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胃癌的过继性免疫治疗研究进展*

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摘要:胃癌是目前世界上发病率及致死率较高的恶性肿瘤之一,在东亚地区尤其显著。针对胃癌的治疗手段仍是传统的手术联合化疗、放疗为主,尽管靶向药物治疗提供了新的选择,但其对晚期胃癌的疗效仍然有限。胃癌的免疫治疗作为独特的治疗手段,在近十多年发展较为活跃,特别是过继性免疫治疗手段不断有创新。过继性免疫治疗主要依赖回输具有抗肿瘤活性的细胞,目前回输的细胞由具有非特异性抗肿瘤作用向具有特异性抗肿瘤作用演变,特别是嵌合性抗原 T 细胞治疗的出现,为进展期胃癌患者提供了一种潜在的选择。本文对胃癌过继性免疫治疗中采用的不同免疫活性细胞的作用机制、临床应用等进行总结,并针对其不足提出利用基因工程技术增强治疗靶向性、降低免疫逃逸的研究方向。

关键词:胃癌;过继性免疫治疗;免疫活性细胞

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Advances in Adoptive Immunotherapy of Gastric Cancer*

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ABSTRACT: Gastric cancer is one of malignant tumors with high incidence and mortality in the present world, especially in East Asia. The main therapeutic method is the traditional surgery combined with chemotherapy and radiotherapy. Although the targeted therapy is a new choice for patients with advanced gastric cancer, the treatment outcomes are still limited. Immunotherapy is an unique treatment for cancers and has been developed actively in the last ten years. As a part of immunotherapy, we have made new progress in adoptive immunotherapy. As a common treatment of adoptive immunotherapy, adoptive cell therapy is the transfusion of antitumor immunocompetent cells into a cancer patient. The Chimeric Antigen Receptor (CAR) T cell therapy is a potential treatment for advanced gastric cancer patients. We summarized functional mechanism and clinical applications when adopting different kinds of immunocompetent cell in this article. The further research is needed to improve tumor targeting and to avoid immune escape by genetic engineering technology.

Key words: Gastric cancer; Adoptive immunotherapy; Immunocompetent cell

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前言

胃癌作为最常见的消化道恶性肿瘤之一,在我国其发病率和死亡率均较高^[1]。目前我国胃癌的早期诊断仍有待完善,确诊的胃癌患者中多为进展期胃癌,主要治疗手段仍是传统的根治性手术辅以术后化疗、放疗等综合治疗,新辅助化疗对于晚期肿瘤负荷较大者的预后改善仍有限,靶向治疗也仅仅是为一部分患者提供了新的选择^[2-4]。恶性肿瘤的免疫治疗为肿瘤患者提供了一种更具潜力的治疗手段,它主要通过调节患者自身的天然免疫机制或刺激机体内的抗肿瘤免疫反应,从而达到控制和杀伤肿瘤细胞的目的^[5-6]。迄今为止,肿瘤的免疫治疗主要有细胞因子治疗、单克隆抗体疗法、过继性免疫治疗等。胃癌因其抗原的异质性特点,使其肿瘤疫苗、单克隆抗体在制备上存在较大困难,过继性免疫治疗则是一种被动性免疫治疗,主要依赖

用于回输的效应细胞发挥抗肿瘤作用,部分规避了机体免疫防御机制中效应细胞无法有效识别、杀伤肿瘤细胞的问题^[6,7]。嵌合性抗原受体的出现为过继性免疫治疗的发展提供了新的契机,它使得回输的效应细胞具备了更强靶向性^[8],进一步提升了杀伤肿瘤的效果。本文将就过继性免疫治疗的概念,主要采用的免疫活性细胞分类、作用机制及其在胃癌治疗中的应用进行归纳总结,分析当前过继性免疫治疗在胃癌临床治疗中存在的特异性、靶向性低,肿瘤免疫逃逸等不足,并对其发展前景进行综述,这对提高胃癌患者疗效及预后有着重要意义。

