·综　　述·

间充质干细胞联合他汀类药物在糖尿病视网膜病变中的应用研究进展

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【摘要】 糖尿病视网膜病变（DR）是糖尿病患者常见的眼部并发症，也是成人盲的主要原因之一。DR 现有的治疗方法包括手术和激光治疗等不能从根本上治疗 DR。近年研究发现应用间充质干细胞（MSCs）对 DR 进行细胞治疗具有广泛的应用前景。MSCs 具有再生潜能并在视网膜的修复中起作用，但移植后 MSCs 的生存能力及归巢能力差，降低了其治疗效率。他汀类药物除具有调脂作用外，还能促进 MSCs 的增生并抑制 MSCs 凋亡。本文就 MSCs 联合他汀类药物在 DR 治疗中的应用及机制进行综述。

【关键词】 糖尿病视网膜病变/治疗；间充质干细胞；他汀类药物；细胞治疗；移植

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Application researches of mesenchymal stem cells combined with statins in diabetic retinopathy　*Wu Bin, Chen Song*

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[**Abstract**] Diabetic retinopathy (DR) is a common complication of eye in diabetics and is one of the major causes of blindness in adults. The current treatments of DR include surgery and laser therapy, but this does not fundamentally cure DR. Recent studies have found that mesenchymal stem cells (MSCs) for cell therapy to DR have a wide range of applications. MSCs have regenerative potential and play a role in the repairment of the retina, but the survival and homing ability of MSCs are poor after transplantation, which reduces the therapeutic efficiency of MSCs. Statins have a variety of beneficial effects independent of lipid regulation, which can promote the proliferation of MSCs and inhibit the apoptosis of MSCs. This paper reviewed the application and mechanism of MSCs combined with statins in the treatment of DR.

[**Key words**] Diabetic retinopathy/therapy; Mesenchymal stem cells; Statins; Cell therapy; Transplantation

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糖尿病视网膜病变（diabetic retinopathy，DR）是糖尿病导致的视网膜微血管病变，高血糖诱导神经胶质细胞、视网膜神经元、内皮细胞产生病理改变及血-视网膜屏障（blood retinal barrier，BRB）受损，造成视网膜的缺血、缺氧，引起视网膜新生血管生成，导致玻璃体大量出血，出现不可逆性盲[1]。现今大多数的治疗方法是建立在抑制或破坏新生血管的基础上的[2]，但其效果不甚理想。间充质干细胞（mesenchymal stem cells，MSCs）具有多向分化潜能、低免疫原性和免疫赦免等特性[3-4]，被广泛应用于多种疾病的预防和治疗。近年来，MSCs 移植治疗 DR 表现出良好的应用前景[5]，但其存在体内存活率低、分化效率低、归巢能力差的缺点[6-8]。近年来研究发现，他汀类药物与 MSCs 的联合应用可以增强治疗效果。现将 MSCs 联合他汀类药物治疗 DR 的进展进行综述。

1　MSCs 治疗 DR 的研究

高血糖是 DR 的主要致病机制，MSCs 能够在体外分化为成熟的胰岛样细胞簇及胰岛素分泌细胞，MSCs 来源的胰岛素分泌细胞移植糖尿病模型鼠肝脏后，血内胰岛素水平显著提高，血糖水平显著下降[9-10]。MSCs 通过全身静脉滴注对 2 型糖尿患者进行移植后，可增加患者自身胰岛素的分泌，减少体外胰岛素的使用。MSCs 能够分化成胰岛细胞并分泌胰岛素；

MSCs 定植至胰腺可以分化为血管内皮细胞，改善胰腺组织血液供应，恢复胰岛细胞功能；MSCs 还可以分泌大量的细胞因子，如胰岛素样生长因子（insulin-like growth factor，IFG）、血管内皮生长因子（vascular endothelial growth factor，VEGF）和肝细胞生长因子（hepatocyte growth factor，HGF），这些细胞因子可能在胰腺组织修复中发挥作用[11-12]。这些已知 MSCs 的潜在作用充分说明了其可以多向、高效地治疗糖尿病，从而改善 DR。

