

胰岛移植的应用及新方法

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摘要 1型糖尿病是由自体免疫系统破坏胰腺胰岛β细胞引起的, 可导致胰岛素严重缺乏。当β细胞被大量破坏时, 胰岛素分泌不足引起血糖升高甚至出现酮症酸中毒症状。近年来, 胰岛细胞移植发展成为一种有效的治疗1型糖尿病的方法。该文对胰岛移植治疗1型糖尿病的发展史、胰岛移植方法以及面临的问题进行讨论, 并详细阐述了提高胰岛移植效率新方法的研究进展。这些方法包括扩大供体来源、胰岛细胞和间充质干细胞共移植、应用纳米技术包装胰岛、在胰岛细胞中诱导保护性基因表达等方面。这些新方法可以显著提高胰岛细胞移植效率, 不仅可以应用在异体胰岛移植中, 也可用在自体胰岛移植过程中。

关键词 1型糖尿病; 胰岛移植; 间充质干细胞

Application and Progress of New Methods on Islet Transplantation

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Abstract Type 1 diabetes mellitus (T1D) is caused by the autoimmune destruction of pancreatic beta (β) cells, resulting in severe insulin deficiency. High blood glucose and Ketoacidosis symptoms are caused by insulin deficiency when beta cells are damaged. Islet cell transplantation is the most promising method for the T1D treatment. In this review, we summarized progresses and problems on islet isolation and transplantation in the T1D treatment. It also introduced the recent advance in current methods used to improve the efficacy of islet transplantation including using xenograft as islet donor, islet co-transplantation with mesenchymal stem cells, islet encapsulation with nanoparticles and induction of protective genes in islets.

Keywords type 1 diabetes; islet transplantation; mesenchymal stem cells

近年来, 随着人们生活水平的提高、人口老化、生活方式的改变, 糖尿病患者人数迅速增加。糖尿病是一类由于胰岛素分泌缺乏或胰岛功能障碍引起的糖代谢紊乱性疾病。世界卫生组织预计, 至

2025年, 全球糖尿病患者将上升至近3亿^[1], 并将成为威胁人类健康与生命安全及发病率和死亡率最高的五大疾病之一。糖尿病主要分为1型糖尿病和2型糖尿病, 其中1型糖尿病患者约占糖尿病总数的

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十分之一左右。1型糖尿病是一种自身免疫性疾病。患者机体的免疫系统选择性地破坏分泌胰岛素的胰岛 β 细胞,导致胰岛素的绝对缺乏,从而产生一系列代谢障碍,尤其会削弱人体血糖稳态功能^[2]。由于1型糖尿病病人体内胰岛细胞的缺失而不能产生正常生理功能所需的胰岛素,因此必须通过注射外源性胰岛素的途径来提供胰岛素。虽然外源性胰岛素在一定程度上可以控制血糖,但较难发挥像自身分泌的胰岛素那样严格按照自身血糖的高低来调节血糖浓度的作用,从而不能从根本上治愈糖尿病。20世纪60年代,胰腺移植技术迅速发展,并成为治疗1型糖尿病的一种新方法。但由于手术风险较大、并发症多,临床效果并不理想,因此很难开展大量的临床治疗工作。相比较而言,胰岛移植技术具有手术操作简单、安全性高、并发症少、可重复进行的优点,重要的是它能够延缓或逆转糖尿病进程^[3]。因此,胰岛移植在治疗1型糖尿病方面有很好的应用前景。

