细胞的体内环境,显著促进细胞的增殖^[11-12]。同时,越来越多的学者结合气体发泡、3D打印、电喷雾、短纤维自组装

等技术实现3D纳米纤维支架^[13-16]。

2 ENF在口腔相关疾病治疗中的研究现状

ENF在口腔中多用于组织工程支架和药物输送载体。ENF直径与天然细胞外基质类似,为细胞黏附、增殖、迁移和分化提供理想的微环境^[12],同时,其具有比表面积大和孔隙率高等特性,可以有效负载各种生物活性成分,如药物、生长因子、无机纳米颗粒等,有助于药物包封和控释^[17]。ENF在口腔领域应用广泛,本文具体从以下应用进行讨论。

2.1 颌面部组织缺损修复

伤口的愈合是软组织动态修复的过程,保持无菌状态和生长因子的适宜浓度在其中发挥重要作用^[18-19]。Schäfer等^[20]使用丝蛋白电纺(静电纺丝)膜负载纳米银颗粒或庆大霉素对比不同抗菌丝蛋白基膜效果,结果表明:庆大霉素组的细菌菌落生长和DNA计数显著降低,并且具有更好的细胞相容性。Ekambaram等^[21]使用磺化聚醚醚酮、胺官能化氧化锆纳米颗粒和姜黄素合成的纤维膜能有效促进伤口愈合和组织再生。Elshazly等^[22]将生物活性玻璃通过低温溶胶-凝胶和静电纺丝结合制作出新型软组织修复敷料,应用中发现血管内皮生长因子表达显著增加,证明糖尿病兔模型口腔软组织加速愈合的有效性。这些能够赋予伤口抗菌和再生特性的ENF在软组织修复方面具有很大的潜力。

骨缺损常用的修复方法为自体骨、异种骨、同种异体骨和骨替代材料修复,但由于自体骨供体局限性,而异种骨和同种异体骨可能引起免疫排斥反应和传播疾病,其临床应用均受到限制^[23]。引导骨再生(guided bone regeneration, GBR)是骨缺损修复有效和可靠的治疗方法,被广泛用于牙槽骨、颌骨的缺损修复^[24-25],但仍存在成骨欠佳的问题。Yao等^[26]报道:使用丝素蛋白和聚乙醇酸作为聚合物制备2种不同孔径的GBR膜用于骨缺损修复,大孔径组较高水平的缝隙连接蛋白43表达和碱性磷酸酶活性表明成骨增殖效果更好。Al-Bishari等^[27]将维生素D和姜黄素负载于聚己内酯(poly-caprolactone, PCL)制作的纤维膜显著增加血管生成和成骨基因(血管内皮生长因子和骨形态发生蛋白2)的表达。此外,钙、镁、锶或锌等营养元素的加入已被证明是增强骨免疫调节的一

种有效方式。Song等^[28]发现：将人类尼尔样-1型(Nel-like molecule-1, NELL-1)生长因子和纳米羟磷灰石结合制作成的双层膜能有效延长NELL-1释放并促进诱导成骨分化能力。Zhu等^[29]构建掺有鸟粪石(磷酸铵镁)纳米线的电纺层并将其附着在非溶剂诱导相分离法所制备的微孔层,结果表明:该双层膜有效促进骨修复过程中间充质干细胞的聚集、增殖和分化。Ren等^[30]发现:将基于锶离子(Sr^{2+})的金属-酚类网络复合物形成的生物填料与PCL混合所制备的电纺膜可以调控骨免疫环境,并证实酚配体和 Sr^{2+} 在改性膜上的可持续释放。Xing等^[31]通过同轴静电纺丝制备的纳米纤维负载3种纳米活性颗粒,实验表明:负载溶血磷脂酸对小鼠胚胎成骨细胞前体细胞MC3T3-E1具有良好的增殖和分化能力,并在氧化锌和去铁胺纳米颗粒的加入下具有协同成骨作用。牙槽骨的数量和质量在缺失牙修复中也起着至关重要的作用。He等^[32]基于静电纺丝和原位矿化开发PCL/明胶(gelatin, GEL)纳米纤维支架,已被证实在大鼠牙槽骨缺损模型中其新生牙槽骨的毛细血管密度、骨量和胶原基质与天然牙槽骨相当。Ho等^[33]开发了一种负载多西环素的外消旋聚乳酸和负载釉质基质衍生物的壳聚糖制成的3层复合膜,可以加速大鼠牙槽骨截骨模型的伤口愈合并促进牙槽骨再生。

