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干细胞及外泌体治疗新生儿缺氧缺血性脑病的研究进展

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摘要 新生儿缺氧缺血性脑病(hypoxic-ischemic encephalopathy, HIE)由围生期缺氧窒息和缺血引起, 是新生儿死亡和出现持久神经发育缺陷的主要原因。HIE的病理生理机制涉及分子与细胞层面多重损伤的级联反应。亚低温治疗(therapeutic hypothermia, TH)作为HIE的标准疗法, 可有效降低死亡率和严重神经发育障碍的风险。然而, TH治疗后严重神经发育障碍的发生率仍较高。近年来, 干细胞(stem cells, SCs)及其衍生的外泌体(exosomes, Exos)在HIE治疗领域展现出巨大潜力, 但其作用机制及临床治疗方案尚不明确。该文旨在综述近年来SCs及Exos在HIE治疗中的研究进展, 并探讨潜在的治疗策略, 以期为HIE患儿的临床治疗提供新思路。

关键词 干细胞; 外泌体; 新生儿缺氧缺血性脑病

Research Progress of Stem Cells and Exosomes in Neonatal Hypoxic-Ischemic Encephalopathy

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Abstract Neonatal HIE (hypoxic-ischemic encephalopathy) results from perinatal hypoxia, asphyxia, and ischemia, and is the main cause of neonatal death and persistent neurodevelopmental defects. The pathophysiological mechanisms of HIE involve multiple molecular and cellular damage processes. As the standard treatment for HIE, TH (therapeutic hypothermia) can effectively reduce mortality and the risk of severe neurodevelopmental disorders. However, the incidence of severe neurodevelopmental disorders after TH treatment is still high. In recent years, SCs (stem cells) and their derived Exos (exosomes) have shown great potential in HIE treatment research, but their mechanism of action and optimal treatment regimen still need further exploration. This article aims to review the research progress of SCs and Exos in the treatment of HIE in recent years, and explore potential therapeutic strategies, in order to provide new ideas for the clinical treatment of children with HIE.

Keywords stem cells; exosomes; neonatal hypoxic-ischemic encephalopathy

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新生儿缺氧缺血性脑病(hypoxic-ischemic encephalopathy, HIE)是一种由于胎儿或新生儿期脑部缺氧缺血(hypoxic-ischemic, HI)导致的神经系统疾病, 主要发生在围生期[1]。其主要表现为脑水肿、基底节及丘脑损伤、脑室或脑实质及蛛网膜下腔出血和脑梗死等[2]。HIE的发病率较高, 尤其在早产儿和低出生体重儿中更为常见, 全球发病率约为5‰, 20%~25%的患儿在新生儿期死亡, 幸存者中25%存在长期神经系统后遗症[3]。HIE的病理生理过程涉及氧化应激、炎症反应和神经元凋亡等多个环节[4]。亚低温治疗(therapeutic hypothermia, TH)目前是HIE标准的临床治疗手段, 但其疗效有限, 尤其在重度HIE患儿中存在副作用及治疗风险[5]。近年来, 包括氙气、促红细胞生成素、高压氧和褪黑激素等新的治疗手段取得了一定进展[6], 但脑瘫、智力受损和精神发育迟滞等多种并发症仍未得到有效解决。干细胞(stem cells, SCs)及其衍生的外泌体(exosomes, Exos)作为一种新兴的治疗手段, 在一些早产儿高发疾病, 如坏死性小肠结肠炎[7]、支气管肺发育不良[8]、视网膜病变[9]、脑室内出血[10]等疾病中取得了成功。越来越多的研究证实, SCs及Exos在HIE治疗中具有潜在的应用价值。然而, 目前其在HIE中的具体作用机制尚未被完全阐明, 治疗方案仍需进一步优化。现总结目前各类SCs及Exos在HIE治疗中的最新研究进展, 并探讨优化治疗策略, 以期为HIE的治疗提供新的思路和方向。

1 干细胞(SCs)和外泌体(Exos)

1.1 SCs的分类及生物学功能

干细胞是一类未分化的细胞, 其具有自我更新及多向分化的潜能[11]。按其来源可分为: 胚胎干细胞(embryonic stem cells, ESCs)、成体干细胞(adult stem cells, ASCs)及诱导多能干细胞(induced pluripotent stem cells, iPSCs)[12]。