MSCs 具有抑制细胞凋亡和炎症反应的作用，促进了治疗细胞的定位和归巢，刺激内源性细胞的分化和增生[5,13]。链脲佐菌素诱导的糖尿病大鼠经尾静脉注射 MSCs，不仅可以降低其血糖水平，MSCs 还可以归巢于受损的视网膜并分化为光感受器细胞、神经胶质细胞，修复受损的 BRB，以改善 DR[2]。MSCs 感知周围的信号，并适当回应，以满足组织的需求；例如，MSCs 在视网膜缺氧状态下产生具有神经保护作用的分子，通过旁分泌作用使周围的细胞在不佳的条件下生存。另有研究表明，链脲佐菌素诱导的糖尿病大鼠玻璃体腔移植人类 MSCs 对其 DR 有防治作用，此作用由 MSCs 产生的神经生长因子介导，如玻璃体腔内的碱性成纤维细胞生长因子、神经生长因子、脑源性神经营养因子、睫状神经营养因子和胶质源性神经营养因子[14]。

随着 DR 的进展，高血糖导致视网膜毛细血管周细胞丧失、血小板聚集、白细胞激活和黏附，使其血流量减少，基底膜增厚。研究发现血小板衍生生长因子（platelet-derived growth factor，PDGF）在周细胞的聚集上发挥了本质作用，MSCs 可以增加许多营养因子，包括 PDGF，而 PDGF 间接通过周细胞和内皮细胞间的相互作用使内皮细胞存活[15-16]，可以推测 MSCs 通过旁分泌的效应保护周细胞和内皮细胞。也有证据表明，MSCs 产生的 HGF、IFG、VEGF 可以激活磷脂酰肌醇 3 激酶/蛋白激酶（phosphatidylinositol 3 kinase/protein kinase，PI3K/Akt）通路[17]，PI3K 是内皮细胞存活和周细胞迁移和增生的关键[18-19]，而 PI3K/Akt 通路是促进细胞增生和抑制细胞凋亡的主要信号通路之一[20]。周细胞和内皮细胞大量死亡，促进视网膜血管闭塞，导致视网膜缺氧。缺氧可诱导缺氧诱导因子 1 及其下游分子 VEGF 的表达升高[21-23]。VEGF 水平的增加导致增生性 DR 恶化，发病机制为血管通透性的增加、BRB 的破坏和血管的再生[24-26]。我们推测，MSCs 经过提高存活率和归巢力的处理后可以消除 VEGF，对预防和管理增生性 DR 是有价值的。

预防增生性 DR 的策略是治疗 DR 的主要工作。MSCs 疗法有降低 DR 致病因素的潜力。然而 MSCs 疗法所遇到的困难，包括移植后 MSCs 的生存能力差，归巢性差，更重要的是，缺氧条件下诱导产生强大的 VEGF，促进新生血管生成和增生性 DR 的进展[26]。研究表明，VEGF 在 DR 的血管损伤中起核心作用，阻断 VEGF 被认为是作为治疗 DR 的有效方法[27]。我们假设，对于增生性 DR，联合 MSCs 和药物制剂，以增加移植后 MSCs 的存活力和归巢性，防止缺氧条件下 VEGF 的产生，将增加 MSCs 的疗效。

