·牙髓干细胞专栏·专家论坛·

牙髓干细胞与牙髓再生

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【摘要】 完整且有活力的牙髓对牙体硬组织健康和稳态的维持至关重要。因感染或外伤等原因致牙髓坏死的患牙,失去了牙髓的支持和营养,即使常规根管治疗远期仍容易出现根折,这也是临床失牙的重要原因。如何诱导牙髓再生并延长患牙的使用寿命是临床面临的挑战。牙髓干细胞(DPSC)和乳牙牙髓干细胞(SHED)分别来源于恒牙和脱落乳牙的牙髓组织,具有高增殖、多向分化和成神经血管的能力,为牙髓再生的最佳"种子"细胞。多项临床前研究和基于自体干细胞移植的临床研究均证实,DPSC和SHED移植可在髓腔原位重建生理性牙髓结构。本述评重点阐述牙髓干细胞的特性和牙髓再生的研究现状,旨在为未来临床牙髓疾病治疗提供新的思路。

【关键词】 牙髓干细胞; 乳牙牙髓干细胞; 牙髓再生

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Dental pulp stem cells and pulp regeneration

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【Abstract】 An intact and healthy dental pulp is crucial to maintain the integrity of tooth. A variety of impairments such as infection and trauma cause irreversible pulp damage, which require removal of pulp tissue and conventional root canal filing. However, this type of treatment fails to restore vital pulp. It is still a clinical challenge that how to regenerate pulp and prolong the lifespan of tooth. Dental pulp stem cells (DPSCs) and stem cells from human exfoliated deciduous teeth (SHED) are isolated from the dental pulp of permanent teeth and exfoliated deciduous teeth, respectively. They are more suitable and practical kinds of seed cell sources for dental pulp regeneration due to their superior proliferation capacity, excellent neurogenic / angiogenic differentiation capability, and dental tissue origin. A few preclinical and clinical studies showed that implantation of autologous DPSCs or SHED can re-establish physiological pulp tissue structures. This review article sought to introduce the innate characteristics of DPSCs / SHED and the current state of dental pulp regeneration research.

【Key words】 Dental pulp stem cells; Stem cells from human exfoliated deciduous teeth; Dental pulp regeneration

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牙髓是位于根管系统内,被高度矿化的牙本质包围的疏松结缔组织,由细胞、细胞间质和细胞间液组成,含有丰富的神经、血管和纤维组织,主要有形成、营养和感觉功能[1]。牙髓受到创伤和感染后,易导致不可逆牙髓炎或牙髓坏死,严重者可致根尖周炎或颌面部感染[2]。目前,牙髓炎症或坏死的常规临床处理是根管治疗,即清除感染或坏死的牙髓组织,用牙胶材料充填并封闭根管,其实质为生物材料在空间上简单替代牙髓组织[3]。牙齿失去了牙髓的支持和营养后,牙体硬组织结构理化性质发生改变,易出现牙冠变色或冠根折裂,并遭受结构性破坏[4]。因此,探索功能性牙髓的完整再生和维持牙体硬组织的完整与健康是牙体牙髓相关疾病治疗的难点和重要方向。

牙体硬组织经受龋损或在受伤后,相对应部位牙髓受到刺激能够形成修复性牙本质,不难推测牙

髓中可能存在常驻的干细胞群。2000年研究证实了恒牙中牙髓干细胞(dental pulp stem cell, DPSC)的存在[5],2003年在乳牙中也发现了乳牙牙髓干细胞(stem cells from human exfoliated deciduous teeth, SHED)[6]。随后20多年来,牙髓干细胞的一系列功能表征[5-7]和功能机制[8-13]相继被证实和发现,这些基础研究推动了牙髓干细胞临床前研究[14-24]和临床研究[25-26]的发展,见证了牙髓干细胞相关研究的巨大进步,展示了牙髓干细胞独特的组织再生前景,开创了口腔科学研究的新领域。如今,将牙髓干细胞作为"种子"细胞介导功能性牙髓的再生已成为共识。本述评中,我们将回顾和总结牙髓干细胞从最初发现到牙髓再生方面的研究进展,并讨论未来的方向和面临的挑战。