目前可以投入临床研究应用的主要是ASCs中的一类: 间充质干细胞(mesenchymal stem cells, MSCs), 这种具有多种潜能的基质细胞, 因其低免疫原性和强大的免疫调节功能, 使其适用于同种异体移植。现已经被证明MSCs具有强大的抗炎和免疫抑制作用, 可增强人体的内在组织修复与愈合能力。相比较之下, ESCs较易发生免疫排斥, 而且还存在伦理难题, iPSCs则具有遗传不稳定性, 很难分析和提取用于研究[13]。SCs除了增殖及分化的功能外, 还具有抗炎、抗细胞凋亡等特性, 这些特性使得SCs在组织修复、再生医学和疾病治疗中具有重要价值[14]。

1.2 Exos的定义及生物学功能

细胞外囊泡(extracellular vesicles, EVs)是由细胞分泌的一类具有磷脂双分子层结构的纳米级颗粒, 在细胞间通讯、器官稳态以及疾病调控中发挥重要作用[15]。Exos是细胞外囊泡的重要亚型之一, 具有独特的生物学特性和功能。它是一类直径在40~160 nm(平均约100 nm)的磷脂双层囊泡, 通过质膜的连续内陷形成多囊泡体, 随后与细胞膜融合并释放到细胞外。Exos几乎可以由所有类型的细胞分泌, 内含有丰富的生物活性分子, 包括DNA、RNA、脂质、代谢物以及胞质和细胞表面蛋白等, 这些分子能够通过Exos在细胞间传递信息, 调控受体细胞的生物学功能[16]。

Exos作为细胞间通讯的重要介质, 在多种生理和病理过程中发挥关键作用, 主要包括细胞间通讯、免疫调节、组织修复与再生、疾病诊断与监测、药物递送等功能[17]。Exos相较于其母体细胞具有多重优势: 其免疫原性显著降低, 且可通过修饰进一步提升生物利用度和靶向特异性。此外, 外泌体在冷冻保存过程中能够保持活性, 同时规避了伦理争议、法律限制以及致瘤性风险[18]。这些特性使得Exos在早产儿疾病治疗领域展现出巨大的潜力, 成为极具前景的治疗候选物。

2 HIE的发生机制

HIE的发生机制涉及一系列的级联反应, 包括: 氧化应激、细胞内Ca^{2+}累积、线粒体功能障碍、细胞兴奋毒性和炎症加剧等[19]。HIE的发生根据病理进程主要分为三个阶段。

缺血缺氧发生后的前6小时。此阶段主要表现为流经胎盘的血流量减少、脑组织缺氧缺血、细胞代谢由有氧转为无氧、三磷酸腺苷(adenosine triphosphate, ATP)的产生效率显著降低。ATP生成不足, 导致Na^+/K^+-ATP酶功能障碍, 细胞膜平衡电位丧失、Ca^{2+}调节机制受损, 最终胞内Na^+、Ca^{2+}和水累积过量, 进而引发细胞水肿及凋亡[20]。

缺血缺氧后的6至72小时。此阶段, 由于细胞膜平衡电位改变, 神经元处于长时间去极化状态, 高浓度谷氨酸和其他兴奋性神经递质在细胞外释放后

累积, 导致谷氨酸受体过度刺激并引发Na^+和Ca^{2+}进入细胞, 同时胞内自由基不断释放, 导致细胞水肿及线粒体功能障碍[21]。线粒体功能障碍进一步削弱能量供应, 氧化应激逐渐启动, 活性氧和活性氮水平升高, 导致细胞凋亡[22]。

缺血缺氧后的72小时后。部分神经细胞开始启动内源性修复机制[23], 但内源性修复能力有限, 且小胶质细胞及星形胶质细胞增生, 释放大量炎性因子, 如肿瘤坏死因子-α(tumor necrosis factor α, TNF-α)、白细胞介素-1β(interleukin 1β, IL-1β)和白细胞介素6(interleukin 6, IL-6), 加剧神经炎症反应, 破坏血脑屏障完整性, 损伤神经元和轴突, 最终导致HIE的发生[24]。

3 SCs/Exos可能的治疗机制

3.1 抗炎及调节免疫微环境

HIE发生后, 小胶质细胞和星型胶质细胞激活, 释放促炎因子(如TNF-α、IL-6、IL-1β)加重脑损伤[25], SCs及Exos抑制小胶质细胞的过度激活, 减少促炎因子的释放, 同时上调抗炎因子IL-10或TGF-β的表达, 从而减轻神经炎症[26]。此外, SCs通过细胞间接触或旁分泌作用, 抑制过度激活的免疫细胞来减轻继发性神经损伤[27]。WANG等[28]研究发现Exos通过携带miR-146a、miR-132等miRNA, 抑制TLR4/NF-κB等炎症通路的活性来减轻神经元损伤。GUAN等[29]发现Exos还可调控巨噬细胞的极化, 促进抗炎性M2型巨噬细胞的形成, 进一步缓解炎症反应。

