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述评 EDITORIAL

胰腺癌免疫治疗的挑战与前景

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Prospects and challenges of immunotherapy for pancreatic cancer

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Abstract

Pancreatic cancer is a highly malignant digestive system tumor with an extremely poor prognosis. It has been reported that pancreatic cancer has now surpassed breast cancer as the third leading cause of cancer death in the United States. Due to its low early diagnosis rate, most patients have lost the chance of surgery at the time of diagnosis. However, various treatment strategies (like radiotherapy, chemotherapy, targeted therapy, *etc*.) have not been able to significantly improve their survival rate. A large body of evidence suggests that an important cause of high lethality in pancreatic cancer is the immune privilege of tumors driven by factors such as immunosuppressive microenvironment, low T cell infiltration, and low gene mutation load. In recent years, tumor immunotherapy has become a hot spot in the field of oncology, and significant progress has been made in the treatment of pancreatic cancer. At present, various new immunotherapies such as immunological checkpoint blockers, adoptive cell therapy, and tumor vaccine have entered the clinical or preclinical stage, and all of them have hope to become a new treatment strategy to improve the treatment of patients with pancreatic cancer. Here, we briefly summarize the recent advances in immunotherapy for pancreatic cancer that is being researched and promising in recent years, as well as the challenges and prospects, with an aim to open up new horizons for the development of new and effective immunotherapy for pancreatic tumors.

Key Words: Pancreatic cancer; Immunotherapy; Immune checkpoint; Cancer vaccine; Adoptive cell therapy

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摘要

胰腺癌是一种恶性程度极高的消化系统恶性肿瘤, 预后极差. 有报告称胰腺癌当前已超过乳腺癌成为美国第三位的癌症死亡病因. 由于胰腺癌早期诊断率较低, 大多数患者在确诊时已失去手术的机会, 而且各种现有的治疗策略(如放疗、化疗, 靶向治疗等)尚无法显著提高其生存率. 大量证据表明导致胰腺癌高致死性的一个重要原因是由免疫抑制微环境, T细胞浸润低和基因突变负荷低等因素驱动而获得的肿瘤免疫特权. 近年来, 肿瘤免疫治疗已成为肿瘤学领域的热点, 在胰腺癌的治疗方面也取得了显著的进展. 目前, 各种新的免疫治疗策略如免疫检查点阻断剂, 过继性细胞疗法和肿瘤疫苗等已进入临床或临床前期阶段, 都有希望成为提高胰腺癌患者救治率的新治疗手段. 因此, 本文简要概括近些年正在研究且有希望的胰腺癌免疫疗法的最新进展, 以及当前所面临的挑战与前景, 为以后研发新的高效的胰肿瘤免疫治疗手段开阔视野.

关键词: 胰腺癌; 免疫治疗; 免疫检查点; CAR-T疗法; 肿瘤疫苗

核心提要: 研究表明胰腺癌高致死性归因于由免疫抑制微环境, T细胞浸润低和基因突变负荷低等因素驱动而获得的肿瘤免疫特权. 目前, 各种新的免疫治疗的手段如免疫检查点阻断剂, 过继性细胞疗法和肿瘤疫苗等已进入临床或临床前期阶段, 都有希望成为提高胰腺癌患者救治率的新治疗策略.