一、牙髓干细胞的发现

牙髓干细胞根据来源的不同,可分为DPSC和SHED。2000年和2003年,DPSC和SHED两种牙髓来源的间充质干细胞(mesenchymal stem cell, MSC)被先后分离鉴定[5-6],它们均具有典型的MSC特性,即在体外培养中表现贴壁生长、自我更新、克隆形成和具有多向分化的潜能[7]。在牙胚和新生牙中提取的牙髓干细胞与DPSC相比表现出更强的增殖效率[27-28],脱落乳牙中发现的SHED相较于DPSC表现出更强的克隆形成、增殖和成骨分化能力[6],并具有更高的端粒酶活性、碱性成纤维细胞生长因子、骨形态发生蛋白2基因表达水平等[29]。以上结果均提示,发育早期或年轻的牙髓可能提供性能更优于成年恒牙牙髓的干细胞。DPSC是第一个被分离和鉴定的口腔颌面组织来源的MSC,随后一系列口颌面部组织来源的MSC相继被发现,如SHED[6]、牙周膜干细胞[30]、根尖乳头干细胞[31]、牙龈干细胞[32]和牙囊干细胞[33]等。牙髓干细胞因其具有可再生分化潜能且容易体外获取和扩增,也被视为理想的MSC来源参与生物组织工程的应用[34]。不同来源的MSC可能具有不同的生物学特性,而牙髓干细胞独特的生物学性质使得其在组织再生,特别是牙髓再生和稳态调节等方面,得到了广泛研究应用。

二、牙髓干细胞的生物学特性

牙髓干细胞作为一种牙髓来源的MSC,与经典的骨髓来源的MSC(bone marrow mesenchymal stem cell, BMMSC)相比,表现出更强的克隆形成和体外增殖能力,且能够直接分化为成牙本质细胞,体内移植后能异位再生牙本质-牙髓复合体外[5,7]。除稳定表达经典MSC标志物外[6,24,35-36],也表达血管神经相关的特殊标志物等[37-38],标志物包括但不限于CD146[6,39]、αSMA[38]、Gli1[37]、PD-1[40]和Stro-1[6,39]。研究者通过相关标志物对DPSC进行了亚群研究,例如,标记CD31、CD105、CD146或流式结果中的阳性/阴性表达区分细胞亚群,获得相对功能性更好的细胞[18,24,41]。而在最新的功能验证中发现,CD146的表达水平与牙髓干细胞的增殖、分化和免疫调节能力呈正相关,提示CD146可作为关键功能性标记物来评估牙髓干细胞的效能[42]。此外,牙髓干细胞表达负责维持早期胚胎和胚胎多能性的转录因子OCT4、SOX2和NANOG等[43-44],提示牙髓干细胞在组织再生方面可能具备多能性。细胞的功能与细胞自身在体内的起源和定植密切相关,早在2003年已有研究阐述了神经嵴和颅颌面的密切关系[45],后来逐渐发现DPSC来源于颅颌早期发育外胚层组织中神经嵴细胞[46],直至2014年,谱系追踪进一步揭示了DPSC起源于周围神经相关胶质[47],该研究发现在成年小鼠的切牙中,周围神经相关的神经胶质细胞能够支持和分化为牙髓细胞,这也为牙齿的器官发生和生长动态提供了新见解。神经源性标志物如c-fos、γ-烯醇化酶、巢蛋白、βⅢ微管蛋白、A2B5、musashi-1和微管相关蛋白2等在牙髓细胞中均能被检测到[41,48-50]。2018年发现,来源于神经嵴的牙髓干细胞特殊表达可维持中枢和外周免疫耐受的抑制性信号通路分子程序性死亡受体1(programmed death-1, PD-1),该结果显示PD-1是控制牙髓干细胞增殖和多向分化的关键分子[40]。以上证据均提示,牙髓干细胞在引导神经再生方面可能具备独特性。此外,血管周围通常是各种类型MSC的独特生态位[51],牙髓干细胞则定位于牙髓组织的血管周围[39]。随后,人们在体内实验中证实了牙髓干细胞参与血管形成[18,21],发现牙髓干细胞具有强大的血管生成能力以促进牙髓再生[52],指出经典Wnt/β-catenin通路与牙髓干细胞成血管能力密切相关[53]。2018年,人们发现持续生长的小鼠切牙中存在以动脉和神经为中心的特殊龛位,使得小鼠切牙以血管神经束为中心伴随生长,在不断生长的小鼠门牙中牙髓干细胞位于小动脉周围,并由$Gli1^+$标记的神经血管束支持[54]。牙髓干细胞表现出成血管和成神经的极大优势和潜能,并可根据不同的表现分为不同的功能亚群。牙髓干细胞所表现出的细胞群体多样性和互补统一性可能是修复和维

