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KRAS靶向药研究进展

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摘要 自1982年首次鉴定*KRAS*原癌基因以来, KRAS长期被视为“不可成药”的靶点. *KRAS*在胰腺癌、结直肠癌和肺癌等高致死性癌症中高频突变, 是驱动肿瘤进展的关键分子, 被誉为“癌症跳动的心脏”. 野生型KRAS依赖生长因子激活, 通过快速水解GTP来失活; 而致癌型KRAS水解酶活性受损, 激活型KRAS癌蛋白水平升高, 过度激活增殖信号通路, 驱动肿瘤发生发展, 因此成为精准治疗的重要靶点. 近年来, 结构生物学和药物化学的突破推动了KRAS靶向药的发展, 以$KRAS^{G12C}$共价抑制剂的变革性成功为代表, 深刻改变了肿瘤靶向治疗的研究格局. 本文回顾了KRAS靶向药物的策略演进, 梳理抑制剂的结构设计与作用机制, 探讨耐药性带来的新挑战, 并展望KRAS靶向治疗的未来方向.

关键词 分子开关, $KRAS^{G12C}$, GTP酶激活蛋白, 靶向药, PROTAC, 分子胶, 耐药性

肿瘤治疗是全球公共卫生领域面临的重大挑战之一. 世界卫生组织数据显示, 恶性肿瘤已连续十年位居全球死因首位, 预计2040年新发病例将突破3000万例[1]. *KRAS*(Kirsten rat sarcoma viral oncogene homolog)是*RAS*家族中最常见的致癌成员, 编码分子量约为21 kD的小GTP酶, 在调控细胞增殖、生长与存活等生命活动中发挥关键作用[2]. *KRAS*基因突变广泛存在于胰腺癌、结直肠癌和肺癌等高致死性实体瘤中, 是驱动肿瘤发生与发展的核心遗传事件[3~6]. 野生型KRAS通过GTP酶激活蛋白(GTPase-activating proteins, GAPs)加速GTP水解, 形成动态“开-关”循环的调控模式, 然而突变型KRAS蛋白通常逃逸GAP(依赖“精氨酸指”arginine finger)介导的失活机制, 导致其无法快速转变为失活状态, 从而过度激活MAPK, PI3K-AKT, RALGDS等致癌信号通路, 驱动肿瘤发生发展[7,8]. KRAS位于信号转导网络的核心, 其下游通路具有显著的冗余性与补偿机制, 使得单靶点干预难以实现持久抑制[9]. Wittinghofer团队解析了HRAS的三维晶体结构, 揭示RAS蛋白表面光滑, 缺乏典型的小分子结合口袋, 为其“不可成药”的特性提供了结构依据[10,11]. 此外, 突变型KRAS以皮摩尔级别的超高亲和力结合胞内高浓度的GTP, 进一步排除了传统竞争性抑制策略的可能性[12]. 结构障碍与调控机制的双重限制, 使RAS长期被视为精准治疗领域最具挑战性的靶点.

系统性癌症基因组研究反复验证了*KRAS*是多种实体瘤中最核心的驱动基因, 且缺乏功能显著、靶向

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性强的替代靶点, 正是这种不可替代的“驱动地位”, 促使学界持续探索其可成药性(图1). 2013年, Shokat实验室[13]基于KRAS^{G12C}突变的结构特征, 首次开发出能够共价结合Switch-II口袋、并将KRAS“锁”定于非激活态的小分子, 打破了长达数十年的药物设计困局, 推动全球首个KRAS^{G12C}抑制剂进入临床并获批上市. Adrian团队[14~16]也推进了面向激活态KRAS的新型三元复合物设计策略, 采用“beyond Rule of 5”分子架构, 实现了对激活态KRAS的选择性干预. RAS研究的复兴早已超越了新药临床开发的范畴, RAS生物学与药物发现已成为炙手可热的研究前沿. 临床经验也不断提醒我们, 关于RAS的生物学机制仍有大量未知亟待探索. 尽管面临诸多挑战, RAS研究正站在新一代癌症治疗策略的前沿. 借助机器学习与结构生物学推动药物发现, 开发新型激活免疫系统的方式来靶向新抗原与克服免疫抑制, 尝试阻断KRAS表达, 探索应对耐药的新方法, 以及评估靶向RAS以外独立通路的策略, KRAS靶向治疗正迎来前所未有的创新突破.

1 KRAS的结构特征与活化机制

RAS蛋白由高度保守的N端G结构域和决定蛋白亚型特异性的C端超变区组成. G结构域包含: Switch-I, Switch-II和P环[10]. KRAS的核心功能依赖其G结构域与GTP或GDP的结合能力. 当KRAS处于GDP结合的非激活态时, 其Switch-II区域会发生构象变化, 暴露出一个疏水性的隐匿口袋(Switch-II pocket, 简称SIIP), 为小分子药物设计提供了重要靶点[2,7,13,17,18]. KRAS作为细胞内的“分子开关”(图2), 其功能可概括为两种状态:

(ⅰ) “开”(ON)激活状态: KRAS与GTP结合时处于激活状态, 启动信号转导, 促进细胞增殖、存活和迁移;

(ⅱ) “关”(OFF)非激活态: KRAS与GDP结合时处于失活状态, 信号终止.

