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造血干细胞移植治疗儿童慢性肉芽肿病进展

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摘　要

慢性肉芽肿病是一种原发性免疫缺陷病。由于gp91^{phox}、p22^{phox}、p47^{phox}、p67^{phox}、p40^{phox}、GTP酶-RAC相关基因突变，导致吞噬细胞内NADPH氧化酶复合物缺陷。CGD临床表现特异性不高，主要为反复细菌、真菌感染、自身炎症性疾病、肉芽肿形成。NBT及DHR实验、基因诊断可以确诊CGD。传统的预防性使用抗生素、抗真菌药物、IFN-γ预防感染等治疗进展显著地改善了CGD患者的生存。包括IL-1β受体拮抗剂、PPAR-γ等药物治疗自身炎症疾病的实验也在进行中。造血干细胞移植为目前治愈CGD的主要方法。近十年因为预处理方案、供者选择、移植后护理等方面的改善，移植治疗的生存率显著提高，OS可以达到84%~93%，半相合供者等可能成为合适的供者选择。基因治疗中载体的改善、新的基因编辑技术能够在保证治疗效果的同时降低致基因突变的风险。

关键词

造血干细胞移植，慢性肉芽肿病

Progress in Treating Chronic Granulomatous Disease with Hematopoietic Stem Cell Transplantation

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Abstract

Chronic granulomatous disease is a primary immunodeficiency. The deficiency of NADPH oxidase

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complex in phagocytes was caused by mutations in genes of gp91^{phox}, p22^{phox}, p47^{phox}, p67^{phox}, p40^{phox} and RAC. The clinical manifestations of CGD are not specific, mainly including repeated bacterial and fungal infections, autoimmune inflammatory disease, and granuloma formation. Diagnosis can be confirmed by NBT, DHR test, and gene mutation analysis. Conventional prophylactic antibiotic and anti-fungal therapy, and IFN-γ improve the survival significantly. Clinical trials of drugs such as IL-1β antagonists, PPAR-γ to treat inflammatory complications are being conducted. Hematopoietic Stem Cell Transplantation is the major treatment to cure CGD. In the last decades, survival was improved significantly with optimized conditioning regimens, selection of donors and post-care, with OS reaching 84%~93%. Haplo-identical donors can be considered as candidates. Advances in the vector design and gene-editing technology can reduce the risk of gene mutation while ensuring efficacy.

Keywords

Stem Cell Transplantation, Chronic Granulomatous Disease

1. 背景

慢性肉芽肿病(chronic granulomatous disease, CGD)是一种原发性免疫缺陷病，由于编码烟酰胺腺嘌呤二核苷酸磷酸氧化酶复合物(nicotinamide adenine dinucleotide phosphate oxidase complex, NADPH)基因突变，影响胞内活性氧(reactive oxygen species，ROS)的产生，致使活化的吞噬细胞(如中性粒细胞、单核细胞、巨噬细胞等)对于病原微生物杀灭障碍[1]。临床表现为机体遭受反复，甚至致命性感染，自身炎症性疾病以及肉芽肿的形成。CGD 发病率约为 1/250,000~1/130,000 [2] [3] [4]。终身预防性抗感染等传统治疗方法降低了死亡率，但人均每年仍会经历 0.26~0.64 次感染，曲霉等感染为主要死因之一[5] [6]。造血干细胞移植可以治愈 CGD，有效地控制感染及自身炎症疾病，提高患者的生活质量[6] [7]。自体基因治疗也为治愈 CGD 的一种方法。本篇综述拟对近年来移植经验进行总结，并简要回顾 CGD 疾病、传统治疗方法及基因治疗现状。

