

CAR-T 细胞免疫疗法在胃癌治疗的研究进展

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【摘要】胃癌(Gastric Cancer, GC)是世界上死亡率第三的恶性肿瘤, 传统方法治疗效果欠佳。研究表明, 嵌合抗原受体T细胞(Chimeric Antigen Receptor T-cell, CAR-T)免疫疗法是很有前景的治疗方法, 利用基因工程方法改造T细胞靶向肿瘤抗原可以促进T细胞的抗肿瘤活性。因此, 找寻在肿瘤细胞高表达、在正常细胞低表达或不表达的特异性抗原是提高CAR-T疗法的主要因素。本文介绍了在胃癌中比较重要的CAR-T治疗靶点, 目前已经开展临床研究的靶点主要有: NKG2D, EpCAM, CLDN, MSLN, FOLR1, HER2, MUC1等, 虽然这些靶点已经取得了一些研究成果, 但远远不够, 新的CAR-T治疗靶点是目前研究的热点。

【关键词】胃癌; 细胞免疫疗法; 治疗靶点

中图分类号: R457.2, R735.2

文献标识码: A

文章编号: 2096-8965(2021)01-0064-06

The research progress of CAR-T cell immunotherapy for gastric cancer

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【Abstract】Gastric cancer (GC) is the third leading cause of cancer mortality in the world. Unfortunately, traditional treatments have limited efficacy. Recent research shows that CAR-T immunotherapy is a promising treatment for GC. Using genetically engineered T cells designed to target a tumor specific antigen, researchers are able to harness the natural anti-tumor activity of T cells. Therefore, it is essential to choose specific antigens that are highly expressed on tumor cells but not on healthy cells. In this review, we present an overview of the most important antigens for CAR-T therapy in the context of GC. A number of clinical studies point to the following as important markers: NKG2D, EpCAM, CLDN, MSLN, FOLR1, HER2, MUC1. Although these markers have been met with some success, the search for new and improved targets continues.

【Keywords】Gastric cancer; Cellular immunotherapy; Therapeutic targets

前言

胃癌是最常见的消化系统恶性肿瘤之一, 在癌症中发病率排名第五, 致死率排名第三^[1]。由于胃癌组织的异质性较高, 手术、化疗及放疗等传统

治疗手段效果不够理想, 进展期胃癌五年生存率不足30%, 临床治疗主要以氟尿嘧啶或铂类联合化疗为主, 但治疗效果欠佳^[2]。嵌合抗原受体T细胞(Chimeric Antigen Receptor T-cell, CAR-T)免疫疗法是目前治疗肿瘤的新方法。主要应用于血液

基金项目: 兰州大学第二医院萃英科技创新项目(CY2017-ZD03, CY2017-QN18)

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肿瘤^[3], FDA已批准三款CAR-T产品。CAR-T疗法在实体瘤领域进展较慢, 主要原因是CAR-T细胞在浸润至实体肿瘤组织后会被抑制性肿瘤微环境(Tumor Microenvironment, TME)抑制。因此, 研究靶向实体瘤及其微环境的CAR-T疗法是未来该领域有待突破的难点。

与传统疗法相比, CAR-T细胞免疫疗法能够直接识别肿瘤细胞表面抗原, 直接杀伤肿瘤, 从而减轻机体的排异反应^[4]。近年来, 细胞免疫疗法已由单纯CAR-T细胞疗法逐渐发展为联合免疫检查点抑制剂、细胞因子诱导的淋巴细胞及T细胞靶向杀伤等联合治疗方案, 为治疗实体瘤提供了一种新的可能^[5, 6]。因此, 细胞免疫治疗在实体瘤中具有很好的应用前景。目前, 胃癌的细胞免疫疗法均处于临床试验阶段^[7]。