在生理条件下, RAS蛋白大部分时间处于GDP结合的“关闭”状态. 胞外刺激激活膜受体后, 通过鸟苷酸交换因子(guanine nucleotide exchange factors, GEFs)促进RAS释放GDP并结合GTP, 完成从“关”状态向“开”状态的构象转换, 实现RAS蛋白的活化[19,20]. RAS蛋白本身具有微弱的内源性GTP酶活性, 能够将GTP水解为GDP, 从而终止信号转导. RAS蛋白GTP酶水解活性的完全发挥依赖于GAPs的增强作用[21,22]. GAPs通过提供“精氨酸指”关键位点, 促进过渡态稳定, 显著提升GTP水解速率, 使激活态的RAS快速恢复至非激活态, 实现信号输出的精确时空控制[23~26]. 然而, KRAS常见的致癌突变多发生在第12或第13位氨基酸(如G12D, G12V和G13D等), 突变导致空间位阻, 阻碍GAPs促进GTP水解[21,27], 使KRAS长时间保持GTP结合激活态, 导致下游信号持续激活, 驱动肿瘤细胞异常增殖与恶性转化, 成为多种实体瘤中的关键致癌事件[21,26,28~30].

2 早期RAS靶向药研究的挫折与启示

RAS蛋白的C末端均以CAAX四肽序列(C: 半胱氨

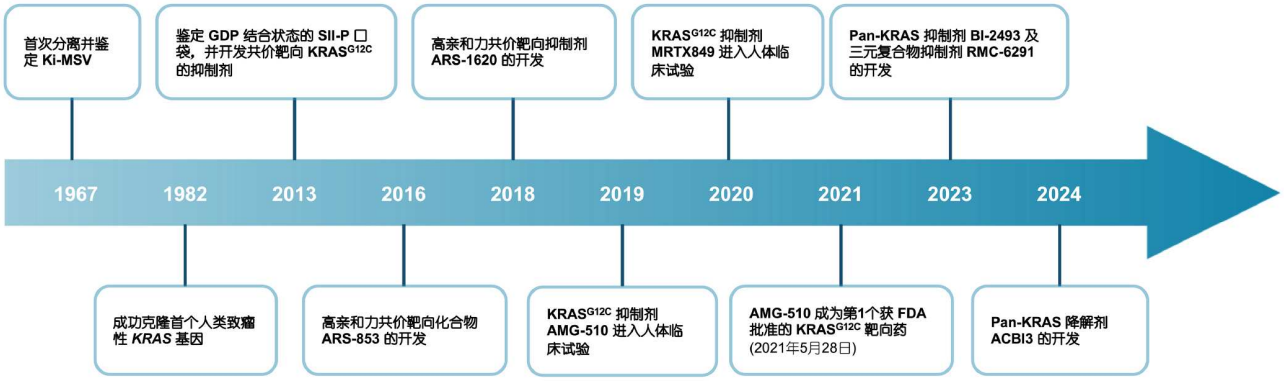


图 1 KRAS抑制剂开发历程示意图[2,13,15,36~40,49,58,76]

Figure 1 Summary timeline of selected milestones in the development of KRAS inhibitors[2,13,15,36~40,49,58,76]

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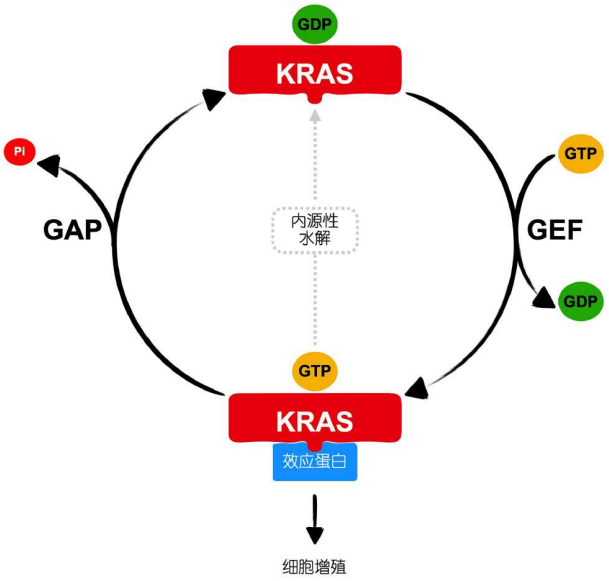


图 2　“分子开关”KRAS蛋白在非激活态与激活态之间的循环. KRAS的激活依赖GEFs促进的GDP/GTP交换; 非激活态则依赖GAPs促进的GTP水解反应

Figure 2　“Molecular switch” KRAS is cycling between inactive GDP-bound and active GTP-bound states. GEFs promote GDP/GTP exchange to activate KRAS, and GAPs enhance the intrinsic KRAS GTPase activity to promote GTP hydrolysis to inactivate KRAS

