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干细胞在治疗糖尿病的应用和进展

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摘　要

糖尿病是一种多因素疾病，影响全世界越来越多的患者。糖尿病分为1型和2型。2型糖尿病(T2DM)是一种代谢功能紊乱疾病，其特征是胰岛敏感性受损，胰岛素分泌相对不足；1型糖尿病(T1DM)是年轻患者中最常见的自身免疫性疾病，其特征是胰腺β细胞的功能损坏，胰岛素分泌绝对不足，身体变得高血糖。外源性给药不能模拟健康胰腺分泌的内源性胰岛素。同种异体胰岛移植已成为长期重建患者血糖正常调节的疗方法。但是这存在很多问题，供体严重不足、移植细胞体内无法长期存活、移植后需长期服用免疫抑制剂。干细胞诱导分化成β细胞成为可解决上述问题的有效方法之一，用于1型糖尿病的治疗。然而，要想干细胞在临床上治疗糖尿病，在这之前仍需要解决许多未解决的问题。在这里，我们讨论了从不同前体细胞中得到胰岛素生成细胞(IPCs)的方式以及干细胞的糖尿病疗法的当前研究进展和面临的问题和挑战。

关键词

糖尿病，干细胞，胰岛β细胞，细胞治疗，内分泌细胞

Application and Progress of Stem Cells in the Treatment of Diabetes

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Abstract

Diabetes is a multifactorial disease affecting an increasing number of patients worldwide. Diabetes is divided into type 1 and type 2. Type 2 diabetes mellitus (T2DM) is a metabolic disorder

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characterized by impaired islet sensitivity and relatively insufficient insulin secretion. Type 1 diabetes mellitus (T1DM), the most common autoimmune disease in young patients, is characterized by functional impairment of beta cells in the pancreas, absolute deficiency of insulin secretion, and the body becoming hyperglycemic. Exogenous administration does not mimic endogenous insulin produced by a healthy pancreas. Islet allotransplantation has become a therapy for long-term reconstruction of normal glycemic regulation in patients. However, there are many problems, such as the serious shortage of donors, the inability of the transplanted cells to survive *in vivo* for a long time, and the need to take immunosuppressants for a long time after transplantation. The induction differentiation of stem cells into β cells is one of the effective methods to solve the above problems and is used in the treatment of type 1 diabetes. However, there are still many unanswered questions that need to be addressed before stem cells can be used to treat diabetes in the clinic. Here, we discuss the ways in which insulin-producing cells (IPCs) can be derived from different precursor cells, as well as the current research progress and problems and challenges facing stem cell therapies for diabetes.

Keywords

Diabetes Mellitus, Stem Cell, Pancreatic Beta Cells, Cell Therapy, Endocrine Cell

1. 引言

糖尿病(DM)是一个全球性的健康问题，影响着全世界 4 亿多人，而且发病率还在上升[1] [2]。糖尿病分为 1 型糖尿病(T1DM)和 2 型糖尿病(T2DM)，常见的 T2DM 是一种代谢功能紊乱疾病，其特征是胰岛敏感性受损，胰岛素分泌相对不足；而 T1DM 是胰岛 β 细胞自身免疫破坏所致，表现为胰岛素绝对不足，需要立即进行胰岛素替代[3] [4] [5]。糖尿病会引起一系列的综合征，如引心血管疾病、失明、酮症酸中毒或高渗性非酮症昏迷(HHNC)、肾衰竭和代谢性紊乱等等[6] [7]。

目前，还没有根治糖尿病的方法，现需要找到一种有效治疗糖尿病的方法，以避免糖尿病及其并发症引起死亡[8]。一般而言，胰岛素类似物可以用于糖尿病的治疗，但其治疗效果有限且有一定的副作用。胰岛移植是一种很有前途的长期治疗糖尿病的方法[9] [10]。从 1966 年进行了第一次胰腺移植以来，到 2015 年全世界超过五万名患者接受了胰腺移植(国际胰腺移植登记中心) [11] [12]。Shapiro 等人报道 1 型糖尿病患者在输注足够的胰岛细胞团块后获得了持续的胰岛素独立。而且，在患者中观察到血糖控制和糖化血红蛋白水平的纠正[13]。在过去的十年多里，随着技术不断改进提高了胰岛移植的存活率，一半左右的 T1DM 患者在胰岛移植五年后实现了胰岛素独立供给[14] [15] [16]。