2. 分子遗传学及临床表现

NADPH 由 6 个亚基组成，包括 gp91^{phox}、p22^{phox} 两个跨膜蛋白(组成催化核心细胞色素 b558)，编码基因分别为 CYBB、CYBA，以及溶于胞质的 p47^{phox}、p67^{phox}、p40^{phox}、GTP 酶-RAC，前三者编码基因分别为 NCF1、NCF2、NCF4。CYBB 基因突变最为常见，约占 2/3，为 X 连锁隐性遗传；其余亚基基因突变为常染色体隐性遗传。此外，NADPH 复合物通过一种由 CYBC1 基因编码的蛋白稳定于细胞器膜上，该基因突变也能够致病。当机体受到病原的刺激时，NADPH 各亚基相互连接，产生并传递电子，产生超氧阴离子(O_2^-)及过氧化氢(H_2O_2)，即呼吸爆发。产生 ROS 的过程中同时发生钾离子向溶酶体内流，激活颗粒蛋白酶与 ROS 共同介导杀死病原微生物[8]。ROS 在此过程中角色有二：可直接作用于杀灭病原，以及作为第二信使影响许多细胞通路。

在欧美[2] [3] [4]、日本[9]及我国华东地区[10]以 X 连锁 CGD 最为常见；部分地区如伊朗、土耳其等地的报导，提示因近亲婚配的影响，AR-CGD 发病率相对更高[11] [12]。一般认为 X 连锁 CGD 较 AR-CGD

起病及诊断时间更早，病情更重，死亡更早发生[2]。但目前也有少量关于起病急、病情重的 AR-CGD 的报导[3] [12]。可能是由于相较于基因突变类型，ROS 残余量决定表型，并与生存直接相关[13]。

CGD 于 1954 年被首次报导，以反复感染并伴随血清丙种球蛋白升高为特征[14]。复旦大学相关报道表示华东地区起病年龄中位数约 1 月，确诊年龄中位数为 8 月[10]，起病年龄及确诊年龄中位数均早于早前其他地区相关研究报道[2] [3] [5] [15] [16] [17]，可能与我国卡介苗接种相关。虽然大多数儿童确诊年龄小于 5 岁，但由于缺陷 NADPH 氧化酶残存活性的影响，部分患者于青少年甚至成人期起病[5] [12] [18]。

感染常为 CGD 患者起病表现。接受传统治疗的患儿人均感染频率约为 0.26~0.64 次/年[5]。常见病原包括金黄色葡萄球菌、洋葱伯克霍尔德菌、粘质沙雷菌、诺卡菌属。真菌以曲霉菌属常见，尤其烟曲霉的感染，被认为是 CGD 患者最常见的死因[19] [20]。在某些结核病广泛流行、人群普遍接种卡介苗的地区，分枝杆菌(包括卡介苗)为 CGD 患者常见病原[21] [22]。常见感染部位包括肺，淋巴结，皮肤，肝脏及消化道[20] [23]，感染形式主要表现为化脓性淋巴结炎、肺炎、肝及肺脓肿[3] [4]。NIH 相关报道指出 CGD 患者肝脓肿发生率较高，约为 14.1% [24]；移植前肝脓肿可能影响患者 HSCT 后总体生存率[25]。卡介苗感染则以局部或肺部的严重感染为主，全身播散性感染少见[26]。

炎症及自身免疫性疾病为 CGD 患者另一大临床表现。Caspase-1 及吲哚胺 2,3-双加氧酶等[27] [28]引起的细胞凋亡缺陷、炎症级联反应失调等可能为 CGD 患者炎症发生的重要因素。消化道、泌尿生殖道等空腔脏器以及肝脏、肺部易受累，其中肠道改变类似克罗恩病。感染的高发、合并异常炎症反应，使 CGD 患者继发巨噬细胞活化综合征的风险增高。既往有文献报道不同基因突变类型合并 MAS [29] [30] [31] [32]。治疗包括糖皮质激素、IVIG、环孢素等，与家族性噬血相比，CGD 继发的 MAS 临床预后相对更好[31] [33]。

3. 诊断

NBT(硝基四氮唑蓝)实验中，NBT 可以与经 PMA 激活后的中性粒细胞内葡萄糖氧化过程中所脱的氢离子结合，使淡黄色的 NBT 染料还原为蓝紫色的甲臜，从而间接测定活性氧的生成[34]。