酸; A: 脂肪族氨基酸; X: 任意氨基酸)结尾, X的氨基酸种类决定了蛋白将被哪种异戊酰转移酶修饰. 当X为M(甲硫氨酸)、S(丝氨酸)、Q(谷氨酰胺)或A(丙氨酸)时, 法呢基转移酶会添加15碳的聚异戊烯修饰; 当X为L(亮氨酸)、I(异亮氨酸)或F(苯丙氨酸)时, 则由GGTase-I添加20碳的脂质, 该序列被修饰后, 增强了RAS蛋白的疏水性, 使其定位于内质网或质膜等亚细胞膜结构, 这是其发挥功能所必需的步骤[31].

RAS家族成员G结构域高度保守, 但其C末端的修饰类型、信号耦合方式及亚细胞定位存在显著差异, 这些特异性在很大程度上决定了各RAS亚型对靶向干预的敏感性与逃逸机制. 由法呢基转移酶介导的法呢酰化被认为是RAS蛋白激活及其致癌功能的关键修饰步骤. 因此, FTase抑制剂(FTIs)曾一度被寄予厚望, 被视为抑制RAS驱动肿瘤的重要治疗策略. 多个FTI药物先后进入针对KRAS突变型肿瘤的Ⅲ期临床试验, 然而, 多项临床试验均未能显示出显著的治疗获益, 随后证实KRAS对FTIs存在生化层面的耐药机制, FTIs的系统性失败使RAS靶向药开发一度陷入低谷, 进一步强化了“RAS不可成药”的学术共识[32~34]. 这段历史为RAS靶向治疗提供了宝贵的教训: 唯有深入理解RAS各亚型的生化和蛋白结构特性, 才能实现结构导向、机制驱动的精准抑制剂设计, 为新一代药物的开发指明方向.

3　$KRAS^{G12C}$抑制剂的开发历程

长期以来, 致癌性KRAS被认为持续处于GTP结合的激活状态, 因此, 非激活态的抑癌策略被普遍质疑, 特别是KRAS致癌蛋白的激活依赖于核苷酸的交换[13,35~47]. 近年来的$KRAS^{G12C}$抑制剂的研究逐步颠覆了这一传统认知. 即使在KRAS驱动的肿瘤细胞中, KRAS蛋白依然能在GTP与GDP状态之间进行动态切换[22,36,48~50], 且这一转化在特定GTP酶激活蛋白, 如非R指依赖的RGS3作用下显著增强, 从而为非激活态抑制剂提供了可结合的“时间窗口”[48,51~53]. 早期尝试利用核磁共振(NMR)寻找可结合KRAS的片段化合物时, 发现了一个可能具有药物开发潜力的口袋, 即SOS口袋[54,55]. SOS结合口袋不是一个理想的靶点, 但是这种靶向策略成功用于“不可成药”蛋白Bcl-2家族的药物开发[56]. 2013年, Shokat团队[13]发现, 在KRAS-GDP构象下Switch-II区域可形成一个疏水性的结合口袋, 为药物设计提供了可成药的结构基础. SIIP位于中央β折叠与α2/α3螺旋之间, 是当前成药性探索的关键结构基础. $KRAS^{G12C}$突变使第12位的甘氨酸残基被半胱氨酸替代, 为小分子共价修饰提供了天然靶点. 半胱氨酸巯基具有优异的亲核性与可极化性, 这使得$KRAS^{G12C}$成为首个实现“不可成药”到“可成药”转变的RAS靶点. 基于$KRAS^{G12C}$-GDP构象的二硫键片段筛选, Shokat团队[13]率先发现了能选择性结合$KRAS^{G12C}$的片段化合物6H05, 并在此基础上优化得到含有丙烯酰胺“弹头”的化合物**12**, 随后进一步发展为携带丙烯酰胺warhead的先导化合物ARS-853和ARS-1620[36~38]. 这些共价抑制剂不可逆结合$KRAS^{G12C}$的半胱氨酸残基, 将其锁定于失活构象, 阻断MAPK通路激活, 有效抑制肿瘤细胞增殖[36]. 基于上述分子机制, AMG-510(Sotorasib, 索托拉西布)作为首个进入临床的共价抑制剂[39,57], 于2021年获得美国FDA加速批准, 用于治疗晚期或转移性$KRAS^{G12C}$突变的非小细胞肺癌(NCT03600883, CodeBreaK 100). Sotorasib可识别SIIP并实现位点共价修饰, 临床数据显

