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# 牙髓干细胞神经向分化方案及机制研究进展

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【摘要】 牙髓干细胞(DPSCs)是一类来源丰富、易获取、具备多向分化潜能和低免疫原性的成体干细胞，近年来因其在神经组织损伤修复中的广泛应用前景而受到高度关注。DPSCs可在特定诱导条件下直接分化为神经元样细胞，并通过旁分泌神经营养因子、免疫调节因子等发挥神经保护、免疫调节、抗炎及抗凋亡作用。DPSCs可与生物支架如水凝胶、壳聚糖、聚乳酸等联合使用，提高其神经分化效率和再生效果。与此同时，DPSCs在神经修复的临床应用中面临微环境适应性差、分化效率低和可控性差、免疫排斥、规模化生产与质量控制难及标准化操作流程缺乏等挑战。未来的研究可能聚焦于优化DPSCs在损伤部位的微环境适应性、提升其神经分化效率、加强免疫调控以确保异体移植安全性、完善符合良好生产规范标准的细胞制备与质量控制体系，以及建立标准化的临床操作流程并结合多中心试验验证疗效等方面入手，从而推动其在神经再生中的高效、安全和可重复的临床转化。本文综述了DPSCs神经向分化的研究进展，重点分析了DPSCs促进神经再生方案及分子机制、临床转化挑战与未来发展方向，为DPSCs神经向分化研究提供理论基础。

【关键词】 牙髓干细胞； 神经分化； 神经元样细胞； 旁分泌作用； 生物支架； 再生医学； 信号通路； 临床转化； 免疫调节

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**Research progress on neural differentiation protocols and mechanisms of dental pulp stem cells**

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【Abstract】 Dental pulp stem cells (DPSCs) are a type of adult stem cell with abundant sources, easy accessibility, multipotent differentiation potential, and low immunogenicity. In recent years, they have attracted considerable attention due to their promising applications in repairing neural tissue injuries. Under specific induction conditions, DPSCs can directly differentiate into neuron-like cells and exert neuroprotective, immunomodulatory, anti-inflammatory, and anti-apoptotic effects through the paracrine secretion of neurotrophic and immunomodulatory factors. DPSCs can also be combined with biomaterial scaffolds such as hydrogels, chitosan, and polylactic acid, thereby enhancing neural differentiation efficiency and regenerative outcomes. However, their clinical application in neural repair still faces challenges, including poor microenvironmental adaptability, low differentiation efficiency and controllability, immune rejection, dif-

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ficulties in large-scale production and quality control, and a lack of standardized operational protocols. Future research should focus on optimizing the adaptability of DPSCs to the injury microenvironment, improving their neural differentiation efficiency, strengthening immune regulation to ensure the safety of allogeneic transplantation, establishing GMP-compliant cell preparation and quality control systems, and developing standardized clinical procedures combined with multicenter trials to validate efficacy, thereby promoting the efficient, safe, and reproducible clinical translation of DPSCs in neural regeneration. This review summarizes the research progress on the neural differentiation of DPSCs, with an emphasis on strategies and molecular mechanisms for promoting neural regeneration, the challenges in clinical translation, and future development directions, aiming to provide a theoretical basis for research on the neural differentiation of DPSCs.

**【Key words】** dental pulp stem cells; neuronal differentiation; neuron-like cells; paracrine effects; biomaterial scaffolds; regenerative medicine; signaling pathways; clinical translation; immunomodulation

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神经系统损伤是神经医学面临的重大挑战。神经组织再生能力有限，在损伤后几乎不具备自我修复能力，如何促进临床神经损伤修复是亟待解决的难题[1-2]。神经损伤的传统治疗包括神经缝合[3]、神经移植[4]、电刺激[5]、药物刺激等方法[6]。尽管部分病例获得不同程度的功能恢复，但整体治疗效果仍有限[7-9]。传统治疗手段存在供体神经来源有限、手术侵入性强、免疫排斥、再生速度慢等缺点，限制了治疗效果[10]。随着再生医学的迅速发展，干细胞疗法已经成为修复神经组织损伤的有效途径[11]。近年来，多种干细胞被应用于神经再生领域，包括神经干细胞（neural stem cells，NSCs）[12]、神经前体细胞（neural progenitor cells，NPCs）[13]、间充质干细胞（mesenchymal stem cells，MSCs）[14]和诱导性多能干细胞（induced pluripotent stem cells，iPSCs）[15]。牙髓干细胞（dental pulp stem cells，DPSCs）是一种具有强大自我更新、多向分化和免疫调节能力的间充质干细胞[16]，近年来在神经再生方面表现出了独特的优势[17-18]。其细胞来源丰富，易于获取，可从智齿或正畸牙中提取，获取过程无创、简便、适合临床应用[19]。DPSCs来源于神经嵴细胞[20-21]，天然具备神经分化的潜力，相比其他干细胞来源，在神经分化方面表现出更强的潜力[22-23]。同时DPSCs细胞具有低免疫原性和良好的生物相容性[24]，非常适合同种异体移植和组织工程，为其修复神经损伤的临床应用奠定了基础。本综述总结了近年来DPSCs在神经分化机制方面的研究进展，重点分析了DPSCs直接神经向分化能力、旁分泌作用及与生物材料的协同作用；并探讨当前研究面临的挑战，以推动DPSCs在神经再生中的临床应用。

