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人脐带间充质干细胞治疗不同疾病的研究进展

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【摘要】 间充质干细胞(mesenchymal stem cells,MSCs)是一类起源于早期中胚层,并且能够自我更新和具有多向分化潜能的成体干细胞。大量的研究证明,MSCs 在再生医学领域中具有巨大潜力,未来可被用于治疗多种类型疾病,如脊髓损伤、肝损伤、肾损伤及自身免疫性疾病等。MSCs 一般来源于胎盘、脂肪、牙髓、骨髓以及脐带和胎儿内脏等器官组织。其中,脐带作为在母体和胎儿之间运输营养物质的纽带,同样含有大量的间充质干细胞。并且相较于易受供体的年龄因素影响的骨髓间充质干细胞和易受到医学伦理限制的胎儿来源的间充质干细胞而言,增殖效率高、供体广泛、病毒感染率低的脐带间充质干细胞(human umbilical cord mesenchymal stem cells,hUCMSCs)可能是临床应用时的更好的选择,这些优势也使得 hUCMSCs 在再生医学领域备受关注。本文重点对 hUCMSCs 目前与疾病治疗相关的研究进展作一综述。

【关键词】 脐带间充质干细胞;干细胞移植;组织修复
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Research progress of human umbilical cord mesenchymal stem cells for treatment of various diseases

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【Abstract】 Mesenchymal stem cells (MSCs) are a type of adult stem cell that originates in the early mesoderm, which are capable of self-renewal and multi-directional differentiation. A large number of studies have shown that MSCs have great potential in the field of regenerative medicine. MSCs can be used to treat many types of diseases such as spinal cord injury, liver damage, kidney damage and autoimmune diseases. They are generally derived from placenta, fat, dental pulp, bone marrow, umbilical cord, and fetal internal organs as well as other organs and tissues. Among them, the umbilical cord as a link between the mother and fetus to transport nutrients contains a large number of MSCs. Compared with bone marrow mesenchymal stem cells that are affected by the donor's age and fetal mesenchymal stem cells that have ethical issues, umbilical cord mesenchymal stem cells (hUCMSCs) have a high proliferation efficiency and wide range of donor sources, and low virus infection rate. Therefore, hUCMSCs are considered to be a better choice for treatment of virous diseases. These advantages also make hUCMSCs attractive in the field of regenerative medicine. This article focuses on the current research progress of hUCMSCs related to disease treatment.

【Keywords】 umbilical cord mesenchymal stem cells; stem cell transplantation; tissue repair

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间充质干细胞(mesenchymal stem cells,MSCs)最早起源于早期中胚层,能够自我更新并具有多向分化的潜能,可从成体骨髓、牙髓、脂肪组织、脐带等组织中分离[1-2]。由于 MSCs 具有免疫调节的作用,因此 MSCs 在损伤组织修复和自身免疫性疾病的细胞治疗领域备受青睐[3-4]。其中,来源于脐带的间充质干细胞(human umbilical cord mesenchymal stem cells,hUCMSCs)因具有多能性、低致瘤性、低免疫原性、增殖率高和获取方便等特点[5-6],成为了同种异体环境中细胞移植的重要适用细胞来源,其亦可能成为干细胞治疗的优先选择。

1 hUCMSCs 的来源及生物学特征

脐带由三部分构成:脐血管,羊膜被覆上皮以及华通氏胶(Wharton's Jelly)[7]。根据脐带的组成结构,人脐带间充质干细胞(human umbilical cord mesenchymal stem cells,hUCMSCs)的来源大致可以分为 4 种:(1)从人脐带华通胶中得到的间充质干细胞(human Wharton's Jelly mesenchymal stem cells,hWJMSCs),(2)来源于人脐带血的间充质干细胞(human umbilical cord mesenchymal stem cells,hUCMSCs),(3)来自人脐带血管周围组织的间充质干细胞(human umbilical cord perivascular mesenchymal stem cells,hUCPV-MSCs),(4)从羊膜中获得的间充质干细胞(mesenchymal stem cells derived from human umbilical cord amnion,hAMSCs)。