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示其在晚期NSCLC患者中达到42.9%的客观缓解率(ORR), 中位总生存期(OS)为12.5个月[58]. MRTX849 (Adagrasib, 阿达格拉西布)于2022年获得FDA加速批准, 在结构上引入了多个优化元素, 其分子中含有一个哌嗪C-2氰甲基基团, 可增强warhead的亲电性, 并通过N-甲基吡咯烷与Glu62侧链形成额外的离子作用, 提高了与$KRAS^{G12C}$的亲和力与选择性[40,59]. MRTX849显示出与Sotorasib相近的ORR(42.9%)和OS (12.6个月), 但在脑转移NSCLC患者中表现出更优异的中枢神经系统穿透性与疗效[60]. 新一代GDC-6036 (Divarasib)是一种共价型$KRAS^{G12C}$抑制剂, 具有高度的效力和选择性. Divarasib的效力是Sotorasib和Adagrasib的5~20倍, 选择性更是高达50倍以上, 并展现出更优的抗肿瘤活性[61]. $KRAS^{G12C}$抑制剂不仅能抑制肿瘤生长, 还能诱导生成半抗原化的肽-MHC Ⅰ类复合物, 从而使肿瘤细胞表面呈现出肿瘤特异性的新抗原. 这些新抗原可以被基于半抗原识别机制的免疫疗法和双特异性抗体所识别和靶向[62,63].

区别于非激活态共价抑制剂, Revolution Medicines公司开发了作用于激活态KRAS的三元复合物抑制剂, 代表药物为RMC-4998[15]. RMC-4998、亲环蛋白Cyclophilin A和$KRAS^{G12C}$-GTP形成三元复合体, 从而靶向激活态的KRAS并抑制其激活信号通路. CYPA-RMC-4998复合物可协同结合SI与SII区域, 干扰KRAS与RAF, PI3K和RALGDS等效应蛋白的相互作用. RMC-4998的进一步优化产物RMC-6291目前正在进行Ⅰ/Ⅰb期临床试验(NCT05462717), 不仅作为单药治疗, 还与“多靶点”RAS三元复合物抑制剂RMC-6236(NCT06128551)联合用于$KRAS^{G12C}$突变实体瘤的临床探索[15]. 另一款候选药物RMC-7977是一类广谱RAS(ON)抑制剂. RMC-7977直接靶向GTP结合态的KRAS/HRAS/NRAS, 实现对癌基因依赖性的抑制, 并在KPC小鼠模型中显著延长生存期, 在多个KRAS驱动的胰腺导管腺癌模型中展现出强效、选择性的抗肿瘤活性, 为后续广谱RAS靶向治疗策略提供了有力的临床前依据[16].

4 KRAS非G12C突变靶向策略

KRAS^{G12C}突变约占全部*KRAS*突变的5%, 这使得能从G12C抑制剂中获益的患者比例有限. 其他高频*KRAS*突变(如G12D, G12V, G13D和Q61K等)由于缺乏高反应性的半胱氨酸, 难以应用传统共价抑制策略, 因此推动了突变选择性抑制剂、广谱KRAS及广谱RAS抑制剂的开发(表1和2).

4.1 $KRAS^{G12D}$小分子抑制剂

受$KRAS^{G12C}$抑制剂临床成功的启发, 研究重心已逐步转向$KRAS^{G12D}$. 与G12C突变中高反应性的半胱氨酸不同, G12D位点的天冬氨酸化学惰性更强, 显著增加了药物设计难度. 然而, 多个机制各异的$KRAS^{G12D}$直接抑制剂已取得关键进展.

MRTX1133是一款基于Adagrasib骨架设计的非共价KRAS抑制剂, 优先结合$KRAS^{G12D}$的GDP状态, 显示出超过700倍的$KRAS^{G12D}$选择性. 该药可有效阻断效应蛋白结合, 抑制$KRAS^{G12D}$突变细胞系的生长, 并在CDX与PDX模型中诱导显著肿瘤退缩[64,65]. 基于良好的临床前数据, MRTX1133已于2023年进入针对$KRAS^{G12D}$阳性晚期实体瘤的Ⅰ/Ⅱ期临床试验(NCT05737706). 另一款与MRTX1133结构类似的HRS-4642在Ⅰ期临床研究(NCT05533463)中也展示出良好的临床活性[66]. 要实现对$KRAS^{G12D}$突变这一最常见KRAS等位突变的共价靶向, 面临的最大挑战在于G12D中的天冬氨酸侧链为羧酸基, 而羧酸是所有含杂原子氨基酸中亲核性最弱的一类. 它不仅本身化学反应活性低, 而且呈负电性, 不易与中性或正电性的电亲试剂高效成键. Shokat实验室[67]采用应力释放型烷基化策略, 利用马来内酯类电亲化合物实现对$KRAS^{G12D}$突变位点的选择性共价修饰. RMC-9805是“分子胶”机制下的三元复合物抑制剂, 通过结合Cyclophilin A共价修饰GTP结合状态的$KRAS^{G12D}$, 从而实现对其活化态的选择性抑制[68]. 该药在多种CDX/PDX模型中表现出良好耐受性和抗肿瘤活性, 并在免疫完整小鼠中与抗PD-1抗体联用显示协同抑制作用, 进行Ⅰ/Ⅰb期临床试验(NCT06040541). ASP3082是一种蛋白酶体靶向嵌合体(PROTAC), 通过促进$KRAS^{G12D}$与E3泛素连接酶的结合, 使其降解于蛋白酶体途径. ASP3082可显著抑制$KRAS^{G12D}$突变细胞的体外生长, 对野生型KRAS细胞影响较小, 并在CDX模型中显示出良好抗肿瘤活性[69]. 该药需静脉注射给药, 目前已进入针对经治$KRAS^{G12D}$突变患者的临床试验阶段(NCT05382559).