颞下颌关节盘损伤自愈能力有限,手术复杂且存在局限性^[34]。适当的细胞源和基于支架或无支架的组合可用于构建颞下颌关节盘结构。Gan等^[35]将一种由PCL、聚乳酸(poly-lactic acid, PLA)和碳纳米管组成的仿生3D椎间盘电纺支架植入兔下颌椎间盘切除模型中,16周后在显微CT下发现骨小梁的厚度和密度增加,实现椎间盘再生和软骨下骨保护。

尽管GBR材料的研究发展迅速,但大多数研究主要集中在ENF支架功能性上,在分子水平上研究细胞内相互作用和成骨机制仍较少。总之,ENF支架可以模仿骨骼生长的微环境,结合表面功能化,能有效推动骨组织工程的发展。

2.2 牙齿再生

脱矿牙本质的再矿化对于提高牙本质结构稳定性和控制龋病的发生至关重要,ENF在促进牙本质再矿化方面优势较大。de Souza Araújo等^[36]运用ENF将寡肽104吸附于PCL支架上,可以直接促进牙髓干细胞分化,促进牙体组织再生。Liu等^[37]

制备了一种浸入二氧化硅和碳酸钙(锶)液体的纳米纤维垫,实现抗酸牙本质的再矿化。这些发现对牙本质的再生矿化提供了一个新的方向。复合树脂作为窝洞充填治疗中常用的材料之一,在其中添加纳米纤维或纳米颗粒可以改善材料的性能^[20]。其中电纺聚丙烯腈纳米纤维可以提高聚合物复合材料的机械性能,降低聚合收缩率,增强材料的美观性^[38-39],同时可以显著提高实验性复合树脂的断裂强度和抗弯强度^[40]。

牙髓疾病的治疗原则主要是彻底清除病变牙髓组织,充填死腔,以达到清除感染病灶,保持咬合强度的作用。传统去除病变的牙髓组织主要通过药物冲洗及根管预备等方法,有残留病变组织的风险。Ribeiro等^[41]将克林霉素和甲硝唑运用电纺技术在低温状态下研磨成纤维颗粒加入光固化甲基丙烯酸酯化明胶中,其可以持续释放抗生素并在感染牙本质切片中有效消除生物膜,控制根管感染。同时,经过根管治疗后的牙齿失去牙髓组织营养供给易于断裂,影响牙齿的存留率。常规治疗方法主要采用热牙胶进行缺损充填,无法促进髓腔正常牙体组织的再生。Terranova等^[42]将电纺PLA和电喷雾PCL与单宁酸微粒制成的复合膜用于支持根管周围组织的细胞迁移,有效促进了牙髓组织再生。此外,电纺PCL纳米纤维膜负载含有纤维蛋白的胶原水凝胶也可以促进人根尖乳头细胞介导的牙髓再生潜力^[43-44]。牙髓治疗的关键是抗炎、抗菌和激活牙髓干细胞的分化潜力,ENF与水凝胶结合通过递送药物为消除根管内感染和牙髓再生提供更多的选择方向。

2.3 牙周组织再生

临床上牙周病治疗目的是去除菌斑生物膜、减少细菌负荷和控制牙周炎症,同时尽可能促进牙槽骨的再生。当牙周组织炎症得到妥善的控制后,受损牙周组织特别是牙槽骨的再生是牙周再生治疗的关键^[45-46]。