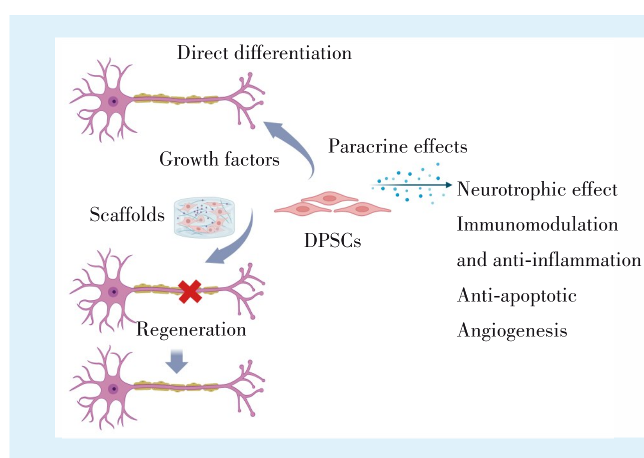
## 1　牙髓干细胞生物学特性

DPSCs具有独特的生物学特性，是神经再生医学的重要候选细胞来源。DPSCs是MSCs的一种，具有贴壁生长、多谱系分化、表达特定MSCs表面标记如CD27、CD29、CD44、CD73、CD90、CD105、CD146、CD166、CD271和间充质干细胞抗原1（stromal cell precursor antigen-1，STRO-1）等特征[25-26]。与此同时，MSCs和DPSCs均不表达CD45（造血细胞标记）、CD14（单核/巨噬细胞标记）、CD19（B细胞标记）或主要组织相容性复合体Ⅱ类分子（major histocompatibility complex class Ⅱ，MHC-Ⅱ）等表面标记[27]，使其区别于其他种类细胞，保持低免疫原性和免疫调节能力，确保其干细胞的身份和多向分化特性[25，28]。DPSCs具有显著的多向分化潜能，可分化为神经细胞、成骨细胞、脂肪细胞及血管内皮细胞等[29]。与其他间充质干细胞来源不同，牙髓组织起源于神经嵴细胞[20-21]。神经嵴细胞经历上皮-间充质转化获得迁移能力从而迁移至胚胎其他区域，包括作为颅颌面器官前体的咽弓[30]。这些神经嵴细胞可分化为口腔神经嵴源性间充质

(即外胚层间充质),进而发育为口腔结缔组织、软骨、肌肉和骨骼[30-31]。研究指出,DPSCs在体外培养的条件下保留了部分神经嵴细胞的特性,可分化为神经嵴细胞衍生组织包括神经元。即使在非诱导的培养条件下,DPSCs也能表达神经祖细胞标志物和成熟神经细胞标志物,包括神经外胚层干细胞巢蛋白(nestin)、β3微管蛋白(tubulin beta 3 class III, TUBB3)、神经营养因子受体(p75 neurotrophin receptor, p75)及神经丝蛋白等[32]。这些证据证明DPSCs本身具有较高的神经分化潜力。相比于牙囊及牙乳头,牙髓来源干细胞表现出更高的神经分化潜力,更合适应用于神经退行性病变[33]。

## 2　牙髓干细胞促进神经再生方案及分子机制

人DPSCs具备多向分化能力,通过多种协同机制表现出显著的神经再生潜力。这些机制包括直接分化为神经元、旁分泌作用和结合生物支架促进神经向分化(图1)。




Dental pulp stem cells (DPSCs) contribute to neural regeneration through multiple mechanisms, including direct differentiation into functional neurons, paracrine effects (including secretion of neurotrophic factors, anti-inflammatory cytokines, anti-apoptotic and angiogenic factors), and synergistic interactions with biomaterial scaffolds. These combined actions enhance the survival, integration, and functionality of regenerated neural tissue

Figure 1　Mechanisms underlying neural regeneration promoted by DPSCs

图1　DPSCs促进神经再生的分子机制示意图

### 2.1　牙髓干细胞直接分化为神经元

DPSCs可通过诱导直接分化为多巴胺神经元、胆碱能样神经元及其他功能性神经元,并在体内模型中被证实存在神经整合能力及治疗效果[32, 34-36]。DPSCs体外神经诱导方案采用不同种类基础培养基、培养补充剂、生长因子、小分子、表面处理及形成神经球方式来精细调节分化过程。如表1所示,分类总结了DPSCs直接分化为神经元的方案。

