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述评 EDITORIAL

食管癌免疫治疗的现状及展望

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Immunotherapy for esophageal cancer: Current studies and future perspectives

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Abstract

Esophageal cancer is one of the most common malignant tumors of the digestive system, and China has the highest morbidity and mortality rates of esophageal cancer in the world. Currently, main therapies for esophageal cancer include endoscopy, surgery, chemotherapy, and radiotherapy. These traditional treatments have appreciated clinical effects, but the prognosis of this malignancy is still poor. There is accumulating evidence that tumor immune microenvironment plays a key role in the development and progression of esophageal cancer. Recent clinical investigations and ongoing studies indicate that immunotherapy might have a great potential in the treatment of patients with esophageal cancer. Future studies will identify treatment strategies that can maximize therapeutic benefits by combining immunotherapies with existing and novel treatment modalities.

Key Words: Esophageal cancer; Tumor immune microenvironment; Immunotherapy

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摘要

食管癌是消化系统最常见的恶性肿瘤之一, 我国食管癌的发病率及死亡率居世界第1位. 目前食管癌的治疗方式主要是内镜、手术、化疗和放疗. 这些传统治疗手段虽然取得了一定的临床效果, 但对生存期的改善并不明

背景资料
2006年美国癌症年会上Steven Rosenberg博士指出: "免疫治疗是目前知道的唯一一种有望完全消灭癌细胞的治疗手段, 有可能取代目前的放化疗手段; 21世纪将是肿瘤生物治疗的世纪". 2013-12-20, 肿瘤免疫治疗被*Science*列为年度科学突破之首.

同行评议者
肖恩华, 教授, 中南大学湘雅二医院放射教研室; 李鹏, 教授, 首都医科大学附属北京友谊医院消化科

研发前沿

肿瘤免疫治疗是通过调节机体的免疫状态进而达到预防和治疗恶性肿瘤的一种治疗方法. 以细胞因子、肿瘤疫苗、过继细胞治疗(adoptive cell therapy, ACT)和免疫检查点阻断剂为代表的免疫治疗已经在临床应用中显示了巨大的临床疗效. 针对食管癌的治疗已经开展了几十项临床试验, 其中食管癌的ACT治疗、T细胞受体转导的T细胞治疗前期的试验结果已显示出这些免疫治疗方法的巨大效益.

显. 目前的多项研究表明, 肿瘤免疫微环境在食管癌发生发展中起着很重要的作用. 已经完成和正在进行的食管癌免疫治疗的临床试验肯定了免疫治疗在食管癌中的巨大潜力. 免疫疗法与现有的或者新的治疗模式相结合将是食管癌治疗的最佳治疗策略.

关键词: 食管癌; 肿瘤免疫微环境; 免疫治疗

核心提要: 肿瘤免疫治疗具有广阔的应用前景, 其在前列腺癌、黑色素瘤、肺癌和肾癌等恶性肿瘤中的广泛应用为食管癌免疫治疗的发展奠定了基础. 免疫治疗与现有的或者新的治疗模式相结合将是食管癌治疗的方向.

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0 引言

食管癌是发生于食管黏膜上皮组织的恶性肿瘤, 其发病率和死亡率分别居于全球恶性肿瘤第8位和第6位[1]. 我国食管癌发病率和死亡率位居世界第1位. 食管癌主要的病理类型有鳞癌和腺癌. 食管癌发病率随年龄增加而增长, 发病高峰年龄为70-80岁. 食管腺癌男性发病率约为女性3-4倍, 而食管鳞癌在性别上没有显著差异[2].

近几十年来, 食管癌诊断和治疗方面的研究取得了一定进展, 但中晚期的食管癌患者5年生存率仍低于15%. 目前化疗在姑息性治疗中起着中流砥柱的作用, 但其客观缓解率仅为20%-40%, 中位生存期约为8-10 mo[3]. 因此, 迫切需要探索出能够显著改善食管癌患者预后的治疗方式.

近二十年来, 随着肿瘤免疫学的研究深入, 肿瘤免疫治疗已经成为国内外研究的热点之一. 2013-12-20, 肿瘤免疫治疗被*Science*列为年度科学突破之首. 目前, 一些用于癌症患者免疫治疗的方案已通过了美国食品和药物管理局(Food and Drug Administration, FDA)和欧洲药品监管机构的审批, 被广泛用于前列腺癌、黑色素瘤、肺癌和肾癌等疾病, 并取得了一定的临床疗效, 为其在食管癌等其他实体瘤的临床研究奠定了基础. 本文将针对食管癌免疫微环境及免疫治疗的主要研究现状及临床应用前景进行综述.