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0 引言

胰腺癌是一种恶性程度极高的消化系统恶性实体肿瘤. 根据美国癌症协会最新数据报告, 目前胰腺癌已超过乳腺癌成为美国第3位的癌症死亡病因, 仅次于肺癌和结肠癌, 5年存活率仅为8%[1]. 近年来, 胰腺癌的发病率和死亡率都在不断增加, 预计到2030年它将成为癌症死亡病因的第2位[2]. 目前, 胰腺癌的临床治疗仍采用以根治性手术为主, 放化疗为辅的综合策略. 由于胰腺癌早期发现困难, 又缺乏有效的筛查指标, 绝大多数患者在确诊时已处于肿瘤晚期, 致使仅有不到20%的患者具有手术根治的机会[3]; 而对于晚期胰腺癌患者多采用姑息性治疗手段如化疗等, 预后更差. 吉西他滨是胰腺癌的一线化疗药物, 有研究表明采用吉西他滨和厄洛替尼联合治疗仅能使胰腺癌患者中位生存期延长约2 wk[4]; 而联合吉西他滨与白蛋白结合型紫杉醇也只能使其中位生存期延长2-4 mo[5]. 另外, 与吉西他滨为主的化疗方案相比, 采用FOLFIRINOX联合化疗虽能使胰腺癌患者的中位生存期延长1倍, 但同时也大大增加了化疗的毒副作用[6].

近年来, 人们发现胰腺癌细胞是通过动员宿主各种免疫细胞, 建立一个免疫抑制性肿瘤微环境, 来逃避宿主免疫监视的. 因此, 靶向和恢复宿主的肿瘤免疫力可作为一种治愈胰腺癌患者强有力的治疗策略. 近年来, 肿瘤免疫治疗已成为肿瘤学领域的热点, 在胰腺癌的治疗方面也取得了显著的进展. 目前, 各种新的免疫治疗的策略如免疫检查点阻断剂, 过继性细胞疗法和肿瘤疫苗等已进入临床或临床前期阶段, 都有希望成为提高胰腺癌患者救治率的新治疗手段. 因此, 本文就近些年正在研究且有希望的胰腺癌的免疫疗法如免疫检查点抑制剂、过继性细胞疗法以及肿瘤疫苗等的最新进展, 以及当前所面临的困境与前景进行简要述评, 为以后研发新的高效的胰肿瘤免疫治疗手段开阔视野.

1 胰腺癌免疫治疗的概况

机体免疫系统与肿瘤细胞的对抗过程主要经历三个不同阶段: 消除期、平衡期和逃避期. 在肿瘤消除期, 机体免疫系统能够识别并消除恶性转化的细胞, 随后逃离消除期的恶性转化细胞会进入平衡期; 在平衡期, 肿瘤细胞通过改变自身的基因组和构建适合生存的肿瘤微环境(tumor microenvironment, TME)使其早期病变能够存活; 最后在肿瘤逃避期, 肿瘤细胞将募集免疫抑制细胞如骨髓衍生抑制细胞(marrow-derived suppressor cell, MDSC), 调节性T细胞(regulatory T cells, Treg细胞)以及肿瘤相关巨噬细胞(tumor-associated macrophage, TAM)营建一个免疫抑制的肿瘤微环境, 逃避宿主免疫监视, 致使肿瘤的发生和发展[7].

肿瘤免疫治疗是一种当前备受瞩目的新型抗癌疗法, 旨在提高肿瘤细胞的免疫原性, 激发和增强机体抗肿瘤免疫应答, 协同机体免疫系统杀伤肿瘤, 抑制肿瘤的生长和进展. 早在19世纪90年代, 美国的外科医生William Coley便开始采用Coley毒素治疗肿瘤, 开启了肿瘤免疫治疗的先河. 目前肿瘤免疫治疗大致分为两种类别: 被动免疫治疗和主动免疫治疗. 被动免疫疗法是通过识别肿瘤相关抗原(tumor associated antigens, TAAs)直接靶向清除肿瘤细胞, 如免疫检查点抑制剂包括PD-1(Programmed cell death-1)/PD-L1(Programmed death-ligand 1)单抗和