1 CAR-T的分子结构及发展历程

CARs由细胞外抗原识别区、跨膜区和细胞内转导区三部分组成^[8, 9]。CARs的细胞外抗原识别区

是特异性识别抗原的基础; 跨膜区通常是由CD3、CD8、CD28或FC ϵ RI的跨膜区域组成(见图1), 其主要作用是将ScFv固定在T细胞表面并将信号转导到细胞中; 细胞内信号转导区由CD8、CD28或CD137细胞内区域和CD3 ζ 组成, 其中包含基于免疫受体酪氨酸的激活基序(Immunoreceptor Tyrosine-based Activatory Motif, ITAM)^[10]。CAR可根据细胞内转导区的信号分子数量将其分为第一代、第二代、第三代CAR(见图2)。第一代CAR是在1993年由Eshhar等人构建, 包含一个单链可变片段(ScFv)和CD3 ζ 结构域^[11]。Finney等人构建的第二代CAR包含了一个共刺激域, 其在第一代的基础上解决了T细胞扩增和不良细胞因子产生的问题^[12]。第三代CAR是以第二代为基础, 创建了包含两个串联共刺激分子, 以此增强其效应功能和体内持久性^[13]。研究者为了进一步增强实体瘤中CAR的靶向抗肿瘤和运输活性, 并降低脱靶毒性和免疫抑制作用, 使用新型机制构建了多种形式的第四代CAR^[14]。