3.2 减少氧化应激与抗凋亡

SCs通过多重路径发挥抗氧化和抗凋亡作用, 从而减轻HI后继发性神经损伤。首先, 通过线粒体功能恢复减少氧化应激, SCs可通过隧道纳米管向受损神经细胞转移功能性线粒体, 这一过程不仅减少了自由基堆积, 还恢复了细胞能量代谢稳态, 为后续的细胞存活创造了有利条件[27]。继而, 通过生长因子分泌或直接抑制凋亡通路实现抗凋亡: SCs通过旁分泌作用释放多种神经营养因子[30]如脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)[31]、胶质细胞源性神经营养因子(glial cell line-derived neurotrophic factor, GDNF)[32]、血管内皮生长因子(vascular endothelial growth factor, VEGF)[33]等, 同时其还能直接抑制caspase-3等凋亡相关蛋白的表达, 防止受损神经细胞凋亡[34]。

3.3 神经保护与再生

SCs具有旁分泌作用, 不仅通过分泌营养因子支持受损神经元存活, 还可促进内源性神经干细胞(neural stem cell, NSC)分化, 修复受损组织, 或通过Exos传递生物活性分子, 如miRNA、蛋白质和脂质, 促进神经细胞增殖、分化和突触形成[16]。MARTINS等[35]发现间充质干细胞衍生的Exos中的miR-133b可激活NSC分化, 并通过调节自噬相关通路帮助修复受损神经元, Exos还可跨越血脑屏障, 直接作用于受损脑组织, 从而增强神经保护作用。

3.4 促进血管再生

Exos一方面通过传递促血管生成因子(如VEGF、FGF)和miRNA(如miR-132、miR-146a)直接作用于内皮细胞和血管前体细胞[36]; 另一方面可通过调节炎症微环境, 如极化巨噬细胞, 降低TNF-α、IL-1β等促炎细胞因子浓度, 增加IL-10、TGF-β等修复性细胞因子水平重构细胞外基质, 间接为新生血管的生成和成熟创造条件[28]。以上机制协同发挥改善HIE患者的脑血流灌注。HEODENG等[37]研究发现, 人类脂肪MSCs-Exos不仅通过激活Rho相关蛋白激酶1(Rho-associated protein kinase 1, ROCK1)、磷酸酶和张力蛋白同源物(phosphatase and tensin homolog, PTEN)抑制脂多糖诱导的炎症表达, 而且其释放的miR-132和miR-146a可上调促血管生成基因的表达, 促进人脐静脉内皮细胞的增殖活性和血管形成。

4 临床前研究进展

4.1 胎盘来源的MSCs(placenta-derived mesenchymal stem cells, PD-MSCs)

ZHAO等[3]研究证实, PD-MSCs移植增强了HIE大鼠的运动协调性, 通过修复病理损伤提高空间记忆能力(表1)。XUE等[38]进一步证实人胎盘绒毛膜板来源的MSCs移植可显著改善HIE大鼠认知和运动功能, 且下调炎性因子IL-3的表达。NOH等[39]重点研究了预处理策略对MSCs治疗潜力的影响, 发现了凝血酶预处理的人源性沃顿氏胶来源的MSCs在SD大鼠和BALB/C裸鼠中既无毒又不致瘤, 具有良好的生物安全性, 更重要的是这些细胞在大脑中存活长达7天, 具有治疗HIE的潜力。

4.2 脐带来源的MSCs(umbilical cord-derived mesenchymal stem cells, UC-MSCs)

