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• 综述 •

牙髓干细胞在周围神经损伤修复中的研究进展

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【摘要】 周围神经损伤(peripheral nerves injury, PNI)是口腔临床常见病,极易造成患者功能丧失和美观异常,牙髓干细胞(dental pulp stem cells, DPSCs)结合组织工程在PNI修复中的应用是目前研究热点。DPSCs具有来源丰富、提取简单、免疫原性低以及体外增殖率高等优点,其可分化成雪旺细胞(Schwann cells, SCs),SCs具有诱导细胞自噬的能力,且能分泌关键的神经营养因子,如神经生长因子、脑源性神经营养因子、睫状神经营养因子、胶质细胞源性神经营养因子等,有利于神经损伤的修复。不同时期的DPSCs在免疫调节、抗炎作用、神经标志物的表达、血管生成等方面具有差异性,该差异性为神经修复提供了更加多样化的选择。目前,组织工程学的引入为DPSCs提供了更加可控的、可改良的微环境,有利于DPSCs在再生医学和组织工程中的应用发展;然而其仍面临着诸多问题亟待解决,例如干细胞的选择、功能链接的恢复阻碍、轴突再生方向不可控、周围神经系统的调节、修复作用机制尚未阐明等。

【关键词】 牙髓干细胞; 雪旺细胞; 乳牙牙髓干细胞; 周围神经损伤; 瓦勒变性; 轴突再生; 组织工程; 神经导管

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【Abstract】 Peripheral nerve injury (PNI) is a common disease in the oral cavity that can easily lead to loss of function and abnormal appearance. The application of dental pulp stem cells (DPSCs) combined with tissue engineering in the repair of PNI is a research hotspot. DPSCs have the advantages of abundant sources, simple extraction, low immunogenicity and a high proliferation rate in vitro. They can differentiate into Schwann cells (SCs). SCs can induce autophagy and secrete key neurotrophic factors, such as nerve growth factor, brain-derived neurotrophic factor, ciliary neurotrophic factor and glial cell-derived neurotrophic factor. SCs are beneficial for the repair of nerve injury. DPSCs in different periods have differences in immune regulation, anti-inflammatory effects, expression of neural markers, angiogenesis and so on, which provide more diversified choices for nerve repair. At present, the introduction of tissue engineering provides a more controllable and improved microenvironment for DPSCs, which is conducive to the application and development of DPSCs in regenerative medicine and tissue engineering. However, there are still many problems to be solved, such as the selection of stem cells, functional link recovery, uncontrollable direction of axon regeneration, regulation of the peripheral nervous system and mechanism of repair.

【Key words】 dental pulp stem cells; Schwann cells; stem cells from human exfoliated deciduous teeth; peripheral nerve injury; Wallerian degeneration; axon regeneration; tissue engineering; nerve conduits

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创伤引起的口腔颌面部周围神经损伤(peripheral nerves injury, PNI)是口腔医学临床常见病,这种伤害常来源于外伤或手术失误,表现为手术部位周围疼痛、功能丧失、美观异常。与中枢神经系统相比,外周神经系统在损伤后具有自行再生的潜力,但是结果并不理想,约有三分之一的PNI患者日常生活仍存在极大困扰^[1]。目前,牙髓干细胞(dental pulp stem cells, DPSCs)治疗是一种极具潜力的PNI修复方法,它不仅具有间充质干细胞(mesenchymal stem cells, MSCs)的特性,还具有分化为中胚层细胞的能力及沿着神经谱系分化的潜力^[2]。DPSCs在组织工程学修复、周围神经再生、疾病重塑和治疗中已经取得了一定的进展,本文就DPSCs同雪旺细胞(Schwanns, SCs)的关系、分类及其在组织工程学方向的研究进展作一综述。

1 DPSCs可分化为SCs

MSCs可以从多种组织中分离出来,它们最可从骨髓或脂肪组织中获得^[3],也可来源于牙髓组织。可从脱落的乳牙中获取人脱落的乳牙牙髓干细胞(stem cells from human exfoliated deciduous teeth, SHED),从第三恒磨牙或正畸拔除的恒牙中获得人恒牙牙髓干细胞(human dental pulp stem cells, hDPSCs),临床应用时不会对患者造成额外的损伤因而更容易被患者接受。研究显示DPSCs同其他类型间充质干细胞相比具有来源丰富、提取简单、免疫原性低以及体外增殖率高等优点^[4],即使经过传代培养或长期冷冻保存,仍具有牙源性、骨源性、软骨源性、神经源性、脂肪源性和肌源性等多向分化能力^[5]。

1.1 SCs在PNI中的作用

当颌面部周围神经截断性损伤后,轴突近端通常可以存活,而远端受损则会迅速闭合并在损伤后3天内发生强制性瓦勒变性^[6]。在瓦勒变性的过程中SCs不但具有诱导细胞自噬的能力,它还能分泌在受损神经的恢复中起关键作用的神经营养因子,如神经生长因子、脑源性神经营养因子、睫状神经营养因子、胶质细胞源性神经营养因子

