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淋巴细胞活化基因 3 在肾癌中的研究进展

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摘要 近年来,肿瘤的免疫治疗获得了前所未有的重视,特别是免疫检查点抑制剂为实体瘤的治疗带来了革命性的进步,其标志性成果包括:第一,使晚期实体瘤患者获得长期生存;第二,使罕见肿瘤患者获得治疗机会;第三,一定程度保全重要器官功能,提高患者生存质量。最近,研究人员发现免疫检查点分子淋巴细胞活化基因 3 (LAG-3)在肾癌中起着重要的作用,已成为一个热门的研究方向,因此,本文重点总结 LAG-3 基因在肾癌中的研究进展,以期为肾癌的治疗提供新的思路 and 策略。

关键词 肾癌;淋巴细胞活化基因 3;免疫检查点

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Research progress of lymphocyte activation gene 3 in renal carcinoma

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Abstract

In recent years, cancer immunotherapy has gained unprecedented attention, particularly immune checkpoint inhibitors, which have brought revolutionary advances in the treatment of solid tumors. The landmark achievements include: (1) Enabling long-term survival for patients with advanced solid tumors; (2) Providing treatment opportunities for patients with rare cancers; and (3) Partially preserving the function of vital organs, thereby improving patients' quality of life. Recently, researchers have found that the immune checkpoint molecule lymphocyte activation gene 3 (LAG-3) plays a crucial role in kidney cancer, which has made it a current focus of research. Therefore, this article focuses on summarizing the research progress of the LAG-3 gene in kidney cancer, aiming to provide new ideas and strategies for the treatment of kidney cancer.

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肾细胞癌即肾癌是泌尿系统最常见的恶性肿瘤之一,其发病率逐年增加^[1]。过去几十年里,肾癌的治疗取得了重大进展,但仍然面临诸多挑战。肾癌的常规一线治疗以手术联合放化疗为主,但大量临床证据显示该策略对晚期病例的疗效欠佳,加之药物不良反应及耐药性的普遍发生,这些因素共同推动了新型治疗方法的研发与应用。目前,比较突出的新治疗方法包括靶向治疗^[2]和免疫治疗,其中免疫治疗中的免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)因其显著疗效而备受关注。该治疗的核心机制在于通过激活患者自身的免疫系统功能,阻断肿瘤细胞的免疫逃逸途径,从而增强机体对肿瘤细胞的免疫识别及清除能力^[3]。目前,临床常用的 ICIs 药物包括免疫检查点分子(immune checkpoint molecules, ICM),如程序性死亡配体 1(programmed cell death ligand 1, PD-L1)、程序性死亡受体 1(programmed cell death protein 1, PD-1)及细胞毒性 T 淋巴细胞抗原 4(cytotoxic T-lymphocyte antigen 4, CTLA-4)的特异性单克隆抗体,这些药物在肾癌的治疗中已展现出一定的疗效^[4-6]。近年来研究^[7-8]表明,新的 ICM——淋巴细胞活化基因 3(lymphocyte-activation gene 3, LAG-3/CD223)在肾癌的发生发展中发挥关键作用,其研究价值不亚于经典的 ICM。基于此,本文拟以 LAG-3 分子在肾癌中的研究进展作一综述。

1 LAG-3 的结构和功能

1.1 LAG-3 分子的基本结构 作为 ICM 中的重要成员之一,LAG-3 与 PD-1、PD-L1、CTLA-4 等在抗肿瘤免疫中共同发挥作用。LAG-3 在结构、功能和作用机制上有别于其他 ICM,在免疫治疗中展现出独特的应用前景^[8]。LAG-3 是与 CD4 同源的 I 型跨膜蛋白,成熟的 LAG-3 结构大致可分为外部结构域、跨膜区域及细胞内区域。其中,外部结构域由多个免疫球蛋白样结构域(immunoglobulin-like domain, Ig-like D)组成,可以与多种配体相结合^[9-11],除了能与主要组织相容性复合体 II 类分子(major histocompatibility complex class II, MHC II)以高亲和力相结合^[12],还可以与半乳糖凝集素-3(Galectin-3, Gal-3)^[13]、纤维蛋白原样蛋白-1(fibrinogen-like 1, FGL1)^[14]和肝窦内皮细胞凝集素(liver

sinusoidal endothelial cell lectin, LSECtin)^[15]等结合;跨膜区则负责锚定于细胞膜并参与下游信号传递;内部结构域含有免疫受体酪氨酸抑制基序(immunoreceptor tyrosine-based inhibitory motif, ITIM)和 KIEELE 序列等,对 LAG-3 发挥抑制功能起到关键作用^[16]。各结构域通过协同作用共同发挥免疫抑制功能,在生理与病理状态中发挥着重要作用。

