•综述•

靶向KRAS突变在胰腺癌免疫治疗中的研究进展

张析妍, 彭宗根, 陈淑珍*

(中国医学科学院 北京协和医学院, 医药生物技术研究所, 天然药物活性物质与功能国家重点实验室, 北京 100050)

摘要: 胰腺癌是消化系统恶性肿瘤中预后最差的类型之一, 其五年生存率仅约13%, 在中国人群中更是低至8.5%。由于早期诊断困难, 大多数患者确诊时已处于晚期, 治疗手段有限, 且对放化疗易产生耐药。Kirsten大鼠肉瘤病毒癌基因同源物 (kirsten rat sarcoma viral oncogene homolog, KRAS) 突变在胰腺癌中发生率高达90%以上, 突变型KRAS不仅驱动肿瘤增殖, 还通过多种机制重塑免疫微环境, 如诱导免疫抑制细胞浸润、上调免疫检查点分子等, 导致免疫逃逸。近年来, 随着KRAS抑制剂进入临床, 靶向KRAS展现出重塑肿瘤免疫微环境的潜力。本文系统性综述了KRAS突变在胰腺癌免疫抑制微环境形成中的作用机制, 靶向KRAS药物的研发进展, 及其与免疫治疗联合应用的研究现状与挑战, 为胰腺癌的精准治疗提供新思路。

关键词: 胰腺癌; KRAS突变; 免疫抑制; 免疫治疗; 靶向治疗

中图分类号: R966 **文献标识码**: A **文章编号**: 0513-4870(2026)09-3292-10

Advances in targeting KRAS mutations for immunotherapy of pancreatic cancer

ZHANG Xi-yan, PENG Zong-gen, CHEN Shu-zhen*

(*State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100050, China*)

Abstract: Pancreatic cancer is one of the digestive system malignancies with the poorest prognosis, with a five-year survival rate of only approximately 13%, and even lower at 8.5% in the Chinese population. Due to difficulties in early diagnosis, most patients are already at an advanced stage at the time of diagnosis, with limited treatment options and a propensity for resistance to radiotherapy and chemotherapy. KRAS (kirsten rat sarcoma viral oncogene homolog) mutations occur in over 90% of pancreatic cancer cases. Mutant KRAS not only drives tumor proliferation but also remodels the immune microenvironment through various mechanisms, such as inducing infiltration of immunosuppressive cells and upregulating immune checkpoint molecules, thereby leading to immune evasion. In recent years, with the introduction of KRAS inhibitors into clinical practice, targeting KRAS has shown potential for remodeling the tumor immune microenvironment. This article systematically reviews the mechanisms by which KRAS mutations contribute to the formation of an immunosuppressive microenvironment in pancreatic cancer, the progress in the development of KRAS-targeted drugs, and the current status and challenges of their combination with immunotherapy, providing new insights for precision treatment of pancreatic cancer.

Key words: pancreatic cancer; KRAS mutation; immunosuppression; immunotherapy; targeted therapy

胰腺癌 (pancreatic cancer, PC) 属于消化系统恶性肿瘤中预后最差的类型之一, 根据最新的统计数据, 胰腺癌患者的五年总体生存率约为13%。而在中国人群中仅为8.5%, 显著低于其他常见恶性肿瘤的生存水平[1,2]。研究预测, 到2030年, 胰腺癌可能超越结直肠癌、乳腺癌等常见恶性肿瘤, 成为癌症死亡的第二大

收稿日期: 2026-04-01; 修回日期: 2026-05-06.
基金项目: 中国医学科学院医学与健康科技创新工程 (2021-I2M-1-030).
*通讯作者 E-mail: bjcsz@imb.pumc.edu.cn
DOI: 10.16438/j.0513-4870.2026-0366

原因[3]。

目前, 胰腺癌治疗手段包括手术和辅助治疗。然而, 由于胰腺癌早期诊断困难, 多数患者在确诊时已处于晚期阶段, 仅有不到20%的患者符合手术切除的条件[4]。化疗和放疗等辅助治疗能暂时缓解病情, 但因其易耐药且复发率高, 治疗效果仍不理想, 临床上迫切需要寻找新的治疗策略[5,6]。

近年来, 免疫治疗在多种恶性肿瘤中取得显著进展, 尤其是免疫检查点抑制剂 (immune checkpoint inhibitors, ICIs) 在黑色素瘤和非小细胞肺癌 (non-small cell lung cancer, NSCLC) 等癌症中展现出良好的治疗效果。然而, 在胰腺癌中的应用效果仍十分有限。临床研究显示, 靶向程序性死亡受体1/程序性死亡配体1 (programmed death 1/programmed cell death ligand 1, PD-1/PD-L1) 抑制剂在晚期胰腺癌患者中的客观缓解率 (objective response rate, ORR) 普遍低于10%[7]。这一疗效局限主要归因于胰腺癌典型的“冷肿瘤”特性, 如肿瘤微环境 (tumor microenvironment, TME) 中T细胞浸润极少, 免疫激活信号微弱, 并伴有显著的免疫抑制环境, 从而造成免疫治疗应答率极低[8,9]。

在这一背景下, Kirsten大鼠肉瘤病毒癌基因同源物 (kirsten rat sarcoma viral oncogene homolog, KRAS) 突变的中心地位愈发凸显。KRAS作为RAS家族的关键成员, 是调控细胞增殖、存活与代谢的核心信号节点。在胰腺癌中, KRAS突变的发生率高达90%以上。其中, G12D是最常见的突变亚型 (约占40%～50%), 其次是G12V和G12R[10]。这些突变导致KRAS蛋白持续处于GTP结合的“开启”状态, 无需上游生长因子刺激即可持续激活下游丝裂原活化蛋白激酶 (mitogen-activated protein kinases, MAPK)、磷酸肌醇3-激酶/蛋白激酶B (phosphoinositide 3-kinase/protein kinase B, PI3K-AKT) 等通路, 从而加剧肿瘤的增殖、迁移及免疫逃逸等恶性行为[11]。

近期研究发现, 突变型KRAS不仅驱动肿瘤恶性增殖, 还通过分泌细胞因子、上调PD-L1等方式塑造免疫抑制微环境[12]。因此, 靶向KRAS被视为调节免疫微环境、克服免疫治疗耐药的新策略。随着KRAS G12C抑制剂上市及G12D等常见突变亚型抑制剂进入临床, 初步研究证实抑制KRAS可减少免疫抑制细胞浸润、增强抗原呈递并促进效应T细胞募集, 从而与ICIs产生协同效应, 为胰腺癌治疗提供了新方向。

