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前列腺癌免疫治疗中癌症疫苗的研究进展

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[摘要] 前列腺癌是目前威胁老年男性生命健康最常见的恶性肿瘤之一。近年来, 以激活抗癌宿主免疫细胞达到杀伤肿瘤效果的免疫治疗成为前列腺癌治疗的一个新的研究方向。癌症疫苗作为免疫治疗的一个重要组成部分, 在恶性肿瘤的精准治疗中具有独特的地位。前列腺癌疫苗主要有单核细胞疫苗、树突状细胞疫苗、病毒疫苗、多肽疫苗和DNA/mRNA疫苗等。其中, Sipuleucel-T作为基于单核细胞的癌症疫苗, 是目前唯一获得美国食品药品监督管理局批准的前列腺癌治疗性疫苗, 在推动前列腺癌免疫治疗的发展中具有独特的地位和作用。然而, 由于Sipuleucel-T自身的局限性, 其尚未被广泛采用。同时, 由于免疫治疗的复杂性和前列腺癌的特殊性, 其余的前列腺癌疫苗并未在大型随机II期和III期试验中表现出良好的临床获益, 仍需进一步深入研究。

[关键词] 前列腺癌; 癌症疫苗; Sipuleucel-T; 免疫治疗

Advances in cancer vaccines for immunotherapy of prostate cancer

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ABSTRACT

Prostate cancer is currently one of the most common malignancies that endanger the lives and health of elderly men. In recent years, immunotherapy, which exploits the activation of anti-cancer host immune cells to accomplish tumor-killing effects, has emerged as a new study avenue in the treatment of prostate cancer. As an important component of immunotherapy, cancer vaccines have a unique position in the precision treatment of malignant tumors. Monocyte cell vaccines, dendritic cell vaccines, viral vaccines, peptide vaccines, and DNA/mRNA vaccines are the most often used prostate cancer vaccines. Among them, Sipuleucel-T, as a monocyte cell-based cancer vaccine, is the only FDA-

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approved therapeutic vaccine for prostate cancer, and has a unique position and role in advancing the development of immunotherapy for prostate cancer. However, due to its own limitations, Sipuleucel-T has not been widely adopted. Meanwhile, owing to the complexity of immunotherapy and the specificity of prostate cancer, the remaining prostate cancer vaccines have not shown good clinical benefit in large randomized phase II and phase III trials, and further in-depth studies are still needed.

KEY WORDS prostate cancer; cancer vaccines; Sipuleucel-T; immunotherapy

前列腺癌是男性最常见的恶性肿瘤之一。全球癌症统计及中国癌症统计^[1-3]显示：近年来世界范围内前列腺癌发病率呈持续增长趋势，已成为重要的疾病负担。目前，前列腺癌的常规治疗均不可避免地会导致去势抵抗性前列腺癌(castration resistant prostate cancer, CRPC)的发生，最终发展为转移性去势抵抗性前列腺癌(metastatic castration resistant prostate cancer, mCRPC)^[4]。在过去的数十年中，免疫疗法通过免疫反应驱动的抗肿瘤效果，给前列腺癌的治疗带来新的转机。特别是随着美国食品药品监督管理局(Food and Drug Administration, FDA)批准Sipuleucel-T用于无症状或轻微症状mCRPC, pembrolizumab用于微卫星不稳定性(microsatellite instability, MSI)或错配修复缺陷(mismatch repair deficient, dMMR)实体瘤，免疫治疗已成为前列腺癌患者临床治疗的重要方法^[5-6]。

癌症疫苗是利用肿瘤细胞相关抗原，诱导机体产生持久和特异性的抗肿瘤免疫应答。癌症疫苗作为免疫治疗的一个重要组成部分，在前列腺癌的治疗中具有独特的地位。前列腺癌疫苗主要有单核细胞疫苗、树突状细胞疫苗、病毒疫苗、多肽疫苗和DNA/mRNA疫苗等^[7]。其中，Sipuleucel-T在推动前列腺癌免疫治疗的进程中作用巨大，因此，本文就前列腺癌疫苗，特别是基于单核细胞的疫苗Sipuleucel-T的最新进展作一综述。

1 单核细胞疫苗

1.1 Sipuleucel-T

Sipuleucel-T(商品名: Provenge[®], 美国Dendreon公司)是一种基于主动免疫细胞的免疫疗法, 可诱导针对前列腺酸性磷酸酶(prostate acid phosphatase, PAP)的免疫反应。通过白细胞去除法采集患者富含抗原递呈细胞(antigen-presenting cells, APC)的外周血单核细胞(peripheral blood mononuclear cell, PBMC), 与PA2024体外一起孵育, 然后重新注入活化的