自 20 世纪 90 年代起，NBT 实验逐渐被流式细胞计数取代，其中以二氢罗丹明-123 (DHR-123)作为荧光探针的流式技术被作为 CGD 诊断的金标准[35]。PMA 激活后的中性粒细胞在髓过氧化物酶(MPO)的参与下产生活性氧，将 DHR-123 氧化为发出荧光的罗丹明-123。测定的平均荧光强度与活性氧产生量正相关[13]。DHR 实验可以区分 X 连锁 CGD、AR-CGD 以及 X 连锁 CGD 女性携带者[35]。ROS 水平可以调控 HSCT 后造血干细胞的生长、分化等[36]，可能影响 CGD 行 HSCT 预后。由于中性粒细胞活性、非特异性激活、实验温度、不同实验室水平[37]、MPO 缺陷[38]等会影响实验结果，应至少进行 2 次 NBT、DHR 实验后确诊 CGD [39]，或者经基因诊断后确诊[35]。

每一位 CGD 患者都应该进行基因检测[40]。基因检测能够确定基因突变类型，从而进行遗传咨询、产前诊断，协助诊断有明确家族史但无临床表现患者、基因携带者[40]，评估预后[13]。

4. 传统治疗

4.1. 预防

复方磺胺甲噁唑(Trimethoprim-sulfamethoxazole, TMP-SMX)及伊曲康唑的使用为预防 CGD 患者感染并发症治疗方案中的两座里程碑。口服 TMP-SMX 预防后，患者的感染频率从十月 1 次下降至 40 月 1 次[41]，1 年无感染的患者从 5%上升至 40% [42]，同时使非真菌感染率明显下降，AR CGD 患者 66% (每 100 个患者月中感染次数从 7.1 下降至 2.4)，X 连锁 CGD 患者下降 56% (每 100 个患者月中感染次数从 15.8 下降至 6.9) [43]。当患者磺胺过敏时，可单独使用甲氧苄啶(TMP)；若患者出现严重副作用难以耐受

时，可考虑更换为氟喹诺酮、二代或者三代头孢菌素、克林霉素等。TMP-SMX 用量为 6 mg/kg/天，分两次口服[44]。

预防真菌感染推荐使用伊曲康唑[45]，不仅有效而且患者容易耐受[46]。预防性使用伊曲康唑显著降低了侵袭性真菌感染的发生率[47]。同时将发生侵袭性真菌感染的中位数时间从 4 年延长至 10 年[48]。伊曲康唑用量为 5 mg/kg/天，<50 kg 上限为 100 mg，≥50 kg 口服 200 mg/天，至少每 6 个月需要随访 1 次肝功[23]。由于耐药菌种的出现，伏立康唑及泊沙康唑等抗真菌药物的使用率逐渐增加[49]。伏立康唑用量：9 mg/kg/q12h，上限 350 mg/次(2~12 岁且<40 kg)；200 mg q12h (≥40 kg) [50] [51] [52] [53] [54]。泊沙康唑用量：q12h，120 mg (10~14 kg)，160 mg (15~19 kg)，200 mg (20~24 kg)，220 mg (25~29 kg)，260 mg (30~34 kg)，280 mg (35~39 kg)，200 mg tid (>40 kg) [55] [56]。

γ 干扰素(IFN-γ)可以从旁路刺激吞噬细胞呼吸爆发产生活性氧，增加 NO 的产生，从而提高细胞的杀菌能力[57]。在伊曲康唑常规预防性应用之前，IFN-γ 的使用可以让重症感染发生次数下降 67%，同时住院时间减少[58]。但在 TMP-SMX 及伊曲康唑预防性使用的基础上加用 IFN-γ 并未降低患者的感染率[59]。虽然是否使用 IFN-γ 仍有争议，但许多专家认为使用 IFN-γ 预防侵袭性真菌感染的风险/受益比是有利的，特别是对于 X 连锁 CGD 的年轻患者和有侵袭性真菌感染史的患者[60]。IFN-γ 的用法为 50 μg/m^2，皮下注射，每周三次。