1.2 LAG-3 的主要功能 LAG-3 在体内通过与各种配体结合发挥各种重要功能。大部分膜结合 LAG-3 与 MHC-II 或 FGL1 结合,抑制 T 细胞的活化与增殖^[12],小部分膜结合型 LAG-3 可被去整合素和金属蛋白酶(a disintegrin and metalloproteinase, ADAM)家族分子剪切裂解,生成可溶性 LAG-3,后者可通过调节抗原呈递细胞(antigen-presenting cell, APC)来间接抑制免疫反应^[17]。LAG-3 可高表达于活化 T 细胞中,尤其在活化的 CD4⁺辅助性 T 细胞(helper T cell, Th)和 CD8⁺细胞毒性 T 细胞(cytotoxic T cell, Tc)上均通过高表达抑制其增殖^[18-20];此外,LAG-3 可增强调节性 T 细胞(regulatory T cells, Tregs)对效应 T 细胞的抑制作用,从而促进免疫耐受的维持^[21-22]。同时,浆细胞样树突状细胞、巨噬细胞与自然杀伤细胞等也能表达 LAG-3,通过调节 APC 活性间接抑制 T 细胞的激活^[23-24]。

LAG-3 在自身免疫性疾病、慢性炎症、急性感染等炎症病变中高表达,发挥控制炎症反应的作用;然而,在各种恶性肿瘤中,LAG-3 的高表达通过介导免疫抑制,促进肿瘤的发生、发展和逃逸。研究^[25]表明:在非小细胞肺癌中,肿瘤浸润淋巴细胞(tumor-infiltrating lymphocytes, TILs)高表达 LAG-3,且与 PD-1/PD-L1 表达相关,LAG-3 阳性或同时 LAG-3 和 PD-L1 阳性与预后差相关;在乳腺癌中,LAG-3 高表达预示肿瘤恶性程度高^[26];在结直肠癌中,LAG-3 表达与总生存期呈显著负相关^[27];值得一提的是,LAG-3 在肾癌中异常高表达^[28],由于这类患者多数在就诊时已进展至晚期,免疫治疗有望成为主要治疗选择。

2 LAG-3 在肾癌中的表达与作用

2.1 LAG-3 在肾癌中的表达 研究^[29]证实,LAG-3 在肾癌中普遍高表达,且在不同组织学亚型间存在差异。LAG-3 在透明细胞肾细胞癌(clear cell re-

nal cell carcinoma, ccRCC)中,尤其晚期或转移患者中表达最高,且集中在TILs和肿瘤相关巨噬细胞(tumor-associated macrophages, TAMs)上;而在肾乳头状细胞癌中,LAG-3的表达相对较低;在嫌色细胞癌中,LAG-3的表达水平居中,且其表达与肿瘤的侵袭性和免疫耐受密切相关^[30-32]。

2.2 LAG-3在肾癌中的作用及机制 在占肾癌绝大多数的ccRCC中,LAG-3蛋白的高表达预示更差的预后^[33]。有报道^[34]指出,LAG-3和粒溶酶K(granzyme K, GZMK)的表达水平结合临床信息能准确预测ccRCC患者的预后。ROUMENINA等^[35]证实,在ccRCC中,通过TAMs以及癌细胞自身产生的补体成分共同促成C1q的生成,后者介导经典补体途径激活从而引发炎症反应,最终导致LAG-3、PD-1及PD-L1等高表达的免疫抑制微环境的产生。KLÜMPER等^[36]发现,ccRCC中的LAG-3受到DNA甲基化的表观遗传学调控。相关研究^[37]还发现,在ccRCC中,*PBRM1*的突变可通过影响LAG-3的甲基化以调节其表达。另外,DANG等^[38]提出,在肾乳头状细胞癌中,LAG-3在高风险组中的表达显著高于低风险组。还有XU等^[39]对干扰素- γ (interferon gamma, IFN- γ)反应簇的关键成员重组蛋白结合蛋白1(recombinant protein binding protein 1, RBCK1)的研究表明:在肾乳头状细胞癌、嫌色细胞癌及ccRCC中,RBCK1高表达组与低表达组的肿瘤微环境免疫状态评分,即TIDE(tumor immune dysfunction and exclusion)评分有显著差异,且RBCK1的表达与LAG-3、PD-L1及CTLA-4等的表达呈显著正相关。