1 胰岛移植的发展历史

胰岛移植可以提供正常的胰岛细胞来代替患者体内已被破坏的细胞,从而维持正常血糖水平。1894年,英国医生Williams等^[4]首次采用部分羊胰腺成分移植到皮下的方法治疗了1个15岁少年发生了酮症酸中毒的病例。1966年,明尼苏达大学Kelley等^[5]第一次成功进行了胰腺移植并取得成功。虽然胰腺移植可以有效地恢复正常血糖水平,但因手术操作较复杂、创伤大、并发症多,所以难于于常规治疗1型糖尿病。1980年,Largiader等^[6]第一次报道了1型糖尿病患者接受胰岛移植后可以不再需要使用外源性胰岛素来控制血糖。2000年,加拿大Alberta大学Shapiro等^[7]提出的Edmonton胰岛移植方案,改良了传统方法,并采用无糖皮质激素的新型低毒高效免疫抑制剂,即他克莫司(tacrolimus)、雷帕霉素(rapamycin)和小剂量塞尼哌(zenapax)。2004年,美国糖尿病学会年会公布的国际多中心胰岛移植的临床研究结果显示,采用Edmonton方案,胰岛移植3年以上不使用外源性胰岛素者达53%^[8]。截至2007年,全球50多家医疗机构实施了700多例胰岛移植^[9]。近年来,国内多家医院开展了胰岛移植,中南大学湘雅第三医院王维^[10]先后进行了20多例胰岛移植,并且取得了明显效果。

2 胰岛的分离

胰岛的分离和纯化是胰岛移植过程的关键环节。目前,胰岛的分离多采用胶原酶消化方法。1988年,Ricordi等^[11]发明了胰岛自动分离系统,不仅解决了胰岛分离和纯化的技术障碍,而且提高了胰岛的回收率。Kenmochi等^[12]进一步改进该分离装置,通过控制消化程度来减轻胰岛分离装置对胰岛的损伤。胰岛分离时,使用新型的混合酶(Liberase释放酶,由I型胶原酶和II型胶原酶以及梭菌蛋白酶混合而成),可以有效地避免胶原酶对胰岛的毒性作用^[13]。目前,胰岛纯化主要采用Ficoll或Dextran密度梯度法^[14]。1989年,Lake等^[15]发明的COBE2991细胞分离器能够一次性大容积连续梯度离心、操作简便、可作为纯化人和大动物胰岛的方法。

3 胰岛移植的体内靶位

胰岛移植部位的选择需考虑手术的安全性、方便性、移植物是否可长期存活,并且能够避免免疫排斥反应等。目前肝脏是最为常用的移植部位^[16-18]。门静脉移植的优点是手术操作相对简便且安全。门静脉营养丰富,肝又是胰岛素的效应器官,利于糖代谢调节。但在肝移植后早期,大量胰岛因发生即刻经血液介导的炎症反应(instant blood-mediated inflammatory reaction, IBMIR)而丧失功能,此非特异性炎症反应是肝内移植所特有的^[19]。因此,探索其他移植部位以代替肝内移植方法也受到重视。目前,用于动物模型中的原位移植包括脾脏、大网膜及腹腔等部位的移植,异位移植则包括皮下、肌肉、睾丸、胸腔、肾包膜下、脑室、骨髓腔、下颌腺等部位的移植^[20-21]。Christofferson等^[22]的试验证明了与肝移植相比较,将胰岛移植到小鼠的肌肉内,可形成大量血管并避免了即刻经血液介导的炎症反应。有报道指出,将胰岛移植到胸腺、颅内以及睾丸等处,可以增强免疫耐受、免疫隔离,但这些体内靶位仍处在实验阶段,距临床应用还有一定距离^[23-24]。

4 胰岛移植所面临的挑战

临床上,尽管胰岛移植成为治疗1型糖尿病最有潜力的方法。但因一些因素限制了此治疗方法在临床上的应用。其一,胰腺供体来源不足。研究显示,1个1型糖尿病患者需要接受2~3个供体提供的胰岛才可达到正常血糖水平^[25]。尽管胰岛分离技术不

