hPSC源少突胶质前体细胞用于脊髓损伤的治疗作用

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摘要 脊髓损伤(spinal cord injury, SCI)是一种严重的中枢神经系统(central nervous system, CNS)疾病, 常导致严重的功能障碍, 因其病理生理机制尚不完全清楚, 仍为世界性的医学难题。随着对少突胶质前体细胞(oligodendrocyte progenitor cell, OPC)在CNS中作用的深入研究, 以此为基础的细胞疗法成为一种有最具前景的治疗策略。动物实验结果表明, OPC移植到损伤脊髓可促进髓鞘再生、改善运动功能。该文介绍了关于OPC治疗SCI的基本情况, 总结了已有的研究成果, 指出了其在临床应用中面临的挑战, 从而为进一步研究和开发有效的治疗策略提供了依据。

关键词 少突胶质前体细胞; 脊髓损伤; 临床试验; 脱髓鞘; 髓鞘再生

The Therapeutic Effect of hPSC Derived Oligodendrocyte Precursor Cells on Spinal Cord Injury

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Abstract SCI (spinal cord injury) is a devastating CNS (central nervous system) disorder that often results in severe functional impairments. Due to the incomplete understanding of its underlying pathophysiological mechanisms, SCI remains a global medical challenge. In recent years, the in-depth understanding of the role of OPC (oligodendrocyte progenitor cell) in the CNS has led to the emergence of cell therapy as a promising strategy. Extensive animal experiments have shown that OPC transplantation into injured spinal cord promotes remyelination and significantly improves motor function. This review provides a foundation of knowledge regarding OPC-based treatment for SCI, summarizes the existing research findings, and identifies the challenges encountered in clinical applications. It serves as a basis for further research and development of effective therapeutic strategies.

Keywords oligodendrocyte precursor cell; spinal cord injury; clinical trial; demyelination; remyelination

创伤性脊髓损伤(spinal cord injury, SCI)是指由交通事故、运动损伤、暴力行为或跌倒等外部力量对脊髓造成的损害。这类损伤可能导致脊髓内神经组织的破坏或断裂, 从而扰乱神经信号的传递和功能。因此, SCI患者会出现包括肢体麻痹、感觉缺失、自主神经系统功能障碍以及膀胱和肠道功能障碍在内的广泛的身体功能障碍[1]。根据世界卫生组织[2]报道, 每年有25~50万例SCI发生, 其中约90%创伤性

收稿日期: 2024-06-12 接受日期: 2024-08-09
伊犁哈萨克自治州科学技术计划(批准号: YKX2023A11、YKX2024A01)资助的课题
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Received: June 12, 2024 Accepted: August 9, 2024
This work was supported by the Technology Plan of Ili Kazakh Autonomous Prefecture (Grant No.YKX2023A11, YKX2024A01)
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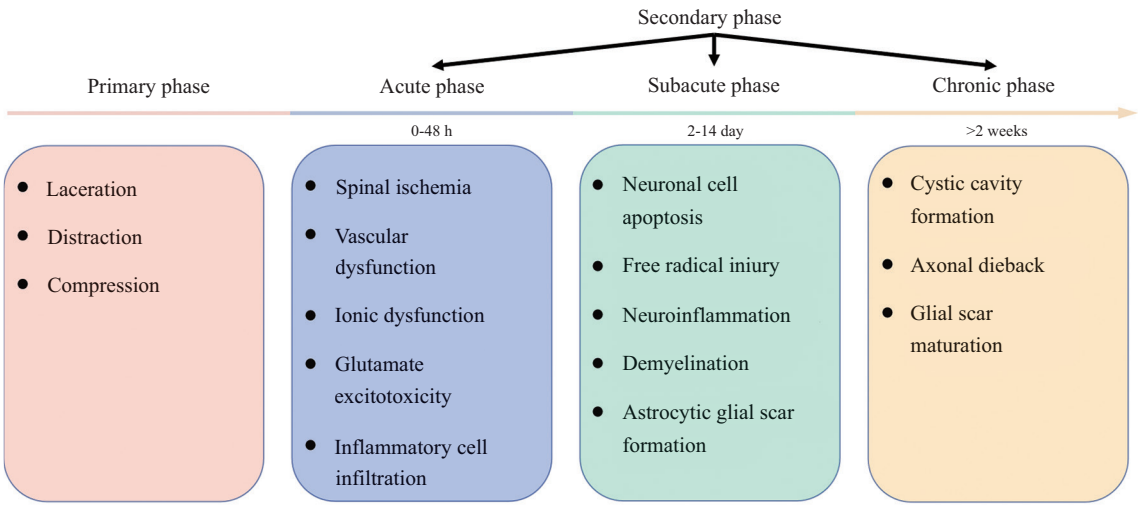


图1　脊髓损伤各阶段病理事件

Fig.1　Pathological events at different stages of spinal cord injury

损伤是由交通事故、跌落或暴力等突发事故引起的。

SCI可分为原发性和继发性阶段(图1)。在原发性阶段, 脊髓受到牵引和压缩等外部机械力作用, 导致椎骨脱位、弯曲和伸展等后果, 引起组织碎裂、神经网络损伤和血管破裂等一系列损伤, 进而导致神经和胶质细胞损伤以及细胞碎片的形成[3], 最终启动继发性阶段。该阶段中的急性阶段(0~48 h)涉及血管损伤、离子平衡紊乱、兴奋性毒性(一种由神经元受过量信号刺激而导致其损伤或死亡的现象)、自由基产生、脂质过氧化、炎症细胞浸润、水肿等, 而亚急性阶段(2~14天)则主要表现为神经细胞凋亡、轴突脱髓鞘、沃勒变性、神经炎症、轴突重塑以及胶质瘢痕(一种主要由反应性星形胶质细胞在损伤部位增殖并紧密交织形成的瘢痕组织)。最后, 慢性阶段(损伤2周后)表现为囊肿形成、轴突枯萎和胶质瘢痕成熟[4]。

由于病理生理机制的复杂性, SCI的治疗仍然是一个重大挑战。目前的治疗策略包括手术、生物活性物质治疗、物理刺激、生物材料移植和细胞移植[5]。其中细胞移植促进损伤修复的功能更加全面, 成为了治疗SCI的热点之一。少突胶质前体细胞(oligodendrocyte precursor cell, OPC)是中枢神经系统(central nervous system, CNS)中负责形成髓鞘的少突胶质细胞(oligodendrocyte, OL)的前体细胞, 具备迁移到损伤部位并分化为OL以使丢失髓鞘的轴突进行髓鞘再生的能力。因此, OPC移植治疗SCI具有广阔的前景。本文通过阐述利用OPC治疗SCI的理论基础, 总结OPC治疗的临床前研究和重要临床进展, 讨论OPC治疗SCI面临的挑战以及潜在的解决措施, 从而为进一步开展临床试验和优化治疗方案提供重要的依据。