表 1 FDA批准用于肿瘤免疫治疗药物或疗法

通用名(商品名)	申请机构	靶点/机制	适应症
Pembrolizumab(Keytruda)	默沙东	PD-1	非鳞状非小细胞肺癌
Nivolumab(Opdivo)	百时美施贵宝	PD-1	非鳞状非小细胞肺癌
Atezolizumab(Tecentriq)	罗氏/基因泰克	PD-L1	转移性非小细胞肺癌
Durvalumab(Imfinzi)	阿斯利康	PD-L1	晚期或转移性尿路上皮癌
Avelumab(Bavencio)	默克/辉瑞	PD-L1	默克尔细胞癌
Ipilimumab(Yervoy)	百时美施贵宝	CTLA-4	晚期黑色素瘤
Tisagenlecleucel(Kymriah)	诺华制药	CAR-T	B细胞前体急性淋巴性白血病
axicabtagene ciloleucel(Yescarta)	风筝制药	CAR-T	非霍奇金淋巴瘤

CTLA-4(cytotoxic T-lymphocyte associated antigen 4)单抗, 以及过继性T细胞治疗包括CAR-T(chimeric antigen receptor T cell)疗法等; 主动免疫疗法如肿瘤疫苗是通过激活患者体内的抗癌免疫细胞, 引发强烈而持久的抗癌免疫应答反应. 目前, 已被美国FDA批准的新型的肿瘤免疫疗法主要包括单抗类免疫检查点抑制剂、CAR-T细胞疗法等(表1).

胰腺癌是一种难治性的消化道实体肿瘤, 其特征性表现在具有一个呈高度免疫抑制状态的肿瘤微环境, 大量的免疫抑制性细胞广泛浸润其中, 包括调节性T细胞、肿瘤相关巨噬细胞(TAM)、骨髓源性抑制细胞(MDSC)等, 同时还有因肿瘤基质增生而形成致密结缔组织屏障包绕, 从而阻碍了抗肿瘤的效应T细胞进入肿瘤内部消灭肿瘤[8-10]. 近年来, 各种新型的肿瘤免疫疗法(如检查点阻断剂、过继性T细胞疗法等)在许多恶性肿瘤的临床治疗中获得了巨大的成功. 不幸的是, 近期的临床试验表明免疫检查点阻断剂如PD-1/PDL-1单抗, CTLA-4单抗治疗胰腺癌的临床效果欠佳; 而对于胰腺癌的肿瘤疫苗而言, 尽管I期临床试验数据比较理想, 但后期临床数据已经证实对胰腺癌治疗无效[11-13]. 最近研究人员发现一小部分瘤内T细胞浸润率高的胰腺癌患者获得更长的生存时间, 这也表明用肿瘤免疫疗法具有治愈胰腺癌的潜力[14]. 虽然目前针对胰腺癌免疫的临床治疗效果不尽人意, 但是在各种免疫治疗策略的研究方面还是取得了很大的进展. 接下来, 我们将总结下当前研究热点的胰腺癌免疫治疗手段的研究进展以及所面临的诸多挑战.

2 胰腺癌免疫治疗的研究进展与挑战

2.1 免疫检查点抑制剂 肿瘤细胞表面抗原可与抗原呈递细胞表面的负性共刺激性的配体或受体(即免疫检查点分子)相结合, 使得体内T细胞凋亡或活性减弱, 从而导致肿瘤细胞逃避免疫系统的监视[15]. 免疫检查点抑制剂作用靶点为免疫检查点分子, 主要包括程序性死亡蛋白-1(PD-1)/程序性死亡蛋白配体-1(PD-L1)和细胞毒性T淋巴细胞相关抗原-4(CTLA-4)等负性调节T细胞功能的分子. 目前理论上认为如果通过有效的手段阻断这些免疫检查点分子的功能, 就能使肿瘤的免疫抑制系统难以维持, 继而解除肿瘤细胞的逃逸机制, 使得机体免疫细胞重新激活而清除肿瘤细胞[16].