4.2. 急性感染

CGD 患者感染表现多样，需与自身炎症疾病区分，炎症指标如 C 反应蛋白、血沉等有助于感染的诊断；相关影像学如 CT、MRI 是必要的。怀疑感染时寻找病原至关重要，病原学结果回示前，需经验性使用抗生素，其中碳青霉烯类可以覆盖 CGD 常见病原谱，在 MRSA 常见地区，可加用万古霉素或克林霉素[23]。

4.3. 自身免疫性疾病

免疫抑制剂的使用可能使 CGD 患者感染风险增加[61]。糖皮质激素会增加真菌感染的风险[62]，但与抗生素联合使用可以加速感染灶的消退[63] [64] [65]、避免外科手术干预[66]。TNF-α 可有效治疗结肠炎，但同时增加重症感染发生率，甚至致死率[67]。IL-1β 受体拮抗剂阿那白滞素、mTORC1 复合物抑制剂雷帕霉素治疗效果不明确[68] [69] [70]。应用于 2 型糖尿病治疗的过氧化物酶体增殖物激活受体 γ (PPAR-γ)激动剂如吡格列酮等，可在小鼠模型上，可以从恢复吞噬细胞线粒体 ROS 产生、抑制急性无菌性炎症、增强细胞杀菌能力等方面[71] [72] [73]治疗 CGD 患者自身免疫性疾病。

5. 造血干细胞移植

由于诊断的进步、预防性抗感染治疗、以及护理、患者随访监测等各方面的进步，接受传统治疗方案的 CGD 患者也能够存活到成年[74]，但其生存质量较接受 HSCT 的患者而言明显下降，后者生活治疗可接近正常儿童[7]。可能与随着年龄的增长，患者的治疗依从性变差，导致并发症发生率升高相关。造血干细胞移植是目前可以治愈 CGD 的方法之一。有报道建议所有 ROS 产生量少的或经历过严重并发症的 CGD 患者，都应该接受 HSCT 治疗[75]。

2017 年 ESID/EBMT (European Society of Immunodeficiencies/European Group of Bone Marrow Transplantation，欧洲免疫缺陷学会/欧洲血液与骨髓移植组)发布了 CGD 移植治疗指征及预处理、供者选择方案，其中指征如下：1) 医疗条件不足；2) 预防性抗感染依从性差；3) 既往发生≥1 次致死性感染；4) 严重肉芽肿病导致器官功能损害；5) 激素依赖性肉芽肿病；6) 治疗过程中感染反复；7) 出现癌前克隆病

变或 MDS。

有 HLA 相合供者的 CGD 患者尽早接受移植治疗[13] [76]。Chiesa [25]等人发现接受 HSCT 治疗的儿童(＜18 岁)患者 OS 及 EFS 显著高于成年患者(86% vs. 76%, 76% vs. 69%, $p = 0.009$)，同时成年患者慢性 GvHD 发生率更高。Yonkof [77]等人报道，15 岁前移植的患者在行 HSCT 前严重感染较少(平均 0.95 次 vs. 2.23 次；$p = 0.047$)。大龄患者疗效欠佳可能与既往反复感染导致器官功能损害、肉芽肿形成、药物毒性相关；同时青少年 CGD 患者自身炎症疾病发生率更高[78]、药物依从性差[79] [80] [81]、青春期激素变化影响免疫功能[82] [83] [84]。在≥15 岁的患者中，移植后患者平均表现得分更高(93.2 v. 85.9; $p = 0.0039$)、残疾率更低(11% vs. 52%; $p = 0.014$)。成年 CGD 患者应经谨慎评估后考虑是否接受移植治疗[85]。