1　OPC治疗SCI的理论依据

为了全面讨论OPC移植治疗SCI的作用及进展, 阐明在这种治疗方法中利用OPC的理论基础至关重要。首先, OPC疗法主要以脱髓鞘为靶点, 脱髓鞘是SCI的关键病理特征, 因为在SCI微环境中, 由于内源性OPC的再生能力有限, 导致髓鞘难以再生[6]; 其次, OPC固有的特性和功能为SCI提供了卓越的治疗潜力[7]。

1.1　SCI后的脱髓鞘以及髓鞘再生的失败

髓鞘是神经系统的重要组成部分, 其以富含脂质的结构包裹神经轴突, 这使其与周围环境相隔离, 并增加动作电位沿轴突传递的速度[8]。SCI后, 髓鞘从轴突上脱离导致轴突失去保护和代谢支持进而变性, 造成运动功能和感觉功能严重受损[9]。此过程可能从原发性损伤阶段持续到慢性阶段[6]。

SCI中的脱髓鞘主要源于OL膜破坏、损伤和死亡, 其次是OPC供应不足。有研究表明, 仅OL的凋亡就足以推动脱髓鞘过程, 这在实验性OL凋亡模型中得到证实[10]。因此, OL的死亡被认为是SCI后CNS脱髓鞘的关键原因。SCI后有多种因素可导致OL死亡, 包括自由基攻击、出血、缺血、离子平衡失调和谷氨酸兴奋毒性[3]。需要注意的是, 由于OL

代谢速率高、铁含量高、谷胱甘肽水平低, 使得它们与OPC一样特别容易受到氧化应激的影响[9]。

成熟的OL缺乏增殖能力, 在其消亡后, 重新补充OL依赖于内源性OPC的招募和分化[11]。然而, 在SCI的微环境中, 这一过程受到了多种因素的阻碍[12](图2)。例如, 在损伤部位, 胶质瘢痕中的某些软骨硫酸蛋白多糖(chondroitin sulfate proteoglycans, CSPGs)显著抑制OPC的生长和分化[13]。同时, SCI后未清除的髓鞘碎片的积累以及SCI后出血引入的纤维蛋白原也能阻碍OPC向OL分化[14-15], 并且血液中的血红蛋白也可能引起OPC线粒体功能失调从而造成影响[16]。

SCI后的自身免疫反应以及炎症反应也可能导致脱髓鞘。当血脊髓屏障(blood-spinal cord barrier, BSCB)受损时, CNS的自身抗原, 包括髓鞘碱性蛋白(myelin basic protein, MBP)、髓鞘相关糖蛋白(myelin-associated glycoprotein, MAG)和髓系OL糖蛋白(myelin-oligodendrocyte glycoprotein, MOG), 被释放到系统循环中, 能够触发特异性抗原T淋巴细胞和B淋巴细胞的激活, 使它们渗透到受损的BSCB并对髓鞘和OL造成损害[17-20]。例如, 有研究表明MBP可以诱导MBP反应性T细胞分泌干扰素γ(interferon γ, IFN-γ)和肿瘤坏死因子α(tumor necrosis factor α, TNF-α), 从而启动自身免疫反应导致脱髓鞘[21-22]。IFN-γ严重损害脱髓鞘脊髓中OPC的增殖和招募[23], 而高剂量的IFN-γ直接诱导OPC凋亡[24]。IFN-γ可以刺激M1型小胶质细胞的产生并释放促炎因子来阻碍OPC的分化[25]。此外, 包括小胶质细胞在内的炎症细胞对OL和髓鞘产生直接影响, 同时释放促炎细胞因子和活性氧化物, 从而导致髓鞘和OL的损伤[26]。TNF-α可诱导OL的死亡以及OPC的凋亡并阻碍其分化[27-28]。

此外, SCI后产生的反应性星形胶质细胞分泌多种细胞外基质成分, 包括CSPG、内皮素-1、透明质酸、纤维连接蛋白, 促炎因子如IL-1β和IL-6, 以及趋化因子CXCL10, 这些因素均可通过各种途径阻止髓鞘再生[29-37](图2)。