本文旨在系统阐述KRAS突变在胰腺癌免疫微环境形成中的作用机制, 并总结当前基于KRAS抑制剂联合免疫治疗策略的研究进展与面临挑战。

1 KRAS突变驱动胰腺癌免疫抑制微环境形成

胰腺癌的TME是一个高度复杂且免疫抑制性极强的系统, 这一特性是其内在治疗抵抗和免疫疗法疗效不佳的根本原因。如图1所示, 该环境中多种细胞成分通过复杂机制相互作用, 共同促进肿瘤生长与免疫逃逸。因此, 深入阐明这些机制是突破胰腺癌治疗困境的关键。

1.1 重塑物理屏障

胰腺癌最显著的组织病理学特征之一是致密的结缔组织增生反应, 在超过92%的胰腺癌病例中, KRAS突变是驱动癌症相关成纤维细胞 (cancer-associated fibroblasts, CAFs) 募集与活化的关键因素。携带KRAS突变的肿瘤上皮细胞通过分泌白细胞介素-1 (interleukin-1, IL-1)、IL-6、转化生长因子-β (transforming growth factor-β, TGF-β) 和C-X-C基序趋化因子配体12 (C-X-C motif chemokine ligand 12, CXCL12) 等多种细胞因子, 激活胰腺星状细胞并诱导其分化为具有肌成纤维细胞特征的CAFs[13,14]。这些活化的CAFs大量分泌细胞外基质成分, 形成高度致密的纤维化屏障, 不仅物理性阻碍免疫细胞向肿瘤核心浸润, 还通过改变趋化因子表达谱, 导致效应性免疫细胞无法被有效招募至肿瘤部位, 从而促进免疫逃逸。此外, CAFs介导的致密细胞外基质造成的组织缺氧会进一步加剧免疫抑制, 缺氧环境稳定了缺氧诱导因子1α (hypoxia-inducible factor 1α, HIF-1α), HIF-1α可上调PD-L1等免疫检查点分子及多种免疫抑制性细胞因子的表达[15,16]。

1.2 免疫细胞招募与极化

肿瘤免疫微环境主要由浸润于肿瘤间质中的免疫细胞及其分泌的细胞因子等活性分子组成。肿瘤细胞与周围间质通过调控免疫细胞的浸润和功能, 形成有利于肿瘤生长的免疫微环境。

研究表明, 携带KRAS常见突变的肿瘤通常表现为$CD8^+$ T细胞浸润减少以及T细胞功能耗竭。作为适应性免疫反应的关键效应细胞, $CD8^+$ T细胞的功能受到KRAS突变状态的显著影响。机制上, KRAS突变可抑制$CD8^+$ T细胞的招募与功能。如KRAS G12D通过减少癌细胞释放CXCL10和CXCL11, 限制了$CD8^+$ T细胞的浸润[17]。此外, KRAS G12D还能通过raf蛋白激酶/丝裂原活化的细胞外信号调节激酶/细胞外信号调节激酶 (raf protein kinase/mitogen-activated extracellular signal-regulated kinase/extracellular signal-regulated kinase, RAF/MEK/ERK) 信号通路提升肿瘤细胞中IL-33的表达[18]; IL-33通过与其受体肿瘤形成抑制因子2 (suppression of tumorigenicity 2, ST2) 结合,

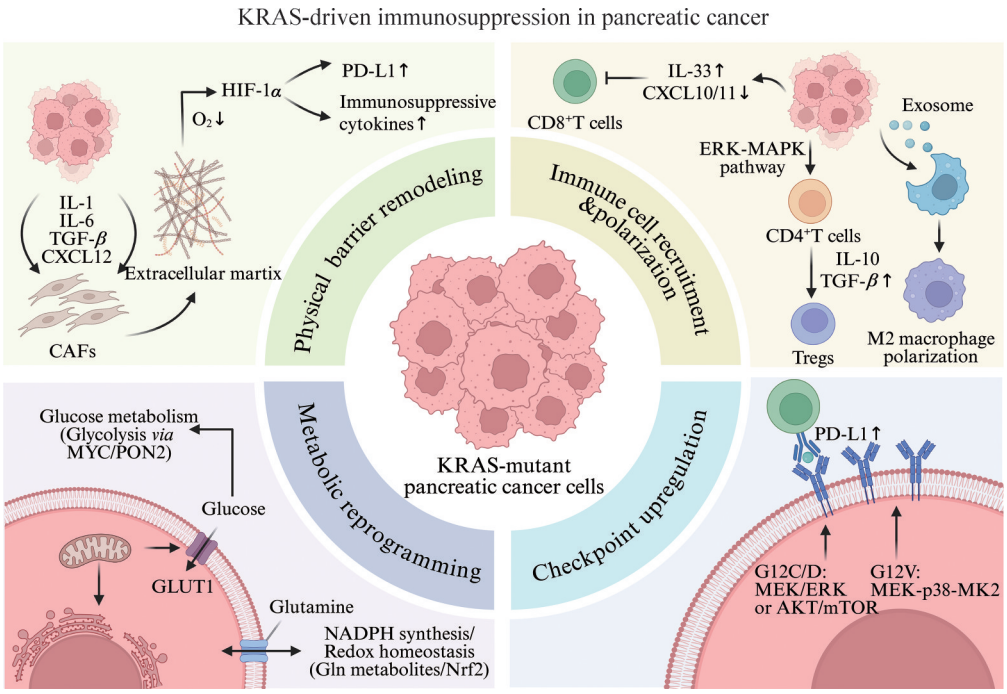


Figure 1 KRAS mutations drive the formation of an immunosuppressive microenvironment in pancreatic cancer. KRAS: Kirsten rat sarcoma viral oncogene homolog; IL-1: Interleukin-1; TGF-β: Transforming growth factor-β; CXCL12: C-X-C motif chemokine ligand 12; CAFs: Cancer-associated fibroblasts; HIF-1α: Hypoxia-inducible factor 1-α; PD-L1: Programmed cell death ligand 1; ERK: Extracellular signal-regulated kinase; MAPK: Mitogen-activated protein kinase; Tregs: Regulatory T cells; MYC: Myelocytomatosis oncogene; PON2: Paraoxonase 2; GLUT1: Glucose transporter 1; NADPH: Nicotinamide adenine dinucleotide phosphate; Nrf2: Nuclear factor erythroid 2-related factor 2; MEK: Mitogen-activated extracellular signal-regulated kinase; AKT: Protein kinase B; mTOR: Mammalian target of rapamycin; p38: P38 mitogen-activated protein kinase; MK2: Mitogen-activated protein kinase activated protein kinase 2 (figure was created with Biorender.com)

