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· 综述 ·

## 再生性牙髓治疗的研究进展

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**【摘要】** 再生性牙髓治疗以牙髓生物学为基础,运用组织工程的基本原则,促进牙髓-牙本质复合体功能性再生,在牙髓坏死或伴根尖周炎的年轻恒牙治疗中已取得良好疗效,近年来也逐渐尝试应用于根尖发育成熟的恒牙治疗。最大限度控制感染并促进组织修复再生是再生性牙髓治疗的关键所在。与年轻恒牙的治疗不同,在根尖发育成熟的恒牙中可适当行根管机械预备;根管冲洗和根管消毒剂的选择,需综合考量抗菌效果、生物安全性及可能引起的牙冠变色、根管钙化等并发症;生物陶瓷材料的发展为冠方封闭材料提供了更多选择,但需进一步临床评估。除传统的血凝块支架外,以富血小板血浆、富血小板纤维蛋白、浓缩生长因子等血小板浓缩制品为代表的新型组织支架不断涌现,其实际临床疗效及与血凝块联用疗效仍需长期、大样本的研究。

**【关键词】** 再生性牙髓治疗; 组织工程; 适应证; 感染控制; 根管预备; 生物陶瓷; 组织支架; 血小板浓缩制品

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**【Abstract】** Regenerative endodontic procedures, based on dental pulp biology, use the basic principles of tissue engineering to promote the functional regeneration of dental pulp-dentin complexes. Good results have been achieved in the treatment of young permanent teeth with pulp necrosis or apical periodontitis. There have also been preliminary clinical explorations of the treatment of mature permanent teeth in recent years. The key to successful treatment is controlling infection as well as promoting tissue repair and regeneration. Moderate root canal mechanical preparation is allowed in the therapy of mature permanent teeth, while it is not recommended in the treatment of young permanent teeth. The choice of root canal irrigation and intracanal antiseptics requires a comprehensive consideration of the antibacterial effects, biological safety, and possible complications, such as crown discoloration and root canal calcification. The development of bioceramic materials provides more options for crown sealing materials, but further clinical evaluation is needed. In addition to traditional blood clot scaffolds, new types of tissue scaffolds represented by platelet-rich plasma, platelet-rich fibrin, concentrated growth factors and other platelet concentrates have been developed. Long-term and large-scale studies are needed to evaluate the actual clinical efficacy of these new scaffolds and the efficacy of their combined application with blood clots.

**【Key words】** regenerative endodontic procedures; tissue engineering; indications; infection control; root canal preparation; bioceramics; tissue scaffolds; platelet concentrates

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再生性牙髓治疗由 Iwaya 等<sup>[1]</sup>首次提出,主要通过有效的根管消毒,保护牙髓干细胞、根尖乳头干细胞等种子细胞,提供再生支架及生长因子,并进行严密的冠方封闭,诱导干细胞迁移和分化生成修复性组织,不仅可改善临床症状,重建牙髓-牙本质复合物体功能,而且能促进感染的年轻恒牙牙根继续发育<sup>[2]</sup>。美国牙髓病学学会(American association of endodontists, AAE)、欧洲牙髓病学学会(European society of endodontology, ESE)均已发布关于年轻恒牙再生性牙髓治疗的操作指南。功能性牙髓-牙本质复合体的再生对牙髓治疗的最高目标保留天然牙列,具有重要影响<sup>[3-4]</sup>。本文就再生性牙髓治疗的适应证、感染控制、再生支架的应用等研究热点,对当前新进展进行综述。

## 1 再生性牙髓治疗的适应证尝试性放宽

### 1.1 根尖发育不全的年轻恒牙

对于牙髓坏死的根尖发育不全的年轻恒牙,再生性牙髓治疗可取得与传统根尖诱导成形术及根尖屏障术类似的疗效,多数病例实现了牙根延长、根管壁增厚、根尖孔闭合,患牙远期根折风险降低<sup>[5]</sup>,并且约50%的病例报道中牙髓活力测试呈阳性反应<sup>[6]</sup>,至少部分恢复了牙髓-牙本质复合体功能,保留其对疾病刺激信号的防御作用。此外,AAE和ESE指南皆指出在病例选择上,需同时考量患者依从性、系统性疾病史、药物过敏史、患牙本身状况及后续修复治疗方案等。