1 过继性免疫治疗的定义和特点

过继性免疫治疗指通过向肿瘤患者体内回输免疫效应细胞,达到提高肿瘤细胞的杀伤和控制作用的治疗方法。为了获得回输所需的效应细胞,需要经过体外的细胞分选,细胞刺激

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以诱导其扩增,进一步确定效应细胞的抗原特异性或免疫表型等,最终获得多种具有抗肿瘤特性的多克隆效应细胞群或高度选择性杀伤肿瘤细胞的 T 细胞群,目前多采用外周血中的淋巴细胞、单核细胞或肿瘤浸润淋巴细胞进行体外扩增,并通过特殊手段如细胞因子诱导等,使得扩增细胞在免疫反应中获得肿瘤的特异性识别和杀伤效能^[9,10]。

2 用于过继性免疫治疗的免疫活性细胞及其在胃癌治疗中的应用

当前临床胃癌治疗中采取的过继性免疫治疗因采用的免疫活性细胞种类不同,其针对恶性肿瘤细胞的作用靶点、免疫调节途径、效应细胞等均有差异,广泛采用的免疫活性细胞包括树突状细胞、自然杀伤细胞、细胞因子诱导的杀伤细胞等。

2.1 树突状细胞(dendritic cell, DC)

DC 多数起源于骨髓 CD34⁺ 细胞,作为专职的抗原递呈细胞,可通过递呈肿瘤抗原以诱导抗肿瘤免疫反应,在肿瘤免疫中发挥着重要的作用,但同时肿瘤组织中的微环境也可以抑制其成熟分化,使其无法自分泌或诱导其它细胞分泌细胞因子、肿瘤趋化因子等,甚至出现凋亡现象,达到免疫逃避的效果^[11,12]。目前应用 DC 的免疫疗法包括单纯的 DC 回输、负载有肿瘤抗原的 DC 疫苗等方式,在多种肿瘤的治疗中取得了一定的疗效,相关的临床研究也证明了 DC 免疫治疗的安全性^[13-15]。在 DC 免疫治疗胃癌领域中,DC 疫苗无论在胃癌细胞学实验还是临床治疗中得到了广泛的应用。此类疫苗的制备仍在不断完善当中,部分采取骨髓来源细胞,多数通过提取人外周血当中 CD14⁺ 细胞作为前体细胞,加入白介素-4(IL-4)和粒细胞-巨噬细胞集落刺激因子(GM-CSF)等不同刺激因子共培养后得到成熟 DC,将其与胃癌细胞株的碎片混合培养后可提高其诱导针对相应胃癌细胞株的细胞毒性 T 细胞(CTL)反应^[16,17]。随着基因修饰技术的进步,通过病毒感染的方式使 DC 获得肿瘤抗原的基因片段(如 SLC gene, 4-1BBL gene 等)成为新的疫苗制备模式,不仅提高了特异性 CTL 反应,还可提高 DC 诱导的机体抗肿瘤免疫反应^[17,18]。有研究表明采用化学诱导的方式,可以控制 DC 激活的时机,从而发挥 DC 的最大效能^[19]。这种经过基因工程技术处理后的 DC,无论在实验还是临床应用方面均取得了较单纯 DC 细胞回输更好的治疗效果,但仍需进一步的临床应用来优化修饰基因片段的选择。