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表 1 部分已上市或正在进行临床试验的KRAS抑制剂(单药治疗)[a)]

Table 1 Selected KRAS inhibitors approved or currently in clinical trials (monotherapy)[a)]

适应症	药物名称	靶点	机制	药物类型	阶段	主要终点
NSCLC	Sotorasib (AMG510)	$KRAS^{G12C}$	$KRAS^{G12C}$ (OFF)	小分子	批准 (NCT03600883)	2026-01-31
NSCLC	Adagrasib (MRTX849)	$KRAS^{G12C}$	$KRAS^{G12C}$ (OFF)	小分子	批准(NCT03785249)	2026-12-31
NSCLC	Divarasib (GDC-6036)	$KRAS^{G12C}$	$KRAS^{G12C}$ (OFF)	小分子	Ⅲ (CTR20254061)/ Ⅲ (NCT06497556)	2027-09-30
NSCLC	Opnurasib (JDQ-443)	$KRAS^{G12C}$	$KRAS^{G12C}$ (OFF)	小分子	Ⅲ (NCT05132075)	2026-02-28
NSCLC	RMC-6291	RAS^{G12C}	RAS^{G12C} (ON)	分子胶	Ⅰ (NCT05462717)	2024-11
CRC	Sotorasib (AMG510)	$KRAS^{G12C}$	$KRAS^{G12C}$ (OFF)	小分子	Ⅰ (NCT03600883)	2026-01-31
CRC	Adagrasib (MRTX849)	$KRAS^{G12C}$	$KRAS^{G12C}$ (OFF)	小分子	Ⅰ/Ⅱ (NCT03785249)	2026-12-31
CRC	RMC-6291	RAS^{G12C}	RAS^{G12C} (ON)	分子胶	Ⅰ (NCT05462717)	2024-11
CRC	Divarasib (GDC-6036)	RAS^{G12C}	$KRAS^{G12C}$ (OFF)	小分子	Ⅰ/Ⅱ (NCT04449874)	2026-09-24
PDAC	Sotorasib (AMG510)	$KRAS^{G12C}$	$KRAS^{G12C}$ (OFF)	小分子	Ⅰ/Ⅱ (NCT03600883)	2026-01-31
PDAC	Adagrasib (MRTX849)	$KRAS^{G12C}$	$KRAS^{G12C}$ (OFF)	小分子	Ⅰ/Ⅱ (NCT03785249)	2026-12-31
PDAC	RMC-6291	RAS^{G12C}	RAS^{G12C} (ON)	分子胶	Ⅰ (NCT05462717)	2024-11
PDAC	Divarasib (GDC-6036)	$KRAS^{G12C}$	$KRAS^{G12C}$ (OFF)	小分子	Ⅰ (NCT044449874)	2026-09-24
NSCLC/CRC/PDAC	MRTX1133	$KRAS^{G12D}$	$KRAS^{G12D}$ (ON/OFF)	小分子	Ⅱ (NCT05737706)	2025-03-10
实体瘤	ASP3082	$KRAS^{G12D}$	$KRAS^{G12D}$	降解剂	Ⅰ (NCT05382559)	2026-10-31
实体瘤	HRS-4642	$KRAS^{G12D}$	$KRAS^{G12D}$ (OFF)	小分子	Ⅰ/Ⅱ (NCT06520488)	2027-3
NSCLC/CRC/PDAC	RMC-9805	RAS^{G12D}	RAS^{G12D} (ON)	分子胶	Ⅰ (NCT06040541)	2026-04-30
NSCLC/CRC/PDAC	RMC-6236	RAS	RAS (ON)	分子胶	Ⅰ (NCT05379985)	2027-05-31
实体瘤	RMC-5127	RAS^{G12V}	RAS^{G12V} (ON)	分子胶	临床前	–
实体瘤	RMC-7977	RAS	RAS (ON)	分子胶	临床前	–
实体瘤	BI-2493	KRAS	KRAS (OFF)	小分子	–	–
实体瘤	ACBI3	KRAS	pan-KRAS	降解剂	–	–
实体瘤	RMC-8839	$KRAS^{G13C}$	RAS (ON)	分子胶	–	–

a) NSCLC: 非小细胞肺癌; CRC: 结直肠癌; PDAC: 胰腺导管腺癌. 截止日期: 2025年12月7日, 来源: https://clinicaltrials.gov