2　他汀类药物促进 MSCs 存活和归巢的研究

他汀类药物，即羟甲基戊二酰辅酶 A 还原酶抑制剂，是目前临床应用广泛的降脂药物，且具有抗凋亡、保护内皮功能及抗炎、抗氧化、促进新生血管生成等作用[28-29]。一氧化氮与细胞凋亡的关系十分密切，除抗凋亡外，其尚具有扩张血管、保护内皮、抑制血小板黏附等多重维持心血管稳态的作用，是体内重要的信号分子之一[30]。他汀类药物可有效提高内皮型一氧化氮合酶（endothelial nitric oxide synthase，eNOS）活性，而 eNOS 恰是内源性一氧化氮生成的主要来源，该作用在他汀类药物的多效性作用机制中占据核心地位[31-32]。Nakanishi 等[33]研究显示，通过腺苷酸活化 Akt、eNOS 途径，阿托伐他汀能够保护 MSCs，使其免受缺氧及脱离血清的损伤。也有证据表明阿托伐他汀在体内、体外均能够通过多种机制促进 MSCs 的存活[34-35]。新近的研究发现阿托伐他汀也与Ⅱ型细胞程序性死亡-自噬密切相关，在去血清等应激情况下，他汀类药物能够诱导保护性自噬以抑制或延缓细胞凋亡[36-39]。近年已有体外实验证实，他汀类药物对在恶劣条件下的 MSCs 有保护作用，抗细胞凋亡是其中重要的作用机制之一。Rv 等[40]和 Nübel 等[41]发现洛伐他汀可抑制紫外线和低浓度电离辐射诱导的 MSCs 凋亡，中国 Xu 等[42]也发现洛伐他汀可抑制低氧和去血清诱导的 MSCs 凋亡。

另有研究表明，高糖、高脂模拟的糖尿病内环境可能促进 MSCs 的凋亡[43]，降低移植后干细胞的存活率。高糖、高脂主要通过合成 N-脂酰鞘氨醇[10]，激活线粒体释放细胞色素 C[44]，凋亡蛋白 Bad、Bid、Bax 过表达等机制诱导细胞凋亡[45-46]，他汀类药物可以促进 MSCs 的增生[47]，增强其黏附力，通过抑制肿瘤坏死因子 α 来减少其凋亡[48]，辛伐他汀可以提高高糖、高脂环境下 MSCs 细胞的存活率，减少其凋亡[49]。近来研究表明，PI3K/Akt 通路可能介导他汀类药物对内皮祖细胞的作用[50-51]。Dimmeler 等[50]通过对内皮祖细胞的研究证实，辛伐他汀可通过激活 Akt 系统促进其增生和分化。Xu 等[42]亦发现洛伐他汀可通过 P13K/Akt 和丝裂素活化蛋白激酶/外信号调节激酶通路发挥抗细胞凋亡作用。

细胞治疗的另一个难点是有效的归巢性和靶向稳定性。基质细胞衍生因子-1（stromal cell-derived factor-1，SDF-1）及其同族受体趋化因子受体 4（chemokine receptor-4，CXCR4）组成的 SDF-1/CXCR4 信号通路是细胞归巢的重要机制，在此机制下，局部损伤组织积累趋化因子，导致 MSCs 呈梯度依赖性向此趋化。其中 CXCR4 是 SDF-1 的配体，CXCR4 是 MSCs 表面表达的一种受体，使细胞能感觉到组织的损伤。据报道，SDF-1/CXCR4 信号通路在 MSCs 的归巢、趋化，黏附分子的表达和植入中发挥重要作用[52]。CXCR4 已被确定为人 $CD34^+$ 细胞一个新的一氧化氮调节基因。在缺氧条件下，阿托伐他汀可以使腺苷磷酸（adenosine monophosphate，AMP）蛋白激酶磷酸化水平显著升高，诱导 eNOS 上调，一氧化氮的合成增加，这可能导致 CXCR4 的表达增加，促进归巢[53-54]。

3　小结

总之，干细胞移植为现阶段 DR 治疗的热点，但是面临移植后 MSCs 生存能力差、归巢性差、缺氧条件下产生强大 VEGF 的缺点。他汀类药物联合 MSCs 可以增加移植后 MSCs 的存活力，促进其归巢和抑制 VEGF 的过度产生，为 MSCs 治疗 DR 提供了新的思路。

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