1 食管癌的诊疗现状

食管癌的治疗和预后依赖于精确评估癌症浸润的深度和淋巴结的侵犯程度, 内镜超声和PET检查的应用进一步完善了分期[4]. 无禁忌证或合并症0期或Ⅰ期的腺癌患者首选内镜治疗[5]. 已经侵犯到黏膜肌层并进入黏膜下层的T1b肿瘤, 根治性食管切除是优先选择的方案[6]. 局部进展期肿瘤最佳治疗手段是根治性食管切除, 根治性放化疗也能达到治疗目的[7], 新辅助化放疗或化疗的应用亦能提高临床治疗效果[8-10]. 姑息性化疗则常用于治疗不能切除的、转移或复发的晚期食管癌[11,12]. 此外, 多西他赛联合雷莫芦单抗也取得一定疗效, 而曲妥珠单抗单一使用增加晚期食管腺癌总生存期(overall survival, OS)和无进展生存期(progression-free survival, PFS)分别为2.7 mo和1.7 mo[13-15].

尽管如此, 中晚期的食管癌患者5年生存率仍低于15%; 局部进展期患者单纯手术治疗5年生存率仅有20%-25%[16,17], 术后联合放化疗或新辅助放化疗的5年生存率也只有30%-35%[18-20]. 食管癌预后较差原因之一是疾病进展较快, 其次是超过50%的患者在确诊时已出现了可见的转移灶[16]. 因此, 进一步探讨食管癌微环境及其对疾病进展的影响将为食管癌早期诊断和治疗改善奠定坚实的理论基础.

2 食管癌的免疫微环境

早在100年前, Paget[21]已提出了“种子与土壤”的假说, 为肿瘤微环境这一概念的提出奠定了基础. 大量数据表明肿瘤微环境中许多免疫相关的细胞和因子及免疫相关的信号通路在肿瘤的发生、转移、复发、血管形成及耐药等各个方面发挥着重要的作用[1,22]. 肿瘤免疫微环境的深入研究是寻找食管癌分子发病机制和新治疗模式的重要环节.

癌细胞周围的各种免疫细胞、成纤维细胞、内皮细胞、血管旁细胞、神经细胞、脂肪细胞及细胞外基质成分构成了肿瘤微环境[23-25]. 其通过抑制癌细胞凋亡、促进增殖、血管形成、耐药及免疫逃逸等机制来发挥促肿瘤作用(图1)[26].