表 2 部分已上市或正在进行临床试验的KRAS抑制剂(联合治疗)[a)]

Table 2 Selected KRAS inhibitors approved or currently in clinical trials (combination therapy)[a)]

适应症	药物名称	客观缓解率	中位无进展生存期	中位总生存期	阶段	主要终点
NSCLC	Sotorasib+atezolizumab/ pembrolizumab	20%(Atezo)/32% ~37%(Pembro)	–	15.7月	Ⅰ (NCT03600883)	2026-01-31
NSCLC	Sotorasib+carboplatin/ pemetrexed	88.99%	5.7月	–	Ⅱ (WJOG14821L)	–
NSCLC	Adagrasib+pembrolizumab	63%	–	–	Ⅱ/Ⅲ (NCT04613596)	2028-10-31
CRC	Sotorasib+panitumumab	30%	5.7月	–	Ⅰ (NCT03600883)	2026-01-31
CRC	Adagrasib+cetuximab	34%	6.9月	15.9月	Ⅰ/Ⅱ (NCT03785249)	2026-12-31
CRC	Divarasib+cetuximab	63%	8.1月	–	Ⅰ (NCT04449874)	2026-09-24
NSCLC/CRC/ PDAC	RMC-6291+RMC-6236	–	–	–	Ⅰ (NCT06128551)	2026-11-30

a) NSCLC: 非小细胞肺癌; CRC: 结直肠癌; PDAC: 胰腺导管腺癌. 截止日期: 2025年12月7日, 来源: https://clinicaltrials.gov

4.2 广谱KRAS抑制剂(pan-KRAS inhibitors)

传统观点认为, 选择性抑制特定KRAS突变可提高治疗指数, 但临床实践中, 一些突变特异性药物仍产生不可预期毒性. 广谱KRAS抑制剂, 如BI-2865和BI-2493可靶向多种KRAS突变体及野生型KRAS[49], 改良分子BI-3706674进入临床试验(NCT06056024). 另

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一类泛RAS抑制剂, 如RMC-6236, 不仅作用于KRAS, 还涵盖HRAS和NRAS多个亚型, 在Ⅰ期试验中显示出初步疗效[70]. RMC-7977是一款靶向GTP结合状态的广谱RAS抑制剂, 对三种RAS亚型的突变型及野生型均具亲和力, 在多种PDAC模型中均显示出显著抗肿瘤活性, 治疗组肿瘤组织出现凋亡及持续性增殖抑制, 正常组织反应温和, 为联合疗法提供新方向[16,71,72].

4.3 RAS降解技术和分子胶抑制剂(molecular glues)

KRAS抑制剂的发现不仅推动了直接靶向KRAS的药物开发, 也为KRAS降解剂(KRAS degraders)的研究开启了新方向. 泛素-蛋白酶体系统是细胞内降解受损或不再需要的蛋白质的主要机制[73], 该策略通过设计双功能分子, 将KRAS靶向至泛素化过程, 从而实现蛋白酶体介导的降解[74]. 早期研究表明, 在非小细胞肺癌细胞系中通过siRNA敲低KRAS不仅能够抑制肿瘤生长, 还可增强肿瘤细胞对靶向治疗的敏感性[75]. PROTAC降解策略可将突变KRAS蛋白引导至泛素-蛋白酶体或溶酶体通路, 诱导其降解. 例如, Popow等人[76]基于BI-2865构建的PROTAC分子(compound 4)通过VHL连接子实现对多种KRAS突变体的降解, 在17种KRAS突变中对13种表现出高效降解活性, 为实现“广谱KRAS”靶向治疗提供可能, 由于其独特的作用方式, 可能引发不同于传统抑制剂的新型耐药机制[76,77]. Revolution Medicines公司推进了面向激活态KRAS的新型三元复合物设计策略, 利用细胞内丰富的伴侣蛋白Cyclophilin A, 将RAS蛋白“黏合”在一个失活的三元复合物中, 从而抑制其活性. 以“分子胶”机制靶向KRAS活性构象已成为新兴策略代表[15,78]. RMC-4998通过与CYPA形成三元复合物, 选择性识别$KRAS^{G12C}$的GTP结合活性态并共价修饰Cys12位点, 从而阻断其下游信号. 通过优化RMC-4998的分子结构开发出了RMC-6291[14,15], 已进入Ⅰ期临床试验(NCT05462717). 在三元复合物抑制剂研究过程中发现一些令人困惑、现有机制无法解释的早期耐药性, 深入的生化研究发现, 有些候选药物具备令人意想不到的功能: 促进突变型和野生型RAS蛋白的GTP水解, 这是RAS研究领域长期以来的追求目标[79], 为开发新型抑制剂开辟新途径.