YANG等[40]研究表明, 鼻腔移植细胞球蛋白转

表1 干细胞及外泌体治疗HIE的临床前研究进展

Table 1 Preclinical research progress on stem cell and exosomes therapy for HIE

类型 Type	来源 Origin	给药途径 Administration	处理方式 Model	研究结果 Results	参考文献 Reference
PD-MSCs	Human	Intravenous injection	*In vivo*	PD-MSCs transplantation enhanced motor coordination and muscle strength in HIE rats and improved spatial memory ability by repairing pathological damage and preventing neuronal loss in the cerebral cortex	[3]
hpcMSCs	Human	Intraventricular injection	*In vivo*	Significant improvements in cognitive and motor functions were observed. It could improve behavioral disorders in HIE rat models, and it was found that after cell transplantation, the expression of inflame-matory factor IL-3 (interleukin 3) was down-regulated	[38]
th-hWJMSCs	Human	Intraventricular injection	*In vivo*	hWJMSCs improved the neurological function of damaged brain tissue in SD rats and BALB/C nude mice by enhancing paracrine effects, reduced the area of injury, and promoted the recovery of motor and cognitive functions	[39]
cYGB-HuMScs	Human	Intranasal transplantation	*In vivo*	cYGB-HuMSCs can act as gene transporters and may play a neuroprotective and anti-apoptotic role in hypoxic-ischemic brain damage via the p38 mitogen-activated protein kinase signaling pathway	[40]
UC-MSCs	Human	Intranasal & intravenous	*In vitro, in vivo, ex vivo*	Nasal delivery of hypoxic pretreated human UC-MSCs significantly reduced brain injury volume and improved motor and cognitive function in HIE rats	[41]
hUC-MSCs	Human	Intranasal transplantation	*In vivo*	Nasal transplantation of UC-MSCs (1.5×10^6) can significantly improve the motor and cognitive abilities of HIBD mice, and achieve the best therapeutic effect	[42]
AD-MSCs	Human	Subcutaneous injection	*In vivo*	AD-MSCs treatment increased the number of striatal medium spiny neurons and reduced the number of striatal microglia without subventricular proliferation	[43]
AD-MSCs	Human	intravenous	*In vivo*	AD-MSCs were injected into HIE rats through the tail vein and the results showed that HASC-treated rats had long-term neuroprotective potential and improved neurodevelopment	[44]
MSCs with unspecified sources	Human	Intravenous injection	*In vivo*	MSCs improve sensorimotor and cognitive functions and promote neuronal growth in rats with perinatal brain injury	[45]
BDNF-eMSC	Human	Intraventricular injection	*In vi*vo	Compared with native MSCs, irradiated BDNF-eMSCs have better paracrine efficacy and improve the therapeutic efficiency of MSCs in neonatal HIE rats	[46]
Muse cell	Human	Intravenous administration	*In vivo, ex vivo*	After infusion of 36 Muse cell preparation CL2020 into neonatal HIE rats, it can target homing to the brain injury area without immunosuppressive intervention	[47]
Neuroblasts	Human	Intraventricular injection	*In vivo*	After CNBs were transplanted into the cerebral cortex of HIE mice, they differentiated into deep cortical neurons, indicating that CNBs can functionally reconstruct the cortical-subcortical neural circuits	[48]
UC-MSC-Exos	Human	Intravenous injection	*In vivo*	UC-MSC-Exos protect rats from SCI by inhibiting inflammatory response via the NF-κB/MAPK signaling pathway. By inhibiting the phosphorylation of P38, JNK, ERK, and p65 in BV2 microglia and SCI rat tissues	[49]
UC-MSC-Exos	Human	Intravenous & local intracerebral injection	*In vivo*	EV-derived microRNA prevents neuronal apoptosis and reduces brain edema and infarct volume by downregulating HDAC1 and increasing EGR2/Bcl2 expression	[50]

续表1

类型 Type	来源 Origin	给药途径 Administration	处理方式 Model	研究结果 Results	参考文献 Reference
UC-MSC-Exos	Human	Tail vein injection	*In vivo*	miR-146a-5p in UC-MSC-Exos reduces microglia-mediated neuroinflammatory response via the IRAK1/TRAF6 pathway	[51]
BMSCs-Exos	Rat	Intracerebral injection	*In vivo*	miR-653-3p inhibits the NF-κB pathway by regulating the TRIM21/p62/Nrf2/CYLD axis. By targeting TRIM21, miR-653-3p affects the ubiquitination of p62, thereby regulating the Keap1/Nrf2 pathway. Nrf2 activates CYLD to inhibit NF-κB pathway, thereby reducing inflammation and apoptosis	[52]
BMSCs-Exos	Human	Intracerebral injection	*In vivo*	hBMSCs-Exos mediate the inhibition of p38 MAPK/p65 NF-κB signaling cascade, leading to the attenuation of the transcription of inflammation-related genes	[53]
ADSC-Exos	Human	Intranasal administration	*In vivo*	Human adipose-derived mesenchymal stem cell exosomes significantly improved the cognitive function of HIBD rats, and significantly reduced apoptotic cells in the hippocampus and increased neuronal cell survival	[54]
AD-MSC	Mouse	Intranasal	*In vitro, in vivo, ex vivo*	AD-MSC-Exos delivers miR-760-3p through intranasal administration, targeting the inhibition of CHAC1 expression and improving neurobehavioral function after ischemic brain injury in mice	[55]
Astrocyte-derived exosomes	Mouse	Intraperitoneal injection	*In vivo*	Astrocyte-derived exosomes carry miR-17-5p that binds to BNIP2, and overexpression of miR-17-5p increases the viability of H19-7 cells and reduces apoptosis, oxidative stress, and inflammation	[56]
hAFEXOs	Human	Tail vein injection	*In vivo*	hAFEXOs alleviate HIBD and enhance angiogenesis in neonatal mice after hypoxia. hAFEXOs also promoted the migration and tube formation of human umbilical vein endothelial cells after oxygen-glucose deprivation *in vitro*	[57]