作用于先天淋巴细胞、调节性T细胞 (regulatory T cells, Tregs) 等, 间接抑制CD8$^+$ T细胞的浸润和活化[19]。

KRAS突变通过诱导多种细胞因子和趋化因子的表达, 系统性塑造免疫抑制性的TME。研究表明, 在KRAS突变型肿瘤中, CXCL1、CXCL2、CXCL3等C-X-C基序趋化因子受体2 (C-X-C motif chemokine receptor 2, CXCR2) 配体的表达显著上调[20]。肿瘤细胞分泌这些趋化因子后, 可募集具有免疫抑制功能的单核细胞和中性粒细胞, 从而抑制抗肿瘤免疫应答。此外, 肿瘤细胞内的KRAS信号通过激活ERK-MAPK通路, 上调IL-10和TGF-β的分泌。这两种细胞因子可促使1型辅助性T细胞 (type 1 helper T, Th1) 型CD4$^+$ T细胞向具有免疫抑制功能的Tregs分化, 进一步损害肿瘤浸润T细胞的效应功能[21,22]。

巨噬细胞在抗肿瘤免疫中具有重要作用, 研究发现, KRAS G12D突变可上调胰腺腺泡细胞中细胞间黏附分子-1 (intercellular cell adhesion molecule-1, ICAM-1) 的表达, 并激活过氧化物酶体增殖物激活受体δ-C-C基序趋化因子配体2/C-C基序趋化因子受体2 (peroxisome proliferator-activated receptors δ-C-C motif chemokine ligand 2/C-C motif chemokine receptor 2, PPARδ-CCL2/CCR2) 信号轴, 促进巨噬细胞和髓源性抑制细胞 (myeloid-derived suppressor cells, MDSCs) 向肿瘤部位浸润[23]。此外, KRAS G12D突变的胰腺癌细胞可通过外泌体将突变型KRAS蛋白传递至巨噬细胞, 激活信号转导及转录激活因子3 (signal transducer and activator of transcription 3, STAT3) 信号通路, 诱导其向M2样表型转化。这些M2型巨噬细胞随后分泌肝素结合性表皮生长因子样生长因子 (heparin-binding EGF-like growth factor, HB-EGF), 与肿瘤细胞表面的表皮生长因子受体 (epidermal growth factor receptor, EGFR) 结合, 在KRAS G12D背景下增强EGFR信号传导, 形成正反馈环路, 进一步强化KRAS的致癌作用, 促进肿瘤进展[24]。

1.3 上调免疫检查点分子

KRAS信号通过多种机制间接促进PD-L1等免疫检查点分子的表达, 增强肿瘤细胞主动抑制T细胞攻击的能力。不同KRAS突变亚型通过多种信号通路差

异性地调控PD-L1的表达。研究显示, G12V突变的KRAS通过MEK-p38丝裂原活化蛋白激酶 (p38 mitogen-activated protein kinase, p38)-MAP激酶活化蛋白激酶2 (mitogen-activated protein kinase-activated protein kinase 2, MK2)信号轴磷酸化mRNA结合蛋白tristetraprolin (TTP), 使其失活, 从而增强PD-L1的稳定性[25]。而G12D和G12C突变主要通过MEK/ERK[26-28]和AKT/mTOR途径上调PD-L1[17-29]。此外, Hashimoto等[30]的研究揭示, KRAS与TP53 (tumor protein 53)突变可通过协同作用上调ADP-核糖基化因子6 (ADP-ribosylation factor 6, ARF6)和AMAP1 (c-MYC-binding protein associated protein)的表达, 从而形成ARF6-AMAP1通路。该通路通过促进细胞内PD-L1的膜循环, 增加肿瘤细胞表面PD-L1的稳定性, 进而增强其对表达PD-1的T细胞的抑制能力。

1.4 诱导代谢重编程

KRAS调控代谢重编程的关键机制之一是调节代谢通路中关键酶的表达。现有研究表明, KRAS可通过激活MEK/ERK信号通路, 促进转录因子MYC (myelocytomatosis oncogene)的表达上调, 进而增强肿瘤细胞的糖酵解代谢水平[31]。此外, 研究发现, 胰腺癌中对氧磷酶-2 (paraoxonase 2, PON2)的过表达可与KRAS突变协同促进葡萄糖代谢, 其主要机制是PON2通过与葡萄糖转运蛋白1 (glucose transporter 1, GLUT1)结合, 增强肿瘤细胞对葡萄糖的摄取能力[32]。

KRAS在维持肿瘤细胞氧化还原稳态方面亦发挥重要作用, 其作用机制具有多样性。其中, 关键机制之一是KRAS参与调控还原型烟酰胺腺嘌呤二核苷酸磷酸 (nicotinamide adenine dinucleotide phosphate, NADPH)的合成过程。在胰腺癌中, 谷氨酰胺被证实为NADPH生成的主要碳来源, 通过其代谢途径为肿瘤细胞提供NADPH, 以维持氧化还原平衡[33]。除参与谷氨酰胺代谢调控外, KRAS还可通过上调核转录因子红系2相关因子2 (nuclear factor erythroid 2-related factor 2, Nrf2)的表达, 进一步增强肿瘤细胞对氧化应激的耐受能力, 维持其氧化还原稳态[34]。

2 靶向KRAS药物的研发突破与分类

KRAS突变是多种癌症的关键驱动因素。近年来, 针对该靶点的药物研发取得显著进展, 从直接靶向特定突变的小分子抑制剂, 到间接干预其信号通路及免疫治疗策略, 已形成多元化研发格局。现将本文涉及的代表性药物汇总于表1[35-47], 并围绕直接靶向与间接靶向两大方面展开详细论述。

2.1 直接靶向KRAS的药物

2.1.1 KRAS小分子抑制剂 KRAS曾长期被视为“不可成药”靶点, 因其表面光滑、缺乏传统小分子可结合的深口袋, 且对三磷酸鸟苷 (guanosine triphosphate, GTP)具有极高的亲和力, 使得直接抑制其活性极具挑战。然而, 随着结构生物学与药物化学的突破, 特别是发现KRAS G12C突变体在非活性二磷酸鸟苷 (guanosine diphosphate, GDP)结合状态下存在一个靶向的“switch-II口袋”, 研究者成功开发出共价抑制剂, 实现了从“不可成药”到“成药”的历史性跨越[48]。随着研究的深入, 一系列KRAS G12C抑制剂被成功开发, 包括早期化合物ARS-853、ARS-1260以及后续的索托拉西布 (sotorasib)和阿达格拉西布 (adagrasib)[35-37]。

MRTX1133是首个进入临床的KRAS G12D选择性非共价抑制剂, 能够以高亲和力结合处于GDP结合状态的突变KRAS蛋白, 从而有效阻断其下游信号传导。临床前研究表明, 该化合物在纳摩尔浓度下即可显著抑制携带KRAS G12D突变的肿瘤细胞增殖, 并在细胞系来源异种移植 (cell line-derived xenograft, CDX)和患者来源异种移植 (patient-derived xenograft, PDX)模型中诱导肿瘤消退, 同时实现对ERK信号通