肿瘤微环境中部分基质细胞抑制免疫效

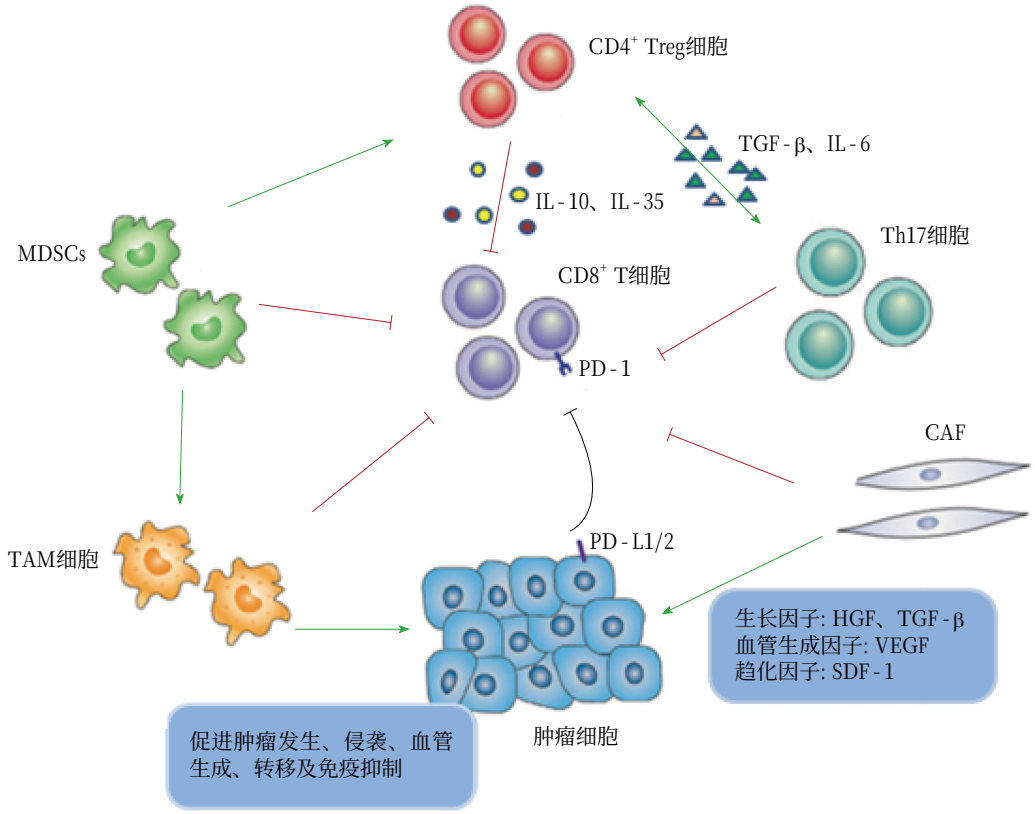

图 1　食管癌免疫微环境. 肿瘤微环境中部分基质细胞抑制免疫效应细胞的功能、促进肿瘤进展. 肿瘤细胞或TAM细胞分泌的趋化因子CCL17和CCL22招募CCR4$^+$ Treg细胞, 后者通过直接接触或分泌细胞因子(IL-10和IL-35)抑制免疫效应细胞. 在IL-6和TGF-β刺激下, Th17细胞可转变为Treg细胞. 炎症和肿瘤衍生因子刺激激活MDSCs, 活化的MDSCs可以直接抑制CD8$^+$ T细胞的活化、诱导Treg细胞等机制来实现免疫逃逸. TAM细胞和CAF细胞通过分泌细胞因子、趋化因子以及各种生长因子促进肿瘤细胞的生长、侵袭、转移及血管形成. 此外, 肿瘤细胞和TAM细胞可表达PD-L1/2, 与PD-1结合后抑制T细胞活化. IL: 白介素; TGF-β: 转化生长因子-β; Treg: 调节性T细胞; MDSCs: 髓系来源的抑制性细胞; TAM: 肿瘤相关巨噬细胞; CAF: 癌相关成纤维细胞.

应细胞的功能、促进肿瘤进展. 肿瘤细胞或肿瘤相关巨噬细胞(tumor-associated macrophages, TAMs)分泌的趋化因子CCL17和CCL22招募CCR4$^+$调节性T细胞(regulatory T cells, Treg), 后者通过直接接触或分泌细胞因子[白介素(interleukin, IL)-10和IL-35]抑制免疫效应细胞. 在IL-6和转化生长因子-β(transforming growth factor-β, TGF-β)刺激下, Th17细胞可转变为Treg细胞. 炎症和肿瘤衍生因子刺激激活髓系来源的抑制性细胞(myeloid-derived suppressor cells, MDSCs), 活化的MDSCs可以直接抑制CD8$^+$ T细胞的活化、诱导Treg细胞等机制来实现免疫逃逸. TAM细胞和CAF细胞通过分泌细胞因子、趋化因子以及各种生长因子促进肿瘤细胞的生长、侵袭、转移及血管形成. 此外, 肿瘤细胞和TAM细胞可表达程序性死亡受体(programmed cell death ligand, PD)-L1/2, 与PD-1结合后抑制T细胞活化.

MDSCs已经被证实在促进肿瘤免疫逃逸、CAF细胞活化及血管形成方面发挥着重要作用[27]. 食管癌微环境中促炎因子如IL-1β、IL-6和前列腺素等的存在可以激活MDSC[28]. MDSC通过直接抑制T细胞的活化[29]、自然杀伤细胞(natural killer cell, NK)的细胞不良反应[30]、精氨酸和半胱氨酸的消耗和诱导Treg细胞等机制来实现免疫逃逸[31,32]. 另一群发挥相似功能的免疫抑制细胞就是Treg细胞. 在生理条件下, Treg细胞可以调节T细胞、B细胞的活化增殖和NK细胞的细胞毒性, 然而在肿瘤微环境中却可以通过分泌免疫抑制相关因子、干扰肿瘤相关抗原(tumor-associated antigens, TAAs)的提呈和抑制免疫效应细胞的细胞不良反应及颗粒酶释放等途径来促进肿瘤的发生和进展[33,34]. 研究表明肿瘤细胞及TAMs可以通过分泌CCL17和CCL22等趋化因子来招募CCR4$^+$的Treg细胞到达肿瘤部位[35,36]. 而肿瘤部位高度聚集的Treg细胞促进肿瘤的浸润和转移, 且与疾病严重程度、化疗后生存率及

■相关报道
随着食管癌诊断和治疗水平的不断进步, 不同角度不同层面对食管癌诊疗的报道逐渐增多, 为大家更深入的了解食管癌提供了有利条件. 如刘维华等系统的分析了*MAGE-A*在食管癌和食管癌细胞系中高度表达的状态, 并进一步说明*MAGE-A*基因编码的抗原肽可由食管癌细胞MHC Ⅰ类分子提呈至细胞毒性T细胞, 进而发挥特异性抗肿瘤活性.