然而，通过移植治疗糖尿病仍有许多困难。供体严重不足、移植细胞体内长期存活困难、移植后需长期服用免疫抑制剂。如要解决这些问题，应寻找合适的种子细胞来代替人体胰岛，以供移植[17] [18] [19]。

干细胞诱导分化成 β 细胞，在一定程度上可解决供体不足和免疫排斥等问题，用以治疗糖尿病。自从人类多能干细胞有望用于再生医学以来，已经对体外干细胞分化成胰岛素生成细胞(IPCs)有了深入研究。体外产生胰岛细胞的来源主要包括胚胎干细胞(ESCs)和诱导多能干细胞(iPSCs))和成体干细胞。当前生成 IPCs 的策略主要基于模拟正常胰腺发育的方法，在过去的十年多中，已经成功设计了许多诱导方法在体外生成 IPCs [20] [21] [22] [23]。

在这篇综述中，我们讨论了不同来源干细胞诱导分化成胰岛素生成细胞及其治疗。本综述还关注了干细胞治疗的封装技术、临床应用、治疗过程中面临的安全伦理和其他问题和挑战。

2. 不同来源干细胞分化成胰岛素生成细胞

2.1. 胚胎干细胞

胚胎干细胞具有巨大的分化潜能，可以产生大量的细胞系，ESCs 包括所有胚层的细胞，且有很多优势如：没有病原体、可以进行不同目的转基因、体外给予合适的生存环境可以分化成不同谱系的细胞。[24] [25]。这些干细胞在 20 世纪末和 21 世纪初首次被用于研究。起初阶段，研究人员主要集中在哺乳动物和鸟类的胚胎上[26]。Thomson 等人于 1995 年首次分离出人类胚胎干细胞(ESCs) [27]。在随后的研究中胚胎干细胞显示出无限增殖能力和自我更新的特点，能够在体外分化成多种类型的成体细胞[28]。

因此，ESCs 体外诱导分化成胰岛素分泌细胞治疗糖尿病是一个很有前途的。在过去的二十年中，已经报道了许多从 ESCs 生成 IPCs 的方法[29] [30] [31] [32] [33]。通常，从 ESCs 产生功能性 IPCs 的方案是基于模拟胚胎胰腺的体内发育。胚胎胰腺发育的关键阶段包括定形内胚层(DE)、原始肠管(PGT)、胰腺祖细胞(PP)、内分泌祖细胞(EP)和表达激素的内分泌细胞的发育。通过在每个阶段添加不同的细胞因子和信号调节剂来激活或抑制参与生成的特定信号通路，诱导分化成 β 细胞[29] [34]。第一个逐步方案来生产能够从 ESCs 合成和释放多种激素的内分泌激素表达细胞，但是分化成的细胞对糖刺激无法做出反应[29]。

众所周知，胎儿胰腺也具有这些特征，以往的研究表明，胎儿人胰腺组织移植到动物体内后，可以正常发育，形成有功能的细胞[32] [35] [36]。

优化的方案生成了胰腺内胚层细胞，然后将它们移植到免疫缺陷小鼠中，胰腺内胚层细胞在体内成功分化并成熟为 β 样细胞，能响应禁食诱导的低血糖和葡萄糖挑战，并维持正常的葡萄糖稳态长达 3 个月[37]。测序技术的发展极大助力干细胞到 β 细胞分化过程的探究，分析鉴定发现分化过程产生不同细胞群，包括 SC-β 细胞、α 细胞、非内分泌细胞和干细胞衍生的肠嗜铬(SC-EC)细胞[38]。

虽然，上述研究已经证实 ESCs 具有分化为 IPCs 的潜力，但由于方案的低分化效率和这些分化产生 β 样细胞的不确定性，这种分化只能谨慎进行。

2.2. 人类诱导多能干细胞

与 ESCs 研究的同时，诱导多能干细胞(iPSCs)的研究越来越多地进入了这一领域。iPSCs 由体细胞重编程，与 ESCs 一样具有类似的增殖和分化能力[39]。iPSCs 源自成年人体细胞，相对于胚胎干细胞中的伦理问题争议更少[40] [41]。从 iPSCs 产生 IPCs 是基于对参与胰腺发育的特定信号通路的深入探究和连续调节。皮肤成纤维细胞衍生的 iPSCs 能够通过模拟胰腺的体内发育在体外产生胰岛样团簇，但其功能并不成熟[42]。但一些体外分化为胰腺 β 细胞的方案已经取得了令人鼓舞的结果[43] [44] [45]。