持牙髓组织局部稳态的关键,这种多样性的细胞群体结构可能也是牙髓干细胞实现真正意义上的功能性牙髓再生的关键。

三、牙髓干细胞的应用

组织学观察显示,牙髓干细胞定植在血管周神经束膜区域,该区域富含神经、体液和气体等交换产物和各种生物因子等,构成紧密关联的内环境并交互影响着牙髓干细胞的功能,同时该区域还链接髓腔和外界环境的交流[54-55]。这种独特的髓腔环境是牙髓干细胞成为特源性MSC的先决条件,使牙髓干细胞不仅具有成血管、成神经的特性且具有更强的增殖分化功能和最小的免疫反应,还因牙的获取没有侵入性而更具广阔的应用可行性,在应用中规避可能的伦理问题,使牙髓干细胞在牙髓再生等口颌疾病甚至全身系统性疾病治疗研究中具有巨大的应用价值。

1. 临床前研究的现状:牙髓干细胞相关的功能特性和机制研究结果提示,牙髓干细胞在牙髓组织中发挥着重要的作用。从DPSC原位再植形成牙本质[22]到SHED异位植入牙根横断切片生成牙髓样组织[56],到2010年首次证实了牙髓干细胞在空根管中可以原位再生牙髓样组织[17],后来研究者们在临床前研究中对牙髓干细胞介导的牙髓再生开展了大量的动物实验研究[57-59],为后续临床研究实现牙髓再生提供了重要的参考价值。牙髓完全再生并具生理功能是牙髓再生治疗和牙齿长期保存的核心关键[58]。目前,临床前研究的牙髓再生策略,主要围绕牙髓干细胞、生物支架和生物因子展开。