**2.1.1　基础培养基**　笔者使用Neurobasal-A作为基础培养基,成功诱导DPSCs表达神经元相关标志物,包括神经细胞黏附分子(neural cell adhesion molecule, NCAM)、神经丝蛋白-M(neurofilament-M, NF-M)及神经丝蛋白-H(neurofilament-H, NF-H)[42]。较早期的研究选择DMEM[61]和αMEM[62]作为DPSCs神经诱导的基础培养基,现在已经较少使用。近年来大多数研究选择无血清培养基方案,学者开发了Neurobasal、Neurobasal-A及DMEM/F-12等作为诱导细胞神经分化的基础培养基[37, 40-41]。使用已知成分的无血清培养基可以抑制DPSCs非神经谱系方向如成骨方向分化,增强神经元向分化效率。同时无血清培养基标准化好,实验重复率高,且不含动物源性成分,可提高临床适用性,是神经分化的首选培养基。

**2.1.2　培养基补充剂**　在DPSCs神经元分化过程中添加培养基补充剂可以减少未分化细胞比例、提高神经分化效率并增加功能性神经元的产生。N2补充剂最初由Bottenstein和Sato于1979年发明,它能够为神经前体细胞培养提供一个成分明确的无血清培养环境,支持细胞增殖,促进轴突生长,增强神经分化[43]。B27是另一种常用于神经元无血清培养的经典补充剂,由Brewer等[63]于1993年开发,用于优化海马体神经元在无血清培养条件下的存活和功能维持。B27可抑制神经胶质细胞增殖,保障神经元营养,提高神经元存活率[34]。胰岛素-转铁蛋白-硒(insulin-transferrin-selenium, ITS)是1979年Bottenstein等[44]为实现无血清培养神经母细胞瘤细胞研发的3组分补充剂,可为细胞提供基本代谢支持,协同促进神经元分化、神经突生长和功能连接。较早期研究中胎牛血清(fetal bovine serum, FBS)也被选择添加到DPSCs的神经元诱导培养基中[38]。近年来,在临床转化需求的推动下,研究人员越来越专注于开发无血清培养基加明确成分的补充剂以获取安全、可控、重复性好的转化方式。培养基补充剂可协同无血清培养基增强DPSCs神经分化潜力[64]。

**2.1.3　生长因子**　神经营养因子[如脑源性神经营

表1　牙髓干细胞直接分化为神经元的诱导方案分类总结

Table 1　Summary of induction protocols for direct differentiation of DPSCs into neurons

| Condition | Specific conditions / components | Main effects & results | Related markers |
|---|---|---|---|
| Basic culture medium | Neurobasal-A[37] | Successfully induces neuronal differentiation | NCAM, NF-M, NF-H |
| | DMEM[37], αMEM[38] | Previously used, now rarely used | - |
| | Serum-free medium (Neurobasal[39], Neurobasal-A[37], DMEM/F12[40-42]) | Inhibits non-neuronal differentiation, increases neuronal differentiation efficiency, with high repeatability and good clinical safety | - |
| Culture supplements | N2[43] | Promotes axon growth and neuronal differentiation | - |
| | B27[34] | Inhibits glial cell proliferation, increases neuron survival rate | - |
| | ITS[44] | Provides metabolic support, promotes simultaneous neuronal differentiation and axon growth | - |
| | FBS[38] | Provides nutrition but affects controllability | - |
| Growth factors | NGF + bFGF[45] | Synergistically promotes neuronal cell differentiation, enhances neuronal marker expression | - |
| | EGF + bFGF [46] | Induces neural progenitor cell differentiation (Sox1, Pax6, NF-M) | Sox1, Pax6, NF-M |
| | BDNF, NT-3, GDNF, BMP-2, BMP-4, Shh[47-49] | Involved in neural development and regeneration | - |
| Small molecules | VPA[50] | Regulates SOCS5, FGF21, JAK/STAT, MAPK pathways, promotes early neural differentiation | - |
| | Repsox[51] | Inhibits TGF-β pathway, improves motor function in Parkinson's mice | - |
| | SB431542+dorsomorphin [52] | Inhibits dual pathways, enhances expression of Sox1, Pax6, and NF200 | Sox1, Pax6, NF200 |
| | CHIR99021[53] | Activates Wnt/β-catenin signaling, maintains stemness and proliferation | - |
| | Forskolin [54] | Regulates cAMP-CREB1-JNK pathways, increases TUBB3, MAP-2, NEUN expression | TUBB3, MAP-2, NEUN |
| | Y-27632[55] | Activates AKT and PAK1 pathways, promotes axon growth | - |
| | ISX-9 [56] | Promotes neuronal differentiation and neuronal marker expression | NeuN, Neurofilament |
| Surface coating | Poly-L-lysine (PLL)[34] | Induces motor neuron differentiation | HB9, Islet-1 |
| | Polyornithine (PLO), PLO+PN[37] | Maintains proliferation, enhances TUBB3, Nestin expression | TUBB3, Nestin |
| | Type IV / Type I collagen, gelatin, PLO/fibronectin, chitosan [57] | Enhances neuronal differentiation efficiency | - |
| Neurosphere culture | No scaffold, non-adhesive culture (DMEM/F12, Neurobasal, serum-free medium)[58-59] | Spontaneously forms neurospheres, survives >15 weeks, highly expresses neuronal markers, can convert to neuron-like cells after 2 weeks | CDH2, NF-M, TUBB3, CD24, HuC/D, p75 |
| | Serum-free MesoCult + bFGF, EGF, B27[60] | Promotes neurosphere formation | - |
| | Coating (PLL, PLO/fibronectin, fibronectin/PLL) + EGF/bFGF[49, 59] | Enhances neurosphere formation and expression of neural progenitor cell markers | - |
| | Neurosphere periphery vs center[39] | Periphery: nestin, TUBB3, O4; center: not expressed | Nestin, TUBB3, O4 |