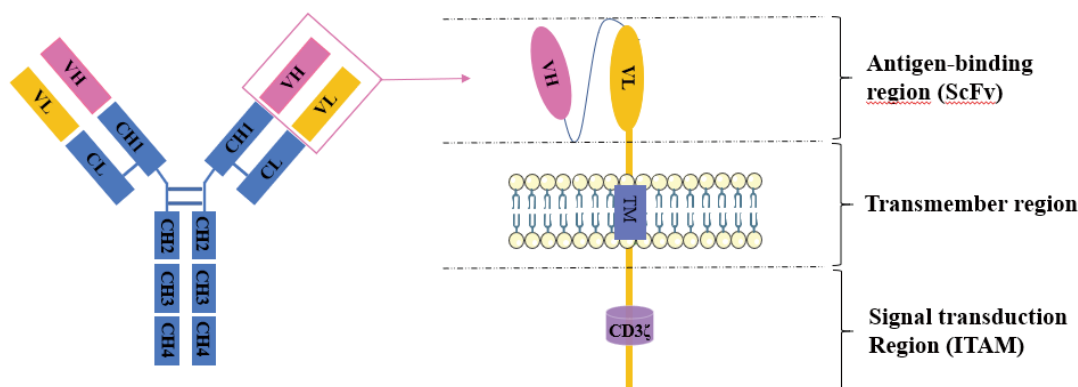


图1 CAR的结构示意图

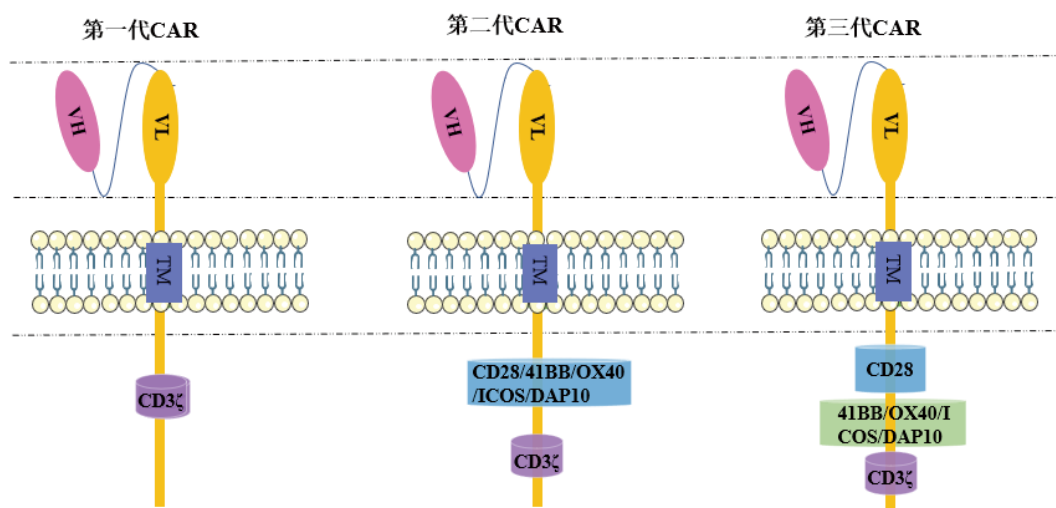


图2 第一代、第二代和第三代CAR结构示意图

2 CAR-T疗法在胃癌中的应用靶点介绍

2.1 NKG2D受体

NKG2D受体是一种凝集素样跨膜糖蛋白,主要表达于自然杀伤细胞(NK细胞)、CD8⁺T细胞和自身免疫抑制的CD4⁺T细胞,它是一个重要的激活受体^[15]。NKG2D受体在正常组织或细胞中呈低表达或不表达,但当NKG2D配体受到病原体感染、基因毒性药物或细胞恶性转化时表达量会迅速增加。因此,NKG2D可以作为CAR-T治疗的理想靶点^[16]。此外Spear等研究发现,NKG2D不仅可以作为CAR-T杀伤的抗原靶点,同时它还可以通过激活宿主自身免疫系统来进行抗肿瘤作用^[17]。目前NKG2D修饰的CAR-T杀伤试验已经在多发性骨髓瘤、恶性胶质瘤及肝细胞肝癌中取得了显著疗效^[18-20],包括胃癌在内的靶向NKG2D的CAR-T杀伤临床试验即将于2021年完成^[21]。

2.2 FOLR1

FOLR1也称为叶酸受体 α 。该蛋白没有胞内区,通过GPI锚定在细胞膜上^[22]。其表达水平与肿瘤进展和细胞增殖密切相关^[23,24]。在卵巢癌、乳腺癌、结直肠癌、肾癌、肺癌和其他实体瘤中高表达,在正常细胞中低表达^[25-27]。该受体能促进增殖,也可能影响有益于肿瘤发生的细胞信号传导,使其成为靶向疗法的良好靶标^[28,29]。大约三分之一的GC患者FOLR1表达较高,在临床前研究中,FOLR1-CAR-T细胞显示出高抗癌活性。这使FOLR1-CAR-T治疗成为一种有希望的治疗方法。在卵巢癌患者中针对FOLR1的CAR-T细胞进行的临床研究表明,该方法有效且安全^[30]。

2.3 HER2

HER2是表皮生长因子受体(Epithelial Growth Factor Receptor, EGFR)家族的表面抗原,由染色体17q21的ERBB2原癌基因编码。HER2由一个包含配体结合位点的结构域,一个跨膜结构域和一个具有酪氨酸激酶活性的结构域组成。EGFR家族的受体在胞内作为信号转导因子,激活后促进细胞增殖并抑制细胞凋亡,致癌并进一步促进肿瘤生长。靶向HER2曲妥珠单抗经常与化疗药物联合应用于HER2阳性胃癌。曲妥珠单抗治疗后约一年可能会出现无法避免的耐药进而导致治疗失败。因此,实施新的、更有效的长期治疗方法是必要的。HER2-CAR-T细胞可以有效消除既定的临床来源

和体外产生的曲妥珠单抗耐药性肿瘤^[31]。研究表明,HER2是胃癌CAR-T细胞疗法中较好的靶点,它的使用减少了对联合疗法的需求。有报道证明HER2-CAR-T细胞可以在体外和小鼠中根除皮肤和葡萄膜黑色素瘤,这也为胃癌的CAR-T治疗提供了思路^[32]。HER2导向的CAR-T细胞对GC细胞具有高亲和力,即使对于HER2表达低的细胞也是如此。有报道称,人源化chA21 scFv的4-1BB共刺激的HER2 CAR的功能表征为广泛采用HER2表达的癌症的过继CAR-T细胞疗法的临床研究提供了基础^[33]。HER2-CAR-T细胞能够在心血管系统中持续发挥作用并在肿瘤环境中蓄积,从而具有永久性抑制肿瘤的作用。

2.4 MUC1

MUC1属于粘蛋白家族,是一种有助于包括胃在内的许多器官的上皮表面形成保护性黏膜屏障的跨膜蛋白。MUC1参与细胞内信号传导并可以充当基质细胞和内皮细胞的粘附配体,影响细胞的移动性并因此影响转移,所以MUC1被应用于监测肿瘤转移和进展的指标,其高水平提示预后不良。癌细胞表面上的MUC-1表现出不同的糖基化模式,这使其成为免疫疗法的理想靶标。有研究表明,第四代人源化MUC1 CAR-T细胞为具有MUC1表达的头颈部鳞状细胞癌患者提供了出色的临床前研究^[34]。也有报道称抗Tn-MUC1 CAR-T细胞在T细胞白血病和胰腺癌的异种移植模型中表现出靶标特异性细胞毒性并成功控制了肿瘤的生长^[35]。由于其参与了肿瘤的发生并且在多种肿瘤的靶向MUC1治疗中高效发挥作用,将其用作GC的治疗靶标非常有前途。