基因人脐带MSCs后, HIE大鼠神经损伤症状明显改善, UC-MSCs可能通过p38丝裂原激活蛋白激酶信号通路, 在缺氧缺血性脑损伤(hypoxic-ischemic brain damage, HIBD)中发挥神经保护和抗凋亡作用。SERRENHO等[41]研究证实经鼻递送低氧预处理的人UC-MSCs可显著减小HIE大鼠脑损伤体积, 改善运动和认知功能, 其通过上调HGF/VEGF/BDNF及激活PI3K/Akt通路抑制神经炎症, 同时促进髓鞘再生。

4.3 脂肪来源的MSCs(adipose-derived mesenchymal stem cells, AD-MSCs)

纹状体中的中型多棘神经元(medium-spiny neurons, MSNs)在HI后易受损, 导致运动功能障碍。BASHAM等[42]研究表明, 雄性HIE大鼠在双次注射AD-MSCs后显著增加了纹状体MSNs的绝对数量, 减少了纹状体中的小胶质细胞数量, 但对脑室下区的细胞增殖没有显著影响, 这表明AD-MSCs通过抑制神经炎症而非增加新的神经元发挥治疗作用。FEBRUARY等[43]研究证实, 尾静脉注射AD-MSCs[(0.5~1.0)×10⁶/0.1 mL生理盐水]的HIE大鼠运动耐力显著提高且受损前肢功能明显改善, 同时大脑皮质萎缩程度显著减轻, 提示该治疗具有长期神经保护和改善神经发育的潜力。

4.4 未知来源的MSCs

TERADA等[44]研究证实, 静脉输注MSCs可改善HIE大鼠的感觉运动和认知功能, 并促进神经元生长, 可能的机制为MSCs分布到受影响的脑组织中发挥抗炎和保护神经保护, 激活残留脑组织的生长并防止神经元减少, 该项研究结果与XUE等[38]一样。AHN等[45]通过新生HIBD大鼠模型评估了辐照处理的BDNF过表达工程化间充质干细胞(BDNF-eMSCs)的疗效。研究发现, 经γ射线处理的高剂量(1×10⁵/mL) BDNF-eMSCs治疗可有效抑制HIBD大鼠脑梗死的进展。UEDA等[46]研究证实, 新生HIE大鼠输注临床级多系分化持续应激耐受细胞(multilineage-differen-

tiating stress enduring cells, Muse cells)制剂CL2020后安全有效, 研究显示, HI后3天(M3组)或7天(M7组)单次静脉输注1×10⁶个CL2020/体, 无需免疫抑制干预, CL2020即可靶向归巢至脑损伤区域, 行为学评估证实两组大鼠运动功能及多动症状显著改善。

4.5 神经母细胞(neuroblasts, NB)

NB是神经系统发育过程中的前体细胞, 能够分化为神经元和胶质细胞[47]。人类胚胎干细胞来源的皮质神经母细胞(cortical neuroblast, CNB)在成人缺血性脑损伤中已显示出巨大潜力。WU等[48]将CNB以不同剂量移植至HIE小鼠脑皮层后证实其分化为深层皮层神经元且无过度生长, 这表明在损伤的未成熟大脑中, CNB可对皮质–皮质下神经回路进行功能重建。

4.6 脐带间充质来源的Exos(umbilical cord mesenchymal stem cell-derived exosomes, UC-MSC-Exos)

LUAN等[49]研究表明, UC-MSC-Exos可通过NF-κB/MAPK信号通路抑制炎症反应, 具体表现为在BV2小胶质细胞和脊髓损伤大鼠组织中, 下调p38丝裂原活化蛋白激酶、c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK)、细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)及核因子κB p65亚基磷酸化, 从而改善大鼠的运动功能。HAN等[50]进一步揭示了UC-MSC-Exos中所含有的miR-410的关键作用: 该miRNA通过下调组蛋白去乙酰化酶1(histone deacetylases 1, HDAC1), 上调早期生长反应因子2/B细胞淋巴瘤因子2(early growth response 2/B-cell lymphoma 2, EGR2/Bcl2)的表达进而抑制神经元凋亡, 减轻脑水肿并减小脑梗死的体积。ZHANG等[51]的研究不仅阐明了人UC-MSC-Exos中的miR-146a-5p通过IRAK1/TRAF6途径抑制小胶质细胞介导的神经炎症反应, 还证实UC-MSC-Exos能到达HIE小鼠缺血损伤部位, 显著抑制小胶质细胞活化并减小脑梗死体积。