创新盘点
本文针对食管癌免疫治疗的现状进行了系统的介绍, 通过现有的或正在进行的具体临床试验结果来说明免疫治疗在食管癌治疗中的应用情况, 并针对食管癌微环境的主要成分在肿瘤发生及治疗中的作用机制进行了评价. 较之前类似的文章更系统、具体、清晰, 对临床应用和研究有较好的借鉴作用.

预后相关[37-39]. 此外, Th17细胞可以通过分泌IL-17和IL-22、激活STAT3相关信号通路来促进血管形成和肿瘤生长[40]. 然而目前Th17细胞的作用仍然存在争议, 究竟是哪些因子影响了Th17的功能也还没有被很好的定义[40,41]. 因此, 我们尚需要更深一步的了解Th17细胞在食管癌中的作用来发掘潜在的治疗靶点.

TAMs有着各种各样的致瘤机制. 巨噬细胞表型频谱范围从M1型到M2型: M1型巨噬细胞代表着经典活化的巨噬细胞, 有分泌细胞因子, 抗原提呈, 抵抗感染和抗肿瘤等功能. 而M2型巨噬细胞则通过分泌Ⅱ型细胞因子、诱导活化COX2/前列腺素E等机制来产生促瘤作用[42-44]. 食管癌患者癌相关成纤维(cancer-associated fibroblasts, CAFs)的存在与微血管密度相关, 也可通过上皮细胞间质化(epithelial-mesenchymal transition, EMT)促进肿瘤进展和转移[45], CAFs也与放化疗后3年生存率和疾病复发有关[46].

PD-1为CD28超家族成员, 是一种重要的免疫抑制分子, 与其配体PD-L1/PD-L2结合后抑制T细胞的活化[47,48]. 多次实验证实PD-L1和PD-L2在食管癌中高度表达[49,50], 其中PD-L1的表达与肿瘤浸润深度和不良预后密切相关, 而PD-L2的表达与$CD8^+$ T细胞浸润减少相关[50]. PD-L2表达的增加可以促肿瘤的Th2细胞因子如IL-4/IL-13分泌[48]. 这些证据表明PD-1的靶向阻断剂在食管癌的治疗中有重大的意义[51].

在食管癌早期阶段, TGF-β信号通过下调*Smad4*和*c-Myc*基因的表达来抑制肿瘤的生长, 而在晚期食管癌中则促进其生长和EMT[52,53]. 这种“开关”作用被认为是衔接蛋白的丢失导致的. 例如β2-血影蛋白就是细胞-细胞相互作用和上皮细胞极性维护中的一种重要衔接蛋白. 在食管腺癌中, 肿瘤细胞中β2-血影蛋白的丢失导致SOX9和c-Myc的表达增加, 但同时也减少了其他TGF-β靶点如E-cadherin和细胞周期调控的p21和p27[54]. 总之, 这些变化使得TGF-β促进了肿瘤的进展并通过促进EMT导致肿瘤的转移.

除了生长因子, 肿瘤微环境中的趋化因子在肿瘤的发生发展中也有着不可忽视的作用. 其中, 主要有成纤维细胞分泌的基质细胞衍生因子-1(stromal cell derived factor-1, CXCL12)[55], 与其相应受体CXCR4或CXCR7结合后可以诱导肿瘤细胞的生长、促进血管生成、刺激运动、侵袭和转移[56]. SDF-1/CXCR4/CXCR7轴与肿瘤侵袭转移以及生存密切相关, 但是用这些独立的组件作为预后分析的指标已经出现了不一致的结果[57]. 尽管如此, 在食管腺癌中SDF-1在体内和体外试验中被证明可以调节CXCR4阳性的肿瘤细胞的迁移. 通过小干扰RNA敲除CXCR4在KYSE-150和TE-13细胞中的表达能够抑制肿瘤细胞的增殖、侵袭和转移能力. 食管鳞癌局部CCL5和CXCL10可招募$CD8^+$ T细胞到达肿瘤部位[58,59].