Table 1 KRAS-targeted therapies in clinical trials

Type of drug	Drug	Target	National clinical trial	Clinical phase	Reference
Direct KRAS inhibitors	ARS-853	KRAS G12C	/	Preclinical	[35]
	ARS-1620	KRAS G12C	/	Preclinical	[35]
	Sotorasib (AMG510)	KRAS G12C	NCT04303780	Approved	[36]
	Adagrasib (MRTX849)	KRAS G12C	NCT06497556	Approved	[37]
	MRTX1133	KRAS G12D	NCT05737706	I	[38]
Pan-RAS inhibitors	Daraxonrasib (RMC-6236)	Pan-RAS	NCT06625320	III	[39]
Tri-complex inhibitors	Elironrasib (RMC-6291)	KRAS G12C	NCT06128551	I/II	[40,41]
KRAS degraders	Setidegrasib (ASP3082)	KRAS G12D	NCT07409272	III	[42,43]
Indirect KRAS inhibitors	Vociprotafib (RMC-4630)	SHP2	NCT05054725	II	[44]
	TNO155	SHP2	NCT07468071	I/II	[44]
	Sitneprotafib (JAB-3312)	SHP2	NCT06416410	III	[44]
	BI-1701963	SOS1	NCT04835714	I	[45]
	Selumetinib	MEK	NCT04924608	Approved	[46]
	MK-2206	AKT	NCT01307631	II	[46]
KRAS-targeted vaccines	ELI-002	KRAS G12D	NCT05726864	I/II	[47]

路的持续抑制[38]。

2.1.2 泛KRAS的小分子抑制剂 除突变特异性KRAS抑制剂外, 靶向罕见变异或缺乏特异性药物突变体的泛RAS抑制剂亦是研发热点。如daraxonrasib可抑制处于活化状态的多种RAS蛋白, 在胰腺癌临床前模型中活性显著。一项I期试验显示, daraxonrasib在KRAS G12X突变胰腺癌患者中ORR达29%, 其他KRAS突变类型为25%[39]。

2.1.3 三元复合体抑制剂 KRAS靶向药的临床应用逐渐暴露出易产生耐药的问题[49]。使用KRAS G12C抑制剂后, 肿瘤细胞可通过获得KRAS二次突变以抵消药物作用[50]。为克服耐药, 新型三元复合体抑制剂被开发。RMC-6291作为分子胶, 通过先结合亲环素A (cyclophilin A, CYPA), 再共同捕获活化状态RAS, 形成三元复合体以阻断下游信号。该机制不依赖传统变构口袋, 有望解决继发突变引起的G12C抑制剂耐药问题[40,41]。

2.1.4 KRAS降解剂 此外, 蛋白降解靶向嵌合体(proteolysis targeting chimera, PROTAC)技术通过招募E3泛素连接酶介导的靶蛋白泛素化与蛋白酶体降解, 为靶向KRAS提供了全新策略。其中, 共价型PROTAC降解剂ASP3082能够特异性识别并诱导KRAS G12D突变蛋白的降解, 代表了一种创新性的治疗思路。临床前研究表明, ASP3082在KRAS G12D突变模型中展现出强效的抗肿瘤活性, 并具有良好的安全性特征[42,43]。

2.2 间接靶向KRAS的药物

2.2.1 靶向KRAS上下游的抑制剂 除直接靶向KRAS突变蛋白外, KRAS上游和下游信号通路中的关键蛋白介质亦被作为抗肿瘤治疗的潜在靶点, 相关靶向药物正处于多项临床试验阶段, 以改善抗肿瘤反应并减轻耐药性。通过靶向KRAS上游的蛋白酪氨酸磷酸酶(src homology 2 domain-containing protein tyrosine phosphatase-2, SHP2)和钠/氢反转运蛋白(son of sevenless homolog 1, SOS1), 可间接抑制泛KRAS蛋白活性。目前, SHP2抑制剂正在开发中, 包括RMC-4630、TNO155、JAB-3312等[44]。BI-1701963是一种SOS1抑制剂[45], 也已进入I期临床试验。

KRAS下游信号通路主要包括MAPK通路、PI3K-AKT通路和雷帕霉素靶蛋白(mammalian target of Rapamycin, mTOR)通路。目前, 针对上述各个蛋白的抑制剂正在进行多项临床试验。司美替尼(selumetinib)与MK-2206可分别抑制KRAS下游信号通路中MEK和AKT蛋白的活化[46]。

2.2.2 靶向KRAS突变的肿瘤疫苗 基于KRAS突变新抗原的疫苗是当前肿瘤免疫治疗中极具前景的研究方向。目前开发的疫苗形式主要包括多肽疫苗和mRNA疫苗。多肽疫苗通过合成包含KRAS特异性突变位点(如G12D、G12V)的短肽序列, 与免疫佐剂联合接种, 旨在激活针对突变KRAS肽段的特异性T细胞应答。mRNA疫苗则利用mRNA编码含有KRAS突变序列的蛋白, 在体内由抗原呈递细胞表达后, 经加工提呈至主要组织相容性复合体(major histocompatibility complex, MHC), 从而诱导更强且持久的细胞免疫反应。

目前, 多项针对KRAS突变的疫苗已进入早期临床试验阶段, 适应症涵盖胰腺癌、结直肠癌等KRAS高突变率的实体瘤。初步临床数据显示, 这些疫苗整体安全性良好, 且能够在部分患者中诱导出可检测的、针对相应KRAS突变肽的抗原特异性T细胞免疫应答, 为后续联合治疗策略的探索奠定了基础。

AMPLIFY-201研究正在评估靶向KRAS的疫苗ELI-002, 该疫苗在接受手术或标准治疗后的高复发风险患者中表现出良好的安全性, 并成功诱导出强烈的免疫应答, 部分患者表现出疾病复发风险降低的趋势[47]。此外, 更为精准的T细胞受体工程T细胞疗法(T cell receptor engineered T cell therapy, TCR-T)也已取得突破, 该疗法通过靶向人白细胞抗原(human leukocyte antigen, HLA)依赖性呈递的KRAS G12D突变肽, 在转移性胰腺癌患者中展现出治疗前景[51]。

3 靶向KRAS与免疫治疗的协同作用

长期以来, ICIs在“冷肿瘤”如胰腺癌中疗效甚微, 而KRAS突变不仅驱动肿瘤发生, 还主动塑造高度免疫抑制的微环境。近年来, 随着KRAS抑制剂的突破, 研究者逐渐认识到抑制KRAS不仅能直接抑制肿瘤细胞增殖, 还可重编程肿瘤免疫微环境, 从而为免疫治疗创造有利条件。将KRAS特异性抑制剂与免疫增强疗法联用, 有望协同打破免疫耐受, 实现更持久的临床获益。