2.5 EpCAM

EpCAM(Epithelial Cell Adhesion Molecule)是一种在基底外侧细胞表面的上皮组织中表达的跨膜糖蛋白,也称为CD326^[36]。研究发现EpCAM在肿瘤的发生及转移中扮演着重要的角色。由于EpCAM在肿瘤细胞的整个表面上均一表达,所以是各种治疗方法(包括免疫疗法)的理想靶标,同时EpCAM的过表达与多数肿瘤患者的预后不良有关,其表达水平可以用来监测和评估肿瘤的发生和预后^[37]。EpCAM在90%以上的GC中过表达,因此将其用作治疗靶点非常合理^[38]。事实证明,针对EpCAM的CAR-T细胞可安全有效地治疗过

表达这种糖蛋白的实体肿瘤,并在临床研究中已取得疗效^[39]。

2.6 CLDN 18.2

CLDN 18 属于 Claudins 蛋白家族成员,由 CLDN 18 基因编码,该蛋白表达在上皮上。上皮细胞是位于皮肤或腔道表层的细胞,主要功能是作为物理和化学屏障,上皮细胞间最主要的连接是紧密连接。Claudin 是构成细胞紧密连接的重要分子,紧密连接决定了上皮细胞的渗透性,也起到阻挡细胞膜表面蛋白和脂质扩散的作用^[40],CLDN 18.2 是 claudine 18 的第二个同工型,位于细胞外膜上。在正常情况下,它在胃黏膜的分化上皮细胞中表达,但它也存在于原发性胃癌中^[41]。在 70% 的原发性胃腺癌及其转移中表达 CLDN 18.2,因此,它被认为是靶向 GC 治疗的潜在治疗靶点^[42]。根据 CLDN 18.2 开发的特异性 CAR-T 细胞,在体内具有良好的持久性,可以有效地穿透癌组织,并且对小鼠没有毒性作用^[43]。因此通过开展针对 CLDN 18.2 的 CAR-T 细胞疗法的更详细研究,有望用于治疗 GC 以及其他 CLDN 18.2 阳性肿瘤^[44]。

2.7 MSLN

MSLN (Mesothelin, MSLN) 是连接糖基磷脂酰肌醇的表面糖蛋白。它是一种分化抗原,在胸膜,心包和腹膜内的间皮细胞中低表达^[45]。MSLN 可能参与细胞粘附,但其功能尚不完全清楚。MSLN 在 30% 的癌症中表达^[46]。在 GC 中观察发现,MSLN 在细胞质中表达高于膜表达,高水平的 MSLN 与肿瘤复发有关,可以用作预测因素^[47]。MSLN 参与肿瘤发生可能与细胞增殖和迁移的加剧,肿瘤细胞侵袭的促进以及 PI3K、ERK 和 MAPK 信号通路的激活转移有关。在肺癌、乳腺癌和胰腺癌中使用针对 MSLN 的 CAR-T 细胞疗法后,已得到良好的治疗效果。而且,MSLN 特异的 CAR-T 细胞疗法可导致小鼠卵巢癌消退,以及胰腺癌转移患者的抗癌反应^[48]。在 CAR-T 治疗中,以 MSLN 为靶点的胃癌治疗也取得了明显的效果^[49]。

3 结论

CAR-T 免疫疗法被认为是目前治疗癌症最有效的方法,在白血病和淋巴瘤中已取得重大突破,但在实体瘤的治疗方面仍面临诸多的挑战和困难^[50, 51]。在实体瘤中,由于肿瘤抗原的异质性、肿瘤免疫微

环境的抑制和肿瘤浸润 T 淋巴细胞的衰竭^[52],使得针对实体瘤的 CAR-T 疗法尚在研发中^[53, 54]。目前,免疫疗法与化学疗法联用已在临床中使用^[55],与单独化疗相比具有显著的治疗效果。本文概述了 CAR-T 细胞免疫疗法在胃癌中的应用靶点和临床治疗前景,以期为胃癌的临床研究提供一定的理论依据。

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[收稿日期] 2020-12-23