hWJMSCs 高表达白细胞分化抗原(cluster differentiation,CD),如 CD29、CD90、CD44、CD105 等,低表达人白细胞 DR 抗原(human leukocyte antigen-DR,HLA-DR),且极少表达 CD45 抗原,因此其免疫原性较低,可用于损伤组织修复和治疗自身免疫缺陷病[8-9];脐带血来源的 hUCMSCs 高表达 MSCs 相关抗原如 CD73、CD90、CDl05 和黏附分子 CD44,不表达造血细胞标志 CD11b、CD14、CD19、HLA-DR[10-11];脐带血管周围的 hUCPV-MSCs 高表达 CD105、CD73、CD90 及 CD44,不表达 CD34、CD235a、VCAM1、IL-3、及 OCT4,由于 hUCPV-MSCs)存在细胞含量少及增殖传代能力较弱的特性[12-13],无法在临床和科学研究中广泛应用,因此相关研究较少;羊膜来源的 hAMSCs 高表达 CD73、CD90、CD105,可诱导分化为成脂和成骨细胞,同时,hAMSCs 具有促血管生成、组织修复及免疫调节功能[14-15]。目前临床研究及应用得最多的是 hWJMSCs 和 hUCMSCs,统称为 hUCMSCs。

2 hUCMSCs 治疗不同疾病的研究进展

2.1 hUCMSCs 治疗肝损伤

hUCMSCs 可减少 $CD8^+T$ 细胞数量,进而减少干扰素-γ 和肿瘤坏死因子的产生;同时可以抑制肝内已经活化的巨噬细胞向抗炎型 M2 细胞转化,并阻止肝内的炎症级联反应[16-17]。2016 年 Bi 等[17]证实,移植进小鼠内的 hUCMSCs 可以通过降低 miR-199 的表达来降低角质细胞生长因子的生成,进而阻止肝星状细胞的活化和聚集,从而起到降低门静脉压力、减少肝纤维化和修复肝损伤的作用。近期在 Shao 等[18]的研究中确定了 hUCMSCs 受到 IL-6 刺激后,会分泌可能靶向作用于 PI3K 信号通路的富含 miR-455-3p 的外泌体。这种外泌体在体内和体外均可抑制脂多糖(LPS)诱导的巨噬细胞活化和细胞因子的产生,并且在化学性肝损伤小鼠模型中,miR-455-3p 的表达增强可以减弱巨噬细胞浸润和局部肝损伤,并降低血清中的炎性因子水平,从而改善肝功能。另外,在 Li 等[19]的研究中,hUCMSCs 已显示出对糖尿病和肝病(如肝硬化和暴发性肝衰竭)的治疗潜力,在临床研究中进行 hUCMSCs 输注可显着改善高糖血症,并降低血液中甘油三酸酯,总胆固醇和低密度脂蛋白胆固醇含量,从而为 2 型糖尿病(T2DM)患者中的非酒精性脂肪肝疾病(NAFLD)患者带来治疗的希望。

2.2 hUCMSCs 治疗肾损伤

急性肾损伤(acute kidney injury,AKI)是临床中常见的肾相关疾病,急性肾损伤后若无法得到及时有效的治疗,肾功能将快速恶化,甚至导致功能性肾衰竭[20]。Andrade 等[21]报道称,体外培养的 hUCMSCs 移植可有效改善急性肾损伤。其作用机制可能是 hUCMSCs 体内定向分化成肾小管上皮细胞,替代已经受损或坏死的肾组织细胞,并改善肾受损程度和减轻受损部位的炎症反应。此外有几项研究都表明 hUCMSCs 可作用于雄性大鼠 AKI 模型并改善其肾受损情况。其作用机制可能是:(1)hUCMSCs 降低趋化因子 CX3CL1 的表达从而减少受损部位炎性细胞的大量激活及浸润,减轻炎症反应,最终抑制肾组织细胞的变异、增生及纤维化;(2)hUCMSCs 分泌的外泌体可通过下调低氧诱导因子-1 的表达而抑制细胞凋亡,同时上调表达血管内皮生长因子,促进血管生成并修复肾损伤组

织[22-23]。除此之外,hUCMSCs 可与胰岛素样生长因子-1(insulin-like growth factors 1,IGF-1)嵌合成 hUCMSCs-IGF-1 复合体,该复合体移植入大鼠 AKI 模型后,可移动至肾受损处同时黏附于血管壁上,促进血管内皮细胞大量增殖;同时 hUCMSCs-IGF-1 复合体可通过激活 PI3K/蛋白激酶 B(protein kinase B,Akt)信号通路从而减少 AKI 模型鼠肾组织中的细胞损伤,增强其抗炎能力,继而缓解肾损伤[24]。因此可以认为,hUCMSCs 的移植将是 AKI 有效的前瞻性治疗方法。