PD-1/PD-L1通路是一种负性调节机体免疫应答重要的信号通路, 在肿瘤的免疫逃逸中发挥着重要作用[17-20]. PD-1蛋白在活化的T细胞表面表达, 与肿瘤细胞表达的配体PD-L1相结合, 抑制效应性T细胞的活化, 从而导致肿瘤细胞逃逸机体的免疫监视[21-24]. 近年来, PD-L1/PD-1单抗已经在黑色素瘤和肺癌等恶性肿瘤免疫治疗中取得了显著的成绩. 然而, 令人遗憾的是其在胰腺癌临床治疗中的单一使用往往不能达到理想疗效[25], 究其主要原因可能是由于胰腺癌具有较低水平的PD-1$^+$T细胞浸润和缺乏新的抗原表位. 有研究发现在一些高微卫星不稳定性(MSI)的胰腺癌患者中, 肿瘤抗原新表位负荷高的患者, 对PD-1单抗治疗是有效的[26]; 而对于未出现肿瘤抗原新表位的患者, 也发现PD-1单抗治疗能够有效促进T细胞浸入到肿瘤微环境中[27]. 然而, 最近有研究发现在一些同时具有活化的T细胞和可检测的肿瘤新表位的胰腺癌患者, 对PD-1单抗治疗则无效[28]. 进一步研究发现胰腺癌细胞高表达多种其他免疫抑制分子如TIM3, TIGIT和LAG3, 它们同样也可以抑制抗肿瘤的效应性T细胞活化, 因此, 联合多种免疫检查点抑制剂的治疗策略可能提高胰腺癌的临床疗效[28].

另一个研究热点的免疫检查点分子是CTLA-4, 其表达于T细胞表面, 对配体B7-1和B7-2具有很高的亲和力[29]. 阻断CTLA-4使得肿瘤相关抗原无法启动足够的活化信号来激活B7/CD28和MHC/TCR共刺激通路, 从而促进T细胞的增殖及活化, 达到抑制肿瘤的效果[30,31]. 早在1996年Allison等[31]人就发现抗CTLA-4的单抗可通过增强免疫力来杀伤肿瘤细胞. 近年来, 研究表明CTLA-4单抗对转移性黑色素瘤[32]和肝癌[33]患者的治疗效果尤为显著, 然而将其运用到胰腺癌的治疗, 却未见显著的临床疗效. Royal等[12]对27例胰腺癌

患者接受单独的CTLA-4单抗(Ipilimumab)治疗的Ⅱ期临床试验, 两周后复查所以患者病情并未得到明显缓解. 然而, Le等[34]在Ib期试验中发现Ipilimumab联合基于GM-CSF的全细胞疫苗(GVAX)胰腺癌患者的中位生存期和1年总生存期明显延长. Allard等[35]研究发现靶向抑制CD73表达可以增强抗PD-1和抗CTLA-4单克隆抗体的抗肿瘤活性. 因此, 联合治疗策略如PD-L1/PD-1单抗辅以化疗、肿瘤疫苗、CTLA-4单抗等可通过增强肿瘤免疫原性, 提高胰腺癌的疗效, 这可能是目前解决胰腺癌免疫治疗困境的最佳策略[36,37].

2.2 过继性T细胞治疗 过继性T细胞治疗(adoptive cell transfer, ACT)是通过复杂的离体培养和细胞工程方法, 将体外大量扩增的具有抗肿瘤反应性的细胞回输到癌症患者体内的新型免疫疗法. 目前, ACT根据扩增T细胞的类型, 可分为肿瘤浸润淋巴细胞(tumor infiltrating lymphocytes, TIL)疗法、T细胞受体(T cell receptor, TCR)疗法和嵌合抗原受体T细胞(chimeric antigen receptor T cell, CAR-T)疗法. CAR-T治疗是目前最具潜力的肿瘤免疫治疗方法, 为患有难治性癌症的患者提供了希望. Beatty等[38]在治疗复发转移性胰腺癌患者中, 采用二代CAR-T回输, 结果成功使一例患者肝转移灶消失. Stromnes等[39]对小鼠T细胞进行TCR编辑并回输给自发性胰腺癌小鼠模型体内, 结果发现TCR编辑的T细胞聚集于肿瘤区, 并能诱导细胞凋亡及基质重塑. 令人可喜的是, CAR-T在B细胞恶性肿瘤中表现出显着的临床疗效, 且治疗反应率高达90%. 最近, 两种CAR-T疗法tisagenlecleucel和axicabtagene ciloleucel分别被美国FDA批准用于B细胞前体急性淋巴性白血病和非霍奇金淋巴瘤.