3.1 联合ICIs

KRAS基因突变是驱动胰腺癌发生发展的关键因素, 并在构建免疫抑制性TME中发挥核心作用。安德森癌症中心开展了一项系统性研究, 整合了16种KRAS G12D突变胰腺癌模型。结果显示, KRAS G12D抑制剂MRTX1133不仅能有效抑制早期胰腺癌的肿瘤生长, 还能显著重塑肿瘤免疫微环境。该药物促进了细胞毒性$CD8^+$ T细胞的浸润与活化, 同时减少了MDSCs的聚集。更重要的是, 将MRTX1133与ICIs抗PD-L1或抗细胞毒性T淋巴细胞相关抗原-4 (cytotoxic T lymphocyte-associated antigen-4, CTLA-4)

抗体联合使用，可协同增强抗肿瘤效果，促进肿瘤消退，并显著延长小鼠的总体生存期[52]。

针对泛KRAS抑制剂BI-2493的研究同样揭示了其免疫调节作用。实验表明，BI-2493治疗可显著提升TME中$CD8^+$ T细胞和$CD4^+$ T细胞的浸润水平，同时降低免疫抑制性细胞如MDSCs、M2型肿瘤相关巨噬细胞的比例。此外，该药物上调了肿瘤细胞中趋化因子CXCL9和CXCL10的表达，通过CXCR3信号轴介导效应T细胞向肿瘤组织的募集。在联合治疗策略中，BI-2493与抗PD-1或抗CTLA-4抗体联用可在低剂量条件下显著延缓肿瘤生长，部分小鼠获得长期肿瘤控制，与抗CTLA-4抗体联用同样显著抑制肿瘤生长并降低肿瘤负荷[53]。

此外，另一项研究发现抑制KRAS突变可通过FOXA1 (forkhead box A1)结合CD47 (cluster of differentiation 47)超级增强子，上调CD47表达，从而促进肿瘤细胞逃避巨噬细胞的吞噬，加入抗CD47抗体则能恢复巨噬细胞吞噬功能，但吞噬后的巨噬细胞会上调PD-L1表达，进而抑制$CD8^+$ T细胞活化。KRAS抑制剂与抗CD47和抗PD-L1抗体的联合疗法可实现协同效应，显著延长小鼠的生存期[54]。

在如图2所示的临床前研究的基础上，KRAS抑制剂与ICIs的联合策略已进入临床探索阶段。目前，多项早期临床试验正在评估该联合方案的安全性与初步疗效。CodeBreak100/101临床试验研究了索托拉西布联合帕博利珠单抗或阿替利珠单抗在58例KRAS G12C突变NSCLC患者中的疗效，在大部分既往接受过治疗的NSCLC人群中，索托拉西布联合免疫治疗的ORR为29%，但在安全性方面，联合治疗导致的3级和4级治疗相关不良事件的发生率高于单药治疗[55]。其中，KRYSTAL-7试验评估了阿达格拉西布联合多塔利单抗在KRAS G12C突变非小细胞肺癌中的疗效，结果显示在整个研究人群中，ORR为44.3%，中位缓解持续时间 (median duration of response, mDOR)为26.3个月。并且在54例PD-L1 ⩾ 50%患者一线治疗中ORR为59%，mDOR达26.3个月，显示出良好的临床治疗效果[56]。另一项I期临床试验的最新数据显示，MK-1084联合帕博利珠单抗治疗非小细胞肺癌患者的ORR达到71%。与MK-1084单药治疗相比，该联合方案显著提高了疗效，且安全性可控[57]。然而，KRAS抑制剂与ICIs的联合策略在胰腺癌中的结果仍较为有限。尽管初步结果具有前景，但临床转化仍面临挑战。

3.2 联合过继性细胞疗法

过继性细胞疗法 (adoptive cell transfer therapy, ACT)虽在血液肿瘤中疗效显著[58]，但在胰腺癌等实体瘤中应用受限，主要归因于肿瘤特异性抗原的缺失、致密间质组织的物理屏障以及强免疫抑制性微环境对ACT细胞浸润与功能的抑制[59]。而KRAS抑制剂可通过重塑基质、减少抑制性细胞、改善代谢环境等方式，为回输的T细胞提供更有利的生存和作用空间。近年来，针对KRAS突变共享新抗原 (如G12D、G12V)的TCR-T疗法取得突破性进展。

基于HLA-A^*11:01转基因小鼠模型，研究团队通过免疫筛选平台鉴定出两种可特异性识别KRAS

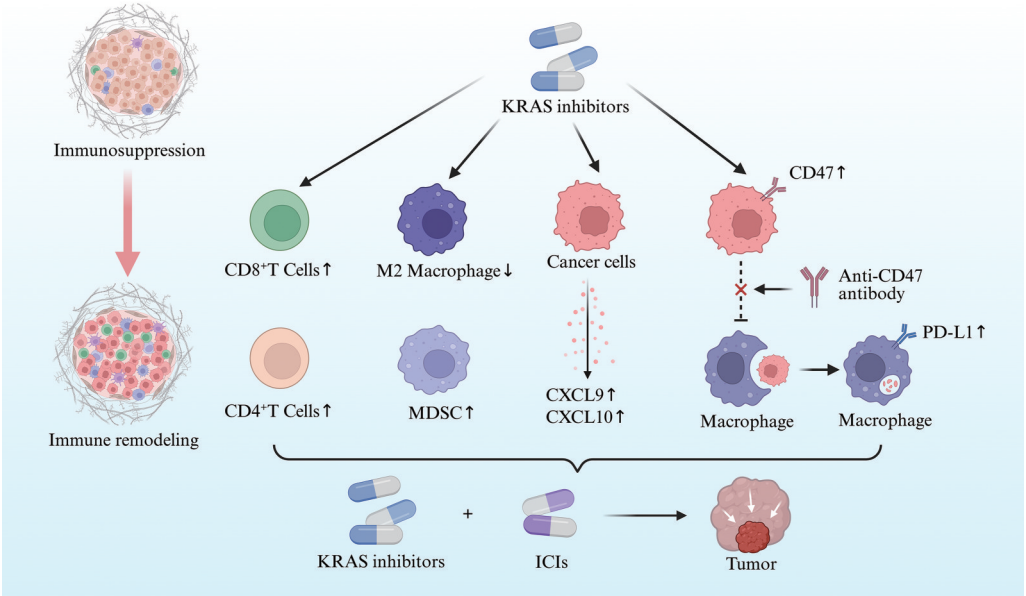


Figure 2 Mechanism of combined KRAS inhibitor and ICIs therapy. MDSC: Myeloid-derived suppressor cells; CD47: Cluster of differentiation 47; ICIs: Immune checkpoint inhibitors (figure was created with Biorender.com)