2.3 hUCMSCs 治疗皮肤损伤

hUCMSCs 近年来由于其具有多能性、低免疫原性和可重建皮肤组织结构等特点而被认为是皮肤损伤的潜在治疗来源。hUCMSCs 移植到皮肤损伤部位后,一方面可通过定向分化成表皮样细胞,促进皮肤角质上皮再生及血管生成,使受损皮肤逐渐愈合;另一方面 hUCMSCs 可通过调节 Wnt4 信号通路,促进 β-连环蛋白核转运,增强表皮细胞的增殖能力,并通过激活 Akt 信号通路来抑制表皮细胞凋亡使损伤皮肤修复[24]。在 Montanucci 等[25]研究中,将 hUCMSCs 置于纤维蛋白双层膜上后进行移植,可以加快受损皮肤的上皮再生。此外,Mejía-Barradas 等[26]发现皮脂切除术后产生继发性慢性溃疡的患者在接受了 hUCMSCs 的皮肤治疗后发现 hUCMSCs 可诱导瘢痕形成和新血管形成,同时可减少产生白细胞和促炎因子,继而发挥其促进皮肤愈合的作用。因此 hUCMSCs 也被提出可作为治疗术后皮肤病变的一种新的方法。

2.4 hUCMSCs 治疗脊髓损伤

急性脊髓损伤(acute spinal cord injury,ASCI)是一类由于高爆发暴力引起的椎体移位或骨折残片侵入人体内椎管,导致脊髓受到严重机械性损伤的疾病,ASCI 的预后通常较差[27]。而 hUCMSCs 易于获得和免疫原性低的特点使它成为治疗脊髓损伤这类疾病的热门选项。2018 年,张陆等[28]通过对比 hUCMSCs 移植前后 ASCI 患者的功能指标后发现,hUCMSCs 可以明显改善 ASCI 患者的神经功能损伤,并且促进其恢复的同时不影响机体本身的免疫功能。另外,人神经干细胞(human neural stem cells,hNSCs)也是在脊髓损伤模型中可用于细胞治疗的移植材料[29]。先前的研究表明,MSCs 可以调节 NSCs 的细胞微环境并提高移植后 NSCs 的存活率,并且与其他干细胞相比,MSCs 移植后相关的肿瘤发生率明显更低[30]。2019 年 Sun 等[31]研究表明,与单独移植 hUCMSCs 和单独移植 hNSC 相比,髓内联合移植 hUCMSCs 与 hNSCs 后治疗效果明显更好。因此虽尚未清楚其作用机制,但可以认为 hUCMSCs 是未来用于临床治疗急性脊髓损伤的一个很有潜力的治疗工具。

2.5 hUCMSCs 治疗 cGVHD

慢性移植物抗宿主病(chronic graft-versus-host diaease,cGVHD)是移植手术后最常见的并发症之一,一般发生在移植 100 d 左右,是手术后患者非疾病复发致死的主要原因[32-33]。而 hUCMSCs 独特的免疫调节能力使其在 cGVHD 相关研究中备受关注。近期张玲等[34]研究报道称,接受 hUCMSCs 治疗后 cGVHD 患者外周血中原本高表达 $CD19^+$的细胞数量有逐渐降低的趋势,并且未观察到和 hUCMSCs 移植相关的不良反应,患者也没有复发原发病以及产生间充质干细胞相关的肿瘤。这意味着 hUCMSCs 用于治疗难治性慢性移植物抗宿主病是有效并且安全的。另外还有实验表明,尽管与对照组小鼠相比,所有类型的间充质干细胞移植后小鼠均具有统计学上显著的存活延长,但仅在接受 hBMMSCs 和 hUCMSCs 的小鼠中观察到了显著的组织病理学改善。即其他类型的 MSCs 在体内的抗炎作用不如 hUCMSCs 和 hBMMSCs[35]。因而可以预见,在未来关于治疗移植物抗宿主病的研究中,hUCMSCs 将成为一个热门选项。

2.6 hUCMSCs 治疗卵巢早衰

作为异质性疾病,40 岁以下的女性中,有 1%~3%的女性患有卵巢早衰(premature ovarian failure,POF),其病理特征包括卵巢功能紊乱、雌激素水平降低和性腺激素水平升高,但目前临床还没有非常有效的治疗手段[36-37]。越来越多的证据表明,hUCMSCs 的移植是治疗 POF 的潜在疗法。研究表明,hUCMSCs 可以上调血红素加氧酶-1(HO-1)的表达,而 HO-1 在卵巢的生理功能和垂体腺分泌促性腺激素功能中具有关键作用[38-39]。但是在 hUCMSCs 治疗 POF 小鼠的相关研究中关于 HO-1 的作用和机制的了解还很少。最近,Yin 等[39]发现在 hUCMSCs 中表达的 HO-1 基因可通过激活 JNK/Bcl-2 信号通路和上调 $CD8^+$ CD28-T 细胞的表达来实现 hUCMSCs 移植后恢复 POF 小鼠的卵巢功能。这些发现为随后的临床上基于 hUCMSCs 的人类治疗提供了新的目标。