APC, 引发抗肿瘤免疫反应。其中, PA2024为PAP的羧基末端和粒细胞-巨噬细胞集落刺激因子(granulocyte-macrophage colony-stimulating factor, GM-CSF)的氨基末端连接而成的重组蛋白(PAP-GM-CSF)。整个过程包括白细胞去除术、细胞活化和回输, 每2周重复1次, 总共3次(第0、2、4周)^[8]。IMPACT(NCT00065442)III期随机、双盲、安慰剂对照的临床试验^[9]中512名患者被随机分配接受Sipuleucel-T或安慰剂(2:1), 中位随访34.1个月, 结果显示: 与安慰剂组(121例, 70.8%)相比, Sipuleucel-T组(210例, 61.6%)的死亡风险相对降低了22%, 调整后的死亡风险比为0.78(95% CI: 0.61~0.98, $P=0.03$); 中位总生存期(overall survival, OS)提高了4.1个月(25.8个月 vs 21.7个月); 36个月的估计生存率为31.7%(安慰剂组为23.0%); 此外, Sipuleucel-T耐受性良好, 最常见的不良事件包括发烧和流感样症状。然而, 值得注意的是, 在无进展生存期(progression-free survival, PFS)或前列腺特异抗原(prostate specific antigen, PSA)下降方面两组差异无统计学意义, 只有不到3%的Sipuleucel-T患者的PSA下降了50%或更高。这一试验对Sipuleucel-T商品化有至关重要的作用。基于IMPACT^[9]、D9901(NCT00005947)^[10]、D9902A(NCT01133704)^[11]3项双盲、对照、多中心III期随机试验, FDA于2010年4月正式批准Sipuleucel-T为治疗无症状或轻微症状mCRPC的首个前列腺癌疫苗^[6], 该药物的临床使用极大推动了癌症疫苗的发展, 但令人遗憾的是, 除Sipuleucel-T外其他前列腺癌疫苗并未在大型随机II期和III期试验中表现出良好的临床获益。

1.1.1 Sipuleucel-T的免疫学作用机制

Sipuleucel-T诱导的免疫反应是多方面的, APC介导的免疫反应是其作用基础, 即诱导机体产生对PAP特异的T细胞和B细胞, 从而激活机体对前列腺癌的免疫反应, 产生杀伤作用。其具体作用机制主要为: 1)APC激活与免疫增强。APC激活是产品效

力和免疫激活的量度, 累积APC激活增加与OS的改善在统计学上显著相关, 第2周和第4周输注Sipuleucel-T会引起APC激活的增加, 这表明第1次输注(第0周)启动了免疫系统, 随后的治疗加强了免疫反应; 同时, 在早期前列腺癌患者中, APC激活效果更好^[12]。2)产生针对PAP和PA2024的特异性免疫反应。3)抗原扩散。Sipuleucel-T在对特定靶抗原的初始免疫反应后会扩大对肿瘤表达的其他抗原的反应, 即发生抗原扩散。在这个过程中, 被抗原特异性T细胞裂解的肿瘤细胞会释放额外的肿瘤相关抗原(tumor-associated antigens, TAA), 最终TAA由APC加工和呈递, 以诱导B细胞和T细胞产生针对二级抗原(如E-RAS、KLK2、K-RAS、LGALS3和LGALS8等)的免疫反应, 这与Sipuleucel-T改善生存益处密切相关^[13-14]。4)T细胞反应性转移与细胞毒性T淋巴细胞(cytotoxic T lymphocyte, CTL)活动。Fong等^[15]研究指出前列腺癌根治术前新辅助Sipuleucel-T会引发全身性抗原特异性T细胞反应, 同时使活化效应T细胞募集到前列腺肿瘤微环境中, 增强免疫效果。Antonarakis等^[16]通过测量PAP或PA2024特异性CD8⁺T细胞表面CD107a的表达证明Sipuleucel-T能够在前列腺癌患者中产生抗原特异性CTL反应, 并发现这与Sipuleucel-T治疗后OS的改善相关。Kibel等^[17]通过视频记录了CTL对表达PAP的靶细胞的细胞溶解活性, 表明通过抗原特异性CD8⁺细胞诱导肿瘤溶解是Sipuleucel-T作用机制的重要组成部分。同时, Sipuleucel-T治疗改变了B细胞受体库, 可以诱导机体产生长期免疫记忆, 使得杀伤作用更为持久^[18]。