2.3 LAG-3与其他免疫检查分子的联合作用 研究^[40]发现,LAG-3与PD-1、CTLA-4、TIM-3等在肾癌肿瘤微环境中存在协同效应,共同促进肿瘤免疫逃逸,抑制PD-1会导致LAG-3明显上调,而双靶点抑制PD-1和LAG-3,能显著增强IFN- γ 的释放,导致双重抑制状态,加速T细胞耗竭^[33];另有研究^[8]表明,LAG-3协同T细胞免疫球蛋白及黏蛋白结构域分子3(T cell immunoglobulin domain and mucin domain-3, TIM-3)影响Tregs活性。研究^[41]也证实,在肾癌中,CTLA-4通过抑制T细胞初始激活,减少效应T细胞生成,而LAG-3则直接抑制其产生的效应T细胞;基于以上各ICM间的协同作效应,以及目前PD-1/PD-L1/CTLA-4单抗抑制剂的耐药问题日益突出,联合用药特别是联合LAG-3抗体与其他ICIs的治疗策略近年来备受研究者关注。

3 LAG-3相关的ICIs在肾癌中的应用及挑战

3.1 LAG-3相关的ICIs在肾癌中的应用 ZHU等^[42]通过对免疫检查点分析表明LAG-3和CTLA4等在高危ccRCC患者中上调,提示其可以作为潜在的治疗靶点;ZHANG等^[43]用CRISPR/Cas9(Clustered Regularly Interspaced Short Palindromic Repeats)技术证实,敲除LAG-3可以明显提高T细胞的抗肿瘤活性;ZELBA等^[40]证实PD-1和LAG-3在肾癌中主导检查点受体介导的T细胞抑制,指出PD-1和LAG-3的双重阻断是治疗肾癌的一种新兴检查点阻断组合。

基于肾癌独特的临床病理特征及ICIs的广泛应用,针对肾癌的免疫治疗的临床试验已在全球范围内广泛开展。根据美国临床试验注册网站数据库(ClinicalTrials.gov)显示,目前已有42项LAG-3抗体相关项目注册研究,涉及多家制药企业(如Merck、Bristol-Myers Squibb、Regeneron、AbbVie等)开发的多种LAG-3单克隆抗体候选药物^[44]。早期研发阶段主要聚焦于重组可溶性LAG-3融合蛋白IMP321(Eftilagimod alpha)的单药治疗,临床数据显示该药在恶性肿瘤包括肾癌的治疗中具有中等程度的抗肿瘤活性^[45]。另外,联合免疫疗法的临床实验也在进行中,如Relatlimab(抗LAG-3抗体)与Nivolumab(抗PD-1抗体)双免疫疗法实验,在晚期肾癌患者临床实验中,结果显示NIVO+RELA组中位随访时间为48.6个月,四分位数间距(IQR)为46.9~51.7个月,客观反应率为30%,中位疾病缓解持续时间(DOR)为33周,24周时的无进展生存率(PFS)为43%。而标准方案NIVO+IPI(抗CTLA-4)组的中位随访时间为48.7个月,IQR为47.1~52.0个月,客观反应率为20%,中位DOR未达到(95%CI: 33周~无法估计),24周时的PFS率为49%。在接受NIVO+RELA治疗的4/30名(13%)患者和接受NIVO+IPI治疗的10/30名(33%)患者中报告了3~4级的治疗相关不良事件。结论是NIVO+RELA组疗效虽未超越标准方案,但其药物安全性显著优于后者^[46]。

3.2 ICIs在肾癌治疗中的局限性及挑战 尽管以LAG-3为靶点的ICIs在肾癌治疗中展现出一定的临床前景,但其临床应用仍面临诸多挑战,包括以下几个方面:首先,药物的副作用和毒性需要进一步明确;其次,精准受益人群标准化筛选方案还有

待确定;再者,药物成本和临床应用的普及性也需要考量。

4 小结和展望

本文对LAG-3分子的生物学特征、在肾癌中的表达特点及临床试验结果等进行了系统归纳,结果表明,LAG-3分子的结构功能特点、在肾癌中的特异性表达模式及其免疫调控机制,为将其作为治疗靶点提供了充分的理论依据。特别是LAG-3抑制剂与其他ICIs的联合疗法已展现出显著的协同效应,预示该靶向治疗在肾癌领域具有重要临床价值。然而,由于肾癌的高度异质性、现有临床试验样本量有限以及随访周期不足等因素,未来仍需通过大规模多中心研究验证长期疗效与安全性,进而优化个体化治疗方案。鉴于以上,未来的研究重点应该为:第一,加强临床前研究,开发和使用更多肾癌特异性的动物模型和细胞模型进一步研究验证;第二,优化出更精确的临床研究方案,来评估LAG-3抑制剂在不同肾癌亚型和不同治疗阶段的疗效;第三,关注耐药及副作用管理,研究耐药机制,评估药物长期安全性并制定有效管理方案。

综上所述,研究LAG-3分子对肾癌的预后及治疗具有重要的意义,特别是包含LAG-3抗体的ICIs联合方案对肾癌的治疗前景值得期待。我们有理由相信,在不久的将来,随着科技的发展,特别是人工智能的快速发展,以LAG-3为靶点的治疗将为肾癌的治疗带来质的飞跃。



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