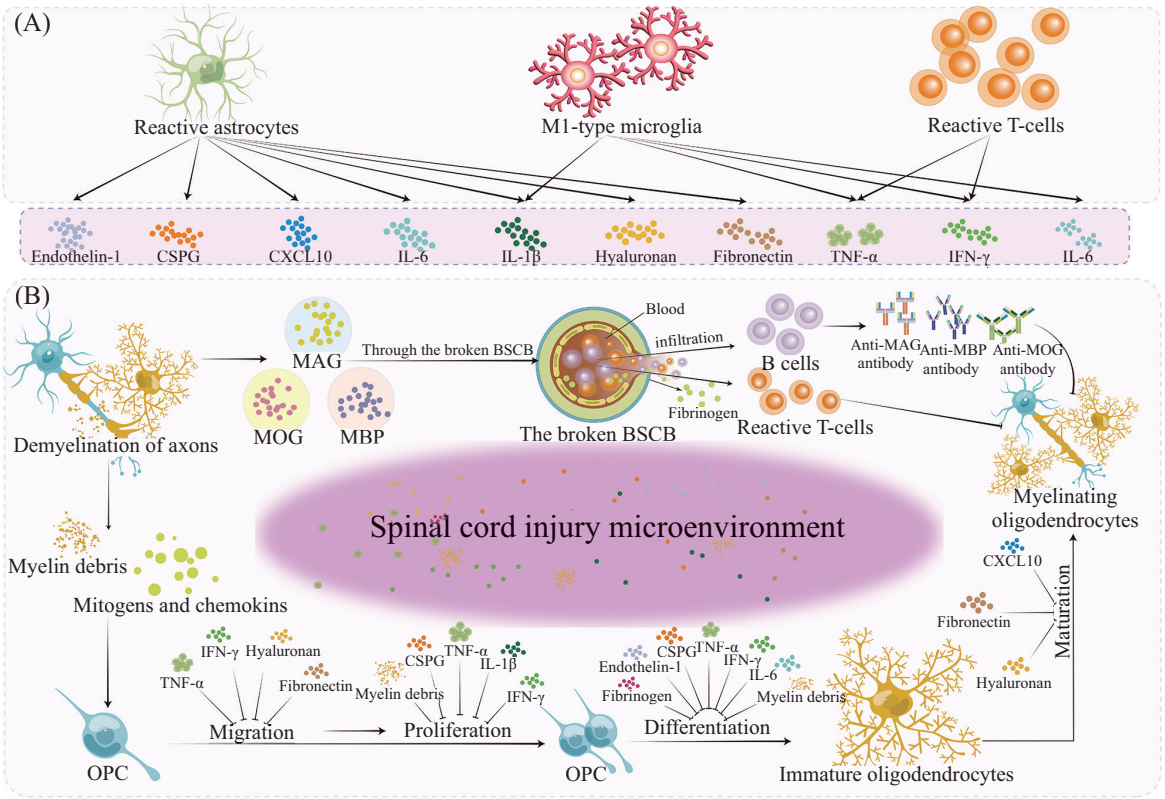
1.2 OPC治疗SCI的潜力

最近的研究揭示了OPC除了在促进轴突髓鞘再生方面的传统作用外还具有显著的治疗潜力[41]、分化能力、与神经元相互作用和免疫调节等能力(图3)。

1.2.1 *多向分化潜能* 受周围微环境影响, OPC可表现出多能性。在SCI环境下, 内源性OPC能够增殖和迁移至损伤部位并分化为OL[39]。而在特定培养条件下补充BMP-2和BMP-4后, OPC可分化为星形胶质细胞[42]。但是在大多数SCI动物模型中, 移植的OPC可成功分化为成熟的OL, 促进运动功能恢复[43-46]。然而, 值得注意的是, 有研究观察到了不同结果。LÜ等[47]将大鼠神经干细胞(neural stem cell, NSC)来源的OPC移植到正常和受伤大鼠的脊髓中, 发现大多数移植细胞分化为星形胶质细胞, 并且大鼠运动功能未能得到明显改善。除此之外, 在特定情况下, OPC也能显示出罕见的神经元分化能力。例如, 小鼠海马中的部分OPC可以分化为γ-氨基丁酸能神经元[48]。而体外培养的大鼠原代OPC也能够分化为表达Tuj1的神经元样细胞[49]。值得注意的是, 研究表明, 诱导多能干细胞(induced pluripotent stem cell, iPSC)来源的OPC在移植后一部分能够分化为神经元[50]。

1.2.2 *与神经元相互作用* OPC表达的*N*-甲基-*D*-天门冬氨酸(*N*-methyl-*D*-aspartate, NMDA)、α-氨基-3-羟基-5-甲基-4-异恶唑烷丙酸(α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, AMPA)和γ-氨基丁酸A型(γ-aminobutyric acid type A, GABAA)受体, 使其能够与神经元建立突触连接, 并在调控OPC增殖和分化方面发挥重要作用[51]。体外实验表明, 使用kainate刺激AMPA受体可抑制OPC增殖, 而使用NMDA刺激NMDA受体可促进OPC分化和髓鞘形成。阻断OPC中的AMPA和NMDA受体信号会减少髓鞘磷脂的形成[52-53]。这些结果表明, OPC能够接受来自神经元的信号调节。相关机制可能涉及生长因子如血小板衍生生长因子(platelet-derived growth factor, PDGF)的释放, 或突触间隙中的其他信号, 从而促进OPC的增殖和分化[41,54]。然而, 目前关于OPC与神经元之间的突触形成与髓鞘再生之间是否直接相关还不清楚。此外, 这些突触连接还使OPC对CNS损伤非常敏感, 从而使它们能够对连接的神经元的健康状况作出反应[51]。

同样, OPC对神经元也具有调控作用。其表面的NG2可通过抑制轴突生长而对神经元产生影响[55]。OPC还表达神经调节蛋白, 包括前列腺素D2合成酶和神经元棘蛋白2, 以及各种神经营养因子, 如TGF-β2、脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)、类胰岛素生长因子1和胶质细胞源性神经营养因子。这些因子有助于神经元的营养、存活和轴突生长, 并积极参与神经元功能的调节[56-59]。此外, 最



A: 反应性星形胶质细胞释放多种因子, 包括CSPG、内皮素-1、透明质酸、纤维连接蛋白、IL-1β、IL-6和CXCL10。M1型小胶质细胞分泌IL-1β、IL-6、TNF-α和IFN-γ。反应性T细胞分泌TNF-α和IFN-γ等炎症因子。B: OPC受到有丝分裂原和趋化因子的刺激, 进行增殖并朝向损伤部位迁移, 分化为OL并进一步成熟为髓鞘化OL。在SCI后, 反应性星形胶质细胞、M1型小胶质细胞和反应性T细胞分泌的因子可通过抑制OPC的迁移、增殖、分化和成熟来妨碍髓鞘再生过程。此外, 脱髓鞘会产生髓鞘碎片和髓鞘蛋白, 如MAG、MOG和BMP。髓鞘碎片阻碍OPC的增殖和分化, 而髓鞘蛋白可以穿过受损的BSCB, 激活特异性抗原的T和B淋巴细胞。这导致产生针对髓鞘蛋白的反应性T细胞和抗体, 最终导致髓鞘破坏和OL死亡。此外, 破损的BSCB还会引入纤维蛋白原阻碍OPC分化。

A: reactive astrocytes release various factors, including CSPG, endothelin-1, hyaluronic acid, fibronectin, IL-1β, IL-6, and CXCL10. M1 microglia secrete IL-1β, IL-6, TNF-α, and IFN-γ. Reactive T cells secrete inflammatory cytokines such as TNF-α and IFN-γ. B: OPC responds to mitogens and chemotactic factors, undergoes proliferation and migration toward the site of injury, differentiates into OLs, and further matures into myelinating OLs. After SCI, factors secreted by reactive astrocytes, M1 microglia, and reactive T cells can hinder the process of remyelination by inhibiting OPC migration, proliferation, differentiation, and maturation. Additionally, demyelination generates myelin debris and myelin proteins, such as MAG, MOG, and BMP. Myelin debris impairs OPC proliferation and differentiation, while myelin proteins can cross the damaged BSCB and activate antigen-specific T and B lymphocytes. This leads to the production of reactive T cells and antibodies against myelin proteins, ultimately resulting in myelin destruction and OL death. Moreover, the compromised BSCB also introduces fibrinogen, which inhibits OPC differentiation.

