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文献综述 REVIEW

间充质干细胞联合胰岛细胞治疗1型糖尿病研究进展

朱从元, 李建平

■背景资料
胰岛移植治疗1型糖尿病, 因炎症介导的免疫反应以及营养因子缺乏导致胰岛细胞存活低下, 而间充质性干细胞与胰岛细胞联合治疗1型糖尿病, 能发挥免疫调控和营养活性功能促进胰岛细胞活性与功能.

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Cotransplantation of mesenchymal stem cells and islet in the treatment of type 1 diabetes mellitus: recent progress

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Abstract
Islet transplantation for type 1 diabetes mellitus (T1DM) is limited by the lack of nutrients and presence of transplantation-associated inflammation. Most patients still need to be given a small dose of exogenous insulin in the following 3-5 years after islet transplantation. Cotransplantation of mesenchymal stem cells (MSCs) and islet holds great promise for the treatment of T1DM, because it can regulate the immune responses and overcome the shortage of trophic molecules. However, cotransplantation-associated tumorigenesis and the potential for metastasis *in vivo* should be also taken into consideration. In this review, we focus on the immunomodulatory properties, trophic effect and the potential side effects of cotransplantation of MSC and islet in the treatment of T1DM.

Key words: Islet transplantation; Mesenchymal stem cells; Type 1 diabetes mellitus

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摘要
近年来, 国内外兴起的胰岛移植术治疗1型糖尿病, 因炎症介导的免疫反应以及营养因子缺乏而导致移植后3-5年内仍需注射小剂量的胰岛素, 而间充质干细胞与胰岛细胞联合, 不仅具有免疫调节作用还能分泌营养因子促进胰岛细胞活性和功能, 但其在体内的致瘤性以及促进肿瘤细胞转移这些潜在不良反应会一定程度影响其临床应用. 本文就间充质干细胞与胰岛细胞联合治疗1型糖尿病的免疫调节与营养活性作用及潜在不良反应方面进行简要综述.

关键词: 胰岛移植; 间充质干细胞; 1型糖尿病

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0 引言
1型糖尿病(type 1 diabetes mellitus, T1DM)是一种T细胞介导的, 以胰岛β细胞破坏为特征的自身免疫性疾病, 其主要原因是由于先天性免疫缺陷而导致自身免疫耐受尚失[1]. 目前T1DM已成为一个全球性难题, 全世界至少有1 300万人罹患此病, 而外源性胰岛素注射不能达到时时控制血糖水平稳定的目的, 最终导致心、脑、眼、肾以及末梢神经系统微血管并发症, 给患者带来极大痛苦[2]. 近年来兴起的胰岛移植术, 虽然手术风险小, 移植成功后可暂时脱离外源性胰岛素, 且能时时控制血糖[3], 但因移植初期炎症介导的免疫反应以及营养因子缺乏, 导致胰岛细胞存活率低下[4], 使得移植后3-5年内仍需注射小剂量的胰岛素[5]. 而间充质干细胞(mesenchymal stem cells, MSC)与胰岛细胞在体外共培养或体内联合移植, 能分泌多种因子发挥

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■研发前沿
目前对于间充质干细胞的免疫调控和营养活性方面作用已越来越受到重视和研究.

免疫调控和营养活化功能, 促进胰岛细胞活性和功能[6,7], 因而成为治疗T1DM的研究热点. 尽管MSC在体内外特定条件下能诱导出胰岛样细胞[8,9], 且MSC单独移植进链脲佐菌素诱导的T1DM模型小鼠体内能发挥降血糖作用[10], 但其作用机制及是否由诱导的胰岛样细胞发挥作用尚存在争议[2], 另外对于MSC与胰岛细胞联合移植治疗T1DM, MSC诱导的胰岛样细胞其功能尚不能令人满意[11]. 因此, 本文仅就MSC免疫调控及营养活化作用及潜在的不良反应方面进行简要综述.

1 MSC免疫调控作用

T1DM是一种T细胞介导的自身免疫性疾病, 通过β细胞自身抗原产生和激活自身反应性CD4+和CD8+ T细胞, 激活的T细胞侵入胰腺组织, 选择性破坏胰岛β细胞[1,12]. 而体内外研究表明, MSC能通过分泌抗炎因子或减少炎性细胞因子释放来抑制T细胞增殖达到免疫抑制作用[13], 另外还能通过调控调节性T细胞(regulatory T cells, Tregs)来发挥免疫调控作用[14].

