·综述·

阿尔茨海默病细胞移植方式研究进展

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【摘要】 阿尔茨海默病是一种神经退行性病变,主要表现为记忆力下降和认知功能受损。传统的药物治疗效果欠佳,细胞治疗是治疗阿尔茨海默病的新途径。目前针对阿尔茨海默病研究多侧重于工具细胞治疗阿尔茨海默病机制和工具细胞筛选。现主要对针对工具细胞移植方式进行总结综述。

【关键词】 阿尔茨海默病; 细胞治疗; 移植方式; 综述

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【Abstract】 Alzheimer disease is a kind of neurodegenerative disorder characterized by memory loss and cognitive impairment. Due to the inefficiency of traditional drug therapy, cell therapy is a new way to treat Alzheimer disease. In view of the fact that current research on Alzheimer disease mainly focuses on the mechanism of tool cell therapy for Alzheimer disease and tool cell screening, there is little summary of transplantation methods. In this paper, the methods of tool cell transplantation are summarized.

【Key words】 Alzheimer disease; Cell therapy; Transplantation method; Review

阿尔茨海默病(Alzheimer disease, AD),又称老年痴呆,是一种神经系统退行性疾病。预计至2050年,全球AD患者的总人数将达到1.32亿[1]。AD的典型特征为进行性记忆力减退和认知功能障碍[2]。在特定的大脑区域(如颞叶、海马体、杏仁核)AD患者多变现为白质变性和髓鞘缺失,而海马区证实为重要的学习和记忆功能区[3-4]。AD传统治疗以药物为主,辅助认知训练。药物治疗主要从神经细胞代谢、脑微循环、氧化应激、调节神经递质代谢等方面入手,但现有的AD药物仅可缓解症状,并不能阻断疾病进展[2]。

目前全球在Clinictrial网站上共有21项已注册的干细胞治疗AD的临床研究[5]。国内干细胞备案项目中浙江医院正在进行宫血干细胞治疗轻度AD的安全性和初步有效性的临床研究[6]。各种类型的细胞治疗中,常见工具细胞有神经干细胞(neural stem cell, NSC)[7-8]、间充质干细胞(Mesenchymal stem cell, MSC)[9-10]、胚胎干细胞(embryonic stem cells, ESC)[11]和诱导性多能干细胞(induced pluripotent stem cells, iPSC)[12]。

AD患者植入细胞后,通过以下途径发挥作用:细胞衍生的神经元,修补残缺神经网络[13];提高乙酰胆碱的水平,改善动物模型的认知水平和记忆力[14];分泌脑源性神经营养因子调节神经细胞重塑和神经纤维再生[15];减少促炎因子的释放,抑制炎症[16];植入的细胞还可以消除AD脑中的淀粉变性斑块[5]。临床前研究的十年经验表明,细胞疗法是一种针对AD有前途的方法[17]。

目前针对AD临床前研究和临床研究较多,且多侧重于工具细胞治疗AD的机制和工具细胞筛选,而对移植方式总结较少。通过有效的移植方式,可以更大地发挥工具细胞的治疗效果,降低工具细胞不良反应发生,现对细胞移植途径进行相关综述。

一、静脉输注

通过静脉途径,将细胞注入外周静脉循环,后进入肺部循环,再泵入动脉系统,细胞直接通过脑

血屏障进入中枢[18]，或由旁分泌作用大量各类因子作用于中枢神经，发挥治疗作用。Harach等[19]将细胞经鼠尾静脉移植AD鼠后1 h，在脑实质(即海马体)中可检测到标记的细胞。Salem等[20]利用骨髓间充质细胞处理的AD模型小鼠的脑组织中sry基因表达，证实了静脉内注入的外源干细胞在脑损伤部位的归巢聚集能力。在另一项研究中，对1月龄AD小鼠静脉内注射1×10^6个脐带间充质干细胞，28 d后进行了淀粉样蛋白(pE3-Aβ)斑块数量和pE3-Aβ斑块大小的组织学分析，观察到AD鼠皮层的小胶质细胞数量和大小明显减少。王永才等[21]对2例AD患者，采用立体定向局部脑内特定核团移植干细胞+腰穿蛛网膜下腔移植干细胞+静脉移植干细胞的方式，初步证明了静脉输注细胞治疗AD患者的安全性。