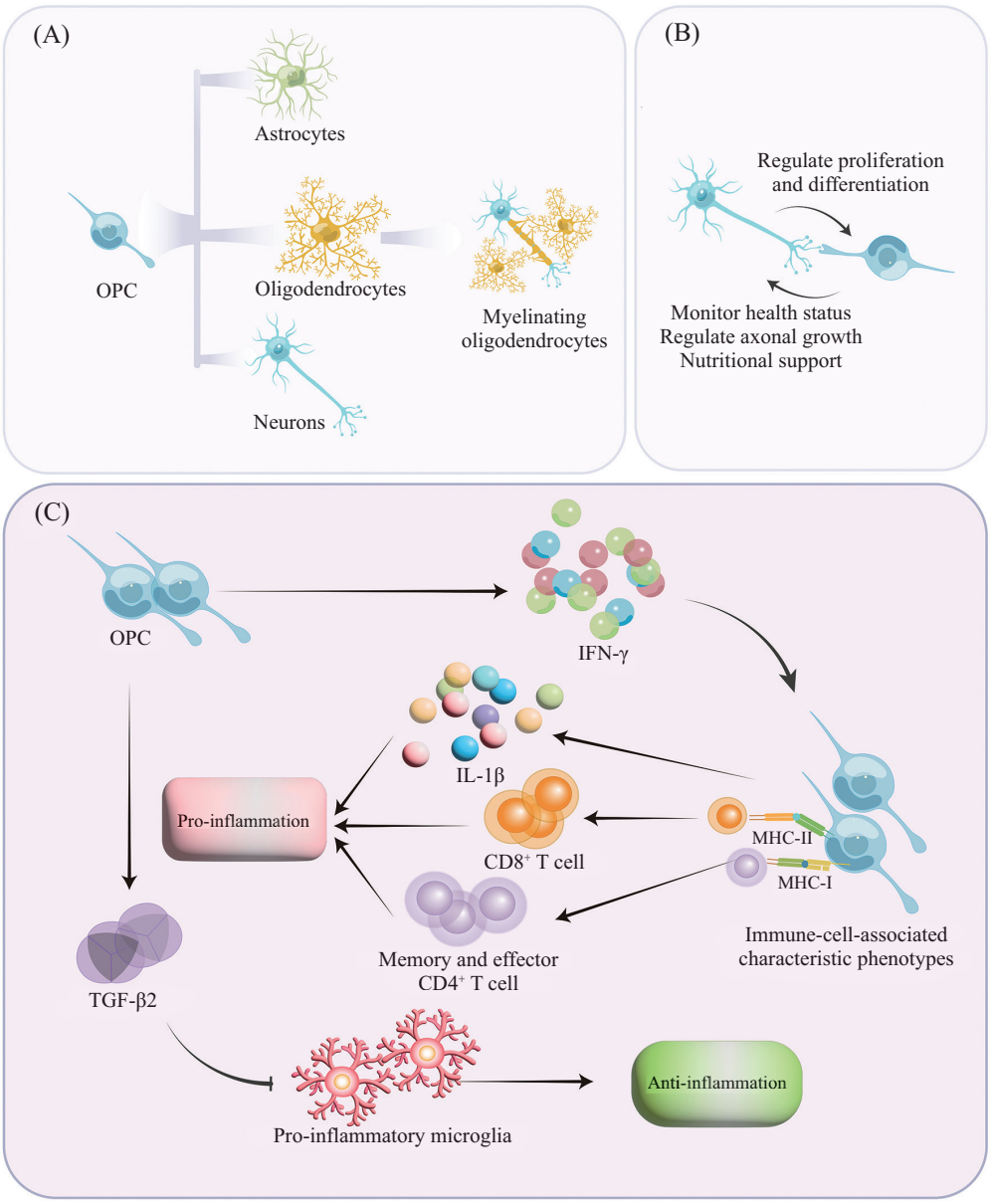
图2　影响OPC髓鞘再生的负面因素(根据文献[14-15,17-40]修改)

Fig.2　Negative factors affecting OPC myelin regeneration (modified from the references [14-15,17-40])

近的研究发现, OPC可通过吞噬神经元轴突和突触来调节神经元回路发展[60]。

综上所述, 移植的OPC有能力通过分泌神经调节因子、神经营养因子以及与神经元相互交流提供一种利于神经组织再生的修复环境治疗SCI。

1.2.3　免疫调节　CNS损伤后, OPC能够参与调节免疫反应, 可能促进或抑制炎症。OPC可以表达IL-β和MHC-I、MHC-II等免疫调节分子, 从而促进炎症的进展[61]。在IFN-γ的刺激下, OPC发生免疫细胞相关表型变化, 包括MHC-I、MHC-II分子的表达以及抗原的处理和呈递[24]。其中, MHC-II分子可促进$CD4^+$ T细胞的存活和增殖, 激活记忆和效应$CD4^+$ T细胞反应[62]。此外, OPC可通过分泌TGF-β2抑制小胶质细胞的促炎活性而使其表现出抗炎特性, 从而产生神经保护作用[63]。尽管内源性OPC在SCI后的免疫调节中扮演的促炎或抗炎角色尚不确定, 但现有数据表明它们在各种神经系统疾病中更倾向于促炎表型[64]。虽然移植OPC在免疫调节中的作用尚不确定, 但了解OPC的免疫调节能力及其对SCI的潜在影响对于阐明OPC的治疗机制具有重要意义。



A: OPC的多能性。在特定条件下, OPC具有分化为髓鞘化OL、星形胶质细胞和神经元的潜力。B: 神经元与OPC之间的相互调控。神经元影响OPC的生长和分化, 而OPC反过来调节神经元轴突的生长, 监测神经元状态, 并分泌神经营养因子和神经调节因子来调节神经元的生长和功能。C: OPC参与免疫反应调节的示例。OPC可以分泌转化生长因子β2(transforming growth factor beta 2, TGF-β2), 抑制炎症性小胶质细胞的活化, 从而发挥抗炎效应。然而, 当暴露于IFN-γ时, OPC可能表现出与免疫相关的特征, 如表达MHC分子, 以呈递抗原给T细胞。此外, OPC可以分泌促炎因子如IL-1β, 促进炎症过程。

A: pluripotency of OPC. OPC possess the potential to differentiate into myelinating oligodendrocytes, astrocytes, and neurons under specific circumstances. B: the reciprocal regulation between neurons and OPC. Neurons influence the growth and differentiation of OPC, while OPC, in turn, regulate the growth of neuronal axons, monitor neuronal status, and secrete neurotrophic and neuromodulatory factors to modulate neuronal growth and function. C: an example for OPC participate in immune response regulation. OPC can secrete TGF-β2 (transforming growth factor beta 2) to inhibit the activation of pro-inflammatory microglia, thereby exerting anti-inflammatory effects. However, when exposed to IFN-γ, OPC may exhibit immune-related characteristics such as the expression of major MHC molecules for antigen presentation to T cells. Additionally, OPC can secrete pro-inflammatory factors like IL-1β, promoting inflammation.

图3 OPC的治疗潜力

Fig.3 Therapeutic potential of OPC

2 OPC移植治疗SCI的进展

在维持CNS正常功能中, 髓鞘的重要作用包括保护轴突信号转导和促进能量代谢需求的满足。进一步的证据表明, 髓鞘再生有潜力恢复轴突信号转导[65-66]。因此, 操纵髓鞘再生被认为是治疗SCI的策略之一[67]。OPC作为成熟OL的祖细胞, 具有自我复