1.1.2 Sipuleucel-T的临床影响

1.1.2.1 疗效评估

IMPACT研究^[9]表明Sipuleucel-T可有效延长mCRPC患者的中位OS。Schellhammer等^[19]指出PSA是Sipuleucel-T治疗效果的强预测因子($P < 0.0001$), 随着基线PSA的降低, Sipuleucel-T治疗效果会更大。基线PSA ≤ 22.1 ng/mL患者的OS风险比为0.51(95% CI: 0.31~0.85), 而PSA > 134 ng/mL患者的OS风险比为0.84(95% CI: 0.55~1.29), 表明在癌症早期使用Sipuleucel-T更有收益。早期使用时肿瘤免疫抑制较少, 同时APC激活较多, 这更有益于Sipuleucel-T刺激长期免疫反应, 获得长期临床效益。

Sipuleucel-T另一个显著的临床特点是延迟效应, 即近端终点如PSA水平、客观疾病进展和疾病相关疼痛的发生没有改变; 相反, 远端终点有所改善^[20]。Small等^[21]对3项Sipuleucel-T随机III期研究汇总时发

现: Sipuleucel-T治疗与疾病相关疼痛时间(time to disease-related pain, TDRP)无关(HR=0.819, 95% CI: 0.616~1.089, $P=0.170$), 与首次使用阿片类镇痛剂时间(time to first use of opioid analgesics, TFOA)延迟相关(HR=0.755, 95% CI: 0.579~0.985, $P=0.038$)。这些晚期结果的变化可能与Sipuleucel-T治疗后发挥免疫抗肿瘤作用需要的时间有关。

在不同种族中, Sipuleucel-T结果也不尽相同。PROCEED研究^[22]结果显示: 与白人相比, 非洲裔美国人接受Sipuleucel-T治疗后的中位OS更高(HR=0.81, 95% CI: 0.68~0.97, $P=0.03$)。这可能与不同种族间免疫系统的差异相关^[23]。

1.1.2.2 联合用药的价值

前列腺癌突变负荷较低, 肿瘤浸润性CD8⁺T细胞数量较少, 使得前列腺癌成为免疫反应的“冷肿瘤”, 导致免疫治疗效果远不如其他实体瘤^[24]。因此, 前列腺癌免疫治疗多采用联合疗法。从理论上来说, Sipuleucel-T治疗后会发生免疫反应的激活和扩散, 加上持久的疗效和安全性, 具有延长抗癌作用的前景, 其联合用药的价值巨大。

一项随机II期开放标签试验评估了Sipuleucel-T与雄激素剥夺疗法(androgen deprivation therapy, ADT)在生化复发(biochemical recurrence, BCR)的转移高危前列腺癌患者中的不同用药顺序的疗效, 结果显示不同给药顺序安全性均良好, 先用Sipuleucel-T比先用ADT的PA2024特异性T细胞反应更高($P=0.001$), 能够诱导更大的抗肿瘤免疫反应^[25]。Jain等^[26]开发的关于前列腺癌对Sipuleucel-T和ADT反应的数学模型结果显示: 在ADT之前接种2剂疫苗是最佳的, 可使癌症病死率降低约45%, 最大限度地提高中位OS。

Small等^[27]评估Sipuleucel-T联合阿比特龙治疗mCRPC的随机II期试验显示: 同时给药不会减弱或改变Sipuleucel-T的免疫效应, 联合使用耐受性良好。

放射治疗(以下简称放疗)和化学治疗(以下简称化疗)可能与免疫疗法产生协同作用, 增强和扩大抗肿瘤免疫反应。然而Sipuleucel-T联合放疗的随机II期试验中, 对无症状或症状轻微mCRPC患者单个转移部位进行高达30 Gy的照射, 并没有增强与Sipuleucel-T治疗相关的免疫反应^[28]。在联合化疗方面, 目前相关研究较少, 而2项评估Sipuleucel-T联合多西他赛治疗先后顺序的临床试验(NCT02793219和NCT02793765)也随着Dendreon被出售而撤回。另外, Sipuleucel-T联合镭223治疗骨转移性mCRPC的随机II期试验显示联合治疗可提高临床疗效, 但免疫