4.7 骨髓间充质来源的Exos(bone marrow mesenchymal stem cell-derived exosomes, BM-MSC-Exos)

SHU等[52]研究发现, 源自BM-MSC-Exos的miR-653-3p靶向调控TRIM21/p62/Nrf2/CYLD信号轴, 抑制HIBD的神经元凋亡。具体调控过程为miR-653-3p通过靶向三重基序蛋白21(tripartite motif-containing protein 21, TRIM21)调控p62泛素化后激活Keap1/Nrf2通路, 激活的核因子E2相关因子2(nuclear factor erythroid 2-related factor 2, Nrf2)核转位, 并转录上调泛素羧基末端水解酶(cylindromatosis, CYLD)的表达, 进而抑制NF-κB信号通路, 最终显著减轻HIBD大鼠的神经功能损伤。另一项研究证实人源BM-MSCs-Exos在HIBD小鼠中抑制P38 MAPK/p65 NF-κB信号级联, 导致炎症相关基因转录水平降低, 从而对小胶质细胞发挥抗炎作用[53]。这些发现为BM-MSC-Exos在HIBD治疗中的抗凋亡与抗炎机制提供了分子依据。

4.8 脂肪间充质来源的Exos(adipose-derived stem cell exosomes, AD-MSC-Exos)

IKEDA等[54]研究表明, 鼻内施用人AD-MSC-Exos可显著改善HIBD大鼠的认知功能, 海马组织中凋亡细胞明显减少且神经元细胞存活率更高, 还发现相比其他给药途径, 鼻内给药效果最佳。WANG等[55]进一步实验表明鼻内给药的AD-MSC-Exos所携带的miR-760-3p可靶向抑制ChaC谷胱甘肽特异性γ-谷氨酰环化转移酶1(ChaC glutathione specific gamma-glutamylcyclotransferase 1, CHAC1)表达, 改善小鼠缺血性脑损伤后神经行为功能。

4.9 其他来源的Exos

DU等[56]研究证实, 星形胶质细胞衍生的Exos通过过表达miR-17-5p改善HIBD大鼠的神经行为, 抑制神经元凋亡, 减轻神经炎症反应, 并减小脑梗死的体积。LI等[57]研究表明人羊水源性外泌体(human amniotic fluid-derived exosomes, hAFEXOs)可减轻HIBD并促进缺氧后新生小鼠的血管生成, hAFEXOs还可在体外氧糖剥夺后促进人脐静脉内皮细胞的迁移和血管形成。还有研究表明, 人母乳富含外泌体miRNA, 可通过哺乳从母亲传递给婴儿, 参与多巴胺能/谷氨酸能突触和神经递质分泌的基因调节、突触小泡运输的生物过程, 可能在神经发育和正常功能中发挥重要作用[58]。

5 临床试验

5.1 同种异体UC-MSCs

在治疗重度HIE患儿的探索中, COTTON等[59]对在TH治疗基础上的6例HIE新生儿单次静脉输注同种异体UC-MSCs(2×10⁶/kg), 其中2例2个月后追加第二剂, 结果显示治疗耐受性良好, 所有患儿存活

且12~17个月随访期发育评分处于平均或低于平均水平, 未观察到严重不良事件, 提示UC-MSCs治疗在HIE患儿中具有良好的安全性与可行性(表2)。进一步的研究中, KABATAS等[60]将脐带华通胶来源间充质干细胞(Wharton's Jelly-derived mesenchymal stem cells, WJ-MSCs)分别通过鞘、肌内和静脉注射(1×10^6/kg), 每月2次, 持续2月, 用于治疗HIE患儿。经12月后随访发现WJ-MSCs植入也显著改善了患儿的神经功能, 进一步支持了间充质干细胞在HIE治疗中应用的安全性与潜在疗效。

