EDITORIAL

The KRAS-G12C inhibitor: activity and resistance

Although it has long been deemed "undruggable", with the development of drugs specifically binding the KRAS-G12C mutant protein, clinical trials that directly inhibit oncogenic RAS have recently made promising improvements. In particular, the covalent KRAS-G12C inhibitors sotorasib and adagrasib are used to treat patients with advanced non-small cell lung cancer (NSCLC) carrying KRAS-G12C mutations. Unfortunately, the vast majority of patients do not respond to KRAS-G12C inhibitor therapy, mainly due to intrinsic or acquired resistance caused by cellular, molecular, and genetic mechanisms. Improving the understanding of drug response in the tumor microenvironment may continue to promote the design, testing, and clinical application of KRAS-G12C inhibitors.

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INTRODUCTION

Cancer is produced through a multi-step mutagenesis process, involving changes in a variety of oncogenes and tumor suppressor genes. In this process, cancer cells acquire a set of common characteristics, including immortal proliferation potential, self-sufficiency of growth signals, and resistance to cell death signals [1]. Although at the turn of the century, the non-surgical treatment of cancer has made great progress, cancer is still a global health problem that requires continuous action to develop new treatment strategies. Immune checkpoints are modulators of immune activation, which not only play a key role in preventing autoimmunity, but also destroy anti-tumor immunity. In addition to immune checkpoint inhibitors that have revolutionized the treatment of certain cancer patients in the past decade [2], recent basic and translational studies have revealed promising results for targeting proto-oncoprotein KRAS-G12C by using small-molecule drugs (sotorasib and adagrasib) in solid cancers [3, 4]. Here, we attempt to highlight the benefits and challenges that oncologists may face when using KRAS-G12C inhibitors.

KRAS mutation and activation

Kirsten rat sarcoma *(KRAS)* gene belongs to a member of the RAS family and its mutations are genetic drivers of multiple cancer types, especially colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), and non-small cell lung cancer (NSCLC) [5]. *KRAS-G12* mutations (89%) predominate in human cancers, followed by *G13* (9%) and *Q61* (1%) mutations [6]. Furthermore, the *G12D* mutation is the most common mutation among three common *G12C* (14%), *G12D* (36%), and *G12V* (23%) mutations [6]. Compared with *G12D* which plays a major role in PDAC [7], *G12C* is the most common mutation subtype in NSCLC (13%) [8, 9]. Identifying specific types of *KRAS* mutations in combination with other gene mutations may provide information about disease aggressiveness or drug sensitivity, which is the basis of precision medicine or personalized care [4].

KRAS protein is a signaling GTPase that switches between the active GTP-bound and inactive GDP-bound conformations [10]. Guanine nucleotide exchange factors (GEF) promote the exchange of GDP to GTP on KRAS, whereas GTPase-activating proteins (GAP) favor the exchange of GTP to GDP (Fig. 1a) [11]. The activation of receptor tyrosine kinases (RTKs) on the plasma membrane, such as epidermal growth factor receptor (EGFR) family, initiates KRAS activation and subsequent multiple effector pathways, especially mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways [10]. As the downstream of RTKs, SOS Ras/Rac guanine nucleotide exchange factor 1 (SOS1) and protein tyrosine phosphatase non-receptor type 11 (PTPN11, best known as SHP2) promote the ratio of GDP-GTP exchange, leading to KRAS activation [12–16]. Comparing the GTP- and GDP-bound structures of KRAS identified two regions, called switch-I and switch-II [17]. The mutant cysteine 12 is located next to the pocket (P2) in the switch-II region [18]. Compared with the wild-type, the *KRAS* mutation disrupts the guanine exchange cycle, thereby locking it in an active GDP-bound form that drives pro-tumorigenic signals [18] (Fig. 1b). The oncogenic KRAS signal establishes the main signal axis of tumor cell proliferation and survival, providing a key target for cancer treatment [19].