反应较低^[29]。

对于前列腺癌的治疗, 由于肿瘤微环境(tumor microenvironment, TME)中缺乏效应T细胞浸润, 因此免疫检查点抑制剂(immune checkpoint inhibitors, ICI)单一疗法效果欠佳。最近, Sinha等^[30]联合Sipuleucel-T和ipilimumab的试验显示: 联合治疗会产生适度的临床反应, 同时不会改变抗原特异性反应。Dorff等^[31]对接受atezolizumab和Sipuleucel-T不同顺序治疗方案的mCRPC患者的Ib期研究显示: 无论其给药顺序如何, 联合治疗安全性良好且可能更为有益。同时, 其他新兴疗法, 如联合细胞因子IL-7的II期试验也取得了令人鼓舞的结果^[32]。

当前, 与其他免疫疗法相比, Sipuleucel-T并未得到广泛应用, 部分原因是其临床成功率有限, 同时其治疗相关的成本难以被大多数患者接受。但是, Sipuleucel-T在联合治疗中表现出的免疫收益, 仍然为更多的大型试验打下了基础。

1.1.3 临床局限性

一项影响美国mCRPC患者使用Sipuleucel-T相关因素的调查^[33]显示: 在接受治疗的7 272名患者中, 仅730名接受了Sipuleucel-T, 其中不同族裔、居住地区、收入及专业人士的推荐是其使用的影响因素。从成本角度看, Sipuleucel-T需要3次输液, 为期1个月。而针对mCRPC患者治疗的成本效益分析发现: 不含sipuleucel-T的治疗策略可以表现出最有利的增量成本效益比(incremental cost-effectiveness ratios, ICER)^[34]。同时, Sipuleucel-T的延迟效应, 导致其在临床试验中缺乏PSA或客观反应, 影响对疾病进展的评估。目前, 除美国外, Sipuleucel-T尚未被广泛采用。由于其复杂的管理、较低的生存获益及高昂的价格等, 这种药在欧洲已经停止使用^[35]。其所有者Dendreon公司因生产能力和资金问题, 最终破产, 而被中国三胞集团完全收购。

2 树突状细胞疫苗

DCVAC/PCa疫苗是一种PBMC衍生的自体树突状细胞疫苗, 可通过单采获得的PBMC与杀死的前列腺癌细胞(LNCaP)进行脉冲, 再将成熟的树突状细胞皮下注射获得^[36]。2项I/II期小样本临床试验^[37-38]表明DCVAC/PCa治疗前列腺癌安全性良好, 可使前列腺特异性抗原倍增时间(prostate-specific antigen doubling time, PSADT)显著延长($P < 0.0018$)。当前, 该疫苗基础和临床相关研究较少。一项评估DCVAC/PCa联合一线化疗(多西他赛+泼尼松)治疗mCRPC患

者安全性和有效性的随机、双盲、III期试验^[39]结果显示: DCVAC/PCa联合一线化疗药物并未延长mCRPC患者的OS(23.9个月 vs 24.3个月, HR: 1.04, 95% CI: 0.90~1.21, $P=0.60$)。

3 癌细胞疫苗

GVAX/PCa疫苗是一种经过基因转染的癌细胞疫苗, 肿瘤细胞为疫苗提供抗原。GVAX/PCa疫苗使用LNCaP和PC-3细胞系以分泌GM-CSF^[40]。一项针对激素初治前列腺癌和PSA复发患者的I/II期试验^[41]表明: 在首次治疗后20周, 76%(16/21)的患者PSA显著降低。Higano等^[42]研究表明mCRPC患者对GVAX产生抗体的比例随剂量增加而增加。这些有希望的结果促成了2项III期试验。VITAL-1试验将未接受过化疗的无症状的mCRPC患者随机分配至GVAX或多西他赛+强的松组; VITAL-2试验将未接受过化疗的有症状的mCRPC患者随机分配至GVAX+多西他赛或多西他赛+强的松组。令人失望的是, VITAL-2试验的初步分析结果表明多西他赛+泼尼松组更有生存优势, 同时GVAX组与其相比死亡人数不成比例, 最终这项试验被提前终止。随后, VITAL-1试验也由于可能无法提高生存率被提前终止^[43]。