### 1.2 根尖发育成熟的恒牙

对于根尖发育成熟的恒牙感染,传统不推荐再生性牙髓治疗,多采用根管治疗术。然而根管治疗术无法恢复牙髓生理功能,且可能出现穿孔、牙根纵裂等并发症。随着临床及基础研究的不断深入,再生性牙髓治疗的适应证正尝试性拓宽,已有学者报道了将其应用于根尖发育成熟的恒牙牙髓坏死及根尖周炎治疗成功的病例<sup>[7-8]</sup>。Nageh等<sup>[9]</sup>随访发现根尖发育成熟的患牙甚至对温度测验、牙髓电活力测试出现反应,提示牙髓-牙本质复合体功能得到了一定恢复。鉴于当前相关研究主

要为小样本临床试验,缺乏大样本的长期追踪随访,其远期疗效仍需进一步评估。

## 2 感染控制的重点环节

### 2.1 根管机械预备的选择

对于根尖发育不全的年轻恒牙,多数学者不建议根管机械预备,因其易损伤残留的干细胞,清除生长因子,削弱薄弱的年轻恒牙根管壁,导致牙根折裂。大量临床研究也表明不进行机械预备,年轻恒牙的再生性牙髓治疗也可获得较好疗效<sup>[2]</sup>。不同的是,应用于根尖发育成熟的恒牙时,大部分病例报道皆进行了根管机械预备<sup>[7-9]</sup>。其目的不仅在于清理感染物质并形成根管,还为了扩大根尖孔直径。传统认为根尖孔直径至少需达1 mm,以保证充足的干细胞、营养物质等转移至根管内促进修复再生。然而,有学者认为人体细胞平均大小为10~100 μm,根尖孔预备至0.25 mm,已能满足干细胞迁移需要<sup>[7]</sup>;也有部分学者选择扩大至0.6~0.8 mm<sup>[9]</sup>。目前关于根尖孔的扩大尚无统一标准,与患牙原始情况、感染程度及患者年龄等潜在因素相关,有待进一步探讨。

### 2.2 根管冲洗

根管冲洗液的选择,需均衡考虑抗菌效能、生物安全性及可能并发症如着色等。AAE推荐将1.5%次氯酸钠(NaClO)溶液与17%乙二胺四乙酸(EDTA)联合应用,而ESE将NaClO溶液浓度范围放宽为1.5%~3%。与上述两种冲洗液相比,氯己定(chlorhexidine, CHX)虽有广谱抗菌效果,但组织溶解力差,易致牙体着色,在再生性牙髓治疗中的直接应用较少。目前新型根管冲洗剂也不断涌现,以QMix为典型代表,其由CHX、EDTA及表面活性剂混合组成,能有效抗菌并清除根尖区玷污层,作为终末冲洗剂时,牙本质着色较CHX显著减弱<sup>[10]</sup>。此外,在保证根管尤其是根尖1/3区清洁效果的同时,应尽量减少冲洗液溢出根尖孔以保护根尖周组织,建议采用侧方开口的冲洗针头或根尖负压冲洗系统。

### 2.3 根管消毒

再生性牙髓治疗中AAE建议采用由甲硝唑、环丙沙星和米诺环素组成的三联抗生素糊剂(triple antibiotic paste, TAP)行根管消毒,而ESE推荐Ca(OH)<sub>2</sub>制剂。不可忽视的是,TAP易导致牙冠变色,有学者提出预先使用牙本质粘接剂封闭牙本质小管,但也只能降低着色程度,并不能抑制变色<sup>[11]</sup>。治疗过程中可将TAP置于釉牙骨质界之下,以减少牙冠变色的风险,对于已产生的牙冠变色可尝试内漂白改善。相比于TAP,在Ca(OH)<sub>2</sub>制剂根管消毒的病例中,根管钙化发生率较高<sup>[12]</sup>。因此,TAP与Ca(OH)<sub>2</sub>制剂各有优劣,目前尚无根管消毒药物选择的统一标准。

### 2.4 冠方封闭

冠方封闭效果对冠方微渗漏、感染控制、再感染的预防具有重要意义。再生性牙髓治疗的临床病例报道中多选用三氧化矿物凝聚体(mineral trioxide aggregate, MTA)作为冠方封闭材料,这也是AAE及ESE的共同推荐,但其固化时间较长、含有铁和铝等金属元素易致牙冠变色<sup>[13]</sup>。通过去除部分MTA和内漂白,可在一定程度上改善变色。随着生物陶瓷材料的发展,越来越多的学者尝试引入Biodentine、iRoot BP Plus等新型生物陶瓷材料替代MTA<sup>[14-16]</sup>。iRoot BP Plus不含金属元素,不易导致变色。相对于MTA,Biodentine及iRoot BP Plus价格较高,临床应用时间短,在再生性牙髓治疗中的生物学效应及安全性评估,多集中于基础研究,仍缺乏大量的临床研究及长期随访。