G12V突变新抗原的T细胞受体。其中, 1-2CTCR被进一步克隆至嵌合抗原受体结构并转导至T细胞中。体外实验显示, 该细胞能够特异性识别并杀伤KRAS G12V突变阳性肿瘤细胞, 具有高度靶向性和细胞毒性。在荷瘤小鼠模型中, 1-2CTCR-T细胞治疗显著抑制了肿瘤生长, 展现出明确的体内抗肿瘤活性。此外, 联合抗PD-1抗体可进一步增强其抗肿瘤效果[60]。

NW-301V是一款靶向晚期实体瘤KRAS G12V突变的新型自体TCR-T疗法, 由经自然选择的TCR转导的自体T细胞组成, 该TCR可特异性识别HLA-A11:01呈递的KRAS G12V新抗原。在近期的I期临床试验初步证实, NW-301V在KRAS G12V突变结直肠癌和胰腺癌患者中兼具良好安全性与抗肿瘤活性[61]。此外, 另一项临床报道显示, 转移性胰腺癌患者在接受靶向KRAS G12D且受HLA-C*08:02限制的转基因自体T细胞治疗后, 其肺转移灶消退[51]。

4 总结与展望

靶向KRAS曾长期被认为难以实现, 但随着2021年首个KRAS G12C抑制剂索托拉西布的获批, 这一局面被彻底打破, 标志着KRAS正式从“不可成药”走向临床可干预。然而, 尽管取得了里程碑式的进展, KRAS靶向治疗在实际应用中仍面临多重挑战。首先, KRAS突变肿瘤具有高度的分子异质性, 导致治疗反应不一, 并且无论是原发性还是获得性耐药都普遍存在。耐药机制多样, 包括KRAS基因本身的二次突变或扩增、上游受体酪氨酸激酶 (receptor tyrosine kinase, RTK) 再激活引发的旁路信号代偿, 以及向Yes相关蛋白1 (Yes-associated protein 1, YAP1) 依赖等非经典生存途径的转化。这些机制常共存演化, 使得单一靶向策略难以长期控制疾病。其次, 当前获批或处于后期研发阶段的药物主要集中于KRAS G12C突变亚型, 更常见的G12D、G12V和G12R等突变亚型仍缺乏高效选择性药物, 广大患者群体尚未从中受益。此外, 为提升疗效, KRAS抑制剂常与免疫治疗或其他靶向药联用, 但这往往引发叠加或独特的毒副作用, 如严重的免疫相关不良反应。如何平衡疗效与安全性, 制定合理的联合方案与毒性管理策略, 是临床实践中的重大挑战。

如图3所示, KRAS突变在胰腺癌中发生率极高, 不仅驱动肿瘤恶性增殖, 还通过重塑物理屏障、调控免疫细胞、上调免疫检查点及代谢重编程等机制构建免疫抑制微环境, 导致免疫治疗耐药。近年来, KRAS抑制剂的临床突破为克服免疫治疗耐药提供了新方向, 其与ICIs和ACT联合应用展现出协同抗肿瘤效应。

面向未来, KRAS靶向治疗的发展将聚焦于多个创新方向。一方面, 新一代药物正致力于突破现有局限, 包括开发覆盖G12D/V/R等高频突变的广谱抑制剂、设计双功能分子以同时阻断KRAS及其上游调控蛋白 (如SOS1或SHP2), 以及利用PROTAC等蛋白降解技术直接清除突变KRAS蛋白, 从而克服传统抑制剂的结构限制与耐药问题。另一方面, 合理化的联合策略将成为提升疗效的关键路径, 如将KRAS抑制剂与化疗、放疗、抗血管生成药物组合, 尤其在胰腺癌等基质致密的肿瘤中, 通过重塑微环境增强药物渗透与免疫细胞浸润。此外, KRAS靶向治疗正逐步与新型免疫疗法融合, 如开发识别KRAS突变肽段的TCR-T或CAR-T细胞、利用溶瘤病毒特异性裂解KRAS突变细胞并激发免疫应答, 或设计双特异性抗体桥接肿瘤细胞与免疫效应细胞。总之, KRAS曾被认为是难以靶向的癌基因, 但随着基础研究、药物技术及临床策略的持续进展, 针对其的治疗正在实现系统性的突破, 有望为更多携带KRAS突变的癌症患者带来长期生存乃至治愈的希望。

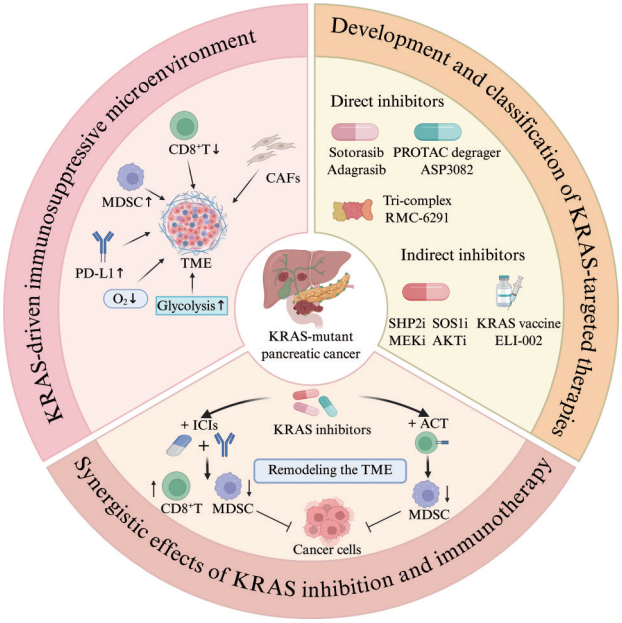


Figure 3 KRAS-driven immune microenvironment and classification of KRAS-targeted therapies in pancreatic cancer. TME: Tumor microenvironment; SHP2i: Src homology 2 domain-containing protein tyrosine phosphatase-2 inhibitor; SOS1i: Son of sevenless homolog 1 inhibitor; PROTAC: Proteolysis targeting chimera; ACT: Adoptive cell transfer therapy (figure was created with Biorender.com)

作者贡献: 张析妍完成文献资料的收集和整理及文章撰写; 彭宗根负责文章的选题与内容指导; 陈淑珍负责文章的选题、内容指导、审阅、修改和校对。

利益冲突: 本文所有作者声明不存在任何利益冲突。

References

[1] Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024 [J]. CA Cancer J Clin, 2024, 74: 12-49.

[2] Zeng H, Zheng R, Sun K, et al. Cancer survival statistics in China 2019-2021: A multicenter, population-based study [J]. J Natl Cancer Cent, 2024, 4: 203-213.

[3] Rahib L, Wehner MR, Matrisian LM, et al. Estimated projection of US cancer incidence and death to 2040 [J]. JAMA Netw Open, 2021, 4: e214708.

[4] Chen H, Zhuo Q, Ye Z, et al. Organoid model: A new hope for pancreatic cancer treatment? [J]. Biochim Biophys Acta Rev Cancer, 2021, 1875: 188466.