4 病毒疫苗

4.1 PSA-TRICOM

PSA-TRICOM(Prostvac)是一种基于病毒载体的疫苗, 通过将带有PSA转基因的重组质粒连同编码3种病毒T细胞共刺激分子(TRICOM)的质粒一起插入痘病毒中制得。患者首先接受重组牛痘的初免疫苗(Prostvac-V), 然后使用重组禽痘进行多次加强免疫(Prostvac-F)^[44]。TRICOM由B7.1、ICAM-1和LFA-3组成, 主要用于提高T细胞亲和力, 增加肿瘤细胞裂解^[45]。II期试验结果显示接受Prostvac-V/F的患者中位OS延长8.5个月(25.1个月 vs 16.6个月), 估计风险比为0.56(95% CI: 0.37~0.85, $P=0.0061$), 病死率降低44%^[46]。这一结果极大地鼓励了后续III期试验的开展, 也掀起了肿瘤疫苗的新高潮。然而, 随后的III期试验表明Prostvac组、Prostvac-GM-CSF组、安慰剂组OS没有差异, 试验提前终止^[47]。

4.2 腺病毒/PSA

腺病毒最初被用作基因治疗的载体。近年来, 随着对转基因产品具有更高安全性和高免疫原性的下一代载体的开发, 其作为疫苗载体的效用不断增

加^[48]。动物试验证明腺病毒/PSA(Ad5-PSA)可以诱导针对PSA的免疫反应,靶向杀伤肿瘤细胞^[49]。一项I期临床试验表明腺病毒/PSA治疗mCRPC患者安全性良好,大多数患者可以产生抗PSA的T细胞反应。然而,当前该疫苗研究仍处于小样本I/II期试验,相关III期试验较少^[50]。

5 多肽疫苗

5.1 个体化多肽疫苗

个体化多肽疫苗(personalized peptide vaccines, PPV)是依据个体遗传基因结构和功能差异,选择个体化的多肽进行疫苗接种制作成的肿瘤疫苗。PPV作用机制是通过将特异性的肿瘤抗原肽输送给APC表面的主要组织相容性复合体(major histocompatibility complex, MHC),在APC内降解为短肽,并形成肽-MHC-TCR复合物,被T细胞所识别,激发相应的CTL反应,从而进行抗肿瘤免疫^[51-52]。一项针对多西他赛化疗后进展的CRPC患者接种PPV的随机、双盲、安慰剂对照III期临床试验^[53]结果显示PPV不能延长患者的OS($P=0.77$),亚组分析表明基线时中性粒细胞比例较低或淋巴细胞比例较高的患者可以从PPV治疗中获得生存获益。

5.2 GX301

GX301是一种由4种端粒酶多肽、2种免疫佐剂(Montanide ISA-51和咪喹莫特)组成的疫苗。I期试验发现其具有安全性和免疫原性^[54]。多中心、随机、平行组、开放标签的II期试验结果显示GX301疫苗在mCRPC患者中具有安全性和免疫原性,免疫应答率与免疫接种次数相关,这为未来研究中的治疗选择提供了参考^[55]。

6 DNA/mRNA 疫苗

DNA疫苗是利用目标抗原设计的闭合的环状DNA质粒,在哺乳动物的强力启动子作用下编码抗原,通过靶向抗原呈递提高免疫原性,杀伤肿瘤细胞。当前基于DNA的前列腺癌疫苗主要有编码PAP、PSMA、PSA等的疫苗^[56]。一项针对编码PAP的I/II期试验^[57]结果显示该疫苗安全性良好,14%(3/22)的患者在治疗后立即产生了PAP特异性IFN- γ 分泌的CD8⁺T细胞,41%(9/22)出现了PAP特异性CD4⁺和/或CD8⁺T细胞增殖,PSADT差异具有统计学意义($P<0.05$)。同样,编码PSMA的DNA疫苗安全性和有效性也在I/II期试验中得到证实,其PSADT显著增加($P=0.0417$)^[58]。最近一项研究^[59]指出将PSMA或T细胞受体 γ 交替阅读框蛋白(T-cell receptor γ alternate reading frame protein, TARP)的肽整合到优化结构的球形核酸(spherical nucleic acid, SNA)疫苗中,可显著影响临床使用的前列腺癌靶点的适应性免疫反应,这或许成为未来新的研究方向。

mRNA疫苗是将合成的编码蛋白质抗原的mRNA序列递送至体内促使机体表达相应的蛋白质,并诱导机体产生针对该蛋白质的免疫应答以实现疾病预防和治疗的目的^[60]。其中,安全、高效的递送系统是mRNA疫苗开发的核心关键技术^[61]。目前,前列腺癌mRNA疫苗正处于研发阶段。针对肿瘤抗原筛选和候选疫苗这一瓶颈问题,Zheng等^[62]研究表明KLHL17、CPT1B、IQGAP3、LIME1、YJEFN3、KIAA1529、MSH5和CELSR3是前列腺腺癌(prostate adenocarcinoma, PRAD)mRNA疫苗开发的潜在抗原,PRAD免疫亚型(PRAD immune subtype, PIS)2型和3型患者更适合接种疫苗。上述不同类型疫苗的作用机制和研究结果见表1。