早在牙髓干细胞被发现时就发现异体牙髓干细胞的移植可在免疫缺陷小鼠的皮下形成无定形硬组织[5],该结果证实了牙髓干细胞具备再生潜能。研究者们通常认为,生物支架能提供对干细胞吸附有利的3D微环境来帮助牙髓干细胞的定植[60-62],所以领域内牙髓再生的相关实验多从牙髓干细胞和生物支架的应用开始。水凝胶是牙髓再生研究中最常用的有机支架,实验证明对其进行改性可增强牙髓干细胞的再生效果[62-65]。最近研究发现,与细胞外基质(extracellular matrix,ECM)样仿生水凝胶一起移植的牙髓干细胞表现出显著增强的存活率以及血管生成和牙源性分化能力[66]。另外,常用的合成材料如羟基磷灰石[67-68]、纳米复合材料[69]、纳米纤维[70]、胶原[14]和凝胶泡沫[71],也可不同程度地促进牙髓干细胞的增殖和分化。以上研究结果显示,牙髓干细胞与支架材料的结合应用可在体内皮下或牙髓腔内形成具有一定形态的类牙髓样组织。除生物支架材料的应用外,生物因子也具有一定的作用参与和调控牙髓组织再生。经典的粒细胞集落刺激因子(granulocyte-colony stimulating factor,G-CSF)能够在诱导细胞成神经成血管的同时发挥抗炎和抗凋亡的作用[72],发现用G-CSF预处理牙髓干细胞可活化细胞的分泌组并增强其再生能力[73]。已知Resolvin E1(RvE1)是一种脂质来源的内源性分子,可通过RvE1在牙髓损伤模型中招募$CD146^+$和$CD105^+$ DPSC亚群来促进受损牙髓组织的修复和再生[74]。此外,生长因子[75]、骨形态发生蛋白2(bone morphogenetic protein 2, BMP2)[22]、γ干扰素(interferon-γ,IFN-γ)[76]、β干扰素(interferon-β,IFN-β)[77]和补体C3a[78],也均可不同程度增强牙髓干细胞的功能。而在非细胞参与的牙髓再生策略中认为,成纤维细胞生长因子、血管内皮生长因子、血小板衍生生长因子、神经生长因子和BMP7[79-81]均可促进机体内源性细胞归巢,然而这些募集细胞的方法虽然形成了充满细胞的结缔组织,但仍难以明确其被招募的细胞来源和远期预后。尽管生物因子对干细胞的调节作用尚未严格可控,单独使用或添加生物因子的应用确实可促使牙髓干细胞在一定的条件下形成类牙髓样组织。值得注意的是,无支架内皮样牙髓干细胞球体也能够在异位植入实验中再生出具有相似形态和血管化的牙髓样组织[82],而单独使用牙髓干细胞聚合体且不借助生物支架或因子的牙髓再生策略可能具有更安全有效的结果[23,26],其中内皮细胞和牙髓干细胞相互作用下或牙髓干细胞的自组装聚合体可形成天然的结构性微环境参与支持组织再生,这种非介入性的微环境可支持得到更多的ECM和血管化组织生成[26,65]。牙髓干细胞衍生的ECM可以充当细胞的生态位,该环境能够自然调节ECM与细胞的相互作用,以模拟生理微环境[66]。此外,由牙髓干细胞组成的无支架三维细胞聚合体能在异位植入的空根管内结构性地重建出具有功能的富含神经血管的牙髓组织,提示依托天然的细胞聚合体所形成的微环境能实现牙髓再生而并不需要额外增加生物支架或因子[23,26]。最新的研究证实,异体的SHED聚合体也能在小型猪牙髓腔中形成完整的神经血管化牙髓组织[83]。在小型猪或比格犬等大动物实验中利用牙髓干细胞成功实现的牙髓再生[84-87],为干细胞临床应用奠定了坚实的基础。

牙髓干细胞作为特源细胞在全身系统性疾病治疗中也取得了一系列的成果,尤其是牙髓干细胞具有免疫调节的特性,已在多种炎症系统性疾病研究中广泛应用,比如SHED介导的T细胞凋亡可改善结肠炎小鼠的情况[88],SHED输注可减弱巨噬细胞和中心粒细胞的浸润,促进肾小管上皮细胞的再生从而缓解急性肾损伤[89],以及SHED还可调节Tregs和Th17细胞改善肾功能[90]。已知炎症反应是组织再生的不利因素[91-92],牙髓干细胞对免疫的调节作用提示其可能也发挥着局部免疫调节的作用以帮助牙髓组织再生,同时SHED也可作为免疫疾病治疗中一种极具价值的细胞来源。此外,不同于中胚层来源的BMMSC,牙髓干细胞源于中胚层的神经嵴,除了在牙髓再生中有利于成神经分化,在神经系统相关的疾病也具有独特的调控功能。系列研究相继发现了SHED可促进神经血管生成以治疗缺血性脑损伤[93];SHED能改善多巴胺水平并促进神经功能恢复,或降低神经毒性以改善帕金森病[94];牙髓干细胞可减少星形胶质细胞增生,抑制神经元凋亡,抑制T细胞进入实质,抑制白细胞介素1β(IL-1β)和肿瘤坏死因子α(TNF-α)表达等参与治疗脊髓损伤[95-96]。最新研究在大动物实验中证实,SHED可以改善自闭症比格犬的社交行为缺陷[97]。此外,SHED在大动物实验的临床前研究中还成功修复了小型猪下颌颌骨缺损[98],在其他疾病如皮肤修复、肝纤维化、缺血再灌注损伤、急性心肌梗死和系统性红斑狼疮等系统性疾病中,牙髓干细胞也发挥着重要的治疗作用[99-101]。