食管癌免疫微环境的基质成分形成了阻碍免疫效应细胞募集和发挥功能的屏障, 同时为肿瘤细胞的增殖、侵袭和转移提供了土壤. 通过各种手段调节机体的免疫状态达到重塑食管癌免疫微环境的作用将是食管癌免疫治疗的主要研究方向.

3 食管癌的免疫治疗

肿瘤免疫治疗是通过调节机体的免疫状态进而达到预防和治疗恶性肿瘤的一种治疗方法. 以细胞因子、肿瘤疫苗、过继细胞治疗(adoptive cell therapy, ACT)和免疫检查点阻断剂为代表的免疫治疗已经在临床应用中显示了巨大的临床疗效[3,60,61]. 在此将集中探讨肿瘤疫苗、ACT和免疫检查点阻断剂3种免疫治疗策略在食管癌治疗中的研究进展. 食管癌免疫治疗相关的临床试验详如表1.

3.1 肿瘤疫苗 肿瘤疫苗治疗是通过向患者体内导入TAAs来激发患者的特异性抗肿瘤免疫反应. Rosenberg等[62,63]针对2004年之前开展的1306项癌症疫苗研究进行全面审查, 发现总体目标反应率仅为3.3%. 猜测可能是免疫细胞亲和力低或者受到内源性因素抑制等原因造成这些不理想的结果.

针对食管癌的治疗, 一些基于疫苗的临床试验报告已经公布. 一项使用肽疫苗治疗10例难治性Ⅲ或Ⅳ期食管鳞癌患者的Ⅰ期临床试验发现9例患者出现了抗原特异性T细胞免疫应答. 其中1例肝转移的患者出现了持续7 mo的完全缓解, 另有1例患者所有的肺转移病灶出现部分缓解, 还有3例患者无进展生存期持续了2.5 mo. 该试验使用的肽疫苗来源于3种HLA-A24限制性癌睾抗原(TTK蛋白激酶、淋巴细胞抗原6复合物基因座K和胰岛素样生长

表 1 食管癌免疫治疗潜在治疗手段近期开展或已完成的临床试验

类别	肿瘤	治疗手段	研究期别	NCT编号
ACT				
	食管癌	CIK	Ⅱ期	NCT02490735
	多种癌症(包括食管癌)	CTL	Ⅰ期	NCT00004178
	食管癌	NY-ESO-1-TCR T细胞	Ⅱ期	NCT01795976
肿瘤疫苗				
细胞疫苗	多种癌症(包括食管癌)	肿瘤细胞疫苗	Ⅰ期	NCT01258868
	多种癌症(包括食管癌)	H1299溶解产物疫苗	Ⅰ/Ⅱ期	NCT02054104
	多种癌症(包括食管癌)	同种异体肿瘤疫苗	Ⅰ期	NCT01143545
肽疫苗	食管癌	IMF-001	Ⅰ期	NCT01003808
	食管癌	LY6K, VEGFR1, VEGFR2	Ⅰ期	NCT00561275
	食管癌	URLC10, TTK, KOC1, VEGFR1, VEGFR2, 顺铂, 氟尿嘧啶	Ⅰ期	NCT00632333
	食管癌	URLC10	Ⅰ期	NCT00753844
	食管癌和胃癌	G17DT, 顺铂, 氟尿嘧啶	Ⅲ期	NCT00020787
	多种癌症(包括食管癌)	癌胚抗原肽1-6D	Ⅱ期	NCT00012246
靶向治疗				
PD-L1单抗	局部进展和转移的实体肿瘤(包括食管癌)	Atezolizumab(PD-L1单抗)	Ⅰ期	NCT01375842
PD-1单抗	食管癌和胃癌	Pembrolizumab(PD-1单抗)	Ⅱ期	NCT02559687
	一线方案耐药的食管癌和胃癌	Pembrolizumab联合化疗药物	Ⅲ期	NCT02564263
	晚期恶性肿瘤(包括食管癌)	PDR001(PD-1单抗)	Ⅱ期	NCT02460224
CTLA-4单抗	食管癌和胃癌	Ipilimumab(CTLA-4单抗)	Ⅱ期	NCT01585987
	食管癌和胃癌	Tremelimumab(CTLA-4单抗)	Ⅱ期	NCT02340975

ACT: 过继细胞治疗; CIK: 细胞因子诱导的杀伤细胞; CTL: 细胞毒性T细胞; VEGFR: 血管内皮生长因子受体; PD: 程序性死亡受体; CTLA-4: 细胞毒性T淋巴细胞相关分子4.