5.2 自体脐带血细胞

SOLANA等[61]对12例胎龄≥36周的中重度HIE新生儿在TH的基础上于产后72小时内输注含有UC-MSCs的自体脐带血细胞(5×10^7核细胞/kg/剂, 注射1~4剂次, 依细胞数量调整), 结果显示, 所有患儿首次输注后均无急性不良反应, 证实该联合治疗方案安全可行。随后, TSUJI等[62]进一步验证该策略, 对6例中重度HIE患儿实施TH联合自体脐带血细胞治疗(减容分3剂, 分别于出生后12~24小时、36~48小时及60~72小时输注), 在无需生命支持的条件下30天存活率达100%, 18月龄随访中4例完成评估者均无神经功能缺损且发育正常。

5.3 Muse细胞

SATO等[63]开展单中心开放标签剂量递增研究来评估Muse细胞CL2020治疗HIE的安全耐受性, 9例接受TH的中重度HIE患儿, 于出生后5~14天接受单次静脉输注CL2020(低剂量组1.5×10^6/kg, 高剂量组1.5×10^7/kg), 结果显示, 给药后12周内无治疗相关不良事件, 证实CL2020在HIE新生儿中安全且耐受性良好。

表2 干细胞治疗HIE的临床研究进展

Table 2 Clinical research progress of stem cell therapy for HIE

类型 Type	来源 Origin	给药途径 Administration	处理方式 Model	研究结果 Results	参考文献 Reference
hCT-MSCs	Human	Intravenous injection	*In vivo*	The combined use of hCT-MSCs and TH in 6 newborns with HIE was safe and without adverse events. Low-titer anti-HLA antibodies developed in 5 of the 6 infants. Bayley-III scores at 12-17 months were within the average range, and MRI showed no evidence of hypoxic-ischemic injury	[59]
hpcMSCs	Human	Intrathecal, intramuscular & intravenous	*In vivo*	The triple infusion of allogeneic hpcMSCs in 6 HIE children was safe and controllable, with only 3 cases experiencing transient low-grade fever/headache/myalgia, which subsided within 24 hours. The neurological function was significantly improved at 12-month follow-up, and the scale, MRI, and laboratory tests all supported the efficacy	[60]
UCBC	Human	Intraventricular injection	*In vivo*	Twelve children with moderate to severe HIE completed the first dose of UCBC infusion within 24 h of birth. Three children with severe HIE died. Follow-up of the surviving children showed that 6/9 had normal early MRI, but 5/8 had abnormal EEG at 4 to 6 months of age. Four children developed epilepsy, of which 3 were relieved	[61]
UCBC	Human	Intraventricular injection	*In vivo*	Six severely asphyxiated newborns were found to be safe and feasible after three intravenous infusions of UCBC on the basis of TH, with no adverse events and no significant fluctuations in physiological indicators and blood parameters. All survived and did not require life support at 30 days of age. Follow-up at 18 months of age showed that 4 cases had normal neurological development and 2 cases had cerebral palsy with developmental delay	[62]
Muse cell	Human	Intravenous injection	*In vivo*	Nine neonates with moderate to severe HIE who received TH were infused with CL2020. There was no death or withdrawal during the 78-week follow-up. The safety was good, and only one case had a transient mild increase in γ-GTP and recovered spontaneously. At 78 weeks, 67% of patients had a KSPD developmental quotient ⩾ 85, MRI scores improved, and 100% of children in the high-dose group had normal motor function	[63]

根据美国临床试验注册库(ClinicalTrials.gov)的数据显示，目前全球范围内仅有一项关于Exos治疗的临床试验，注册号为NCT05490173。该试验由俄罗斯团队开展，研究对象为极低出生体重早产儿(25~27周)，旨在通过鼻腔注射Exos进行早期安全性和临床有效性评估，目前处于招募阶段。然而，该研究对象与足月HIE患者群体存在差异。除该研究外，目前尚无关于Exos用于HIE治疗的临床试验开展。

6 提高SCs治疗效率的方法

6.1 SCs来源选择

妊娠组织(如脐带组织、脐带血、胎盘)来源的MSCs，因其独特的优势在再生医学领域备受关注。这些组织通常在出生后被丢弃，其获取过程不仅简便易行，且避免了伦理争议，因而成为了理想的细胞来源[64]。与AD-MSCs或BM-MSCs相比，妊娠组织来源的MSCs表现出更低的免疫原性，这为其在临床治疗中的应用提供了显著优势[20]。此外，妊娠组织来源的MSCs还具有更强的增殖能力和多向分化潜能，这进一步增强了其在组织修复和再生中的潜力[65]。