NCAM: neural cell adhesion molecule. NF-M: neurofilament-M. NF-H: neurofilament-H. DMEM: dulbecco's modified eagle medium. αMEM: alpha minimum essential medium. DMEM/F12: dulbecco's modified eagle medium/nutrient mixture F-12. N2: N2 supplement. B27: B27 Supplement. ITS: insulin-transferrin-selenium. FBS: fetal bovine serum. NGF: nerve growth factor. bFGF: basic fibroblast growth factor. Sox1: sex-determining region y-box transcription factor 1. Pax6: paired box 6. BDNF: brain-derived neurotrophic factor. NT-3: neurotrophin-3. GDNF: glial cell line-derived neurotrophic factor. BMP-2: bone morphogenetic protein-2. BMP-4: bone morphogenetic protein-4. Shh: Sonic hedgehog. VPA: valproic acid. SOCS5: suppressor of cytokine signaling 5. FGF21: fibroblast growth factor 21. JAK/STAT: janus kinase/signal transducer and activator of transcription pathway. TGF-β: transforming growth factor beta. NF200: neurofilament 200. cAMP-CREB1-JNK: cyclic adenosine monophosphate-cAMP response element-binding protein 1-c-Jun N-terminal kinase. TUBB3: tubulin beta 3 class III. MAP-2: microtubule-associated protein 2. NEUN: neuronal nuclei. CDH2: cadherin-2. AKT: protein kinase B. PAK1: p21-activated kinase 1. ISX-9: isoxazole 9. MAPK: mitogen activated protein kinase. HB9: homeobox gene HB9. PN: poly-N-isopropylacrylamide-co-butyl acrylate. HuC/D: human antigen C/D. p75: p75 neurotrophin receptor. bFGF: basic fibroblast growth factor. EGF: epidermal growth factor. O4: O4 antibody. "-": not specified or not reported

养因子(brain-derived neurotrophic factor,BDNF)、神经营养素-3(neurotrophin-3,NT-3)、胶质细胞源性神经营养因子(glial cell line-derived neurotrophic factor,GDNF)]及胚胎发育信号分子[如骨形态发生蛋白2(bone morphogenetic protein 2,BMP-2)、骨形态发生蛋白4(bone morphogenetic protein 4,BMP-4)和音猬因子(sonic hedgehog,Shh)],在神经系统发育和再生过程中也扮演重要生长因子角色[47-49]。神经生长因子(nerve growth factor, NGF)和碱性成纤维生长因子(basic fibroblast growth factor, bFGF)协同促进DPSCs向神经样细胞的分化,增强神经标志物表达[45]。该过程与调控神经分化的细胞外信号调节激酶通路(extracellular signal-regulated kinase, ERK)和蛋白激酶B信号通路(protein kinase B, AKT)密切相关[65]。此外,表皮生长因子(epidermal growth factor, EGF)与bFGF联合使用时,也可诱导DPSCs分化为神经祖细胞,这些细胞以Sox1、Pax6和NF-M等神经特异性标志物的表达为特征,且在快速分裂的DPSCs亚群中这一效应尤为显著[46]。