应用要点
在食管癌免疫治疗的临床应用分析的基础上提出免疫治疗与现有治疗模式的结合是今后食管癌治疗方向的观点, 并辅以具体试验的证据, 为食管癌免疫治疗在临床具体应用方案的制定提供了有力证据.

因子-Ⅱ mRNA结合蛋白3)[64]. 紧接着, 针对该疫苗的多中心的Ⅱ期临床试验也顺利开展. 该试验评估了HLA-A*2402阳性和阴性食管鳞癌患者在疫苗应用后OS、PFS和免疫应答情况. 结果显示, 在HLA-A*2402阳性患者(n = 35)中观察到了免疫应答, 但是相对于HLA-A*2402阴性患者(n = 25)其OS并没有统计学的差异(4.6 mo *vs* 2.6 mo, P>0.05), 而PFS则有明显的差异(P = 0.032)[65]. 在Saito等[66]主持的一项肿瘤疫苗试验(n = 20)中, 4例自身肿瘤细胞高度表达MAGE-A4或者MHC Ⅰ类抗原的患者在接种疫苗后不仅观察到MAGE-A4特异性免疫应答, 并且相对于没有免疫抗体的患者其OS明显延长. Wada等[67]以NY-ESO-1作为癌症疫苗在8例食管癌患者中进行试验, 结果显示7例患者出现免疫应答. 在参与临床效果评估的6例患者中, 1例患者出现部分缓解, 2例患者持续维持在无进展状态, 另有2例患者出现混合临床反应. 鉴于这些肽疫苗在临床试验中的初步成果, 其安全性检验及与放疗化疗相结合的相关研究也正逐步开展.

3.2 ACT ACT的概念由Dietrich等[68]于1955年最早提出, 是指通过一定手段将自体或异体免疫细胞在体外扩增后回输入患者体内, 直接杀伤肿瘤和调动机体的免疫功能对抗肿瘤的治疗方法. 目前常用效应细胞可分为两类: 第一类为肿瘤抗原非特异性免疫细胞, 包括自体淋巴因子激活的杀伤细胞、细胞因子诱导的杀伤细胞(cytokine-induced killer, CIK)及NK细胞, 这类细胞通过从外周血细胞中分离并经淋巴因子或细胞因子诱导刺激获得; 另一类效应细胞为肿瘤抗原特异性T细胞, 包括肿瘤浸润性淋巴细胞(tumor infiltrating lymphocytes, TIL)、细胞毒性T细胞(cytotoxic T lymphocyte, CTL)以及经基因工程化的T细胞包括T细胞受体转导的T细胞(T cell receptor transferred T-cells, TCR-T)和嵌合抗原受体修饰T细胞(chimeric antigen receptors modified T-cells, CAR-T)[69,70].

首次ACT的人体试验通过回输CIK和重组IL-2来提高转移性癌症患者的生存, 该方

名词解释
肿瘤微环境: 是指癌细胞周围的各种免疫细胞、成纤维细胞、内皮细胞、血管旁细胞、神经细胞、脂肪细胞及细胞外基质成分所构成的癌细胞发生发展的微观环境; 肿瘤免疫: 是指通过调节机体的免疫状态进而达到预防和治疗恶性肿瘤的一种治疗方法. 常见的治疗方法包括细胞因子、肿瘤疫苗、ACT和免疫检查点阻断剂等.

案已成功应用于治疗难治性转移性黑色素瘤, 而对于其他类型的癌症比如脑胶质瘤、肾细胞癌、非小细胞肺癌等, 其客观缓解率从20%-72%不等[16,71,72].

迄今为止, 食管癌的ACT治疗已经有若干临床试验评价. 由Besser等[73]和Toh等[74]首次公布的研究中, 从食管鳞癌患者外周血中分离出单个核细胞, 在体外给予自体肿瘤细胞刺激, 将获得的CTL联合IL-2借助内窥镜注入肿瘤部位或直接注射到转移灶内. 后期结果显示一半的患者出现了客观反应, 其中36%的受试者达到了完全缓解或部分缓解. CTL和TIL细胞是开展实体肿瘤免疫治疗的热点, 其杀瘤机制明确. 但从肿瘤患者的外周血和组织中很难获取足够数量的抗原特异性T细胞用于回输. 基因工程修饰的肿瘤特异性T细胞的开发解决了这一难题, 在恶性肿瘤的ACT中具有巨大的应用前景.