[5] Wainberg ZA, Melisi D, Macarulla T, et al. NALIRIFOX *versus* nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): A randomised, open-label, phase 3 trial [J]. Lancet, 2023, 402: 1272-1281.

[6] Yang H, Li W, Li S, et al. Progress on targets and therapeutic drugs for pancreatic cancer [J]. Acta Pharm Sin (药学学报), 2023, 58: 9-20.

[7] Upadhaya S, Neftelinov ST, Hodge J, et al. Challenges and opportunities in the PD1/PDL1 inhibitor clinical trial landscape [J]. Nat Rev Drug Discov, 2022, 21: 482-483.

[8] Galanopoulos M, Doukatas A, Gkeros F, et al. Room for improvement in the treatment of pancreatic cancer: Novel opportunities from gene targeted therapy [J]. World J Gastroenterol, 2021, 27: 3568-3580.

[9] Zhang H, Xing J, Dai Z, et al. Exosomes: The key of sophisticated cell-cell communication and targeted metastasis in pancreatic cancer [J]. Cell Commun Signal, 2022, 20: 9.

[10] Wei D, Wang L, Zuo X, et al. A small molecule with big impact: MRTX1133 targets the $KRAS^{G12D}$ mutation in pancreatic cancer [J]. Clin Cancer Res, 2024, 30: 655-662.

[11] McDaid WJ, Wilson L, Adderley H, et al. The PI3K-AKT-mTOR axis persists as a therapeutic dependency in $KRAS^{G12D}$-driven non-small cell lung cancer [J]. Mol Cancer, 2024, 23: 253.

[12] Molina-Arcas M, Downward J. Exploiting the therapeutic implications of KRAS inhibition on tumor immunity [J]. Cancer Cell, 2024, 42: 338-357.

[13] Das S, Shapiro B, Vucic EA, et al. Tumor cell-derived IL1β promotes desmoplasia and immune suppression in pancreatic cancer [J]. Cancer Res, 2020, 80: 1088-1101.

[14] di Miceli N, Baioni C, Barbieri L, et al. TGF-β signaling loop in pancreatic ductal adenocarcinoma activates fibroblasts and increases tumor cell aggressiveness [J]. Cancers (Basel), 2024, 16: 3705.

[15] Sadozai H, Acharjee A, Kayani HZ, et al. High hypoxia status in pancreatic cancer is associated with multiple hallmarks of an immunosuppressive tumor microenvironment [J]. Front Immunol, 2024, 15: 1360629.

[16] Dong S, Li W, Li X, et al. Glucose metabolism and tumour microenvironment in pancreatic cancer: A key link in cancer progression [J]. Front Immunol, 2022, 13: 1038650.

[17] Liu C, Zheng S, Wang Z, et al. KRAS-G12D mutation drives immune suppression and the primary resistance of anti-PD-1/PD-L1 immunotherapy in non-small cell lung cancer [J]. Cancer Commun, 2022, 42: 828-847.

[18] Alam A, Levanduski E, Denz P, et al. Fungal mycobiome drives IL-33 secretion and type 2 immunity in pancreatic cancer [J]. Cancer Cell, 2022, 40: 153-167.

[19] Donahue KL, Watkoske HR, Kadiyala P, et al. Oncogenic KRAS-dependent stromal interleukin-33 directs the pancreatic microenvironment to promote tumor growth [J]. Cancer Discov, 2024, 14: 1964-1989.

[20] Awaji M, Saxena S, Wu L, et al. CXCR2 signaling promotes secretory cancer-associated fibroblasts in pancreatic ductal adenocarcinoma [J]. FASEB J, 2020, 34: 9405-9418.

[21] Tay C, Tanaka A, Sakaguchi S. Tumor-infiltrating regulatory T cells as targets of cancer immunotherapy [J]. Cancer Cell, 2023, 41: 450-465.

[22] Deng Z, Fan T, Xiao C, et al. TGF-β signaling in health, disease, and therapeutics [J]. Signal Transduct Target Ther, 2024, 9: 61.

[23] Liu Y, Deguchi Y, Wei D, et al. Rapid acceleration of KRAS-mutant pancreatic carcinogenesis *via* remodeling of tumor immune microenvironment by PPARδ [J]. Nat Commun, 2022, 13: 2665.

[24] Dai E, Han L, Liu J, et al. Autophagy-dependent ferroptosis drives tumor-associated macrophage polarization *via* release and uptake of oncogenic KRAS protein [J]. Autophagy, 2020, 16: 2069-2083.

[25] Coelho MA, de Carné Trécesson S, Rana S, et al. Oncogenic RAS signaling promotes tumor immunoresistance by stabilizing PD-L1 mRNA [J]. Immunity, 2017, 47: 1083-1099.

[26] Chen N, Fang W, Lin Z, et al. KRAS mutation-induced upregulation of PD-L1 mediates immune escape in human lung adenocarcinoma [J]. Cancer Immunol Immunother, 2017, 66: 1175-1187.

[27] Gao Z, Chen JF, Li XG, et al. KRAS acting through ERK signaling stabilizes PD-L1 *via* inhibiting autophagy pathway in intrahepatic cholangiocarcinoma [J]. Cancer Cell Int, 2022, 22: 128.

[28] Peng DH, Rodriguez BL, Diao L, et al. Th17 cells contribute to combination MEK inhibitor and anti-PD-L1 therapy resistance in KRAS/p53 mutant lung cancers [J]. Nat Commun, 2021, 12: 2606.

[29] Lastwika KJ, Wilson W, Li QK, et al. Control of PD-L1 expression by oncogenic activation of the AKT-mTOR pathway in non-small cell lung cancer [J]. Cancer Res, 2016, 76: 227-238.

[30] Hashimoto S, Furukawa S, Hashimoto A, et al. ARF6 and AMAP1 are major targets of KRAS and TP53 mutations to

promote invasion, PD-L1 dynamics, and immune evasion of pancreatic cancer [J]. Proc Natl Acad Sci U S A, 2019, 116: 17450-17459.

[31] Dey P, Li J, Zhang J, et al. Oncogenic KRAS-driven metabolic reprogramming in pancreatic cancer cells utilizes cytokines from the tumor microenvironment [J]. Cancer Discov, 2020, 10: 608-625.

[32] Moldogazieva NT, Mokhosoev IM, Terentiev AA. Metabolic heterogeneity of cancer cells: An interplay between HIF-1, GLUTs, and AMPK [J]. Cancers (Basel), 2020, 12: 862.

[33] Schild T, McReynolds MR, Shea C, et al. NADK is activated by oncogenic signaling to sustain pancreatic ductal adenocarcinoma [J]. Cell Rep, 2021, 35: 109238.