2.2 自然杀伤(natural killer, NK)细胞

NK 细胞表型为 CD3⁺CD56⁺,不具有主要组织相容性复合体限制性,不需预先致敏即可发挥杀伤肿瘤细胞的作用,主要机制是通过释放穿孔素和颗粒酶诱导靶细胞的凋亡,但肿瘤细胞也可通过改变膜表面蛋白成分及结构、调低 NK 细胞激活和增殖来躲避 NK 细胞的杀伤作用^[20-22]。迄今为止,世界上已有多项针对恶性肿瘤应用 NK 细胞过继免疫治疗临床试验已经完成或正在进行,主要方式包括自体 NK 细胞过继治疗和同种异体 NK 细胞过继治疗,其安全性和有效性均得到证实^[23,24]。针对胃癌的 NK 细胞过继治疗已经由单纯的体内注射转变为体外预处理 NK 细胞再回输体内,例如采用 OK432、FN-CH296 等刺激免疫细胞增殖,提高 NK 细胞的杀伤毒性,但其对人体无毒副作用^[25]。Wu 等^[26]研究发现羽扇豆醇可以提高 NK 细胞的

增殖能力和对多种胃癌细胞株的杀伤毒性,其自身也有抑制胃癌细胞株增殖的功效。当前 NK 细胞主要存在靶向性不足,多次回输后肿瘤细胞免疫逃逸就会出现,需要从药物诱导增强免疫杀伤和抑制肿瘤细胞免疫逃逸两方面入手,综合各种手段提高 NK 细胞对肿瘤细胞的识别、杀伤能力。

2.3 细胞因子诱导的杀伤(cytokine-induced killer, CIK)细胞

CIK 细胞是由单核细胞在体外经过多种细胞因子共同刺激、诱导培养出一群异质细胞,主要成分是 CD3⁺CD56⁺ 和 CD3⁺CD8⁺ 细胞,其中 CD3⁺CD56⁺ 细胞具有最大的细胞毒性作用,因为它具有 T 淋巴细胞的抗肿瘤活性和 NK 细胞无主要组织相容性复合体限制性的杀伤特点^[27,28]。Hontscha C 等^[29]最先在国际注册了应用 CIK 细胞治疗多种恶性肿瘤的临床试验,从此 CIK 细胞逐渐被广泛应用于肝癌^[30]、肺癌^[31]、乳腺癌^[32]等多种恶性肿瘤过继性免疫治疗的动物实验和临床实践当中,其在胃癌治疗中的应用也在不断地探索中,目前主要有单纯 CIK 细胞回输、CIK 细胞联合化疗、CIK 细胞联合 DC 或肿瘤疫苗、CIK 细胞联合靶向药物、CIK 细胞联合细胞因子等治疗方式^[33-35]。由于单纯 CIK 细胞治疗在抗肿瘤特异性、杀伤效力等方面仍存在不足,采用联合治疗方式可发挥免疫治疗与其他治疗方式的互补作用,提高免疫杀伤的靶向性,为胃癌晚期患者提供更多的治疗选择。Peng Z 等^[36]利用 IL-15 基因转染 CIK 细胞后,提高了其增殖能力和肿瘤杀伤效果。有随机临床 II 期研究将 CIK 细胞、脐带血来源的 DC 和化疗三种方式联合应用于进展期胃癌患者,显著延长了其无瘤生存期,疗程中对患者无明显的毒副作用^[37]。由此可见,如果要达到充分发挥 CIK 细胞的抗肿瘤作用,就必须积极需要联合其他手段增强其对肿瘤细胞的识别能力,避免脱靶效应。