患者来源的 iPSCs 已被证明在体外研究疾病的发病机制和病理生理学方面具有巨大优势，hiPSCs 可以来源于健康受试者，也可以来源于糖尿病患者。因此，从糖尿病患者身上产生 iPSCs 的研究引起了极大的兴趣。患者特异性 iPSCs 可以克服目前干细胞治疗中的障碍，如免疫排斥，并为建立个性化的疾病模型以研究疾病的发病机制和寻找治疗方法提供平台[46] [47] [48] [49]。

随着进二十年的研究，iPSCs 衍生 β 细胞的方案有了很大的改进，如在胰腺祖细胞期加入基于的 ROCK 抑制剂，对胰岛素表达和分泌的有益影响[50] [51]。通过最后阶段让细胞重新聚类，结果强劲的动态胰岛素分泌，通过驱动线粒体氧化呼吸实现代谢成熟[52] [53]。通过在最后阶段允许 WNT4 信号，结果代谢成熟与强大的胰岛素分泌和高线粒体氧化呼吸[54]。

同样，iPSCs 诱导分化成 IPCs 和 ESCs 诱导分化成 IPCs 存在相同的问题，分化效率低和分化的 β 样

细胞存在不确定性。人类多能干细胞分化而来的β细胞还有很长的路要走。

2.3. 成体干细胞

2.3.1. 间充质干细胞

间充质干细胞(MSC)是非造血多能祖细胞，存在于骨髓中。德国病理学家首次推荐骨髓中存在非造血干细胞，他观察到一类具有成纤维细胞样形态的多能祖细胞，呈纺锤形，塑料粘附，非吞噬，这些细胞也称为多能基质细胞或间充质细胞[55] [56] [57] [58]。自我更新潜力和多能性是MSC的标志。在体外和体内，这些细胞能够分化为多种细胞谱系，如脂肪细胞、软骨细胞、骨细胞、肌腱细胞、成纤维细胞、心肌细胞、骨骼肌细胞、神经肝细胞和基质细胞[59] [60] [61]。

MSC具有发育可塑性以采用胰腺内分泌表型。这被认为是MSC可用于治疗糖尿病的主要机制。研究表明，来自各种组织和器官的MSC能够分化为胰岛样细胞或功能性IPCs。第一个表达胰岛素和巢蛋白的不完全分化的IPCs是通过在具有高葡萄糖、烟酰胺和β巯基乙醇浓度的培养基中培养大鼠骨髓MSC(BM-MSC)获得的[62] [63]。瓦顿氏凝胶间叶干细胞衍生MSC (WJ-MSC)更容易获得和培养，此外它们对成熟胰腺β细胞的分化潜力更高。与BM-MSC相比，分化的WJ-MSC中胰腺和十二指肠同源框1 (Pdx-1)、胰岛素分泌和C肽mRNA表达的更高，表达也表明WJ-MSC诱导的IPCs具有优异的胰岛素分泌特性[64]。

除了再生内源性胰岛β细胞外，MSC还通过分泌各种细胞因子和生长因子来帮助再生内源性胰岛β细胞[65] [66]。MSC还能够通过免疫调节保护这些细胞。这种免疫调节被认为是MSC发挥其抗糖尿病作用的主要机制——通过免疫调节，MSC可以防止T1DM中产生胰岛素的胰腺β细胞的自身免疫性破坏[67]。MSC的免疫调节特性包括以下能力：1) 抑制T细胞对有丝分裂和抗原刺激的反应，2) 抑制树突细胞分化和(3)以剂量依赖性方式抑制B细胞增殖[68] [69] [70]。因此，人们认为MSC的免疫调节特性对于在接受MSC治疗的T1DM和T2DM患者中观察到的恢复作用至关重要[71]。