等^[7]。幸存的SCs和髓鞘能够帮助引导新长出的神经支配目标组织^[8]。Isaacman-Beck等^[9]通过在斑马鱼中使用活细胞成像技术,发现再生的运动轴突对原来的肌肉区域表现出强烈的偏好,并且轴突在选择原路径之前会广泛地向各个方向探测正确的生长轨迹。这一过程中SCs受损后赖氨酸羟化酶3(lysyl hydroxylase 3, LH3)的表达量增加可以恢复轴突靶向再生的能力。此外,在断面附近的SCs能够表达LH3底物胶原蛋白4a5(collagen 4a5, col4a5),在再生过程中col4a5可能通过轴突导向抑制因子Slit1a进行方向探测,使不适当的生长轨迹上的轴突退化,以达到选择性再生的目的。

1.2 DPSCs可向SCs样细胞诱导分化

DPSCs是牙髓中的多能干细胞,可以通过分泌外泌体将信号分子传递给SCs介导细胞间通讯^[10],且在特定神经诱导培养基上扩增良好,其具有神经分化能力可分化为SCs样细胞^[11]。在神经基础培养基中加入碱性成纤维细胞生长因子和表皮生长因子可诱导DPSCs神经向分化^[12]。Hei等^[11]采用整合素 $\beta 4$ (CD104)、S-100蛋白、层粘连蛋白(Laminin)、神经营养因子低亲和力受体(low affinity neurotrophin receptor, p75NTR)免疫细胞化学方法对分化后的DPSCs成功地进行了SCs样细胞的鉴定,且脉冲电磁场的应用更加促进了DPSCs向SCs样细胞的分化。有研究显示,磁性细胞分选方法分选出表达p75NTR、巢蛋白(Nestin)和SOX-10(SRY-related high-mobility-group(HMG)-box protein-10, SOX-10)的Stro-1⁺/cKit⁺/CD34⁺ DPSCs,在体外具有分化为SCs样细胞的能力,与髓鞘分化相关并可在体内促进轴突再生。这一DPSCs亚群容易获得、体外增殖迅速、可成功地整合到宿主组织中,因此可能成为再生医学的优秀候选者,特别是在神经组织工程领域^[2]。

2 DPSCs与SHED在PNI中的作用差异

DPSCs缺乏主要组织相容性复合体Ⅱ类抗原的表达,免疫原性较低,能够抑制同种异体反应的T细胞增殖,不刺激免疫应答;也可以通过抑制促

炎细胞因子的产生和刺激抗炎细胞因子、抗原特异性T细胞的产生来减少体内的炎症反应^[13]。乳牙和恒牙的牙髓干细胞在周围神经中的作用存在相似性,也存在一定的差异。

2.1 免疫调节

SHED可通过分泌单核细胞趋化因子-1调节巨噬细胞迁移和浸润,表现出独特的免疫调节特性,有助于组织修复^[14]。DPSCs通过减少小胶质细胞激活、下调炎症标志物离子钙接头蛋白分子1和活性氧的积累、降低炎症细胞因子的分泌,表现出较强的免疫调节和抗炎能力^[15]。

2.2 抗炎作用

SHED作用于巨噬细胞,上调CC类趋化因子2和白血病抑制因子的表达,使巨噬细胞大量浸润于损伤部位,将巨噬细胞表型从加速组织破坏的促炎M1巨噬细胞转化为促进组织修复的抗炎M2巨噬细胞^[16]。DPSCs表达的白细胞介素-10具有抗炎活性,而且DPSCs表达的巨噬细胞集落刺激因子高于粒细胞巨噬细胞集落刺激因子,可诱导巨噬细胞M2极化^[17],在一定程度上可缓解神经性疼痛和平衡神经损害,最终减少了周围神经损伤后氧化应激和体内稳态调节异常所致的神经炎症反应^[15]。

2.3 神经标志物的表达

DPSC和SHED的神经向分化后可表达成熟的神经元标记物 β -微管蛋白III(β -III-Tubulin)、GA-TA结合蛋白3等^[18],在幼稚状态下也可自发表达早期神经元和神经嵴标记物Nestin等^[19]。基因芯片分析显示,SHED携带较高的八聚体结合转录因子-4(octamer-binding transcription factor-4, OCT4)、SOX2、Nanog等胚胎标志基因^[20],促进成脂、成骨^[21];而DPSCs携带较高的人类配对盒基因(paired-box gene6, PAX6)、Nestin、 β -III-Tubulin等神经源性基因^[20],有利于神经发生^[21]。

2.4 血管生成

在神经损伤部位缺氧条件下SHED可诱导巨噬细胞产生血管内皮生长因子-A(vascular endothelial growth factor-A, VEGF-A)增强了损伤部位新血管的形成,并使SCs迁移促成Büngner带的形成^[16]。DPSCs本身具有较高的血管生成特性,也可分泌VEGF-A刺激血管形成,分化为SCs后仍保留其在内皮细胞的增殖、迁移和血管形成的能力^[16]。