TCR-T细胞是将抗原特异性的高亲和性TCR的α和β链转入T细胞并表达在细胞表面, 进而有效识别并杀伤表达该抗原的肿瘤细胞. 目前食管癌中常见的TAAs有癌睾抗原MAGE-A3/4和NY-ESO-1. 多项研究[75-77]表明MAGE-A3在食管癌中表达比例约为90%, NY-ESO-1在食管癌中表达比例高达40%-90%. 近期, 由Kageyama等[78,79]开展的一项基因工程化T细胞Ⅰ期临床试验前期, 向MAGE-A4阳性的复发的食管癌患者回输TCR-T细胞, 并后续应用MAGE-A4肽疫苗, 连续5 mo检测10例受试者外周血中TCR-T细胞, 其中5例受试者可持续检测到特异性T细胞. 7例受试者在治疗2 mo后出现了进展, 但另外3例受试者存活时间超过了27 mo.

CAR-T细胞为基因工程化T细胞的另一种类型. CARs是将靶抗原相对应抗体的单链可变区和T细胞信号分子融合而成能够特异性识别并结合TAAs的嵌合受体, 将CARs这样一种嵌合抗原受体的结构通过基因工程转入T细胞后获得CAR-T. 1989年Gross等[80]首次将CARs的结构成功构建进入T细胞使其发挥特异性杀伤功能. 截止到目前, 已经公布20余项关于CAR-T治疗恶性血液系统肿瘤的临床试验数据. 以CD19为靶向的CAR-T细胞在淋巴瘤和B细胞白血病的Ⅰ、Ⅱ期临床试验中显示了良好的抗肿瘤作用[81-84]. 针对实体瘤的CAR-T疗法, 早期一代CAR应用于临床并未出现理想的结果[85], 根源在于实体瘤缺乏独特的TAAs, T细胞归巢至肿瘤位点的效率低、持久性差, 瘤内免疫抑制环境强烈抑制CAR-T细胞功能. 应用二代或者三代CAR技术靶向实体瘤的临床试验尽管比较有限, 但一些比较可观的临床试验结果正逐步揭晓. 其中一项针对19例转移或复发HER2阳性肉瘤的患者, 应用HER2-CAR-T治疗后4例患者出现了12 wk-14 mo的病情稳定状态[86]. 近期, Feng等[87]公布的一项EGFR-CAR-T治疗EGFR阳性复发/难治的非小细胞肺癌患者的临床试验结果显示, 11例参与评价的患者中2例患者出现了部分缓解, 5例患者出现了2-8 mo不等的病情稳定状态, 整个临床试验中未出现明显的不良反应. 在食管癌的治疗方面, 目前还未开展CAR-T疗法相关研究. 但食管癌中不断涌出的抗肿瘤靶点如HER2[88], 也为下一步研究的开展提供了参考依据.

3.3 免疫检查点阻断剂 近年来, PD-1/PD-L1阻断剂在黑色素瘤和肺癌的治疗中取得了鼓舞人心的临床效果[89,90]. 关于PD-1阻断剂在食管癌治疗中的潜在作用, 可以透过肿瘤免疫微环境的基因组图谱的分析结果来预测. 从食管癌肿瘤组织中分离出的MDSC上PD-L1的表达有显著的上调, 约60%的食管癌组织TIL中能检测到PD-1的表达[47,91]. 值得注意的是, PD-1及其配体的高度表达与患者较差预后呈明显相关性[49]. 因此, 抑制PD-1/PD-L1通路对于食管癌的治疗有着不可忽视的价值.

目前, 关于PD-1或PD-L1阻断剂治疗食管癌的临床试验的结果尚未公布. 但正在进行研究的初步结果表明PD-1阻断剂Pembrolizumab在PD-L1阳性表达的食管癌患者有可接受的安全性. 中期分析客观缓解率约为30%, 持续反应期长达40 wk[92]. 这些结果为继续完成Pembrolizumab在食管癌患者应用的关键性研究奠定了基础.