1) 成人胰腺干细胞

成人胰腺由两个独特的部分组成：外分泌胰腺和内分泌胰腺，分别具有独特的形态和功能。胰腺起源于沿着后前肠背侧和腹侧的两个独立的原基[72] [73]。然而，如果在成年动物和人类胰腺中存在可检测到的胰腺干细胞，这些细胞如何参与β细胞的再生仍存在争议。该假设最初得到了成年啮齿动物胰管结扎(PDL)后新生发生的组织学观察的支持[74]。然而，成年人的生活中或损伤后出现了内分泌再生没有贡献[75] [76]。总之，成人胰腺干细胞是否存在于成年尚不清楚。单细胞RNA测序的最新事件有望用于绘制成年生命期间或动物和人类胰腺损伤后的动态基因表达变化，构建胰腺/胰岛细胞的分化轨迹，并阐明β细胞再生所涉及的机制。

2) 胰管源性干细胞

从理论上讲，胰管上皮细胞具有产生β细胞的潜力，因为两者都源自相同的胚胎前体[77] [78]。成人胰腺再生过程中会出现β细胞或从导管上皮产生的新胰岛的出芽，并且已有报道[79] [80]。胰腺导管上皮可以在体外基于基质胶的3D培养系统中扩张并进一步分化为功能性胰岛组织[81]。研究表明，CK19+非内分泌胰腺上皮细胞可以在体外分化为β细胞[82]。

2.3.2. 来自胰岛的巢蛋白阳性间充质干细胞

巢蛋白是一种中间丝蛋白，在神经元和肌肉前体细胞中特异性表达[83] [84]。最近的研究表明巢蛋白阳性细胞存在于胰岛中，可以分化为IPCs和胰岛样细胞簇[85]。首次证明在从表达巢蛋白的人胰腺中分离的胰岛中存在不同的细胞群，称为巢蛋白阳性胰岛衍生祖细胞(NIP)。这些NIP显示出干细胞的特征，并且能够在体外产生具有胰腺外分泌或内分泌表型的细胞[86]。

2.3.3. 肝脏干细胞分化

肝脏和胰腺起源于前肠内胚层。肝脏和胰腺的共同胚胎起源引发了一个有趣的猜测，即可能将肝细胞转化为胰腺内皮细胞。几项研究表明，成人或胎儿肝细胞和胆管上皮细胞能够通过诱导内分泌胰腺特异性转录因子的表达重编程为 IPCs [87] [88] [89] [90]。体内数据表明，这些肝细胞衍生的 IPCs 在植入糖尿病小鼠体内后可以改善高血糖。然而，肝脏到胰腺重编程的效率仍然很低，获得的 IPCs 很可能是未成熟的 β 样细胞[91]。

3. 干细胞治疗的封装技术

封装技术基于一种基质，可防止免疫排斥，同时允许营养物质交换，从而增强移植功能。作为封装的载体，应用相对较多的是水凝胶生物材料，水凝胶有良好的生物相容性、与天然的胰腺结构和机械强度相似、而且网格结构有利于物质交换、隔离免疫细胞和胰岛细胞团的黏附[92] [93]。

水凝胶封装主要可分为以下四类：纳米封装、微胶囊化、生物打印和宏观封装。

纳米封装是一种通过界面聚合将水凝胶薄膜置于细胞聚集体表面的技术。最终的交联水凝胶膜会在每个单独的胰岛或细胞聚集体的表面周围形成纳米保形涂层。最常见是通过丙烯酸酯聚合物的光介导界面聚合进行的，最常用的生物材料丙烯酸聚乙二醇(PEG) [94]-[99]。

微囊化技术包括将单细胞或微组织嵌入球形的水凝胶状聚合物[100]。微胶囊化技术应用的主要困难是材料的生物相容性，生物相容性是细胞长期存活所必须[101]。多种生物相容性聚合物已用于微囊化应用，例如胶原蛋白、纤维素、琼脂糖、壳聚糖、明胶等，但它们胰岛封装效率低。藻酸盐是最常用的生物材料，因其对植入部位微环境中的细胞和微胶囊内的胰岛都表现出高度的生物相容性[102] [103] [104]。

生物打印是一种新兴技术，在制造功能性组织结构以替代受伤或患病组织方面具有多种应用。它通过控制细胞、生物材料和载有生物活性物质的生物材料打印出我们需要的形状。这是一种相对较新的方法，它以自动化方式对制造的构造提供高重现性和精确控制，有可能实现高通量生产。所以，生物打印技术在器官移植方面展现出巨大的潜力巨大潜力，有望解决组织和器官修复或替代[105] [106] [107]。多生物墨水制造的可能性允许创建出胰腺组织样结构。目前，已经使用生物打印系统和喷墨挤出打印技术研究了 β 细胞和胰岛生物打印[108] [109] [110]。