2.5 其他作用

SHED在细胞生长动力学方面具有较高的增

殖率,增长速度约为DPSCs的两倍,细胞集落形成特性、集落数量和大小均高于DPSCs^[20];而DPSCs比SHED更好的聚集成神经球,显示出更多地致力于神经元谱系的表达^[20]。hDPSCs具有肌生成潜力,可使营养不良骨骼肌的组织病理得到改善,可用于促进横纹肌萎缩的再生^[22],也可提高糖尿病大鼠的坐骨神经传导速度,使骨骼肌血管密度和神经纤维密度增加^[23]。

DPSCs和SHED在PNI修复过程有两个潜在机制,即直接分化或融合后替换丢失的内源性细胞,以及间接分泌可溶性因子或外泌体介导对存活内源性细胞的支持,这两种机制可能是单独作用或协同作用^[21]。

3 DPSCs组织工程学修复PNI

自体神经移植是PNI修复金标准,它提供了富含SCs的结构来引导轴突再生,虽然免疫排斥反应会极低,但是会造成供体区域神经损伤,导致供区神经功能丧失^[24]。研究者将DPSCs与组织工程神经导管支架相结合,用于传递信号分子、生长因子、药物等。

组织工程近年来逐渐成为研究的热点内容之一,其主要目标是开发能够治愈、修复或再生受伤病变组织和器官的生物材料替代品^[25]。组织工程学将生物相容性材料(如聚四氟乙烯、硅树脂、聚乙烯、胶原、生物聚合物等)与DPSCs、神经生长相关因子、血管生成相关因子等相结合为神经再生提供一个可控的、可选择的、可改良的微环境^[26]。有研究表明,SHED同聚乙醇酸神经导管(polyglycolic acid tube, PGA)联合应用不仅可促进面神经下颌支的再生,由于导管的存在还减少了受损组织之间的粘连^[27];多种材料的联合应用比单一材料的使用存在更多的优势,通过物理性吸附、共价键结合、混纺、同轴电纺等方式对支架进行加工修饰,可改善材料性能,使其更有利于神经修复。Lackington等^[28]用胶原涂层PGA神经导管修复大鼠面神经缺损,结果表明带涂层修饰比不带修饰的导管修复效果好;Hu等^[29]将聚羟基丁酸戊酯和聚环氧乙烷按照9:1的质量比进行混合静电纺得到三维的神经支架,用于神经再生实验,证明后者的加入提高了干细胞与聚羟基丁酸戊酯的生物相容性。大量研究结果显示聚合物的组合改变了导管的物理性质,也改变了它们的神经引导特性。DPSCs同组织工程支架的联合应用维持了受损神

经解剖结构的完整,并提供了方向引导和空间支撑,但在神经导管提供的微环境中轴突再生的分子机制尚不清楚,DPSCs在再生医学和组织工程中的应用仍需要不断的探索。

4 DPSCs应用于PNI修复过程中面临的问题

近年来,研究者开始重视发展DPSCs对PNI的治疗策略,以增强轴突再生、促进靶组织选择性再生并调节周围神经系统的重组^[30],但高质量的功能性恢复面临的问题仍然很多,包括:①干细胞的选择,在有良好适应证的年轻患者中选择合适的健康牙齿,采用改进的干细胞分离、培养技术和神经诱导方案,使DPSCs向着有利于神经分化的方向发展^[31],这一过程需要考虑干细胞的来源、采集方式、免疫原性、增殖效率^[14]等因素^[31];②功能性链接的恢复,由于神经纤维化导致神经瘤的形成^[32]、远端轴突瓦勒变性的发生及目标组织的不可逆性萎缩^[6]等问题的存在,使恢复神经的功能性链接成为一项难题;③轴突再生方向的不可控,神经横断伤破坏了神经和神经基底层的连续性,迫使再生轴突穿过无细胞环境、穿越损伤间隙,这一过程中再生的轴突向各个方向不断发展,其方向具有不可控性^[9];④组织工程材料的选择与应用,神经损伤后结缔组织向缺损部位延伸^[15]、粘连影响神经愈合,而组织工程学修复可以将周围结缔组织分离,保证神经修复空间^[24],但其尚在发展的初期,材料的选择、技术的应用正在研究阶段;⑤动物模型的局限,国内外实验大部分都是建立在动物模型之上,其神经损伤模型表现出的再生潜力与人体不同,将其转化到临床应用用于人体修复仍是一项严峻的挑战;⑥修复机制仍不明确^[33]。

5 总结与展望

DPSCs不但可以分泌细胞因子作用于损伤后残存的SCs,还具有诱导向SCs样细胞分化的潜力;DPSCs与组织工程学联合应用成为PNI修复的新趋势;然而其受患者的年龄、病变部位和类型、手术修复的时机和方式以及轴突再生跨越损伤的距离等多种因素影响。乳牙和恒牙的牙髓干细胞是存在于同一生物体不同时期的两种DPSCs细胞状态,二者除了具有MSC的基本特征外,还具有不同的生物学特性,它们的区别应用为神经修复提供了一个新的选择。

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LH revised the article. Wang XM reviewed the article. All authors read and approved the final manuscript as submitted.

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