断改进, 并且已有单个供体胰岛移植成功的报道, 但供体数量仍远远不能满足临床需求。其二, 移植后胰岛死亡。据报道, 移植早期, 由于缺氧和炎症反应导致高达60%的胰岛坏死和凋亡^[26-29]。其三, 免疫排斥反应。针对胰岛移植后的免疫排斥反应, 使用免疫抑制药物只能发挥局部抑制作用。根据Edmonton提出的使用高剂量雷帕霉素和低剂量他克莫司的方法, 可以有效地治疗1型糖尿病的移植排斥和自身免疫的复发。但是有报告显示, 免疫抑制剂的使用会引起许多副作用^[30]。比如, 雷帕霉素可以引起高血脂、口腔溃疡、外周性水肿等, 联合使用雷帕霉素和他克莫司可引起蛋白尿^[31]。近年来, 针对胰岛移植在临床应用上面临的困难, 研究者们不断地寻求新材料、新方法及新技术, 从而实现胰岛移植在临床上的广泛应用。

5 寻求胰岛移植的新材料、新方法及新技术

5.1 猪胰岛异种移植

在胰腺供体来源不足的情况下, 猪胰岛异种移植成为治疗1型糖尿病的潜在的有效方法。在利用重组胰岛素之前, 猪胰岛素就被用来治疗1型糖尿病。猪是最理想的供体选择的主要原因为: (1)猪胰岛素与人胰岛素氨基酸序列最接近, 仅有一个氨基酸不同; (2)猪的血糖调定点与人类相似; (3)组织来源广泛; (4)猪胰岛能够在新鲜人血清组织培养液中存活、增生^[32]。Dufrane等^[33]利用成年猪的胰岛移植到链脲佐菌素(streptozotocin, STZ)诱导的糖尿病猴的体内, 结果显示, 成年猪的胰岛可以恢复灵长类动物胰高血糖素对胰岛素的敏感性, 但是不能保护糖尿病患者抵抗低血糖症。Lee等^[34]将猪胰岛移植到STZ诱导的糖尿病猴的肝脏内, 2~4个月以后, 静脉糖耐受实验显示, 糖尿病猴恢复正常血糖水平, 并且C-肽水平升高。Matsumoto等^[35]的实验证明了用封装的新生儿猪的胰岛治疗1型糖尿病是安全的。

5.2 胰岛与间充质干细胞共移植

目前, 大量实验研究证明了间充质干细胞与胰岛共移植能够提高胰岛移植治疗1型糖尿病的可行性。间充质干细胞最先是成人骨髓中分离获得的, 并且还发现了其他组织来源, 如脂肪、皮肤以及羊水^[36]。间充质干细胞可以较为容易地从患者身上获得, 而且具有较高的可塑性、减少炎性细胞释放、

免疫调节性和支持细胞生存的能力^[37-38]。这些特性显示了间充质干细胞可以提高移植后胰岛的生存能力^[39-41]。

已有体内研究表明, 将间充质干细胞与胰岛共移植到糖尿病大鼠体内, 可以维持正常的血糖水平, 但间充质干细胞的作用机制仍不清楚^[42-44]。实验证明, 脂肪间充质干细胞可以提高胰岛的生存能力和血管再生^[45]。Figliuzzi等^[46]的体内试验利用骨髓源性间充质干细胞和胰岛共移植(共移植组)与仅将胰岛移植到糖尿病大鼠的肾被膜下相比较, 发现共移植组的糖尿病大鼠在移植后血糖逐渐下降并恢复正常, 而且骨髓诱导的间充质干细胞能够促进胰岛的血管生成以提高胰岛的存活率。Kono等^[47]的体外试验将胰岛与人脂源性间充质干细胞共培养在含有促炎性细胞因子的培养基中, 发现间充质干细胞能够提高胰岛生存能力和功能; 将人脂源性间充质干细胞与胰岛共移植到1型糖尿病模型鼠内, 结果显示, 人脂源性间充质干细胞可以改善小鼠的葡萄糖耐受性, 增强细胞功能, 减少细胞死亡。Rackham等^[48]将肾源性间充质干细胞与胰岛共移植到STZ诱导的糖尿病的C57BL/6小鼠糖尿病模型的肾被膜下, 发现肾源性间充质干细胞可以维持移植后的胰岛细胞的结构和功能, 能够提高胰岛降低血糖的能力, 并且能够诱导生成血管内皮细胞。Berman等^[49]将分离出的食蟹猴的胰岛与猴骨髓源性间充质干细胞共移植到食蟹猴的肝脏内, 结果证明, 间充质干细胞可以增强移植后的胰岛的功能并提高胰岛的存活率。