2.1.4 其他小分子 具有表观遗传调控效应的小分子可通过作用于关键信号通路作为DPSCs神经诱导方案的组分。组蛋白去乙酰化酶抑制剂丙戊酸(valproic acid,VPA)通过上调细胞因子信号抑制因子5(suppressor of cytokine signaling 5, SOCS5)和成纤维细胞生长因子21(fibroblast growth factor 21, FGF21)、下调JAK/STAT通路和激活MAPK级联来促进成体间充质干细胞的早期神经分化[50]。Repsox通过抑制转化生长因子-β(ransforming growth factor-beta,TGF-β)信号通路,将成纤维细胞重编程为神经祖细胞,改善帕金森小鼠运动功能障碍[51]。SB431542和dorsomorphin双重抑制activin/nodal/TGF-β和骨形态发生蛋白信号通路(bone morphogenetic protein signaling pathway, BMP),增强神经元特异性转录因子Sox1和Pax6以及成熟神经元标志物NF200 mRNA的表达,同时刺激神经元特异性γ烯醇化酶的蛋白表达[52]。CHIR99021通过抑制GSK-3,激活Wnt/β-catenin信号通路,维持神经干细胞和前体细胞的干性与增殖能力[53]。Forskolin通过调节cAMP-CREB1-JNK信号通路,上调cAMP-CREB1表达并下调c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK)表达,增加神经元相关标志物TUBB3、微管相关蛋白2(microtubule-associated protein 2, MAP-2)、神经元核抗原(neuronal Nuclei, NeuN)的表达[54]。Rho相关蛋白激酶信号通路(Rho-associated protein kinase pathway, ROCK)抑制剂Y-27632可促进Rac1/NOX1依赖的活性氧(reactive oxygen species, ROS)生成,进而激活AKT和p21激活的蛋白激酶1(p21-activated kinase 1, PAK1)信号通路,促进神经突起生长[55]。特定的神经源性小分子ISX-9可促进神经干细胞向神经元分化,增强神经标志物NeuN及神经丝蛋白的表达[56]。

2.1.5 表面涂层 在涉及DPSCs的神经分化研究中,表面涂层是调节细胞黏附、增殖和定向分化的重要策略,直接影响神经分化效率和功能神经结构的形成[37,66]。DPSCs神经分化诱导实验通常在聚苯乙烯(thermoplastic styrene, TPS)培养皿中进行。Gao等[37]尝试通过增加表面涂层提高神经诱导效率,结果显示,聚-L-鸟氨酸包被的组织培养聚苯乙烯(poly-L-ornithine - coated tissue culture polystyrene, PLO-TCPS)培养板,以及聚-L-鸟氨酸与聚-N-异丙基丙烯酰胺-丙烯酸丁酯(poly-L-ornithine and poly-N-isopropylacrylamide-co-butyl acrylate, PLO-PN)包被的培养板,均可维持DPSCs的稳定增殖。接种于被覆聚赖氨酸孔板的DPSCs可被诱导为运动神经元,表达神经元相关标记物(如HB9及Islet-1)[34]。另外,IV型胶原蛋白、I型胶原蛋白、明胶、多聚鸟氨酸/纤粘蛋白、壳聚糖都被作为表面涂层用于增强神经分化效率[57]。

2.1.6 神经球培养方法 神经球是在无支架、非附着性条件下牙源性干细胞自我聚集形成的三维球状结构,可通过细胞间相互作用和细胞外基质更好模拟体内环境,促进自我更新并维持细胞特性[58,67]。其形成受培养条件和表面涂层影响,常用培养基包括DMEM/F12、neurobasal及商业无血清培养基[68-69]。在无血清培养基中,人DPSCs可自发形成细胞球并存活超过15周,球体中钙黏蛋白-2(cadherin-2, CDH2)、NF-M、TUBB3、CD24等神经标志物的表达高于二维培养,且随时间增加而增强[58-59]。培养DPSCs两周后,球体衍生细胞可自发分化为神经元样细胞,人类神经元蛋白C/D(human neuronal protein C/D, HuC/D)和p75呈阳性[70]。在无血清MesoCult间充质基础培养基中加入bFGF、EGF及B27也可诱导神经球形成[60]。Karbanová等[39]发现,神经球外围细胞表达nestin、TUBB3和O4抗体,而中心细胞不表达这些标志物,提示中心微环境不利于神经元生存与分化。常用涂层包括聚赖氨酸、聚鸟氨酸/层黏连蛋白、纤

连蛋白/聚赖氨酸等，其中EGF/bFGF预处理可在聚赖氨酸及纤连蛋白包被条件下促进神经球形成并增强神经祖细胞标志物表达[59]。聚鸟氨酸/层黏蛋白涂层配合神经诱导培养基也能诱导神经球形成[49]。

DPSCs神经元分化的效率可以通过检测神经元标志物的表达来验证。常见的方法包括使用免疫荧光染色、qRT-PCR检测nestin、微管相关蛋白2（microtubule-associated protein 2，MAP2）、TUBB3和胶质纤维酸性蛋白（glial fibrillary acidic protein，GFAP）等标志物的表达[71]。然而，由于DPSCs起源于神经嵴，可以不经诱导固有地表达某些神经元标志物，因此需要额外的检测，例如电生理学特征检测才能确保真实实现了神经向分化。Arthur等[42]发现分化后的DPSCs中存在电压依赖性钠（$Na^+$）内流，尽管没有观察到动作电位发生。随后，Gervois等[71]成功发现DPSCs神经分化后发生类似动作电位的去极化。然而，迄今为止，暂无研究表明神经诱导的DPSCs可以在共培养系统中成功建立功能性突触接触，表明目前DPSCs神经元分化方案仍有待优化。