细胞毒性T淋巴细胞相关分子4(cytotoxic T lymphocyte antigen-4, CTLA-4), 也称为CD152属于免疫球蛋白超家族, 可作为免疫检查点. 当活化$CD4^+$辅助性T细胞表面表达CTLA-4, 该类细胞就会向T细胞发送抑制性信号[93]. 而高度表达CTLA-4的$CD4^+$ Treg细胞则通过减少IL-2的分泌和下调IL-2受体的表达将T细胞阻滞在细胞周期的G_1期[94,95]. Ipilimumab和Tremelimumab两个完全人源化的单克隆抗

CTLA-4抗体已获得FDA批准用于治疗黑色素瘤和间皮瘤[96,97]. 近期一项调查Tremelimumab针对晚期胃癌和食管癌治疗有效性的Ⅱ期临床试验(n = 18)已经完成. 尽管只观察到了5%的反应率, 但其中4例患者病情得到控制, 1例患者在8周期(25.4 mo)治疗后出现了部分缓解并持续了数月[98]. 正在进行的临床试验结果预计将进一步凸显出单克隆抗CTLA-4抗体在食管癌中的临床应用价值.

4 食管癌的综合治疗

肿瘤的治疗目前已经进入了综合治疗的时代, 临床实践证明采用任何单一的治疗方法都难以取得最佳的效果. 因此, 除一些早期肿瘤和个别特殊类型的肿瘤以外, 绝大多数肿瘤的治疗原则是综合治疗. 新近的研究结果表明, 免疫治疗和化疗的联合使用在多种肿瘤治疗中取得了较单一疗法更优的效果. 大量的研究证明, 免疫治疗与化疗的联合使用具有多项优点, 他不仅能逆转肿瘤晚期导致的免疫抑制、提高肿瘤抗原的交叉提呈作用、促进杀伤性T细胞增殖并使其更易杀伤肿瘤细胞, 还可以在一定程度上减少化疗的不良反应以及减缓肿瘤细胞耐药性的发生[99-101]. 在免疫治疗与手术相结合的研究中, 多项研究[102,103]发现DC-CIK细胞治疗在清除微小残留病灶、预防肿瘤复发转移、提高治愈率方面具有良好的临床价值. 而在食管癌治疗中, 免疫治疗与放疗的结合则显示出更加突出的临床效果. 放射治疗是食管癌治疗的关键组成部分, 通过水分子和羟自由基介导的DNA链的断裂来杀伤肿瘤细胞. 在这过程中, DNA的损伤可改变基因的表达, 进而使肿瘤细胞表型发生了变化, 相当于为破坏免疫系统的肿瘤细胞进行“标记”[104]. 大量数据表明放疗能改变局部肿瘤的微环境, 这为放疗与免疫治疗的结合提供了有力证据[105,106].

5 食管癌免疫治疗的机遇与挑战

免疫疗法在一些肿瘤中取得成功是多年来对免疫系统进行研究的结果, 也表明其在癌症治疗中作出了贡献. 更值得一提的是, 若干种免疫检查点阻断剂也已经或正在被FDA批准, 预计下一步将加快步伐以单药或者与其他治疗模式相结合应用于临床[107,108]. 然而, 机遇与挑战并存, 在免疫治疗中仍有些关键问题并未回答. 首先, 许多治疗癌症的靶向分子药物, 如何确定以最小的毒性取得最大临床获益的生物学剂量仍需探究; 其次, 鉴于当前大多数的免疫疗法主要是通过激活免疫系统来发挥抗肿瘤效应, 他要求患者在接受初始免疫治疗之前存在一定程度的免疫力. 因此, 全面评估患者的免疫状态和寻找预测免疫治疗效果的生物标志物势在必行. 此外, 大量证据表明辐射和化疗药物的暴露可能影响肿瘤细胞DNA突变率, 促使一些新抗原的形成. 当前的免疫治疗与放化疗联合应用时, 确定放疗的剂量、强度及持续时间, 或者定时放化疗是联合治疗取得最大效益的先决条件.

6 结论

免疫治疗在恶性肿瘤的治疗中具有广阔的应用前景. 食管癌细胞高频率的突变以及在其他胃肠道恶性肿瘤中免疫治疗凸显的有效成果为食管癌免疫治疗的研究提供了有力证据. 采取免疫疗法与现有的或者新的治疗模式相结合的治疗策略将是今后食管癌治疗的方向.

同行评价

食管癌是消化系统最常见的恶性肿瘤之一, 本文系统评价了不同免疫疗法目前现状及发展的前景, 较全面论述免疫治疗在食管癌治疗中的巨大潜力. 认为采取免疫疗法与食管癌的传统治疗手段(内镜、手术、化疗和放疗)是今后食管癌治疗的方向. 信息量大, 比较新颖, 对临床应用和研究有较好的借鉴作用.

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• 消息 •

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