2. 临床研究的进展:2017年日本报告了一项试点临床研究,招募了5例不可逆牙髓炎患者并在其原位移植经G-CSF预处理的自体DPSC后进行了24周的监测[25]。牙髓活力测试结果显示,5例患者中有4例表现出阳性反应,该结果提示再生的牙髓中恢复了感觉神经功能,而这种感觉功能性重建的成功明显优于牙髓血运重建,然而CBCT和磁共振成像显示,5例患者中仅有3例患者表现功能牙本质的形成和完整的牙髓再生。2018年,我国报道了一项植入自体SHED聚合体的临床随机研究,提供了更可靠的牙髓再生证据[26]。在该研究前期两种动物模型实验中,研究者利用自体SHED的植入成功再生出具有成牙本质细胞层、血管和神经的全牙髓组织。随后,在临床研究中纳入36例牙髓坏死患者,其中治疗组26颗牙,使用SHED干细胞聚合体,另10颗牙作为对照组,所有患者均接受12个月的随访。该研究中激光多普勒流量测试和牙髓电活力测试证实了再生牙髓中神经血管化的牙髓活性。随后的放射检测和组织学结果均显示三维全牙髓组织的成功再生,包括成牙本质细胞层,结缔组织、血管和神经等。令人振奋的是,锥形束CT(CBCT)结果显示SHED聚合体可以继续促进牙根发育,接受SHED干细胞聚合体移植的发育未完成的恒牙牙根长度显著增加,且同时根尖孔宽度减小,这些结果证实了SHED聚合体能介导真正意义上的功能牙髓的再生并促进牙根的发育,与生理性牙髓一样具有维持血供、提供感觉和支持牙根持续发育的正常功能。

在这两项临床研究中,前者利用来源于成人自体第三磨牙的牙髓干细胞实现牙髓再生,提示牙髓再生应用可适用于更广泛的年龄范围,而不限于混合牙列期。然而,试点临床研究纳入的病例数量极少并仅表现为60%的成功率,故该方法被广泛应用于临床之前有必要扩大患者数量进行进一步的随机临床试验。而后者在随机临床试验中取得了更令人信服的结果,可能归功于细胞来源于未成年人SHED缔造的良好的再生微环境,其中SHED相对于DPSC可能表现更强的增殖分化能力[6,40,102],而SHED聚合体自形成的基质结构模拟了天然牙髓生长的环境[102]。该研究中自体SHED聚合体的移植适用人群年龄范围相对较局限,且研究中仅纳入门牙作为参考,同时通过干细胞获得的牙髓再生仍需临床长期随访。

除以上两项临床研究使用牙髓干细胞参与单根牙的牙髓再生外,近日最新发布的病例研究报道了2例应用在成人多根牙的牙髓再生[103],该研究分别取自体智齿中的牙髓干细胞移植到患牙根管中进行牙髓再生治疗。临床检查结果显示,随访1年内牙髓完全再生且未出现不良反应,证明了自体牙髓干细胞在多根磨牙的牙髓再生治疗中的有效性,但仍需进行随机临床试验的进一步验证。