制、迁移、分化为OL并形成髓鞘以及促进神经元生长存活的显著能力。因此，这些独特特性使其成为治疗干预的有前景选择之一。

2.1 OPC疗法的研究现状

OPC移植治疗SCI已经引起了极大关注。多项动物实验(表1)表明，移植的OPC能够在损伤部位成功存活和增殖，分化为OL，并促进髓鞘再生、轴突功能和运动功能的恢复。然而，移植的OPC的确切细胞行为，比如细胞如何在CNS内迁移和驻留，仍然不清楚。根据FRANKLIN等[68]的观点，内源性OPC通过激活、招募和分化三个阶段介导CNS的髓鞘再生。在激活阶段，OPC基因表达发生变化，并变得更具增殖能力；在招募阶段，OPC在趋化因子的作用下迁移到损伤部位；之后，OPC退出细胞周期，分化为OL，形成髓鞘。根据目前的研究，移植的OPC无法在完整的CNS内存活或迁移[69]。然而，当移植到脱髓鞘区域时，OPC表现出显著的存活率升高并迁移到受损区域[70]。这些发现意味着移植的OPC容易受到病理环境的影响，在受损区域内存活和迁移，而不是整合到健康的CNS中。尽管移植的OPC可能经历与内源性OPC类似的阶段来促进髓鞘再生，但损伤微环境对移植的OPC的影响以及是否与内源性OPC观察到的效应相似，尚不确定。

由于OPC、OL和髓鞘对损伤微环境的高度敏感性，OPC移植的时机至关重要。OPC在亚急性损伤阶段的移植被认为是最有效的。KEIRSTEAD等[77]分别在大鼠SCI 7天和10个月后移植人胚胎干细胞(human embryonic stem cell, hESC)来源的OPC，观察到了强力有效的髓鞘再生和显著的运动能力改善，但在10个月后的移植组中并没有观察到这种效果。类似于OPC，NISHIMURA等[85]也发现在慢性期SCI中，NSC的移植是无效的，这是由于胶质瘢痕限制了移植NSC的迁移以及M2型巨噬细胞的浸润导致的。这些发现表明了慢性期SCI对移植细胞存活的不利影响。OGATA[86]

表 1 OPC治疗SCI的动物实验

Table 1 Animal experiments on OPC therapy for SCI

细胞类型 Cell type	动物 Animal	损伤位点 Injury site	移植细胞量 Transplanted cell volume	移植时间点 Transplantation time point	移植部位 Locations	移植效果 Results	参考文献 Reference
miPSC-OPC	SD rats	T9	5.0×10^6	7 days after injury	Injured site	Increased the formation of myelin sheaths; alleviation of motor function and sensory function	[71]
miPSC-OPC	SD rats	T9-T11	1.0×10^6	7 days after injury	The rostral and tail end of the injury	Improve motor recovery and relieve mechanical allodynia	[72]
hESC-OPC	Athymic nude rats	C5	2.4×10^5	7 days after injury	The spinal cord parenchyma adjacent to the injury site	Significantly improved locomotor performance; reduced parenchymal cavitation and increased sparing of myelinated axons	[73]
hESC-OPC	Lewis rats	T8	1.0×10^6	2 hours after injury	The grey matter posterior to the central canal; 4 mm above and 1 mm to the left of the epicenter; 4 mm below and 1 mm to the right of the epicenter	Functional improvements in SSEP amplitudes and latencies	[74]
Newborn (P0) SD rats OPC	SD rats	T9-T10	7.5×10^5	5 days after injury	The site of injury	Improved axonal conduction and spinal cord function in the injured spinal cord	[75]
2-day-old neonatal SD rats OPC	SD rats	T10	1.0×10^6	7 days after injury	Lesioned cord	Enhanced myelination in the lesioned area and substantial improvement of motor function and nerve conduction	[76]

续表1

细胞类型 Cell type	动物 Animal	损伤位点 Injury site	移植细胞量 Transplanted cell volume	移植时间点 Transplantation time point	移植部位 Locations	移植效果 Results	参考文献 Reference
hESC-OPC	SD rats	T8-T11	2.5×10^5 or 1.5×10^6	7 days after injury 10 months after injury	The midline of the spinal cord at a depth of 1.2 mm into one site 4 mm cranial to the lesion epicenter and one site 4 mm caudal to the lesion epicenter	Enhanced remyelination and promoted improvement of motor function No enhanced re-myelination or locomotor recovery	[77]
hESC-OPC	SD rats	T8-T11	1.5×10^6	7 days after injury	The cranial end of the laminectomy and the caudal end of the laminectomy	Robust remyelination	[78]
hESC-OPC	SD rats	C5	1.5×10^6	7 days after injury	1.2 mm into one site cranial and one site caudal to the lesion epicenter	Attenuated lesion pathogenesis and improved recovery of forelimb function	[44]
hESC-OPC	SD rats	T8	5.0×10^5, 1.5×10^5	3 and 24 hours after injury	1.0 mm into the white matter at T7 and T9; 1.5 mm into the gray matter at the T8 epicenter	OPCs survived for a minimum of 8 days after injury and integration into the spinal cord with contusion injury without disruption to the parenchyma; increased neurological responses	[46]
hESC-OPC	Athymic nude rats	T10	2.4×10^6 or 2.4×10^5	6-8 days after injury	The dorsal spinal parenchyma adjacent to the contusion epicenter	Myelination *in vivo* and did not cause any adverse clinical observations, toxicities, allodynia or tumors	[79]
2–3-day-old Lewis rat OPC	Lewis rats	C3	6.0×10^4	3 days after injury	Lesion site	The reversed functional deficits associated with demyelination	[80]
hESC-OPC	Rats	T8	6.3×10^5	2 hours after injury	Lesion site; 4 mm cranial and caudal to the lesion center	OPCs survive and proliferate; improvement of conduction marked by the increased SSEP amplitude	[81]
P2 rat brain derived O-2A cells	SD rats	T9	5.0×10^5	7 days after injury	Lesion center	A significant improvement in hindlimb performance	[82]
hiPSC-OPC	Rats	T8	5.0×10^2	24 hours after injury	Lesion site	Reduced cavitation, scars formation, and microglial proliferation; remyelination in the lesion; BBB scores improvement after the first month	[83]
miPSC-A2B5$^+$OPC	Rats	T10	5.0×10^2	7 days after injury	2.5 mm rostral or caudal to the epicentre of the injured site	Reduced cavitation, promoted improvement of motor function	[84]

miPSC-OPC: 小鼠诱导多能干细胞衍生的少突胶质前体细胞; hESC-OPC: 人胚胎干细胞衍生的少突胶质前体细胞; SD rats: Sprague-Dawley大鼠; SSEP: 体感诱发电位; BBB评分: Basso Beattie Bresnahan评分; O-2A cell: 少突胶质细胞2型星形胶质细胞祖细胞; hiPSC-OPC: 人诱导多能干细胞衍生的少突胶质前体细胞。

miPSC-OPC: mouse induced pluripotent stem cell-derived oligodendrocyte progenitor cells; hESC-OPC: human embryonic stem cell-derived oligodendrocyte progenitor cells; SD rats: Sprague-Dawley rats; SSEP: somatosensory evoked potential; BBB score: Basso Beattie Bresnahan score; O-2A cell: oligodendrocyte-type-2 astrocyte progenitor cells; hiPSC-OPC: human induced pluripotent stem cell-derived oligodendrocyte progenitor cells.