6.2 MSCs预处理

研究表明，通过体外预处理(如缺氧环境、脂多糖刺激、生长因子诱导或药理/化学试剂处理)可显著增强MSCs的旁分泌活性及其治疗效能。不同预处理方案会显著影响MSCs分泌蛋白组的组成和功能特性，从而产生多样化的旁分泌效应[66]。凝血酶预处理能够更有效地促进Exos的生物合成，并显著富集其分泌蛋白组的活性成分，从而在加速伤口愈合方面表现出更优异的治疗效果，这一发现为优化MSCs预处理策略提供了重要依据[39]。

6.3 确定给药的最佳途径

MSCs可以通过多种方式输注，包括静脉、脑内、腹腔和鼻内。然而，每种方法都有其局限性。静脉给药受限于肺等器官的拦截，导致到达脑部的MSCs数量有限。脑内给药虽然直接且高效，但HIE患儿的脑损伤不稳定，风险较大。腹腔给药操作简单，但效率较低。鼻内给药则无创、快速，可能成为最佳途径[67]。IKEDA等[54]研究表明，鼻内递送MSCs时Exos可快速穿过血脑屏障，1小时内富集于脑损伤区域，显著改善大鼠模型的长期认知功能。鼻内给药的优点在于非侵入性、脑靶向性强且避免全身副作用，但其递送效率受鼻腔环境影响，长期疗效和安全性仍需进一步验证。

7 Exos临床应用的挑战

Exos疗法向临床转化的过程中，尽管在预临床研究中显示具有抗炎、神经保护及促进组织再生等多方面的显著潜力，但仍面临诸多挑战：首先，对Exos治疗HIE的机制认识尚不完善，其次安全性评估仍需进一步强化，最后需要构建高效、可控的工程化制备平台。

Exos通过携带miRNA、蛋白质及脂质等生物活性物质介导细胞间通讯，以达到抗炎、抗凋亡和促进神经再生的目的，但其具体作用靶点和信号通路尚未完全系统阐明。此外，动物实验中常用的Exos剂量与人类新生儿的可耐受窗口差异较大，体内外环境差异使得机制研究难以直接外推。

在目前绝大多数Exos临床试验中，安全性评估仍以成人为主，新生儿群体的安全性数据匮乏。临床前研究虽提示Exos低免疫原性，但新生儿免疫系统发育未成熟，可能对外源Exos产生不同程度的免疫反应或细胞毒性[68]。迄今为止，尚无报道临床试验测试过Exos作为新生儿HIE疗法的安全性，对于这一脆弱的患者群体，需在I期试验中设计严格的安全监测及神经发育量表的综合评价体系。

大规模、可重复的Exos生产是临床转化的根本瓶颈。当前的超速离心、密度梯度和亲和层析等方法产量低、纯度参差不齐，难以满足药品生产管理规范要求[69]。WANG等[70]指出，需要开发高通量一致性平台，并建立关键质量属性和关键工艺参数，以保障各批次之间生物活性和安全性一致性。在此基础上，生物反应器培养与微流控分离等新兴技术有望提升其产能，但其标准化及成本效益仍待评估。同时，在不破坏膜结构的前提下高效装载诊疗分子并实现可控释放，也是Exos工程亟待解决的核心问题[71]。

8 结语与展望

本文综述了近年来SCs和Exos在HIE治疗中的研究进展，临床前研究及临床试验均表明，SCs和Exos通过多种机制，在安全可行的基础上显著改善了HIE的神经功能并延缓了疾病进展。然而，目前仍缺乏对其具体作用机制的深入理解，以及最佳治疗方案的确定。为使这种有潜力的研究方式早日投入

到临床使用中, 未来的研究应着重于以下几个方面。一是对机制研究: 要进一步深入探讨具体的治疗机制, 特别是其在调节炎症反应、促进神经再生和血管生成方面等详细的分子机制。这将为开发更有效的治疗策略提供理论依据。二要优化治疗的方案: 明确最佳的SCs来源、最佳的途径等, 以提高治疗效果。三要探索联合治疗策略, 如结合TH或其他药物治疗, 这可能会进一步改善HIE的预后。四要积极跨学科合作: 结合基因编辑、纳米技术等新兴技术, 优化SCs和Exos的治疗效果。例如, 通过基因修饰增强SCs的分泌功能, 或利用纳米材料提高Exos的靶向递送效率等。最后要在上述几个方面的基础上扩大临床试验的规模和范围, 以验证SCs和Exos在HIE治疗中的疗效和安全性。特别需要关注长期随访结果, 以评估其对患儿神经发育的远期影响。总之, 尽管SCs和Exos在HIE治疗中展现出巨大的潜力, 但仍需进一步的研究来克服现有挑战。随着研究的深入和技术创新, 相信这一领域将为HIE患儿带来更为有效的治疗方案, 也为HIE患儿的预后带来曙光。

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