4.4 靶向RAS-MAPK通路

MAPK通路垂直联合用药在KRAS突变肿瘤中尚未显示出良好的疗效或安全性. 在正常细胞中, 经典RAS蛋白及其亲缘蛋白, 如RRAS, MRAS, RIT和RAP家族成员所介导的信号通路是相互独立且特异的; 而当致癌突变体出现时, 信号通路之间便可能发生非生理性的交叉激活. 靶向阻断KRAS突变体对PI3K效应子的激活, 为临床治疗提供有效的治疗窗口[80]. RAF激酶的激活同样在RAS驱动的癌症中至关重要. 早期通过抑制RAF激酶以降低RAS信号活性的尝试失败了, 因为某些RAF抑制剂会引起RAF激酶的补偿性激活[81~84]. MEK和ERK的抑制也未能成为有效的治疗策略, 可能是由于它们无法提供一个对正常细胞有利的治疗窗口. 然而, MEK抑制剂Selumetinib已被批准用于治疗NF1蛋白neurofibromin缺陷所导致的良性丛状神经纤维瘤[85], 另一种MEK抑制剂Cobimetinib也已被批准用于组织细胞增生症的治疗[86]. 因此, 对于接受KRAS靶向治疗的患者来说, 正交联合策略可能是最优路径, 有助于缓解垂直抑制策略带来的重叠毒性, 提升治疗效果.

5 耐药机制

近年来, Sotorasib与Adagrasib等针对$KRAS^{G12C}$突变的共价抑制剂在非小细胞肺癌患者中展现出显著抗肿瘤活性. $KRAS^{G12C}$抑制剂在初始阶段能够有效抑制KRAS信号通路, 但该抑制作用通常在用药后24~72小时内有效. 随后, 活性KRAS蛋白重新积累, 伴随ERK信号再度激活. 这一现象符合“适应性反应”的经典模式[41], 类似于RAF或MEK抑制剂所引发的反馈激活过程. 机制上, 活性KRAS的重新积累提示细胞通过补偿性激活受体酪氨酸激酶及其下游的SOS1/2实现适应性反馈, 而这些因子在ERK通路被激活时通常受到反馈抑制[87~89]. 此外, ERK的抑制也会导致MAPK磷酸酶表达下调, 从而进一步增强ERK信号强度[90]. 然而, 初始应答率普遍低于50%, 且多数患者在治疗6个月内出现获得性耐药并复发, 表明靶向KRAS治疗的持久性仍受限, 耐药问题日益凸显[58,60]. 临床研究表明, 继发性耐药突变集中于RAS-RAF-ERK通路相关基因, 通过绕过或削弱抑制剂的信号阻断作用, 重新激活下

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游增殖信号. 某些基因共突变可能削弱KRAS^{G12C}抑制剂的治疗效果. 其中, KEAP1, SMARCA4和CDKN2A的共突变与疾病早期进展及较差的预后密切相关. 因此, 系统解析影响KRAS抑制剂疗效的遗传标志物与耐药机制, 是提升治疗持久性和临床获益的前提.

获得性耐药最直接的机制是*KRAS*本身发生二次突变, *KRAS*基因的获得性突变会显著影响KRAS^{G12C}抑制剂的治疗反应. 一些突变位于药物结合位点, 例如H95D/Q/R, Y96C等, 会直接削弱抑制剂与KRAS的结合能力; 另一些突变则通过生成不同KRAS变体(如G12D/R/V/W, G13D与Q61H)使其逃避抑制剂的选择性. 此外, 还观察到*KRAS*^{G12C}等位基因或MET的扩增, 以及RAS-MAPK信号轴旁路激活, 包括NRAS, BRAF, MAP2K1/MEK1等的突变. 更复杂的获得性机制还包括*ALK*, *RET*, *BRAF*, *RAF1*与*FGFR3*等驱动融合基因的出现[41,91]. 研究表明, 新合成KRAS^{G12C}更易被核苷酸交换激活, 从而绕过抑制恢复信号活性, 解释了G12Ci治疗的疗效递减现象. 抑制新生KRAS的表达、促进其降解或阻断其向活性构象的转化, 有望实现更持久的药效维持. 多项临床前研究表明, 联用KRAS^{G12C}抑制剂与SHP2抑制剂可实现对RAS通路的持续抑制[92,93]. KRAS的激活依赖于GDP与GTP之间的交换过程, 该过程由SOS介导. 因此, 抑制SOS能阻断其与KRAS的结合, 有效抑制KRAS的信号转导活性. BI1701963是一款可阻断SOS1与KRAS相互作用的pan-KRAS抑制剂, 可削弱KRAS结合GTP的能力, 该药物与MEK抑制剂Trametinib联用在临床前模型中显示出良好的抗肿瘤活性, 适用于携带任意KRAS突变的肿瘤患者[94,95]. 在KRAS^{G12C}突变肿瘤模型中, 将SOS1抑制剂与Sotorasib联用, 可进一步增强抗肿瘤作用[96]. 有研究观察到在KRAS^{G12C}抑制剂处理后, FGFR1的磷酸化水平上升, 提示FGFR激活也是反馈反应的一部分; 进一步研究表明, FGFR抑制剂与KRAS^{G12C}或MEK抑制剂联用具有协同抗肿瘤效果[97,98].