分析认为在急性期，受损组织暴露于各种炎症因子，如TNF-α、IFN-γ、自由基等可干扰髓鞘形成或诱导OPC、OL凋亡；在后期，胶质增生或胶质瘢痕出现，可阻止轴突再生和OPC迁移分化；在慢性期，轴突周围大量的抗髓鞘再生信号被认为是损伤恢复的主要障碍；因此，亚急性期被认为是髓鞘再生的最佳时间窗，其特点是炎症反应减弱和不明显的胶质细胞增殖。然而，有几项研究报道了OPC在SCI急性期移植的积极效果。例如，ALL团队[46,81,83]在SCI后24 h移植了hiPSC来源的OPC，观察到了包括细胞存活、部分髓鞘再生、运动功能改善和病理特征减轻等有益效果。虽然他们在损伤2 h后进行了OPC移植并观察到了显著的细胞死亡，但这不会影响细胞的长期增殖和存活以及宿主的病理改善[74]。然而，值得注意的是，大多数关于OPC移植治疗SCI的实验研究主要集中在亚急性期。实际上，ALL团队的研究结果支持OPC在SCI急性期移植的可行性，但症状改善及治疗程度与亚急性期移植相比如何尚不清楚。

可通过对OPC进行基因编辑以及OPC与其他药物或细胞联用等方法来提高OPC治疗SCI的效果。如将过表达miR-219的OPC移植到SCI模型中后发现其更容易分化为表达MBP的成熟少突胶质细胞，以促进疗效[87]。将表达睫状神经营养因子(ciliary neurotrophic factor, CNTF)的OPC移植入SCI模型可促进髓鞘再生和功能恢复[88]。将hiPSC-OPC与人脐静脉内皮细胞联合移植也促进了SCI后的功能恢复[89]。或者将OPC与音猬因子(Sonic hedgehog, Shh)联用治疗SCI动物模型比单独移植OPC或单独使用Shh治疗之后的运动功能恢复及病理特征改善效果更好[75]。这些研究结果表明，通过基因编辑和联合治疗的策略，可以进一步提高OPC治疗SCI的疗效。然而，在实际应用之前需要充分评估其潜在的风险和临床应用的可行性。

开发获得大量OPC的方法以满足临床应用的需求至关重要。人多能干细胞(human pluripotent stem cell, hPSC)因其无限增殖并可以多向分化的特性，成为临床治疗所需OPC的最主要来源之一。通常，通过模拟OPC在体内的自然发育模式可以实现稳定且大量的OPC供应。例如，使用FGFs和视黄酸处理，然后加入Shh，接着加入PDGFα以及促进少突细胞谱系成熟的胰岛素生长因子和甲状腺激素的方法，可获得OPC以及OL[90]。也可以通过重新编程方法如在hPSC中过表达SOX10等表型特化转录因子或在人成纤维细胞中过表达OCT4并与小分子联用等方法获得OPC[91-92]。人类细胞直接重新编程为OPC已显示出潜力，但其仍然存在肿瘤发生的风险以及获得率低等问题，在临床应用之前需要进一步研究。

2.2 OPC治疗SCI的临床进展

OPC在SCI动物模型中的试验已经显示出其显著的临床治疗潜力。Lineage Cell Therapeutics是第一家在SCI临床试验中应用hESC-OPC的公司。hESC-OPC最初是由Geron Corporation公司发明的，随后在2013年该公司将干细胞资产转让给了Asterias Biotherapeutics(BioTime的子公司)。在2019年BioTime收购了Asterias Biotherapeutics并将其更名为Lineage Cell Therapeutics。目前，他们的旗舰产品LCTOPC1由OPC、神经前体细胞以及少量成熟神经元细胞和其他独特的细胞类型组成，该产品针对急性SCI治疗的I/IIa期多中心临床试验已经成功完成[93]。

2.2.1 OPC1的发展历史　OPC1的开发可以追溯到2005年，当时NISTOR等[43]首次提出了一种从hESC中获取高产OPC的方法(图4)。将hESC-OPC移植到一个髓鞘发育异常的颤抖小鼠模型中后，可观察到致密髓鞘形成，表明这些细胞显示出功能性表型。随后他们将hESC-OPC移植入大鼠SCI模型中，并证明了其在SCI后早期时间点的治疗潜力[77-78]。对hESC-OPC的特征分析表明，它们表达midkine、肝细胞生长因子、激活素A、TGF-β2和BDNF，并且表现出弱免疫原性[57,94]。

2010年，通过使用颈椎SCI模型对hESC-OPC进行了一项临床前研究，结果显示在组织学结果和功能恢复方面取得了显著改善[44]。随后，Geron公司进行了hESC-OPC的I期临床试验(NCT01217008)。最初由于动物实验中观察到囊肿形成而面临监管方面的挫折。然而，释放标准的修订和额外的前瞻性动物研究减轻了这些担忧，最终于2010年6月解除了临床限制[99]。试验开始一年后，在4名接受治疗的患者中报道了细胞治疗的安全性的初步结果。不幸的是，由于资金短缺和不确定的经济环境，试验后来被终止[100]。值得注意的是，该临床试验由于分化OPC的方案缺乏可重复性、分化方案中含有动物源成分以及啮齿类动物模型不足以模拟人类的SCI等原因而备受争议。两年后，该公司公布了一种基于vitronectin衍生的合成肽丙烯酸包被基质用于支持hESC生

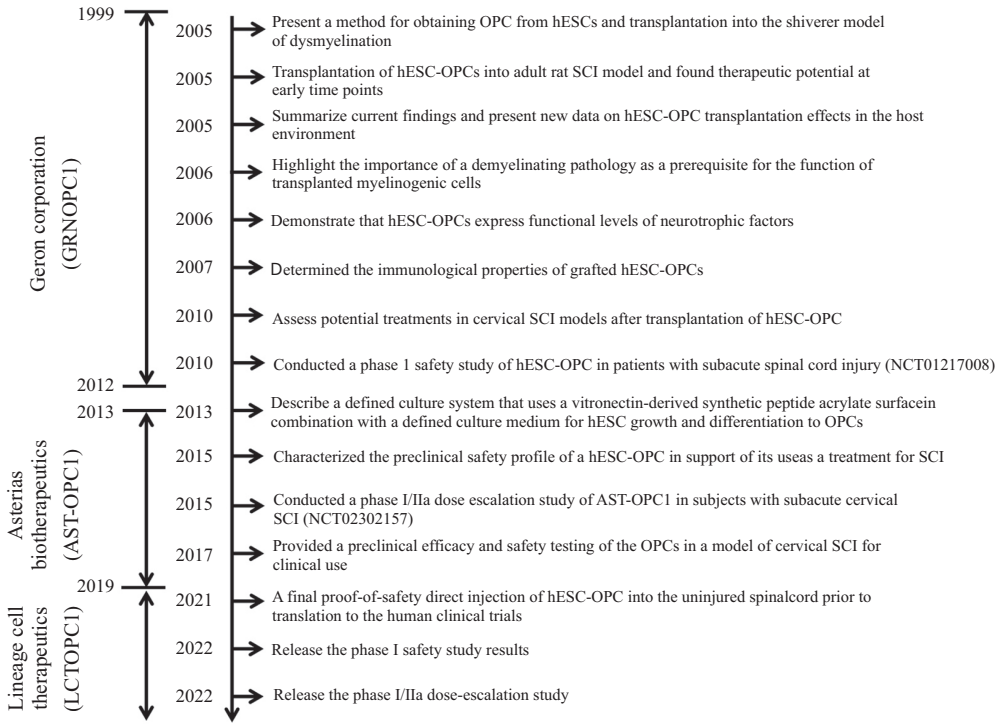


图4 LCTOPC1(先前被称为GRNOPC1和AST-OPC1)产品的研发历史(根据文献[43-44,57,73,77-79,93-98]修改)