二、腰穿鞘内注射

通过腰穿的方式，将细胞注入蛛网膜下腔，细胞随着脑脊液循环，进入中枢神经系统，发挥作用。王永才等[21]研究中，老年性痴呆、遗传性共济失调患者采用腰穿蛛网膜下腔移植干细胞的方式。每次给予干细胞量按$(2\sim3)\times10^2$个/kg计算，每周给予1次自体骨髓干细胞移植，共4周。老年痴呆患者其老年痴呆症状得到明显改善，并能在搀扶下行走，与旁人进行正常的交流。杨华强等[22]通过腰穿鞘内注射方式移植脐带血间充质干细胞治疗10例神经系统退行性变患者，症状得到不同程度改善，同时也初步证明了腰穿鞘内注射方式移植细胞的安全性。AD研究中的腰穿一般是安全的，患者耐受性良好[23]。

三、鼻内途径植入

将细胞通过鼻内途径植入颅内的方法作为一种新兴的移植手段越来越受到关注。细胞滴入鼻腔后可以通过以下3个途径进入中枢神经系统[24-25]：(1)通过嗅球途径；(2)通过呼吸道黏膜上皮细胞途径；(3)鼻部具有丰富的脉管系统，同时植入细胞发挥旁分泌作用，可以分泌大量各种类型因子，如神经生长因子、血管内皮生长因子、肝样细胞因子、肿瘤坏死因子等，因子可以通过鼻腔黏膜直接进入颅内，或进入脉管系统，从而进入外周循环，对中枢神经和周围神经功能起到调节的作用[11]。鼻内途径植入细胞的途径已经用于缺血缺氧脑病、帕金森病、多发硬化、脑干损伤、肌萎缩侧索硬化等疾病[26-28]的研究。对于AD患者，鼻内给药证实是提高AD患者脑内药物浓度最有希望的给药途径[26]。Danielyan等[29]通过鼻内途径将骨髓来源的间充质干细胞输送到AD小鼠的皮质、杏仁核、纹状体、海马、小脑和脑干中，认知功能和记忆力得到改善。

四、头部立体定向注射

头部立体定向注射是指脑内注射或脑室内注射细胞。细胞的脑内移植可以穿过血脑屏障，并且可以到达大脑深部病变部位。AD的主要病变部位在海马和颞叶深部[3-4]，定向种植细胞在这些病变部位，可避免细胞的浪费，在病变部位聚集高浓度的工具细胞，更好地发挥细胞替代和旁分泌作用。最初研究是通过脑室内灌注细胞，对小鼠神经元细胞死亡和记忆损伤起到抑制作用，从而改善记忆[30]。进一步试验将神经生长因子通过脑部立体定向注射在10例AD患者Meynert的核基底核，验证了安全性和初步有效性[31]。另一项临床研究，脐带血间充质细胞头部立体定向注射治疗AD的Ⅰ期试验已经完成，试验中共治疗9例患者，在海马和颞叶深部(丘脑)进行定向移植，每侧海马组织选择2～3个靶点，每个靶点细胞量控制在$(2.5\sim5)\times10^5$个，证明AD患者脑内注射具有一定的安全性[32]。然而，与静脉途径相比，脑内定向注射属于将干细胞植入特定大脑区域的有创植入性方法[33]，所以在选择头部立体定向治疗AD患者时，要根据患者病情、心肺功能、术后不良反应的预判等谨慎选择。

总之，细胞治疗为AD的治疗提供了一个崭新思路。每种移植途径都有其优缺点，对于AD患者要根据病情选择。王永才等[21]治疗AD患者的报道中，多采用几种移植途径相结合的方式移植细胞，如静脉输注+腰穿鞘内注射或腰穿鞘内注射+头部立体定向+静脉输注等。要合理选择工具细胞，并控制细胞剂量，避免不良反应的出现。根据细胞在脑内存活时间和对AD病理的影响[32]，还可以选择重复注射细胞。对于AD细胞治疗机制的研究、AD患者治疗前评估、微创有效移植方式甄别、不良反应的防止，还需要进一步积累和研究。

利益冲突 文章所有作者共同认可文章无相关利益冲突

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