移植前应抗感染治疗。移植前急性感染可能会导致移植后 TNF-α 升高[86]，从而导致急性 GvHD 发生率增高[87]。对于≥2 岁感染烟曲霉或者巢曲霉的 CGD 患者，推荐使用伏立康唑，<2 岁者可使用两性霉素 B，但后者易发生巢曲霉耐药[88] [89]。抗真菌疗程至少 6~12 周[90]，复发侵袭性曲霉病(Invasive Aspergillosis, IA)可换其他抗真菌药继续治疗，包括两性霉素 B 脂质体、米卡芬净、卡泊芬净、泊沙康唑、艾莎康唑、伊曲康唑等，同时建议有 HLA 10/10 相合供者 HSCT 前保守治疗<3 月，随后随访肺部影像学，推荐使用 MRI [91]。

最理想的供者为 HLA 全相合同胞供者(Matched Sibling Donor, MSD)。但是欧美等地只有不到 30%的 CGD 患者能得到 MSD [92] [93]，鉴于国情不同，中国 CGD 患者获得 MSD 相对更难。近年来随着预处理、移植后护理技术的进步，HLA 全相合无关供者(Matched Unrelated Donor, MUD)与 MSD 移植后效果相差无几[74]。不全相合无关供者(HLA-Mismatched Unrelated Donor, MMUD)植入失败(Graft Failure, GF)、慢性 GvHD (chronic Graft-versus-Host Disease, cGvHD)发生率更高[85]，从而影响生存。一例 712 例大样本报道[25]显示不全相合供者较相合供者 OS 显著降低(MSD 89%及 MUD87% vs. 76%, $p = 0.02$)，HLA 不合位点越多会导致 EFS 下降越明显。半相合供者(Haploidentical Donor, HID)易获得，便于供者淋巴细胞输注(Donor Lymphocyte Infusion, DLI)，从而缩短移植前等待时间。近期来自北京[94]的 28 例半相合移植(Haploidentical HSCT, haplo-HSCT)的报道显示了良好的治疗效果。28 例中，供者 HLA 包含 9 例 5/6、13 例 4/6、6 例 3/6 相合，采用 MAC 的预处理方案，无原发性 GF 发生，有继发性 GF1 例，3 年预计 OS 为 94.1%，EFS 为 84.7%，治疗相关死亡率为 5.9%。另有多例小样本试验中[95] [96] [97] [98]共报道了 9 例 haplo-HSCT，有记载的 4 例供者为患者父亲，无死亡发生，有记载的 8 例患者当中，7 例达到了完全嵌合。虽然取得较为良好的效果，但 HID 是否能作为常用的供者仍需要长期的随访观察。女性供者干细胞回输入男性受者体内后，Y 染色体上编码的微小 HLA 可能会导致急性变应反应的发生，从而使 GvHD、移植相关死亡风险增加[99] [100] [101] [102]。建议选择患者父亲作为 HID。非恶性疾病如 CGD 采用 UCBT 可能降低 GvHD 发生概率及严重程度[103]。相关报道以小样本为主，有单中心[94]报道了 10 例接受 UCBT 治疗的 CGD 患者，使用 MAC 预处理，CsA 及 MMF 预防 GvHD 发生，中位随访时间 600 天中无 GF 发生，3 年预计 OS 为 80%，EFS 为 80%，UCBT 可能是对 CGD 患者有益的一个备选[104]。

依据 2017 ESID/EBMT 共识，清髓性(Myeloablative conditioning, MAC)预处理方案建议用于脐血移植、半相合移植；减强度性预处理(Reduced intensity conditioning, RIC)方案建议用于同胞供者及无关供者移植。然而 MAC 方案用于 MSD、MUD 也能够取得良好效果。ESID/EBMT 报道了欧洲首例大样本多中心研究[86]，27 例 CGD 患者于 1985~2000 年间接受 MAC 预处理方案的 HSCT 治疗，其中移植时没有明显的自身炎症、急性感染的患者 OS 为 100%，而移植时存在持续感染的患者的 TRM 为 44% (9 人中有 4 人)。总体 OS/EFS 分别为 85/81%。GF 和慢性移植物抗宿主病率分别为 7%和 11%。存活患者中绝大多数为超过 95%的供体来源细胞。这篇重要的论文表明，基于白舒非/环磷酰胺和无体内 T 细胞耗尽的 MAC 造血