1.1 抑制自身反应性T细胞增殖 在T1DM发生过程中, β细胞自身抗原通过激活T细胞, 破坏胰岛β细胞最终导致T1DM的发生[12], MSC能通多种方式来抑制T细胞的活化与增殖, 如细胞-细胞直接接触, 通过释放可溶性因子或免疫抑制因子来直接或间接调控T细胞相关受体或配体, 达到抑制T细胞的活化与增殖[13,15-19]. Augello等[15]研究表明, MSC可通过活化的T细胞分泌的IFN-γ正性调节MSC分泌的抗炎因子程序性死亡配体-1(programmed death 1, PD-L1), 从而达到抑制T细胞增殖目的. PD-L1是由MSC在炎性条件下分泌的抗炎因子, 可调控自身免疫和耐受, 而非炎性环境下, MSC检测不到PD-L1[16]. Nauta等[17]研究认为MSC还能通过促进IL-10分泌和抑制炎症因子IL-12和IFN-α的产生, 来促进DC的分化进而达到抑制功能效应性T细胞功能的作用. 另外MSC还可以通过分泌基质金属蛋白酶-2(matrix metalloproteinase-2, MMP-2)和金属蛋白酶-9(matrix metalloproteinase-9, MMP-9)来抑制T细胞的增殖[13]. MMP通过裂解T细胞胞外白介素-2受体α(IL-2 receptor α, IL-2Rα), 从而减少IL-2的生成, 达到抑制T细胞活化的功能[18]. 但对于MSC释放可溶性细胞因子如转化生长因子-β(transforming growth factor-β, TGF-β)等来抑制T细胞增殖尚存争议, Di Nicola等[19]研究表明中和MSC释放的TGF-β可恢复T细胞增殖活性, 然而Le Blanc等[20]认为中和TGF-β无此功效. 这种差异可能是由于MSC所处的微环境不同引起[18], 其作用机制尚需进一步研究论证.

1.2 调控Tregs活性 Tregs是T细胞的一种特殊亚群, 在维持内环境稳定和自我耐受发挥着重要作用, 其通过表达转录因子FOXP3[21]以及抑制自身反应性T细胞[22]来降低免疫反应, 从而达到调控自身免疫性疾病的目的. 在糖尿病患者和NOD小鼠动物模型研究表明, 不管是数量还是功能异常的Tregs都与T1DM的发生、发展密切相关[23]. Madec等[24]体外研究表明, MSC能通过分泌IL-10诱导产生Tregs, 阻止激活的T细胞对胰岛β细胞的损伤, 减少糖尿病的发生. Zhao等[14]在NOD小鼠动物模型中研究发现, MSC能通过修正功能缺陷的Tregs发挥免疫调控作用, 且这种调控是持续的. Ge等[25]研究认为, MSC能通过分泌吲哚胺2, 3-双加氧酶(indoleamine 2, 3-dioxygenase, IDO)来达促Tregs生成. IDO是一种与调控T细胞反应与免疫耐受密切相关的酶, 能促进Tregs产生, 另外对胰岛细胞移植存活有重要意义, 但其具体作用机制尚未完全弄清楚. 而体内研究中, Haller等[1]将15例T1DM患儿注入富含Tregs的自体脐血, 结果14例患儿能1 mo内能完全脱离外源性胰岛素, 也说明Tregs的免疫调控作用. Di等[26]通过外周血与MSC培养, 发现MSC通过下调能抑制FOXP3表的CD127分子的表达, 从而达到促进FOXP3表达, 进而达到免疫抑制功能.

2 MSC营养活化功能

胰岛细胞移植后凋亡除了炎症介导的免疫反应外, 另外一个很重要的原因就是营养因子的缺乏[7]. 生理状况下, 胰岛细胞由致密的毛细血管网所包绕, 尽管这些毛细血管网只占整个胰腺组织的1%-2%, 但血流量却占到5%-10%[27,28]. 足够的血流量对维持胰岛细胞功能有着极为重要的作用, 而胰岛细胞分离是去血管的, 移植后新生血管网再生要14 d[29], 使得这段时间成为早期胰岛细胞成活的关键. 在与胰岛细胞共培养/联合移植, MSC能分泌多种营养因子, 如: VEGF-A、肝细胞生长因子(hepatocyte growth factor, HGF)等[7]来促进胰岛细胞活性与功能, 从而提高胰岛细胞移植后存活率. TGF-β与IL-6也被认为是MSC分泌的营养因子[7], 但TGF-β主要是通过诱导FOXP3发挥免疫调控作用[30], 而IL-6

■创新盘点
本文重点介绍间充质干细胞与胰岛细胞联合治疗1型糖尿病免疫调控和营养活化方面的作用.

也是一种炎性调节因子, 主要发挥免疫调控作用[31], 故未列入营养因子范畴.