尽管CAR-T细胞疗法对血液肿瘤表现出显著的临床疗效, 但是仍存在许多障碍阻碍了其立即应用于人类实体肿瘤, 包括胰腺癌. 目前, 虽然许多通过胰腺癌过表达的自身抗原如CEA, PSCA, 间皮素和HER等构建的CAR-T细胞已在小鼠胰腺癌模型中证实是有效的, 但是大多数CAR-T疗法的后期临床试验数据却都不尽人意. 通常认为肿瘤治疗的关键点在于能否保证CAR-T细胞在肿瘤部位的持续存在. 因此, 我们推测CAR-T疗法治疗胰腺癌失败可能存在多方面的原因. 首先, CAR-T细胞必须能够有效地进入肿瘤才能保证其治疗效果. Ward-Kavanagh等[40]联合淋巴耗竭全身照射(WBI)和抗CD40激动剂(αCD40)治疗原发性神经内分泌胰腺肿瘤, 研究发现联合WBI和αCD40治疗可显著延长T细胞的增殖并增加供体T细胞在小鼠淋巴器官和胰腺中的积累. 近来, 针对其他实体恶性肿瘤的研究表明加入乙酰肝素酶或肿瘤靶向细胞因子受体的CAR-T疗法可显著改善其肿瘤内运输和抗肿瘤反应. 此外, 多项针对间皮瘤的研究表明CAR-T的区域性给药比全身给药更有效[41]. 因此, 保证CAR-T细胞能够顺利进入肿瘤内部的措施可能有利于增强CAR-T疗法的疗效. 其次, 目前许多正在研究中的针对胰腺癌的CAR-T疗法多是含有部分鼠源性单链可变片段, 易于通过抗体介导反应而消除, 影响CAR-T细胞持续发挥其治疗作用. 因此, 可能需要构建完全人源性CAR或联合清除B细胞才能解决此难题. 另外, CAR-T细胞很快就被胰腺癌的免疫抑制肿瘤微环境所消耗, 也阻碍了其最大程度发挥其治疗效果. 近来, Chapuis等[42]研究表明增加阻断CTLA-4的肿瘤特异性T细胞可诱导黑素瘤患者体内的T细胞持续存在并具有记忆性, 这也为提高CAR-T疗法在胰腺癌中的疗效提供了新的思路.

此外, CAR-T疗法所面临挑战主要在于由于T细胞输注引发的诸如不完全肿瘤靶向特异性, 神经毒性和严重细胞因子释放综合征的挑战引起了显着的安全性问题. 此外, 肿瘤抗原丢失和肿瘤异质性也是目前CAR-T细胞疗法所面临的难题. 为了应对以上这些挑战, 人们已经开始研发具有更多功能的CAR-T细胞, 包括门控系统的CAR-T细胞, 自杀系统的CAR-T细胞以及诱导基因表达的CAR-T细胞等, 可以在空间和/或时间上精密调控CAR-T细胞的效能, 减少CAR-T疗法的相关并发症.