Fig.4 LCTOPC1 (previously known as GRNOPC1 and AST-OPC1) product development history (modified from the references [43-44,57,73,77-79,93-98])

长及向OPC分化以取代复杂的动物源性基质胶[96]。

在Asterias Biotherapeutics收购Geron的干细胞资产后, AST-OPC1(前身为GRNOPC1)在大鼠SCI模型中进行的安全性和毒性测试支持了针对完全性胸部SCI患者的I期临床试验的启动[79]。2015年, OPC1的I/IIa期剂量递增研究(NCT02302157)开始进行。随后, 在2017年, OPC1在裸鼠颈椎SCI模型中的临床前疗效和安全性测试结果被发表, 进一步支持了临床试验[73]。在2021年, 将OPC1(即GRNOPC1或LCTOPC1)直接注射到解剖学上类似于人类脊髓的未损伤脊髓中, 作为其最终的安全性证明, 为人类临床试验的转化铺平了道路[97]。最终, 来自人类临床试验的初步数据, 以及I/IIa期剂量递增研究的结果[93], 明确证明了OPC1应用于人类SCI的安全性和显著的治疗效果。

目前, Lineage Cell Therapeutics在保持OPC1功能活性的同时, 取得了生产和质量方面的显著进展, 包括开发了一种新的即用型注射制剂、生产规模大幅增加、纯度提高以及生产过程无动物源成分[101-103]。

2.2.2 OPC1的临床试验 Lineage Cell Therapeutics围绕OPC1进行了两项临床试验。第一项是I期安全性研究, 该试验旨在评估在受伤后7至14天内对T3到T11神经功能完好的SCI患者进行OPC1治疗的安全性。5名参与者在注射OPC1后, 使用他克莫司免疫抑制治疗60天, 通过检测与OPC1注射、注射程序以及伴随的免疫抑制相关的不良事件的频率和严重程度, 来评估OPC1的安全性, 此外, 通过感觉评分、下肢运动评分测量、SCI神经学分类国际标准检查神经功能的改善程度。结果表明, 在10年中无神经功能减退、肿块增大、脊髓进一步损伤或空洞形成。MRI结果显示, 80%的患者表现出T2信号改变。这项研究首次提供了OPC1人体安全性数据, 表明了患者可以很好地耐受这种细胞类型, 无不良事件期长达10年[98]。

基于临床I期安全性研究结果, Lineage启动了一项针对亚急性颈椎SCI的I/IIa期剂量递增试验。其目标是评估在受伤后21至42天之间的单个时间点给予递增剂量的OPC1治疗的安全性, 包括亚急性颈椎SCI患者在内的5个分组。此外, 该试验还评估了OPC1治疗后神经功能的变化。共招募25名C4-7 AIS A或B级受伤患者, 接受了3个不同剂量的OPC1治疗, 并给予低剂量他克莫司直至第60天, 检测不良事件和神经功能。在1年的随访期间, 共报道了与研究相关的32个不良事件, 其中2个严重的事件(一名

患者脑脊液泄漏和另一名患者细菌感染)与注射过程和他克莫司免疫抑制相关，但这些问题随后被解决。未观察到额外与注射相关或OPC1相关的损伤。令人鼓舞的是，96%的参与者在神经功能方面出现明显改善，至少在身体的一侧恢复了一个或多个运动功能，32%的人出现2级或以上的神经功能改善。值得注意的是，这项试验存在一定的局限性，包括缺乏对与OPC1相关的神经学或功能改善进行评估的对照组，缺乏他克莫司或手术注射程序(如假手术对照)的对照组，以及缺乏与OPC1相关的神经学改善的评估[93]。

目前，Lineage和Neurgain Technologies将合作对Neurgain的新型实质输送注射(parenchymal delivery injection, PDI)系统进行临床试验。该系统的设计目的是在不停止患者呼吸的情况下将细胞注入脊髓。在手术过程中无需停止呼吸有望降低将细胞注入损伤区域的复杂性、风险和可变性[104]。随后，在2024年2月13日，美国食品药品监督管理局批准了Lineage Research的新药申请修正案。该修正案着重评估了一种新型脊髓递送装置在亚急性和慢性SCI患者中的安全性和可行性[105]。此外，在前期临床试验的基础上，Lineage公司在2023年开展了两项观察性研究(NCT05919563、NCT05919563)，分别监测注射了GRNOPC1或AST-OPC1的SCI患者15年的长期安全性。

3 挑战与展望

为了成功实施髓鞘再生策略，需要存在无髓鞘包裹且完好无损的轴突。然而，关于SCI后内源性OPC是否能有效促进此类轴突形成髓鞘以及损伤后脱髓鞘轴突是否持续存在，仍存在争议，SCI后是否存在这样的治疗靶点还不确定[106]。POWERS等[107]和LASIENE等[108]的研究结果均表明，在啮齿动物中出现了有效的内源性髓鞘再生，该现象引发了关于以髓鞘再生为目标的治疗策略是否合理的讨论。尽管动物实验和临床试验显示OPC移植具有有益的治疗效果，但目前尚不清楚观察到的运动功能改善是由于髓鞘再生还是其他因素(如神经营养因子分泌)导致的。因此，未来的研究需重点探索OPC治疗SCI的机制，以更好地指导治疗策略的设计和优化。

在OPC移植时，细胞递送方式也面临一些问题。目前使用的标准方法包括静脉注射和蛛网膜下腔注射，但这些方法无法有效控制细胞的分布、迁移和归巢至损伤部位，可能导致到达脊髓损伤部位的细胞数量不足[109]。解决这个问题的方法之一是直接注射细胞到受损脊髓内部。然而这也面临着包括针头和注射速度的影响以及移植体积等挑战[110]。为了控制细胞移植中的各种不利因素，目前存在3类主要的精密控制注射系统，包括脊柱固定系统、手术台固定系统和外科机器人。脊柱固定装置可以解决呼吸问题，但仍可能受到脊髓脉动的影响[111]。浮动导管系统可以进一步改善目标定位。手术台固定注射器在3个轴上提供高稳定性，但不能解决由心血管脉动、通气或患者移动引起的脊髓运动[112]。外科机器人配备的工具可以提供高度精确的定位，但仍需要在规范审批、高可靠性、无菌性以及适应人体剂量的灵活调整等方面进行改进[113]。