2.1 VEGF-A VEGF-A作为一种与新生血管生长相关的重要因子, 在胰岛新生血管形成过程中通过与VEGF受体-1结合而发挥着重要的作用[32,33]. 不管是在体外与胰岛细胞共培养还是体内联合移植实验研究, MSC都能分泌VEGF-A因子, 促进胰岛细胞活性和功能的作用[34,35]. Jung等[34]将胰岛细胞与骨髓来源MSC(bone marrow derived mesenchymal stem cells, BM-MSC)体外共培养与胰岛细胞单独培养比较, 结果显示共培养组VEGF-A水平更高, 而Sakata等[35]在体内将胰岛细胞与骨髓细胞联合移植, 也表明MSC能分泌VEGF-A有效促进胰岛细胞活性与功能, 从而提高胰岛细胞移植后存活率. Rackhamt等[36]不仅从功能学方面阐释MSC联合移植效果相比其他非联合移植组效果更好, 更从形态学角度说明MSC更能维持和促进胰岛细胞移植后新生血管形态. MSC与胰岛细胞联合, 能有效促进胰岛血管内皮细胞集聚, 这点与生理状态下胰岛细胞血管形态相似, 而胰岛细胞单独移植, 血管内皮细胞则散在分布. Figliuzzi等[37]则通过RT-PCR技术, 从基因表达水平证实出MSC与胰岛细胞联合移植高表达血管生成因子$VEGF_{165}$. 但Wu等[38]通过腺病毒介导的HGF转染MSC与胰岛细胞联合移植, 仅检测到少量VEGF-A, 并认为此含量不足以促血管生成. 因而对于携带HGF基因的腺病毒载体是否影响MSC促VEGF-A生成, 尚待进一步研究.

2.2 HGF HGF是MSC分泌的另一种促进胰岛细胞生长的重要因子. HGF最初从成熟肝细胞中分离纯化而来, 能促进多种细胞生长, 如: 肝细胞、肾小管细胞、软骨细胞、成骨细胞等[39]. 对于胰岛β细胞, 体外研究表明, HGF在体外能有效促进胎儿和成人β细胞分裂[40], 而体内研究显示, HGF通过上调葡萄糖转运分子-2、葡糖激酶、胰岛素基因的表达, 从而达到促进β细胞活性和功能的目的[41]. 另外体内外研究还证实, HGF可作保留胰岛细胞生理性葡萄糖应答反应的刺激增殖物[37], 从而达到促进β细胞活性的效果. Park等[42]通过体外MSC与胰岛细胞共培养, 证实MSC能分泌HGF, 促进胰岛活性与功能. Berman等[43]将MSC与胰岛细胞联合移植进灵长类动物体内, 也观察到HGF表达明显优于其他非联合移植组. 另外HGF也能促进胰岛血管重建功能[38,44].

3 不良反应和潜在的风险

虽然MSC与胰岛细胞联合, 具有上述多种单纯移植无可比拟的优势, 但也同样存在不良反应和潜在的风险. 研究表明, MSC对体内外肿瘤细胞发挥着不同的作用[45-47], 在体内MSC可导致肿瘤发生[45], 同时可促进肿瘤细胞转移[46], 其原因可能是由于MSC有潜在分化能力而宿主机体免疫力相对低下[48], 另外也与其促进肿瘤细胞血管生成作用有关[49], 而体外MSC可使肿瘤细胞停留在G_1期从而抑制其生长[47]. 由于体内的致瘤性及可促进肿瘤细胞转移, 使得MSC的临床应用蒙上一层阴影, 若能进一步研究体内MSC作用的异同点, 从中找到突破口, 进行预防和干预或许能有效避免或降低其导致肿瘤发生的机率. 另外因MSC的潜在分化能力, 其在特定条件下能能诱导分化为分化为骨、软骨、脂肪组织[50], 若与胰岛细胞联合应用于临床, 其是否会诱导出上述细胞以及对机体产生何种影响尚未可知, 还有MSC对全身和局部免疫系统的影响也需考虑[51], 因此应用于临床前, 应对MSC进行严格筛选和监测, 确保其安全性和有效性.

4 结论

尽管MSC联合胰岛细胞治疗T1DM, 在免疫方面和营养活性方面显现出良好的作用, 但尚处于动物实验研究阶段, 其作用机制仍需进一步证实和完善. 另外若要应用于临床, 还需注意其潜在的不良反应, 进一步研究如何避免其致瘤作用及促进肿瘤细胞转移等方面, 在保证安全有效的前提下, 才能被临床所接受. 总之, MSC联合胰岛细胞为治疗T1DM提供了一个新方向, 也显示出良好的应用前景, 若要应用于临床, 尚待时日.

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■应用要点
若能解决诸如致瘤及促进肿瘤细胞转移等不良反应, 间充质干细胞联合治疗1型糖尿病有良好的应用前景.

■同行评价
本文在选题上较新, 间充质干细胞技术联合治疗糖尿病是近年来较新较热的一个基础研究方向, 并有较强的临床应用价值及前景.

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• 消息 •

《世界华人消化杂志》入选《中国学术期刊评价研究报告 – RCCSE权威、核心期刊排行榜与指南》

本刊讯 《中国学术期刊评价研究报告-RCCSE权威、核心期刊排行榜与指南》由中国科学评价研究中心、武汉大学图书馆和信息管理学院联合研发, 采用定量评价和定性分析相结合的方法, 对我国万种期刊大致浏览、反复比较和分析研究, 得出了65个学术期刊排行榜, 其中《世界华人消化杂志》位居396种临床医学类期刊第45位. (编辑部主任: 李军亮 2010-01-08)