表1 前列腺癌疫苗概述

Table 1 Overview of prostate cancer vaccines

| 疫苗 | 类型 | 作用机制 | 临床阶段 | 结果 | 状态 |
|--------------|---------|---|------|--------------|------|
| Sipuleucel-T | 单核细胞疫苗 | 基于主动免疫细胞的免疫疗法,可诱导针对前列腺酸性磷酸酶(prostate acid phosphatase, PAP)的抗肿瘤免疫反应 | III期 | 提高中位生存期4.1个月 | 上市 |
| DCVAC/PCa | 树突状细胞疫苗 | 通过单采获得的外周血单核细胞(peripheral blood mononuclear cell, PBMC)与杀死的前列腺癌细胞(LNCaP)进行脉冲,再皮下注射成熟的树突状细胞,进而获得抗肿瘤免疫反应 | III期 | 未延长患者的中位生存期 | 完成 |
| GVAX/PCa | 癌细胞疫苗 | 经过基因转染,使用LNCaP和PC-3细胞系以分泌粒细胞-巨噬细胞集落刺激因子(granulocyte-macrophage colony-stimulating factor, GM-CSF),产生抗肿瘤免疫反应 | III期 | 未延长患者的中位生存期 | 提前终止 |

表 1(续)

| 疫苗 | 类型 | 作用机制 | 临床阶段 | 结果 | 状态 |
|-----------------------|-------------|---|--------|-------------|-------|
| PROSTVAC (PSA-TRICOM) | 病毒载体疫苗 | 将带有 PSA-TRICOM 的质粒插入痘病毒中制得, 患者首先接受重组牛痘的初免疫苗(Prostvac-V), 然后使用重组禽痘进行多次加强免疫(Prostvac-F) | III 期 | 未延长患者的中位生存期 | 提前终止 |
| 腺病毒/PSA | 病毒载体疫苗 | 利用腺病毒/PSA 可以诱导针对 PSA 的免疫反应, 靶向杀伤肿瘤细胞 | I/II 期 | 疫苗具有免疫原性 | 正在进行中 |
| PPV | 多肽疫苗 | 将特异性的肿瘤抗原多肽输送给抗原提呈细胞(antigen-presenting cell, APC)表面的主要组织相容性复合体, 形成肽-MHC-TCR 复合物, 从而激发细胞毒性 T 淋巴细胞(cytotoxic T lymphocyte, CTL)反应, 产生抗肿瘤免疫 | III 期 | 未延长患者的中位生存期 | 完成 |
| GX301 | 多肽疫苗 | 由 4 种端粒酶多肽、2 种免疫佐剂(Montanide ISA-51 和咪喹莫特)组成的疫苗 | II 期 | 疫苗具有免疫原性 | 正在进行中 |
| DNA/mRNA 疫苗 | DNA/mRNA 疫苗 | DNA 疫苗是利用目标抗原设计的闭合的环状 DNA 质粒, 在哺乳动物的强力启动子作用下编码抗原, 通过靶向抗原呈递提高免疫原性; mRNA 疫苗是将合成编码蛋白质抗原的 mRNA 序列递送至体内, 导致机体表达相应的蛋白质, 并诱导机体产生针对该蛋白质的免疫应答 | I/II 期 | 疫苗具有免疫原性 | 正在进行中 |

PCa: 前列腺癌; PSA: 前列腺特异抗原; PPV: 个体化多肽疫苗。

7 结 语

近年来, 前列腺癌免疫治疗取得了显著的进展, 各种新型疗法层出不穷。Sipuleucel-T 作为迄今为止唯一被运用于临床的前列腺癌疫苗, 在推动前列腺癌免疫治疗的进展中有至关重要的作用。然而, 癌症疫苗限于其自身的特点, 与其他疗法相比, 并未有更大的临床获益。这需要我们进一步完善癌症疫苗接种策略, 改进 Sipuleucel-T 设计, 寻找评价指标。相信随着 Sipuleucel-T 的不断优化, 其在前列腺癌靶向治疗中的优势将越发显著, 未来更合理的联合治疗方式也将不断提高免疫治疗杀伤肿瘤的效果。

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