干细胞移植在同胞移植中总体上是有效的，但在移植时遭受持续感染的患者中却会引发强烈的炎症影响移植效果。来自英国的 Soncini 等人[105]报道了自 1998 至 2007 年间接受 HSCT 治疗的 20 例患者。14 例患者移植前经历过 2 次及以上的侵袭性感染，并接受了抗生素、抗真菌药物甚至手术处理。3 例接受粒细胞回输。有 12 人有自身炎症疾病，接受了激素及氨基水杨酸衍生物治疗。20 例患者中有 2 人在造血干细胞移植时有急性真菌感染，10 人有活跃的持续自身炎症的迹象。20 例患者中有 10 例接受了 MSD 移植，8 例接受了 MUD 移植，2 例接受了 MMUD (9/10，1 例 UCB，1 例 PBSC)移植。预处理方案主要是全剂量的白舒非/环磷酰胺清除骨髓，URD 加用阿伦单抗治疗。观察内容包括难治性感染的恢复情况，炎症性器官功能障碍的缓解情况，以及生长发育追赶情况。10 例移植前结肠炎在 HACT 后 8 周内症状消失。中位随访时间 61 个月，OS/EFS 分别为 90/90%。无 GF 发生，慢性移植物抗宿主病发生率为 10%。这篇论文说明使用 MAC 预处理方式进行 MSD/URD 移植是有效的，能够缓解结肠炎，实现生长发育追赶，GvHD 及死亡发生于移植前患炎症及感染的患者当中，说明尽早移植治疗的重要性。

相较于 MAC 方案的高毒性，包括肺出血、肝静脉阻塞病(hepatic veno-occlusive disease, HVOD)以及生殖腺的影响，RIC/RTC 方案能够显著降低预处理毒性、急性 GvHD 发生率，同时获得良好的生存效果[74]。Gungor 等人[106]报道了一项针对 56 例儿童/成人 CGD 患者的 10 年(2003~2013)前瞻性研究 ，其中 42/56 (75%)的患者被定义为高风险，即有反复难治性感染或者自身免疫性疾病。该研究使用 RIC 预处理方案，采用亚清髓的白舒非(半剂量或 45~65 mg/L × h 的 cAUC)治疗，确实产生了良好的治疗结果。其中有 14/44 的(32%)患者需要调整白舒非剂量。联合氟达拉滨和血清治疗，后者包括 ATG 或阿仑珠单抗，清除患者免疫功能。在中位随访时间 21 个月后，OS/EFS 分别为 93%和 89%。5%的患者发生 GF。III-IV˚ aGvHD 及 cGVHD 发生率分别为 4%、7%。93%的存活患者嵌合稳定于 90%以上。MSD 与 MUD 移植效果无显著统计学差异。9/10 HLAMUD (n = 10)与 10/10 HLA MUD (n = 25)移植后生存效果无显著差异，但因为样本量相对较小，效果有待观察。两位男性患者移植后成功孕育了后代。该研究展现了 RIC 良好的生存效果，cAUC 控制下采用 RIC 也能达到良好的嵌合，生殖系统毒性可能较小，同时说明 9/10 HLA MUD 可以考虑为供者备选。Morillo-Gutierrez 等人[107]在一项 EBMT 包含 70 例 CGD 儿童的大型回顾性研究中发现，以苏消安为基础的 RTC 预处理 HSCT 效果良好。93%的患者移植前有急性感染、自身炎症性疾病，被定义为高风险患者。预处理采用苏消安(42 g/m^{2}或 36 g/m^2，D-6~D-4，3 剂/天)、氟达拉滨、血清学治疗 ± 噻替哌，中位随访时间 34 个月，OS/EFS 分别为 91.4%/81.4%。12%的患者发生继发性 GF。III-IV˚ aGvHD 发生率为 12%。80%的存活患者获得稳定于 95%以上的嵌合。苏消安是一种烷基化药物，具有清髓和免疫抑制作用，在 CGD 移植中表现出较低的急性毒性。如果作为单一的烷基化剂使用，苏消安比其他的烷基化剂更少的性腺毒性。