2.2　*旁分泌作用*

研究表明，DPSCs移植优势可能不仅是直接替换受损部位的神经元细胞，而是归功于旁分泌效应[72]。DPSCs通过神经保护作用、免疫调节及抗炎、抗凋亡及血管生成发挥旁分泌效应增强神经分化效率。表2分类总结了DPSCs旁分泌作用机制。

**表2**　牙髓干细胞旁分泌作用机制分类总结

Table 2　Summary of paracrine mechanisms of DPSCs

| Effect type | Specific mechanism | Main role | Related factors |
|---|---|---|---|
| Neuroprotective effect | Secretes neurotrophic factors[47, 72] | Promotes neurogenesis, neuronal maintenance, and repair | NGF, BDNF, NT-3, GDNF |
| Immunomodulatory and anti-inflammatory effect | Secretes anti-inflammatory cytokines to regulate immune responses[73-74] | Reduces inflammatory response, improves therapeutic efficacy in neurological diseases | IL-6, IL-10, TGF-β1, IL-1β, IFN-γ, IL-2, IL-12, TNF-α |
| | Inhibits microglial activation and polarizes macrophages toward anti-inflammatory M2 phenotype[75-76] | Improves neural microenvironment, alleviate inflammation, and promotes tissue regeneration | - |
| Anti-apoptotic effect | Upregulates anti-apoptotic proteins and downregulates pro-apoptotic factors[77-78] | Protects neurons, reduces apoptosis | Bcl-2, Bax, p53, Caspase-3, VEGF, Fractalkine, GM-CSF |
| | Increases endogenous survival factor Bcl-2 and decreases Bax to enhance cell viability[79-80] | Improves cell survival rate | - |
| Angiogenesis | Secretes angiogenic factors to promote blood vessel formation[81] | Promotes endothelial cell migration and angiogenesis, supports neural regeneration | VEGF, PDGF-A, ANG-1 |

DPSCs: dental pulp stem cells. NGF: nerve growth factor. BDNF: brain-derived neurotrophic factor. NT-3: neurotrophin 3. GDNF: glial cell line-derived neurotrophic factor. IL-6, IL-10, IL-1β, IL-2, IL-12: interleukin-6, interleukin-10, interleukin-1 beta, interleukin-2, interleukin-12. TGF-β1: transforming growth factor beta 1. IFN-γ: interferon gamma. TNF-α: tumor necrosis factor alpha. Bcl-2: b-cell lymphoma 2. Bax: bcl-2-associated X protein. p53: tumor protein p53. Caspase-3: cysteine-aspartic acid protease 3. VEGF: vascular endothelial growth factor. GM-CSF: granulocyte-macrophage colony-stimulating factor. PDGF-A: platelet-derived growth factor subunit A. ANG-1: angiopoietin-1. M2: M2 phenotype (alternatively activated macrophages). “-”: not specified or not reported

2.2.1　神经保护作用　DPSCs分泌神经营养因子，在神经发生、神经维护和修复中发挥重要作用。DPSCs分泌NGF、BDNF、NT-3和GDNF促进轴突生长[47]。DPSCs可向神经向分化，经神经诱导后可表达NGF、BDNF及GDNF等神经营养蛋白，并能促进神经诱导后DPSCs的增殖，为周围神经损伤提供有效且长期的治疗，促进功能恢复和解剖修复[72]。

2.2.2　免疫调节和抗炎作用　DPSCs的分泌组通过多种机制发挥免疫调节和抗炎作用。DPSCs条件培养基（conditioned medium，CM）和细胞外囊泡（extracellular vesicle，EV）含有丰富的免疫调节因子，可调控炎症反应达到提高神经系统疾病疗效的作用。DPSCs分泌抗炎细胞因子白细胞介素-6（interleukin 6，IL-6）、IL-10、转化生长因子β1（transforming growth factor beta 1，TGF-β1），抑制促炎细胞因子IL-1β、干扰素-γ（interferon γ，IFN-γ）、IL-2、IL-12和肿瘤坏死因子-α（tumor necrosis factor α，TNF-α）等的表达[73-74]。DPSCs分泌组抑制小胶质细胞

的激活，并促进巨噬细胞从促炎的M1表型到抗炎M2表型的极化[75-76]。DPSCs免疫调节及抗炎作用改善了神经微环境，减轻炎症并增强组织再生，突出了其分泌组在神经修复治疗中的潜力[77，80]。