以上临床研究中通过自体牙髓干细胞的移植在前牙或后牙中实现生理功能牙髓的再生,标志着细胞治疗走向器官再生变成现实,研究结果不仅是细胞治疗的重大突破,也是器官再生领域发展的巨大飞跃。虽然有一定的风险,但牙髓再生因其实现了真正意义上的功能再生,并具有巨大的社会效益,将会成为临床牙髓生物治疗未来的方向。虽然,在2014年印度报道了1例利用同种异体DPSC有效治疗放射性骨坏死患者的病例[104],但相对于干

细胞在牙髓再生中的有效应用,其在颌面组织再生中可能涉及更多的全身复杂性因素,比如随机临床研究中自体牙周膜干细胞治疗牙周骨内缺损虽然安全无不良反应,但基于干细胞的牙周治疗的有效性仍需进一步验证[92]。值得注意的是,牙髓干细胞在全身系统性疾病的临床研究中也走在前沿。2021年,我国长海医院首次使用系统性输注SHED治疗糖尿病,该临床研究证实了异体SHED输注可显著降低患者的糖基化血清白蛋白水平和糖基化血红蛋白水平,从而改善2型糖尿病患者的葡萄糖代谢和胰岛功能[105]。2022年,日本药物开发公司对系统性输注牙髓干细胞治疗急性缺血性中风也做了安全性和有效性的临床Ⅰ/Ⅱ期评估[106]。

四、总结和展望

从在体外分离发现牙髓干细胞到将牙髓干细胞真正应用在临床患者身上,领域已累积了20年的研究成果(图1),为进一步的探索奠定了坚实的基础。牙髓干细胞作为一种牙髓组织来源的特源性