[34] Rapozzi V, Comuzzi C, Di Giorgio E, et al. KRAS and NRF2 drive metabolic reprogramming in pancreatic cancer cells: The influence of oxidative and nitrosative stress [J]. Front Cell Dev Biol, 2025, 13: 1547582.

[35] Janes MR, Zhang J, Li LS, et al. Targeting KRAS mutant cancers with a covalent G12C-specific inhibitor [J]. Cell, 2018, 172: 578-589.

[36] Hong DS, Fakih MG, Strickler JH, et al. $KRAS^{G12C}$ inhibition with sotorasib in advanced solid tumors [J]. N Engl J Med, 2020, 383: 1207-1217.

[37] Jänne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in non-small-cell lung cancer harboring a $KRAS^{G12C}$ mutation [J]. N Engl J Med, 2022, 387: 120-131.

[38] Wang X, Allen S, Blake JF, et al. Identification of MRTX1133, a noncovalent, potent, and selective $KRAS^{G12D}$ inhibitor [J]. J Med Chem, 2022, 65: 3123-3133.

[39] Ignacio GL, Brian MW, Wungki P, et al. Safety, efficacy, and on-treatment circulating tumor DNA (ctDNA) changes from a phase 1 study of RMC-6236, a RAS(ON) multi-selective, tri-complex inhibitor, in patients with RAS mutant pancreatic ductal adenocarcinoma (PDAC)[J]. J Clin Oncol, 2025, 43: 722

[40] Schulze CJ, Seamon KJ, Zhao Y, et al. Chemical remodeling of a cellular chaperone to target the active state of mutant KRAS [J]. Science, 2023, 381: 794-799.

[41] Cregg J, Pota K, Tomlinson ACA, et al. Discovery of elironrasib (RMC-6291), a potent and orally bioavailable, RAS(on) G12C-selective, covalent tricomplex inhibitor for the treatment of patients with RAS G12C-addicted cancers [J]. J Med Chem, 2025, 68: 6041-6063.

[42] Tolcher AW, Park W, Wang JS, et al. Trial in progress: A phase 1, first-in-human, open-label, multicenter, dose-escalation and dose-expansion study of ASP3082 in patients with previously treated advanced solid tumors and KRAS G12D mutations [J]. J Clin Oncol, 2023, 41: TPS764.

[43] Yoshinari T, Nagashima T, Ishioka H, et al. Discovery of $KRAS^{G12D}$ selective degrader ASP3082 [J]. Commun Chem, 2025, 8: 254.

[44] Khan N, Raza U, Ali Zaidi SA, et al. Drugging the 'undruggable' KRAS: Breakthroughs, challenges, and opportunities in pancreatic cancer [J]. Cancer Biol Med, 2025, 22: 762-788.

[45] Hamilton G, Stickler S, Rath B. Targeting of SOS1: From SOS1 activators to proteolysis targeting chimeras [J]. Curr Pharm Des, 2023, 29: 1741-1746.

[46] Herrick WG, Kilpatrick CL, Hollingshead MG, et al. Isoform- and phosphorylation-specific multiplexed quantitative pharmacodynamics of drugs targeting PI3K and MAPK signaling in xenograft models and clinical biopsies [J]. Mol Cancer Ther, 2021, 20: 749-760.

[47] Pant S, Wainberg ZA, Weekes CD, et al. Lymph-node-targeted, mKRAS-specific amphiphile vaccine in pancreatic and colorectal cancer: The phase 1 AMPLIFY-201 trial [J]. Nat Med, 2024, 30: 531-542.

[48] Ostrem JM, Peters U, Sos ML, et al. $KRAS^{G12C}$ inhibitors allosterically control GTP affinity and effector interactions [J]. Nature, 2013, 503: 548-551.

[49] Liu KX, Wu RL, Yuan T, et al. Recent advances in mechanisms of $KRAS^{G12C}$ inhibitors anti-tumor resistance and relevant overcoming strategies [J]. Acta Pharm Sin (药学学报), 2022, 57: 271-276.

[50] Awad MM, Liu S, Rybkin II, et al. Acquired resistance to $KRAS^{G12C}$ inhibition in cancer [J]. N Engl J Med, 2021, 384: 2382-2393.

[51] Simnica D, Kobold S. Neoantigen T-cell receptor gene therapy in pancreatic cancer [J]. N Engl J Med, 2022, 387: 573.

[52] Mahadevan KK, McAndrews KM, LeBleu VS, et al. $KRAS^{G12D}$ inhibition reprograms the microenvironment of early and advanced pancreatic cancer to promote FAS-mediated killing by $CD8^+$ T cells [J]. Cancer Cell, 2023, 41: 1606-1620.

[53] McAndrews KM, Paradiso F, Stalnecker CA, et al. An allele-agnostic mutant-KRAS inhibitor suppresses tumor maintenance signals and reprograms tumor immunity in pancreatic cancer [J]. Sci Transl Med, 2025, 17: eadt5511.

[54] Hirade K, Tanaka N, Kajino T, et al. Inhibiting KRAS with CD47 and immune checkpoint overcomes intrinsic resistance to combined KRAS and immune checkpoint inhibitor therapy [J]. Cell Rep Med, 2025, 6: 102317.

[55] Li BT, Falchook GS, Durm GA, et al. OA03.06 CodeBreaK 100/101: First report of safety/efficacy of sotorasib in combination with pembrolizumab or atezolizumab in advanced KRAS p.G12C NSCLC [J]. J Thorac Oncol, 2022, 17: S10-S11.

[56] Jänne PA, Smit EF, de Marinis F, et al. LBA4 preliminary safety and efficacy of adagrasib with pembrolizumab in treatment-naive patients with advanced non-small cell lung cancer (NSCLC) harboring a KRAS G12C mutation [J]. Immunooncol Technol, 2022, 16: 100360.

[57] Rojas CI, Lugowska I, Juergens R, et al. 44O updated results from a phase I study evaluating the KRAS G12C inhibitor MK-

1084 in solid tumors and in combination with pembrolizumab in NSCLC [J]. ESMO Open, 2024, 9: 102273.

[58] Tang L, Huang Z, Mei H, et al. Immunotherapy in hematologic malignancies: Achievements, challenges and future prospects [J]. Signal Transduct Target Ther, 2023, 8: 306.

[59] Yeo D, Giardina C, Saxena P, et al. The next wave of cellular immunotherapies in pancreatic cancer [J]. Mol Ther Oncolytics, 2022, 24: 561-576.

[60] Lu D, Chen Y, Jiang M, et al. KRAS G12V neoantigen specific T cell receptor for adoptive T cell therapy against tumors [J]. Nat Commun, 2023, 14: 6389.

[61] Bai X, Shen Y, Zhang T, et al. 1514O First-in-human phase I study of TCR-T therapy targeting KRAS G12V in metastatic solid tumors [J]. Ann Oncol, 2025, 36: S844.