## 3 再生支架的应用选择

### 3.1 血凝块

血凝块(blood clot, BC)通过刺激根尖区组织出血后凝结而形成,可作为基质营养、支持新生组织,是最常用的再生支架<sup>[2]</sup>。ESE建议在BC之上放置一层厚约2~3 mm的胶原基质,使其浸润液体避免形成空腔,再进行冠方封闭,可防止冠方材料塌陷影响支架成型和引导组织生长。然而,临床操作中较难准确控制出血速度及出血量,且部分病例未能成功诱导BC形成<sup>[17]</sup>,可能与根尖周组织破坏严重或所使用的麻药含有肾上腺素导致血管收缩有关。为兼顾麻醉效果与BC形成,局麻时推荐使用良好渗透性且不含肾上腺素的麻药。

### 3.2 富血小板血浆

与传统BC相比,富血小板血浆(platelet-rich plasma, PRP)含有更丰富的生长因子如转移生长

因子、血管内皮生长因子、表皮生长因子及类胰岛素生长因子等。Alagl等<sup>[18]</sup>研究表明PRP与BC在改善临床症状及根尖区骨密度上无明显差异,但PRP能更显著地诱导牙根继续发育。然而,另有学者将PRP应用于根尖孔开放的恒牙根尖周炎再生性牙髓治疗时,发现牙根并未继续发育<sup>[19]</sup>。因此,PRP有助于促进根尖阴影消失,根尖区钙化,但在诱导牙根发育上具有不稳定性。

### 3.3 富血小板纤维蛋白

富血小板纤维蛋白(platelet-rich fibrin, PRF)是继PRP后第二代血小板浓缩制品,简化了制备过程,无需添加抗凝剂,且具备完整的免疫生物相容性,能形成三维纤维蛋白支架,更缓慢、持久地释放生长因子。Lv等<sup>[17]</sup>研究发现PRF与BC疗效类似,可有效改善临床症状,促进根尖周病变愈合及牙根发育。Ulusoy等<sup>[20]</sup>临床及影像学评估结果表明,BC、PRP、PRF疗效相近,但后两者无需诱导根尖出血,且根管闭塞倾向明显降低。因此,PRF可取得不逊色于BC的疗效,但其呈凝胶状,难以完全适应复杂的根管形态。随着低速离心概念的提出,可注射富血小板纤维蛋白(injectable platelet-rich fibrin, i-PRF)被研发,其降低了离心速度及时间,初期保持液体流动状态以适应根管形态,凝固后可形成更均匀、稳定的三维纤维蛋白网络,富含高浓度的血小板、白细胞和生长因子<sup>[21]</sup>,其良好的生物活性提示具有较好的潜在应用前景。

### 3.4 其他新型再生支架

浓缩生长因子(concentrated growth factors, CGF)是第三代血小板浓缩制品,通过变速离心提升纤维蛋白拉伸强度及黏合度,形成高渗透性的三维立体纤维蛋白网结构,获得了更高浓度的生长因子释放。研究表明,CGF能促进牙髓干细胞增殖、迁移和分化,并可诱导比格犬发育未成熟的单根牙牙本质-牙髓复合体再生<sup>[22]</sup>。Brizuela等<sup>[23]</sup>创新性地将异源性人脐带间充质干细胞载入贫血小板血浆,用于成熟恒牙根尖周炎的再生性牙髓治疗,也获得了良好的临床疗效,随访12个月50%患者甚至出现牙髓电活力测试阳性。

## 4 总结与展望

再生性牙髓治疗较传统的根尖诱导成形术、根尖屏障术及根管治疗术能部分恢复牙髓-牙本质复合体功能,具有一定的优越性,但新生组织是否为牙髓样组织仍存有争议,多数研究认为主要是纤维结缔组织、类牙骨质组织、类骨质组织等,并

非生物学意义上的牙髓再生。值得注意的是,这类硬组织的沉积易导致髓腔钙化,而髓腔钙化对牙髓根尖周病变的转归、牙髓-牙本质复合体的恢复、再感染时后续治疗的影响还有待评估。

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