预处理方案的选择仍有争议。MAC 预处理方案因为预处理毒性、严重 GvHD 发生率较高，目前欧洲以 RTC、RIC 预处理为主[85]。然而来自 Chiesa 等人[25]的 712 例大样本报道则显示不同预处理后患者 OS、EFS 及 GvHD 的发生无显著统计学差异。MAC 相较于 RIC/RTC 而言植入率更高，嵌合相对稳定。而且非肿瘤性疾病移植后 GF 发生率为肿瘤性疾病的 3 倍[108] [109]，RIC 方案患者 GF 的发生率为 MAC 方案的 3~4 倍[94]，Oshrine 等人的 3 例 CGD 患者接受 MUD 移植，采用 RIC 方案后均发生 GF [110]。在苏消安为主的预处理方案当中，有中心建议加用噻替哌减少 GF 发生率[111]，但同时也可能导致性腺毒性增加[112]。为了保证有效性、安全性，RIC/RTC 方案中使用治疗药物浓度监测(Therapeutic drug monitoring, TDM)是必要的[113]。

6. 基因治疗

自体基因治疗(Gene Therapy, GT)可部分修复受损的吞噬细胞，是一种潜在的 CGD 治愈方法。GT 后

可能发生 GF，但 GvHD 的发生率为 0 [114] [115] [116]。自 2000 年以来，由于 γ-逆转录病毒的基因治疗出现插入性肿瘤后，基因治疗的发展从 γ-逆转录病毒转向慢病毒载体[116] [117]。近期 9 名年龄介于 2~27 岁的 X 连锁 CGD 患者，接受了自失活慢病毒载体 GT 治疗[114]。在保证有效性的前提下，应用该载体旨在降低突变风险。所有患者存在 gp91phox 基因严重缺陷，治疗前 NADPH 氧化酶无活性表达。随访时间至 12 个月时，6/7 的存活患者体内能够稳定产生活性氧的中性粒细胞占总体中性粒的 16%~46%，同时存在稳定的载体拷贝数(每个中性粒细胞存在 0.4~1.8 个拷贝数)。1 例患者治疗失败，产生活性氧的中性粒细胞<5%。2 例患者于 3 个月内因严重肺部疾病及出血而死亡。没有证据表明克隆性失调或转基因沉默。存活的患者没有出现新的 CGD 相关感染，6 例已经能够停止抗生素预防。随访时间超过 12 个月，OS/EFS 分别为 78/66%。尽管在载体设计上取得了进步，但基于整合一个额外的野生型基因拷贝的基因治疗存在不可避免的插入突变风险[118]。

在体内外实验中，新的基因组编辑技术可以介导基因添加、基因消融、基因修正和其他高针对性的基因修饰。通过特异性位点内切酶，如锌指核酸酶(Zinc Finger Nucleases, ZFN)、转录激活因子样效应核酸酶(Transcription Activator-like Effector Nucleases, TALEN)、或 CRISPR (clustered regularly interspaced short palindromic repeat)/Cas9 核酸酶等有可能取得良好的治疗效果[67] [119] [120]。

7. 结语

在过去的二十年中，传统治疗中有效的感染预防方案和积极的急性期治疗的发展改善了预后。造血干细胞移植取得了良好的治疗效果，建议有合适供者的 CGD 患者尽早接受移植治疗。虽然预处理的选择仍有争议，应依据患者移植前状态、供者 HLA 相合程度、移植物类型做出最优选择，以实现安全性和更高水平的供体嵌合，同时防止感染和炎症并发症的发生。半相合供者及脐血可能成为未来寻找供者困难的 CGD 患者的备选方案。基因治疗前景良好，同时需要更多的实验来控制致突变、致癌等并发症。我们需要进一步的研究观察随访 CGD 患者的长期管理，同时逐步完善现有的治疗措施，寻找可能的新的靶向治疗等。

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