目前,引导组织再生和GBR治疗是再生功能性软硬组织最常用的方法。Xu等^[47]将电纺PCL/GEL纳米纤维堆叠和固定制备出的3D支架植入大鼠牙槽骨缺损模型,结果显示骨密度明显增高,形成的新纤维方向及胶原纤维表达量与天然牙周膜类似。Abdalla等^[48]研究植入小鼠成牙骨质细胞OCCM-30的PCL支架可以促进OCCM-30细胞的增殖和分化,调节成牙骨质细胞标志物的表达,并增强细胞外基质沉积和钙沉积。完全的牙周组织

再生具有挑战性,因为不仅需要抑制介导组织损伤的炎症免疫反应,还需要诱导骨组织和软组织在内的复杂组织再生^[49],通过单纯的临床操作无法实现。Ferreira等^[50]制备的一种负载甲硝唑和四环素的抗生素支架,在大鼠牙周损害的三壁骨缺损模型中,可以增加骨形成、减少骨丢失并且降低炎症反应。He等^[51]制备壳层茶多酚(tea polyphenol, TP)和芯层脂联素受体激动剂(adiporon, APR)的同轴纳米纤维膜,结果显示:TP/APR序贯释放给药能在初期持续抑制炎症和破骨细胞形成,后期促进骨再生。然而,抗菌和成骨是牙周病治疗的关键,抗菌的外层和成骨的内层这种多功能梯度ENF支架是未来研究的重要方向。

综上所述,ENF的应用有可能使牙周软硬组织完全再生,在抗炎、抗菌和促进生长方面应用广泛。

2.4 种植体表面修饰

种植牙种植成功的关键因素是实现种植体骨结合和避免种植体周围感染。为使种植体表面更具生物活性和骨传导性,常使用种植体表面修饰对种植体进行改性^[52]。Mathur等^[53]将GEL和银纳米颗粒结合制作的电纺支架附着到钛合金表面来增强种植体的抗菌性,与未修饰涂层的钛盘相比,涂层钛盘48 h内培养基中金黄色葡萄球菌和大肠杆菌的数量明显减少。Cochis等^[54]将电纺角蛋白纳米纤维膜沉积在钛表面再浸入硝酸银溶液中获得富含银离子的抗菌纳米涂层,结果表明:含银角蛋白涂层样品在降低金黄色葡萄球菌生物膜活力方面提高11倍。然而,如何使种植体表面兼具抗菌活性和骨结合能力是种植体涂层研究的热点。Chowdhury等^[55]开发的纤维膜是以聚乙烯醇、碳化硅、二氧化钛、石墨烯和印楝等为原料共混静电纺丝合成,碳化硅与石墨烯修饰增强了种植体表面粗糙度和亲水性能,从而提高骨结合能力,印楝与二氧化钛表面涂层后提高种植体抗菌、抗腐蚀性能。因此,静电纺丝涂层技术的应用可以赋予种植体特定性能,提高种植体植入的成功率。

2.5 口腔局部药物递送

临床上常用的牙周局部抗菌剂由于抗菌时间短、作用位点不确切等原因常无法实现牙周炎的长效药物治疗。Chen等^[56]开发出负载氯己定的纤维膜,可以延长氯己定释放时间,并在体外对牙周致病菌表现出较高的抗菌活性。Andrei等^[57]通过电纺PLA、纳米羟磷灰石和多西环素制备的新型

抗菌材料在体外抗菌试验中发现可以持续释放多西环素,适用于牙周袋清创术后反复感染的情况。口腔黏膜贴片可实现局部治疗,是治疗口腔溃疡和口腔念珠菌病的有效手段^[58]。Edmans等^[59]制作出黏膜双层纳米贴片将抗肿瘤坏死因子 α 直接输送到口腔黏膜溃疡,成功递送了抗体F(ab),中和了肿瘤坏死因子 α 的活性,同时降低了与疾病有关的T细胞趋化因子浓度至基线水平。Teno等^[60]将PCL、PLA和盐酸环丙沙星进行分层电纺制作出3层复合膜,被证实具有优异的抗菌性能并且在志愿者中平均释放药物7 h。Li等^[61]制备出负载乳铁蛋白的氟康唑/GEL膜,结果发现:氟康唑在6 h内迅速释放,总计可持续释放120 h,能有效抑制白色念珠菌。Clitherow等^[62]将饱和脂肪酸负载在电纺膜用来克服抗真菌药的耐药性,结果显示:含有十二烷酸的口腔贴片对白色念珠菌抗菌活性最高。ENF贴片有效解决了药物的递送和吸收问题,在口腔黏膜局部药物应用方面前景广阔。