6　总结与展望

KRAS长期被视为“不可成药”靶点, “表面光滑、缺乏可成药口袋”等特征使药物开发困难重重. G12C特异性共价抑制剂的成功问世, 标志着RAS靶向治疗取得历史性突破. 该类药物通过识别Switch-II可诱导口袋并选择性结合G12C突变位点, 首次实现了对KRAS构象状态的功能性调控, 不仅打破了RAS类GTP酶“难以成药”的传统观点, 也建立了“构象选择性抑制”这一全新药物开发范式, 为RAS家族其他成员的靶向开发奠定了理论与技术基础. 临床上, Sotorasib与Adagrasib的相继获批, 验证了突变型KRAS蛋白在肿瘤细胞中仍维持GDP/GTP动态转换的生理属性, 挑战了“突变型KRAS持续活化”的经典模型. 然而, KRAS^{G12C}抑制剂的临床疗效受限于耐药快速发生和缓解率偏低等问题, 暴露出KRAS作为靶点的复杂性与适应性. 第二代抑制剂正在通过优化药代动力学特性、增强靶点结合稳定性等策略, 力图提升疗效并延缓耐药的发生. 与此同时, β-内酯、环丙烯酮等新型亲电子片段为靶向低亲核性残基(如G12D)提供了全新化学空间; 共价与非共价策略协同推进, 广谱抑制剂和突变选择性抑制剂的研发不断拓展KRAS靶向谱. 考虑到不同KRAS突变在信号依赖性、功能效应和肿瘤微环境适应性方面的高度异质性, 机制导向的联合治疗成为提升疗效、延缓耐药的关键路径. 围绕SHP2, SOS1, EGFR, MEK/ERK及免疫检查点等多靶点联合干预方案, 正在多项临床研究中积极推进(表1和2).

KRAS靶点的产业化进程也展现出从靶点验证到药物转化的快速响应能力. AI和量子计算等新兴技术正在赋能新药设计. 在KRAS靶向药物设计与蛋白质结构预测领域取得突破性进展. 英矽智能联合多伦多大学开发的量子生成对抗网络模型(QCBM-LSTM), 实现了KRAS突变体抑制剂的高效生成与筛选, 并成功完成从虚拟筛选到临床前研究的全流程验证[99]; 国内研究团队提出的高斯玻色取样(GBS)量子处理架构, 已在分子对接、RNA结构解析等方面展现出药物研发应用潜力, 预示着量子计算有望成为“难成药”靶点突破的关键技术支撑, 展示了量子计算在新药研发中的应用潜力[100]. KRAS靶向药物的研发已从孤立突变靶向迈向多机制、多维度干预的新阶段. 实现广谱、持久且高效的KRAS靶向治疗仍面临诸多挑战, 未来的研究应重点聚焦以下方向: (ⅰ) 深化突变异质性解析, 系统研究不同KRAS突变的结构功能特征及其在肿瘤发生、信号调控和免疫逃逸中的作用; 探索等位基因选择性降解剂是否可提升KRAS突变肽段在MHC分子上的呈递能力, 为个体化T细胞免疫治疗提供新策略; (ⅱ) 推动跨技术融合创新, 整合人工智能分子

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生成、量子模拟与天然产物资源，构建面向“难成药”靶点的创新药物发现平台；(ⅲ) 拓展RAS超家族靶点研究，以KRAS靶向策略为范本，延伸至NRAS, HRAS及其他GTP酶驱动的恶性疾病治疗探索.

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Unlocking drug sensitivity in KRAS

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Since the *KRAS* proto-oncogene was first identified in 1982, KRAS has long been regarded as an "undruggable" target. *KRAS* mutations frequently occur in highly lethal solid tumors such as pancreatic cancer, colorectal cancer, and lung cancer, representing a key driver in tumor progression; thus, KRAS was coined "the beating heart of cancer". Wild-type KRAS relies on growth factors for activation and GTP hydrolysis accelerated by GAPs for inactivation. Oncogenic KRAS proteins are GAP-insensitive, resulting in prolonged activation that excessively stimulates downstream pathways, drives tumor initiation and progression, and consequently makes KRAS a major focus of precision therapy research. Recently, breakthroughs in structural biology and medicinal chemistry have propelled the development of innovative KRAS-targeted drugs. The transformative success of $KRAS^{G12C}$ covalent inhibitors has profoundly reshaped the landscape of targeted cancer therapy. This review summarizes the evolution of KRAS-targeted drug strategies, outlines the structural design and mechanisms of inhibitors, discusses challenges related to drug resistance, and prospects new precision treatment strategies targeting KRAS.

molecular switch, $KRAS^{G12C}$, GTPase-activating proteins, targeted drugs, PROTAC, molecular glue, drug resistance

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