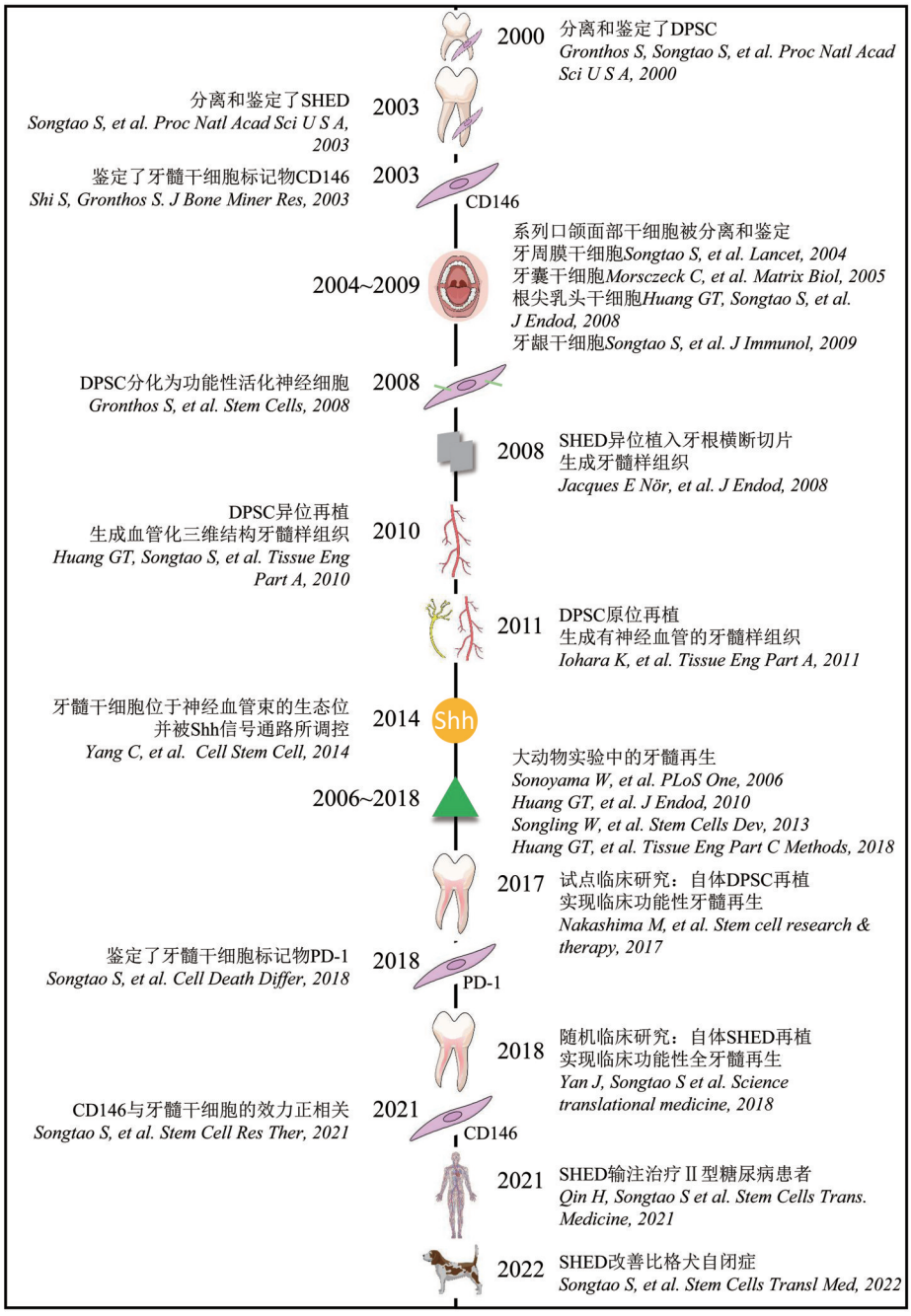

图1 牙髓干细胞与牙髓再生基础研究、临床前和临床研究中重要事件时间轴 SHED为乳牙牙髓干细胞;DPSC为恒牙牙髓干细胞;PD-1为程序性死亡受体1。

MSC,不仅在牙髓组织中扮演着重要角色,也因其独特的生物学特性,在口颌及全身系统应用中展示了重大的应用价值。同时,牙髓干细胞因来源丰富(智齿、正畸拔除牙和脱落乳牙等)、易获取、无创、免疫源性低和尚无伦理限制等优点,其作为生物组织工程种子细胞具有极大优势。其中,SHED可以来源人类生长发育过程中的脱落器官,且表现出比DPSC更高的增殖能力以提供更足够的体外扩增细胞数量,从而具有更显著的转化优势,而乳牙作为脱落器官仍具有高功能活性的干细胞,值得领域进一步探索其生理意义。除此之外,牙髓干细胞因其神经亲和性,向神经分化的作用明显,将其作为细胞治疗范例参与神经类疾病的治疗已成为共识。

牙髓干细胞与牙髓再生的临床研究取得的突破性成就引发了领域内广泛的关注,再生不仅实现了牙髓三维结构的重建,也恢复了其重要的形成、营养和感觉功能,这种具有完整功能的全牙髓再生标志着人类历史上首个真正意义上器官再生的成功,这项突破性的研究也进一步塑造了我们对器官再生的认识:想要获得似自然生理状态的器官再生,找到最佳的干细胞"种子"和适宜的"土壤"环境至关重要。但是,基于牙髓干细胞的牙髓再生的安全性和长期稳定性仍需临床长时随访监测,另外,干细胞的来源、风险和质量控制也需要进一步改进,异体SHED移植的牙髓再生可延伸干细胞应用范围,该临床研究的实践也亟待开展。当务之急,领域应该推动临床研究成果转化,向常规的临床治疗迈进,而干细胞独特的生物学性质使得干细胞介导的牙髓再生标准的制订迫在眉睫,该标准也将是把牙髓干细胞主导的牙髓再生推向临床牙髓常规治疗策略的关键。

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