2.2.3　抗凋亡作用　DPSCs分泌组在神经分化过程中表现出显著的抗凋亡作用。这主要是通过上调抗凋亡蛋白B细胞淋巴瘤-2（B-cell lymphoma 2，Bcl-2）和下调促凋亡因子［Bcl-2相关X蛋白（Bcl-2-associated X protein，Bax）、p53和半胱氨酸天冬氨酸蛋白酶3（cysteine-aspartic acid protease 3，Caspase-3）］来保护神经细胞[77-78]。DPSCs分泌组含有较高神经营养因子，如血管内皮生长因子（vascular endothelial growth factor，VEGF）[82]、趋化因子Fractalkine[79]和粒细胞-巨噬细胞集落刺激因子（granulocyte-macrophage colony-stimulating factor，GM-CSF）[83]，这些因子可以降低暴露于β淀粉样蛋白（Amyloid-beta peptide，Aβ）的细胞毒性和细胞凋亡。DPSCs分泌组通过刺激内源性存活因子Bcl-2和减少凋亡调节因子Bax提高细胞活力[79，84]。大鼠脊髓损伤模型中移植载有bFGF及DPSCs的水凝胶可抑制Bax和Caspase-3蛋白表达抑制凋亡[85]。

2.2.4　血管生成　生长因子BDNF，NGF和VEGF可以通过DPSCs旁分泌作用促进内皮细胞迁移和血管生成，同时增强神经细胞分化和轴突生长[86]。DPSCs表达VEGF[78]、血小板衍生生长因子-AA型（platelet-derived growth factor-AA，PDGF-AA）[87]和血管生成素-1（angiopoietin-1，ANG-1）[88]等血管生成的相关因子，这对于血管形成至关重要。在神经分化过程中，DPSCs通过旁分泌机制促进新血管的形成，增强局部微环境营养供应，提高细胞存活率，同时为神经元的迁移和功能整合提供了物质与信号支持，增强干细胞神经分化和神经元神经修复能力。

### 2.3　干细胞疗法与生物材料支架之间的协同相互作用

如何将DPSCs准确有效地输送到神经受损位置参与修复，并为干细胞建立有利于细胞分化的微环境是干细胞修复神经损伤的关键问题。选择合适的生物支架有助于将DPSCs输送至指定区域并向神经向迁移和分化。天然高分子、合成聚合物、石墨烯、水凝胶等材料已被广泛应用于支持和诱导干细胞向神经方向分化[57，89]。

水凝胶具有良好的生物相容性、可调节的力学性能及高含水量，能够模拟神经组织的柔软特性[90]。甲基丙烯酰化明胶（gelatin methacryloyl，GelMA）水凝胶通过调节交联密度可精确匹配脊髓等软组织的低刚度特性，有助于维持DPSCs的形态和促进神经分化[91]。Qian等[89]利用数字光处理3D打印技术制备GelMA微球，显著提高了DPSCs的定向黏附与存活率，增强了神经标志物生长相关蛋白43（growth associated protein 43，GAP43）和MAP2的表达，并在大鼠脊髓损伤模型中促进了脊髓再生。Luo等[92]采用10% GelMA水凝胶与bFGF及DPSCs填充纤维素/大豆分离蛋白复合膜管，构建神经再生导管，成功修复了大鼠坐骨神经缺损。水凝胶的高可塑性还允许其作为生长因子递送平台，通过可控释放促进DPSCs的神经分化。

壳聚糖是来源广泛的天然多糖，具有良好的生物降解性、抗菌性和成膜性。在神经组织工程中，它可被加工成导管或多孔支架，为DPSCs提供支持和引导。载bFGF的壳聚糖支架在体内可通过降解或扩散缓慢释放生长因子，激活ERK信号通路，增强DPSCs中GFAP、S100钙结合蛋白β（S100 calcium binding protein β，S100β）和TUBB3的表达，从而促进神经分化[93]。壳聚糖导管结合干细胞因子与DPSCs在兔面神经损伤模型中促进了面神经再生、髓鞘重建及功能恢复[94]。壳聚糖支架的机械强度适中，可通过表面改性提高细胞黏附性，并与其他材料复合以改善神经诱导效果。

聚乳酸（polylactic acid，PLA）是一种可生物降解的合成高分子，具有良好的机械强度和可设计性，特别适合通过3D打印制备具有方向性结构的神经支架。定向PLA支架模拟神经组织中轴突的排列方向，引导DPSCs沿特定方向延伸，促进细胞极性形成和轴突样突起生成，同时显著提高成熟神经元标志物MAP2的表达[95]。PLA支架可与其他功能材料（如导电聚合物或石墨烯）复合，进一步提升神经诱导能力。