3 过继性免疫治疗在胃癌治疗中存在的问题

过继性免疫治疗虽然在胃癌治疗中得到了广泛的应用,但是临床治疗当中仍然存在着很多问题需要注意。首先,过继性免疫治疗以免疫活性细胞向体内回输为主要方式,其治疗对象有一定的限制。患者如果具有严重的自身免疫性疾病、脏器移植病史、哺乳期或妊娠期内、对细胞因子过敏、罹患 T 淋巴瘤等情况中的一种或几种时,是不适于接受过继性免疫治疗的,需要医师在临床工作中注意排查^[5,9]。其次,过继性免疫治疗过程中免疫活性细胞的制备、扩增、回输等环节就会在免疫效应产生之前对治疗效果发生显著影响。目前不同种类免疫活性细胞的制备就无统一的标准,不同医院或研究单位选用的材料、方法就不同,细胞扩增后需要达到的数量、质量无法保障,特别是在胃癌作为实体性恶性肿瘤,究竟应该回输多少细胞才能达到有效的效应细胞和靶细胞比例,也是当前临床试验需要解决的问题。有研究对 DC+CIK、TAL、NK、 $\gamma\delta$ T 等细胞治疗的临床研究进行统计,为保证治疗效果,虽然每次回输的细胞量约 $1-5 \times 10^5$ 个不等,但是相应的回输细胞次数与回输细胞量呈反比,一般采用 3-5 次为 1 个疗程^[38]。再次,在临床治疗中接受过继性免疫治疗的胃癌患者的选择也会影响最终的治疗效果。胃癌不同的发展阶段其肿瘤负荷不同,患者原发病灶能否根治性切除、有无远隔脏器的转移等因素都会对预后产生影响。很多临床医师在胃癌的常规治疗中仍是首选手术后的化疗、放疗

等传统治疗,过继性免疫治疗仅仅作为晚期患者的补充治疗手段^[33,34]。如果患者肿瘤进展至晚期,肿瘤负荷过大,即便接受了过继性免疫治疗,由于应用时机、自身免疫力等问题也会导致疗效欠佳,无法有效延长患者的生存期。目前已有研究将胃癌 I、II 期患者也纳入到研究中以全面评价疗效^[35]。最后,过继性免疫治疗技术尽管仍在不断发展,在胃癌治疗中其应用方式也在不断探索,但胃癌作为基因复杂性和异质性很强的恶性肿瘤,其免疫逃逸的能力也很强^[39],现有的过继性免疫治疗也只能是综合治疗手段的一个重要组成部分。

随着基因工程技术的进步,针对传统免疫活性细胞的诸多不足,过继性免疫治疗的改良研究有了新进展。嵌合性抗原受体(CAR)通过在 T 淋巴细胞膜直接表达肿瘤抗原的受体,使得 T 淋巴细胞的激活不再依赖 MHC 分子就能激活相应的效应细胞,从而达到杀伤肿瘤的作用^[40]。现有的 CAR 技术已经发展了三代,从仅有抗体可变区发展到串联有共刺激分子区,使得其修饰的 T 细胞在存活时间和活化效果上均有增强^[41,42]。以此技术为基础的 CAR T 细胞治疗已成功应用于多种血液系统恶性肿瘤^[43-45],针对实体恶性肿瘤治疗的临床试验也在开展^[41,46],但是针对胃癌治疗的 CAR T 细胞治疗仍在探索当中,其主要难点在于肿瘤抗原的选择。目前已有研究针对 CEA、HER-2/neu、NKG2D 等作为胃癌肿瘤抗原靶点设计了相应的 CAR^[47-49],但均以针对胃癌细胞株的体外实验、动物实验为主,部分项目启动了临床入组计划(NCT02349724、NCT02416466),大规模的临床应用研究尚未进行。

4 小结与展望

现行广泛应用的过继性免疫治疗在胃癌治疗领域得到了充分验证,除了发热、腹痛、关节痛等不良反应外,在其临床疗效的研究中体现了良好的发展潜力。由于所采用的免疫活性细胞在机体免疫反应中所具有的自身特点,在针对胃癌患者的治疗中仍存在着靶向性不足,肿瘤细胞免疫逃逸机制使其无法发挥杀伤作用等缺点。CAR T 细胞治疗作为一种新兴的过继性免疫治疗手段,发挥了基因工程技术的优势,使得 T 细胞在抗肿瘤免疫反应中的靶向性得到了显著提高,为传统过继性免疫治疗中应用的 DC、NK 细胞、CIK 细胞等提供了改进的新思路。随着新的过继性免疫治疗方式不断涌现,特别是经过基因工程改良后,过继性免疫治疗在胃癌临床治疗中的适用范围、治疗方式也会逐步拓展,具有广阔的发展前景。

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