宏封装系统的研究重点是开发能够为移植的胰岛或产生胰岛素的细胞提供足够的氧气和营养的策略和设备配置。这是因为大量移植时胰岛细胞供养和营养交换有限，往往导致细胞活力降低和功能的丧失。[111]-[116]。

4. 移植的免疫反应

干细胞衍生 4 的 β 细胞临床应用的另一个主要障碍是由移植物免疫排斥。患者目前依赖免疫抑制药物来预防同种异体移植免疫。这些药物可能有副作用，有些是轻微的，如口腔溃疡、腹泻和痤疮，有些是严重的，包括增加严重感染和恶性肿瘤的风险[117] [118] [119]。如果移植患者特异性 iPSCs 衍生物，则可以防止同种异体移植排斥。然而，个体患者生产这种个性化细胞将非常昂贵、耗时，并且不太可能在短期内成为糖尿病的通用解决方案。

为此，目前正在设立 HLA 库。这些库包含精选的细胞系，这些细胞系经过精心挑选以匹配大多数人群。细胞系库的建立减少了匹配所需的细胞系数量，以允许在遗传上无关的供体和受体之间进行移植，从而使干细胞治疗更广泛地应用[120] [121] [122]。

调节性 T 细胞疗法代表了一种有吸引力的方法，可以建立对同种异体移植物的免疫耐受性，并在移植时绕过正在进行的自身免疫。T1DM 患者的临床试验已经证明了这种方法的治疗效率和安全性[123]

[124]。

另一种诱导免疫耐受的策略涉及选定细胞类型的共同移植，例如间充质干细胞(MSC)，其具有有益的特性，包括血管生成潜力和免疫反应的调节。因此，胰岛与 MSC 的共同移植提高移植物存活率。在不同的实验模型中已执行的研究中，从小鼠，大鼠，和甚至非人类灵长类动物，表明胰岛与 MSC 的共同移植可通过调节性 T 细胞和减少促炎细胞因子的产生来防止免疫排斥[125]-[130]。

另外分子水平上减轻免疫反应的方法是利用基因干扰技术使人类多能干细胞产生低免疫原性[131] [132]。

5. 干细胞治疗进展中的困难、挑战

尽管对再生药物进行了大量的研究，但干细胞治疗糖尿病的应用仍处于发展阶段。

干细胞诱导分化成 β 细胞存在以下困难和挑战：

首先，诱导产生的 β 细胞功能相对幼稚，如何从 hPSCs 体外产生功能更成熟的 β 样细胞；干细胞诱导分化效率较低，如何提高干细胞诱导分化效率；如何保护植入的 IPCs 免受自身免疫攻击。自身免疫是移植过程中面临的一个主要问题。神经和血管支持的变化微环境中与移植细胞存活和稳定性相关的障碍[133] [134] [135] [136]。

其次，安全问题和伦理问题。ESCs 应用于细胞治疗糖尿病存在恶性肿瘤的潜在风险，这些患者有可能发生畸胎瘤。此外，一些试验表明 ESCs 对甲状腺有内分泌破坏作用[137]。干细胞治疗一直争论不休。目前的进展在诱导多能干细胞的研究领域使其使用一个人自己的细胞成为可能，有望缓解伦理问题冲突[137] [138] [139]。

最后，诱导分化步骤繁复，成本较高，规模量产问题短时间内难以解决[140] [141]。

6. 结论

基于干细胞的疗法被认为是一种很有前景的治疗糖尿病的潜在治疗方法，尤其是对于 T1DM。正如本综述中提到的，从干细胞分化成胰岛素生成细胞的研究取得了重大进展，使糖尿病患者重构葡萄糖反应性胰岛素分泌成为了可能。封装技术可防止免疫排斥，同时允许营养物质交换，从而增强移植功能。然而，由于免疫反应仍然存在和移植技术的限制，干细胞治疗糖尿病的临床试验结果仍不令人满意，还有很多问题和技术障碍需要进一步解决，但干细胞治疗糖尿病未来仍可期。

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