除此之外，OPC疗法还存在其他问题。由于受到微环境影响，细胞移植只在损伤的早期阶段如亚急性期可行，限制了其在慢性阶段患者以及急性期患者中的使用。未来的策略可以考虑将细胞移植与清除细胞疗效受阻因素(如胶质瘢痕的清除)的方法相结合，以治疗慢性阶段患者。对于急性期患者，由于微环境存在大量不利于细胞存活的因素，因此可以考虑细胞移植与细胞保护性或炎症抑制性药物联用，以提高疗效。

在移植后，OPC再生的髓鞘往往比原始髓鞘更薄[77]，这一结果的原因尚不清楚。尽管再生的髓鞘厚度较薄，但DUNCAN等[114]的结果表明在犬类动物中薄髓鞘仍然能够长期存在并继续支持正常的轴突功能，然而在人体内薄髓鞘对轴突功能影响如何尚不清楚。除此之外，移植的OPC在CNS中的迁移和驻留机制尚未被完全阐明，并且其迁移到其他区域并产生后续影响的可能性尚待确定。

虽然OPC1在临床试验中显示出有效性且没有明显异常，但其安全性问题不能被忽视。例如，MANLEY等[73]在移植部位发现了少量软骨异位结构，推测OPC可能分化为少量的间充质或上皮细胞，表明存在一定的干细胞特性。尽管这不会引起不良反应，但潜在的致肿瘤风险不能被忽视。此外，细胞纯度也是一个问题，因残留的未分化的ESC细胞增加了致瘤风险，因此，获得具有稳定性、均质性、功能性的OPC仍具有挑战性，未来需要开发新分化技术来提高获得的OPC的纯度。由于OPC治疗涉及异体移

植, 存在免疫排斥现象, 需要进行免疫抑制, 然而, 这种免疫抑制可能会削弱患者的免疫系统并引发细菌感染等问题[93,98]。为此, OPC的来源非常重要。用于治疗SCI的细胞药物, OPC难以从CNS组织来源获得, 因为它们在很大程度上依赖于供体自身因素如细胞适合性。此外, 供体年龄、获取条件和供体遗传因素等共同影响CNS组织来源OPC的有效性[90]。虽然将人体细胞如成纤维细胞直接重编程为OPC的方法已经出现, 能够克服免疫排斥以及成本高、步骤繁琐等问题, 但存在产率低、肿瘤风险等不利因素, 难以进行临床应用。使用经重编程的患者自体细胞产生的iPSC来源的OPC具有较低的免疫原性, 是一个可行的选择。然而, 由于重编程iPSC涉及致癌基因的过表达, 其分化为OPC也具有一定的致瘤风险[115], 仍然需要进行严格的质量把控。目前, 从hPSC分化为OPC通常需要漫长的诱导期, 而患者自体细胞重编程iPSC分化的OPC难以在最佳治疗窗口期进行移植, 因此采用经基因编辑改造的低免疫原性通用型hiPSC分化的现货型OPC更具有应用前景。

需要注意的是, 使用hESC进行研究时的伦理问题不能忽视[116]。相比之下, 使用iPSC或其他成体干细胞产生的细胞面临较少的伦理挑战。然而, 尽管如此捐赠者和受益者必须自愿提供知情同意, 无损于自身生命或健康, 并避免利益冲突和强制遵循特定科学立场。受益者享有平等权利, 需提供知情同意并接受伦理审查, 明确选择和分配标准, 并了解手术预期结果。捐赠者不应获得额外补偿, 决策过程应全面评估风险–利益考虑、伦理影响和技术可行性[117](表2)。

SCI的治疗是全球性的医学挑战, 而OPC疗法提供了希望。动物模型、临床前研究和临床调查已经证明了OPC移植可促进轴突髓鞘再生, 促进运动功能恢复, 并且在安全性方面表现出良好的特性, 没有明显的副作用、畸胎瘤或肿瘤形成, 也没有组织学损伤。这些发现为进一步探索OPC在治疗SCI中的治疗效果奠定了坚实的基础。但OPC的治疗效果和安全性尚需在更多的临床研究中进行验证。然而, OPC治疗也面临着一些障碍, 包括长时间的分化

表2 目前OPC疗法面临的问题与建议[73,93,98,106,110,115-118]

Table 2 Current problems and suggestions of OPC therapy [73,93,98,106,110,115-118]

面临的问题 Problems faced	建议 Suggestions
The application of cell transplantation is limited in the chronic stage	Combining cell transplantation with strategies aimed at alleviating factors that impede the efficacy of cell therapy
Considering the pluripotency of hPSCs-OPCs, including the potential risk of generating other heterogeneous cell types, there may be safety concerns such as tumorigenicity	Prior to cell transplantation, rigorous quality control measures are necessary to ensure the safety and functional status of OPCs
Cell purity issues, such as residual hPSCs or other cell types, can potentially result in immune rejection or tumor formation; implementing immunosuppression may be associated with potential risks, including compromised immune function, increased susceptibility to infections, and other related complications	New technologies need to be developed to further enhance purity and reduce the immunogenicity of hPSCs-OPCs
The exact mechanism of OPCs transplantation therapy remains unclear; the migration, engraftment, and retention mechanisms of OPCs in the CNS are not yet fully elucidated	Need to gain a deeper understanding of the mechanisms underlying the therapeutic effects of OPCs and their behavior following transplantation; Need to develop accurate methods for monitoring the dynamic development of transplanted OPCs *in vivo*
The differentiation of hPSC into OPCs is time-consuming and resource-intensive, which poses significant limitations for clinical research applications	Need to develop faster and more efficient differentiation methods, such as optimizing culture conditions and utilizing small mole-cule-based transdifferentiation techniques
Cell delivery faces challenges such as the difficulty in controlling distribution and the risk of secondary damage	One could consider directly injecting cells into the site of spinal cord injury, optimizing the injection system to enhance accuracy and stability, as well as developing innovative cell delivery technologies
Ethical issues	Both donors and recipients should provide voluntary informed consent, undergo ethical review, and ensure absence of conflicts of interest; the decision-making process should consider a comprehensive assessment of risk-benefit, ethical implications, and technical feasibility

过程、复杂的手术程序、伦理问题、移植细胞的致肿瘤潜力、免疫排斥以及移植后生物学行为不明确等。未来的研究应在兼顾伦理道德的基础上集中于深入研究OPC治疗机制, 细胞移植最佳窗口期, 移植剂量、频率和移植方案的优化以及移植细胞的安全性等问题, 同时可联合其他治疗方法, 以建立高质量的“现货型”的OPC产品并促进其在临床中的成功应用。这些努力将为SCI患者提供更有效和安全的治疗选择, 以帮助他们恢复运动功能和提高生活质量。

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