2.7 hUCMSCs 治疗帕金森和阿尔茨海默症

MSCs 可用于治疗神经退行性疾病引起了临床研究领域极大的关注,因为大部分神经退行性疾病都极其影响患者的生活质量,并且暂时没有其他有效的药物治疗手段[40-41]。Lo 等[42]研究表明,通过颈动脉移植 hUCMSCs 能够明显使帕金森(Parkinson's disease, PD)患者的 UPDRS 评分和 Webster 评分升高。hUCMSCs 治疗神经退行性疾病的作用机制尚不明确,目前提出的可能有:hUCMSCs 能够分化成促使神经再生及修复的神经元;hUCMSCs 旁分泌作用产生的细胞因子可以缓解黑质纹状体的损伤,并抑制 PD 患者多巴胺神经元的凋亡[43-44]。此外也有报道提出,hUCMSCs 可以使外周神经损伤后的轴突再生,并且可以到达神经起到修复再生的作用[45-46]。

阿尔茨海默症(Alzheimer's disease, AD)的病理特征目前主要认为是由 β-淀粉样蛋白聚集体引起的,但尚不清楚这些蛋白质聚集体与临床症状之间的致病机制[47-48]。hUCMSCs 分泌的神经营养因子也许可以改善这种复杂的细胞环境并抑制神经细胞凋亡[49],同时 hUCMSCs 可能通过逆转大脑中的小胶质细胞神经炎症而产生持续的神经保护作用[50]。此外 Oh 等[51]研究证实,hUCMSCs 可以减少 β-淀粉样前体蛋白转基因小鼠大脑中的淀粉样沉积。因此虽然 PD 和 AD 这两种神经退行性疾病的致病机制尚不完全清楚,但 hUCMSCs 已经给我们带来了治愈神经退行性疾病新的希望。

2.8 hUCMSCs 治疗阻塞性肺疾病

在美国,死于慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)的人数仅次于癌症和心血管疾病[52]。根据世界卫生组织(WHO)的估计,全世界目前有 6500 万人患有中度至重度 COPD[53]。目前用于治疗 COPD 的药物包括支气管扩张药、吸入类固醇、口服类固醇、磷酸二酯酶 4 抑制剂、茶碱和抗生素。临床上还使用肺疗法治疗 COPD,例如氧气疗法;此外还有进行减少肺体积的手术,以及肺移植来治疗 COPD。然而,这些疗法疗效有限且存在严重不良反应[54-55]。Le 等[56]研究发现 hUCMSCs 的移植显着改善了 COPD 患者的生活质量和临床状况,并且结果表明 hUCMSCs 的全身给药相对安全,这可能是由于 hUCMSCs 具有较强的免疫调节能力。尽管这是一项初步研究,但这些结果为进一步对 COPD 患者进行 hUCMSCs 的临床研究提供了重要的参考。

3 小结与展望

从人脐带分离的 hUCMSCs 是目前再生医学领域备受瞩目的研究热点,与其他来源的 MSCs 相比,它们具有较高的增殖能力、较快的自我更新能力、较低的免疫原性以及更可靠的获得方式。虽然目前对 MSCs 的功能机制的研究还不够深入,但其治疗的有效性和安全性已在科学研究、临床前和临床试验中得到了初步的验证。然而,细胞的移植剂量、递送途径、移植时间窗的选择、注射速率和移植频率等技术问题依然是临床试验中函待解决的问题,尤其由于 hUCMSCs 移植存在血管栓塞、hUCMSCs 传代过程中遗传物质改变及潜在致瘤致畸等风险极大等问题限制了其目前的发展。此外 hUCMSCs 供体的隐性健康问题亦存在很大隐患。因此研究人员不仅需要在移植前进行供体细胞的基因检测和规范细胞处理流程,而且还需要长期随访监控受体患者的健康状况。这使 hUCMSCs 的大规模临床应用面临更多的挑战,并且未来还需要做大量的工作才能充分揭开 hUCMSCs 的面纱。但随着细胞规模化培养、高通量测序等技术的发展以及临床试验研究体量的增加,相信不久的将来,hUCMSCs 将在转化医学领域带给我们更多惊喜。

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