复合导电支架（石墨烯、导电聚合物等）神经组织具有高度电活性，因此支架的导电性对于模拟神经微环境和促进神经分化至关重要。Seonwoo等[96]开发的还原氧化石墨烯-聚己内酯（reduced graphene oxide-poly ε-caprolactone，RGO-PCL）复合纳米纤维支架中，有序排列的纤维显著促进了DPSCs的神经分化，在0.1%RGO浓度下TUBB3表达显著增加。Gao等[37]通过在导电合成聚合物表面涂覆细胞外基质蛋白，成功诱导DPSCs分化为神经元样细胞，显著上调神经标志物表达。这些材料不仅提供结构支撑，还通过电化学信号调控细

胞行为，增强神经诱导效率。表3总结了干细胞疗法与生物材料支架之间的协同作用机制。

**表3** 干细胞疗法与生物材料支架之间的协同相互作用机制

Table 3 Synergistic interaction mechanisms between stem cell therapy and biomaterial scaffolds

| Scaffold type | Mechanism | Main function | Related markers |
|---|---|---|---|
| Hydrogel scaffold | Enhances expression of neural markers by tuning crosslinking density to match the low stiffness of the spinal cord[89] | Improves directed adhesion and survival of DPSCs | GAP43, MAP2 |
| | Loads and continuously releases growth factors[92] | Repairs rat sciatic nerve injury | - |
| Chitosan scaffold | Good biodegradability, antibacterial property, and film-forming ability; supports DPSCs migration and differentiation[93] | Slow release of βFGF promotes neural differentiation of DPSCs and activates ERK signaling | GFAP, S100β, TUBB3 |
| | Merges with stem cell factors[94] | Promotes rabbit facial nerve regeneration | |
| PLA scaffold | Directionally fabricated by 3D printing to mimic axon arrangement [95] | Guides DPSCs migration along specific directions and promotes cell polarity formation and axon growth | MAP2 |
| Composite conductive scaffold | Conductive scaffold modulates cell behavior via electrochemical signals to promote neural differentiation[37] | Provides electrical activity support and enhances neural differentiation efficiency | TUBB3 |
| | RGO-PCL composite nanofiber scaffold promotes DPSCs neural differentiation[96] | Enhances neural induction | TUBB3 |

DPSCs: dental pulp stem cells. PLA: polylactic acid. GAP43: growth associated protein 43. MAP2: microtubule-associated protein 2. βFGF: basic fibroblast growth factor. ERK: extracellular signal-regulated kinase. GFAP: glial fibrillary acidic protein. S100β: S100 calcium binding protein β. TUBB3: tubulin beta 3 class III. RGO-PCL: reduced graphene oxide-poly ε-caprolactone.“-”: not specified or not reported

## 3 小结与展望

目前，DPSCs在神经损伤修复的临床研究仍处于初步阶段，主要集中在动物模型中的应用，其临床转化仍面临诸多挑战。①微环境适应性差：DPSCs在体内修复神经损伤时，其功能可能受到损伤部位微环境的限制。这些病理状态显著影响干细胞的存活、归巢能力以及分化潜力，从而限制了再生效果[97]。②分化效率和可控性差：虽然DPSCs具有较强的神经分化潜力，但如何高效且稳定地诱导其分化为功能性神经细胞仍是一个挑战。目前的分化诱导方法存在效率低、可控性差的问题，难以满足临床需求[98]。③免疫排斥问题：尽管DPSCs具有较低的免疫原性，但在异体移植中仍可能引发免疫排斥反应，影响其临床应用的安全性。如何有效控制免疫反应，保证移植的长期安全性，是临床转化的关键问题[99]。④规模化生产与质量控制：大规模扩增DPSCs以满足临床需求仍存在困难。细胞批次之间的差异性可能影响治疗效果，并且现有的生产标准和质量控制体系尚不完善，导致治疗结果的不一致性[100]。⑤缺乏标准化操作流程：目前缺乏统一的临床操作流程和相关的标准化治疗方案，导致不同研究和治疗之间存在较大差异[101]。

针对以上挑战，未来研究可以从以下几个方向推动DPSCs在神经再生中的临床转化。①优化微环境适应性：通过预适应处理、联合使用生物支架及抗炎因子等方法，改善DPSCs的微环境适应性，增强其在神经损伤部位的生存和功能发挥[102]。②提升分化效率：开发新的诱导方案，如生长因子组合、小分子调控及基因编辑等技术，以提高DPSCs的神经分化效率和可控性，从而获得更多的功能性神经细胞[103]。③免疫调控与安全性研究：通过调控免疫反应、使用免疫抑制剂或对细胞进行基因编辑等方法，降低免疫排斥反应，确保异体移植的安全性和长期效果[104]。④细胞制备与质量控制：建立符合良好生产规范标准的大规模扩增平台，制定统一的质量控制体系，确保DPSCs的高效扩增和稳定性，以保障治疗效果的可重复性和一致性[105]。⑤标准化治疗流程：制定规范化的临床操作流程，结合多中心临床试验，进一步验证DPSCs在神经再生中的疗效与安全性，推动其早日进入临床应用[106]。

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