5.3 胰岛包装

几十年来, 大量的实验证明, 包裹胰岛的相容性生物材料可起到促进同种移植、同种异体移植、异种移植胰岛存活的免疫隔离作用^[50-52]。胰岛封装后, 被隔离的胰岛通过利用表面的补体分子、IgG和宿主免疫细胞呈递保护细胞分子来发挥“隔离”和“调节”作用, 防止细胞凋亡。胰岛移植后, 由于产生免疫排斥反应和大量炎症因子浸入导致细胞死亡。因此, 胰岛移植后, 利用含有保护性因子的生物材料包装的胰岛会保持其功能和提高生存能力。目前, 在开发用于胰岛包装的具有可靠生物相容性、力学、化学稳定性和选择通透性的生物材料方面, 取得了显著进展^[53-61]。有研究报道指出, 乳酸-羟基乙酸共聚物作为胰岛的涂层材料, 可以增强其功能和减少

细胞凋亡^[57]。Bhaiji等^[58]利用纳米涂层的胰岛与间充质干细胞共培养后治疗1型糖尿病,可以提高胰岛的胰岛素分泌功能和有效地避免免疫排斥。Dong等^[59]研究表明,纳米材料包裹的胰岛可以克服免疫排斥、减少细胞死亡等问题。Liao等^[60]发现,将悬浮在糖多肽水凝胶中的胰岛移植后,糖多肽水凝胶不具有细胞毒性,反而具有维持胰岛正常结构的功能,还能隔离胰岛受到免疫排斥,从而保持其功能。Jaroch等^[61]报道了胰岛移植治疗1型糖尿病时,胰岛表面包裹一层多孔的二氧化硅,可以对胰岛起到免疫保护和提高存活率的作用。

5.4 保护性基因的诱导表达

研究证实,保护性基因的诱导表达可以避免移植后的胰岛因应激而导致的凋亡^[62]。保护性基因是一种通过特定的信号级联反应和转录因子来调节应激反应的基因,参与促进细胞生存^[62]。目前,已发现多种保护性基因,包括血红素氧化酶-1(hemeoxygenase, *HO-1*)、锌指蛋白A20、B淋巴细胞瘤(如*Bcl-2*)、热休克蛋白、胆绿素还原酶(biliverdinreductase, *BVR*)、抗氧化酶等在胰岛细胞中表达,并且这些基因被激活后可以防止细胞凋亡^[62-66]。Pileggi等^[67]的研究表明,在啮齿动物的胰岛移植的模型中,血红素氧化酶-1可以提高胰岛的功能。Yamashita等^[68]的研究结果显示,在移植接受者中,*HO-1*的表达对于移植物的长期存活和提高移植物的耐受性是必不可少的。Lee等^[69]的实验证明了血红素氧化酶-1可以延长移植后的胰岛的存活时间并且能够提高胰岛的存活率。Li等^[70]的研究指出,在临床胰岛移植中,具有潜在的价值*HO-1*可以抵抗TNF- α 和CHX介导的细胞毒性和减少胰岛细胞凋亡。Chen等^[71]的实验证明了血红素氧化酶-1能够明显地提高移植后的胰岛功能,并且延长正常血糖水平和减少淋巴细胞浸润。大部分保护性基因是通过它们的抗炎性和防止细胞凋亡来发挥作用。

6 结论

近年来,在胰岛移植治疗1型糖尿病方面的研究取得了很大进展,并且治疗1型糖尿病有很好的效果,给患者带来了福音。但是在临床应用上,胰岛移植面对诸多问题,如胰岛分离纯化技术不够完善、尚未筛选出优质的免疫抑制剂、免疫隔离材料的组织相容性差等。通过国内外学者们有的放矢地努力、

加强基础及临床的协作研究,相信胰岛移植必将成为治愈1型糖尿病的有效手段之一。

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