2.3 肿瘤疫苗 肿瘤治疗性疫苗具有诱导强大的抗肿瘤免疫应答的潜力, 也是当前研究胰腺癌免疫治疗的热点方向之一. 肿瘤疫苗主要包括肿瘤细胞、肿瘤相关蛋白或多肽、表达肿瘤抗原的重组基因等, 旨在激活循环中的肿瘤特异性T细胞, 达到消灭肿瘤目的[43]. GVAX是一种由肿瘤细胞组成的癌症疫苗, 经基因修饰可分泌粒细胞-巨噬细胞集落刺激因子. Jaffee等[44]对14例胰腺癌患者采用GVAX疫苗, 其中3例患者生存期大于25 mo. Le等[45]在早期临床试验中发现, 使用GVAX能够提高癌症患者的总体生存期. 然而, 近来的Ⅱb/Ⅲ期临床数据证实GVAX尚不能显著提高胰腺癌患者的生存率[13]. Middleton等[46]运用源自肿瘤相关自身抗原人端粒酶(hTERT)的单肽疫苗的Ⅲ期临床试验显示, 对于转移性肿瘤的患者并没在生存时间上获益, 甚至未发现有免疫应答反应. 另外, 超急性胰腺癌疫苗(Algenpantucel-L)由表达鼠α-1,3-半乳糖基转移酶的经照射的同种异体胰腺癌细胞组成. Hardacre等[47]研究发现胰腺癌患者在术后接受吉他西滨和基于5-氟尿嘧啶的放化疗及Algenpantucel-L疫苗, 能够显著提高患者1年生存率并且降低肿瘤复发率. 然而, 不幸的是其与GVAX具有同样的结局, 在最近的Ⅲ期临床试验中也未能表现出显著提高胰腺癌患者的存活率[48].

最近, 研究发现肿瘤疫苗在佐剂辅助下发挥更大的疗效. Mehla等[49]利用肿瘤抗原靶向抗体mAb-AR20.5、抗PD-L1和PolyICLC联合免疫治疗, 诱导抵抗表达人自身抗原MUC1的胰腺肿瘤, 并产生持久的MUC1特异性的细胞免疫应答反应. Arlen等[50]将表达癌胚抗原(CEA)和MUC1的肿瘤疫苗接种晚期胰腺癌患者, 并以粒细胞-巨噬细胞集落刺激因子(GM-CSF)为佐剂, 研究结果表明接种肿瘤疫苗的晚期胰腺癌患者的生存时间明显延长. 另外, Abou-Alfa等[51]报告的Ⅰ/Ⅱ期临床数据表明, 接种表达K-ras突变基因编码肽段的肿瘤疫苗, 辅以GM-CSF佐剂, 能够显著提高胰腺癌患者的免疫应答反应强度, 并且显著延长患者的中位生存期. 最近的研究数据表明, 佐剂可能不像之前认为的那样有利于肿瘤疫苗发挥疗效. 研究发现佐剂不仅可能降低肿瘤疫苗的整体免疫反应的强度, 而且还在肺癌术后肿瘤微环境中表现出强烈的免疫抑制作用[52,53].

3 结论

胰腺癌当前依然是一种难治性消化道实体癌, 预后极差. 尽管当前针对胰腺癌的各种新型免疫疗法的临床效果仍尚未明确, 但是很多疗法已经展现出非常光明的应用前景. 近些年来, 经历大量单一免疫治疗策略的临床试验失败的教训, 使我们充分认识到由于胰腺癌的分子生物学变异比较大, 单个靶点的阻断不足以完全阻断活化的肿瘤增殖通路. 因此, 将目前已经证实的临床有效的免疫疗法的联合应用可能取得更好的临床疗效. 此外, 基于目前的大数据和二代基因测序技术的发展, 探寻更多更具有特异性的肿瘤生物标志分子, 研发新的靶向药物和肿瘤疫苗, 这些都是将来具有广阔前景的肿瘤免疫治疗的研究方向. 尽管目前胰腺癌的免疫治疗面临着许多困难与挑战, 但我们仍有希望克服重重困难, 开发更为有效的胰腺癌的免疫疗法, 最终战胜这种令人胆寒的绝症.

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