高发生率的口腔鳞状细胞癌常用的治疗手段主要为手术切除辅助放射治疗和化学治疗^[63]。通过纳米系统递送化学治疗药物可以有效增强药物的靶向性和减少不良反应^[64]。Nam等^[65]已将已证明有抗癌活性的当归提取物加入聚合物中形成的电纺膜可以快速湿润、崩解和分散到口腔黏膜中,实现对口腔鳞状细胞较少的抗癌活性,同时对正常组织和器官的不良反应低。Ravichandran等^[66]开发出负载羽扇豆醇的PCL/GEL纳米纤维,结果显示:羽扇豆醇在抗癌活性试验中对人口腔癌和肾细胞癌细胞株显示出较高稳定性和抗癌活性。同样,该学者还将夹竹桃根苷甲醇提取物负载在电纺膜上作为抗菌剂、抗癌剂和抗氧化剂,有效延长化学治疗药物的释放^[67]。

除了传统化学治疗方法以外,还有一些利用光热转换方式来控制药物释放的纳米材料。Liu等^[68]在一项研究中发现:PCL和无细胞真皮基质混合的电纺膜在近红外辐射下可以按需释放褐藻糖胶以抑制口腔肿瘤生长,在3轮照射后,恶性肿瘤标志细胞明显降低活力和提高凋亡率。这种热控材料增强细胞靶向特异性,空间上控制药物的释放,在治疗和预防口腔癌复发方面具有很大的潜力。

总之,负载抗肿瘤药物的ENF膜可以增强药物的靶向性,结合光动力、声动力等疗法,能有效治疗口腔癌及降低其复发率。

3 结论与展望

目前, 静电纺丝技术已经在口腔疾病应用领域方面被广泛研究。在口腔组织工程学中, ENF可以重建口腔软硬组织, 如在牙本质、牙髓、牙周组织及骨组织等的再生方面具有巨大的潜力; 在药物输送方面, ENF可以控制药物释放速率和释放部位, 处理口腔致病菌带来的各种口腔疾病, 如龋病、牙髓病、牙周病、黏膜病和颌面感染等。由于口腔疾病常处于复杂的微生物环境中, 常需要多种药物联合使用, 与单一流体静电纺丝相比, 多流体静电纺丝可以避免材料之间的相互影响, 可以开发出功能多样、性能可调的复合纳米纤维。此外, 可以对ENF进行智能化改造, 使其可以在特定刺激下释放药物, 如pH、温度、光照等, 达到精准释放的效果。另外, 还可以通过物理和化学表面改性技术, 提高ENF的生物相容性和功能性。

然而, ENF应用于口腔疾病治疗等方面仍面临挑战。首先, ENF在口腔的研究多局限于体外实验, 缺乏体内和临床研究, 且体内研究模型多是小型动物, 和人类真实口腔环境有很大的不同, 未来需开展更多的临床试验。其次, 3D支架具有层状结构, 放置在牙槽窝等空腔缺损处可增加界面相互作用, 是未来支架的发展方向之一, 而ENF多为二维结构, 电纺成精确尺寸和形态的3D结构具有一定的挑战。最后, 静电纺丝工艺的量产和成本控制仍旧是未来发展的难点之一。量产的同时还要控制纳米纤维附着的药物和生物活性分子分布均匀, 以达到临床中所需求的材质强度。因此, 如何克服这些限制, 是静电纺丝材料未来发展的关键。

总之, ENF在口腔医学领域的应用具有广阔的前景, 但想要获得相对理想的材料还需要进一步的探索与研究。

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