Activity of KRAS-G12C inhibitor

A series of strategies try to indirectly target KRAS, such as inhibiting farnesyltransferase by blocking KRAS post-translational modification or by inhibiting downstream KRAS effectors [19]. However, these efforts have not been successful in clinical trials over the past 30 years. Today, Amgen and Mirati Therapeutics have developed two direct KRAS-G12C inhibitors, namely sotorasib (also known as AMG 510 or Lumakras) and adagrasib (also known as MRTX849), which act by selectively forming a covalent bond with cysteine 12 within the switch-II pocket of KRAS-G12C protein (Fig. 1b), thereby locking KRAS in the inactive state to arrest cell proliferation [3, 4, 20]. The idea that the cysteine residues in KRAS-G12C can be used to produce covalent inhibitors came from the pioneering work of Shokat and colleagues in 2013, using protein mass spectrometry to screen 480 tethered compound libraries for KRAS-G12C in the GDP state [18]. Preclinical studies have shown that sotorasib and adagrasib selectively impair the viability of *KRAS-G12C* mutant cell lines, but do not affect cell lines with other *KRAS* mutations in vitro and in vivo [21–24]. Both sotorasib and adagrasib have long half-life (5.5–24 h) and extensive tissue distribution in human [25]. Unexpectedly, neither sotorasib nor adagrasib affects PI3K signaling, indicating that the upstream pathway independent of KRAS-G12C facilitates the activation of PI3K, which provides an explanation for the formation of KRAS-G12C inhibitor resistance

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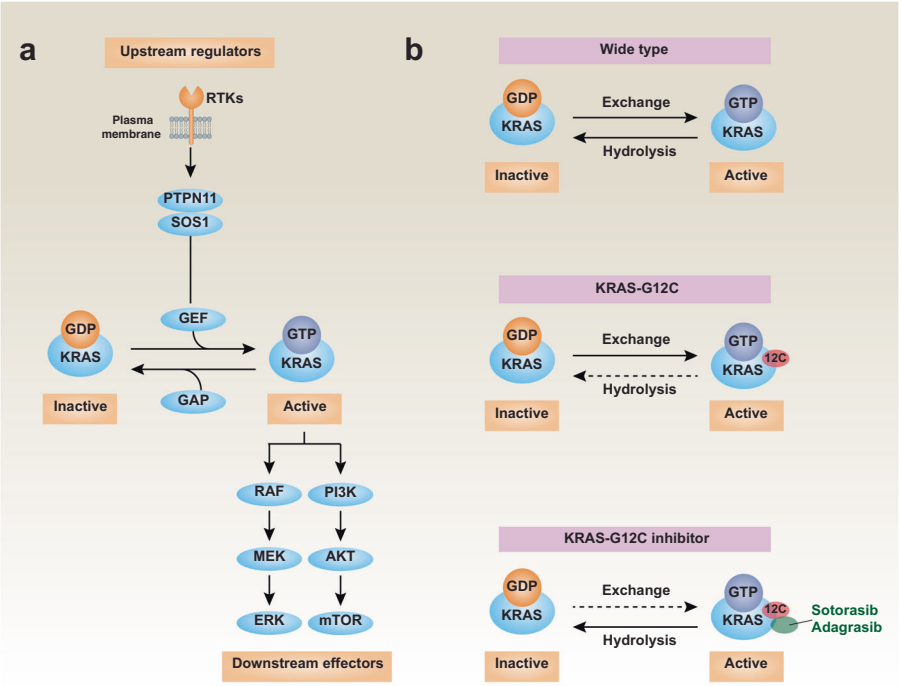

Fig. 1 Oncogenic KRAS signal transduction. a KRAS has GTPase activity and can convert GTP into GDP by hydrolyzing the gamma phosphate on GTP. The inactive and active states of KRAS are regulated by GAP and GEF, respectively. RTKs are the second major type of cell surface receptors with a wide range of functions, including promoting KRAS activation and subsequent multiple effector pathways, especially the RAF-MEK-ERK and PI3K-AKT-mTOR pathways. **b** Compared with wild-type KRAS, which maintains a balance between inactive and activated states, cysteine 12 (C12) mutations destroys GTPase activity of KRAS and locks in the GTP-bound state. In contrast, the small molecule drug sotorasib or adagrasib can form a covalent bond with C12 in the KRAS-G12C protein, causing KRAS to be in an inactive state.

(discussed later) [26]. Of note, compared with immunodeficient mice, sotorasib has enhanced anti-cancer activity in immunocompetent mice, highlighting the role of KRAS-G12C inhibitor in the triggering of pro-inflammatory tumor microenvironment to sustain T cell infiltration and activation in response to immune checkpoint inhibitor (anti-PDCD1/PD-1 antibody) [23]. These recent studies also underscore that KRAS-G12C inhibitor may elicit robust adaptive immune responses against rechallenged tumors [27], although the precise mechanism of this process remains to be elucidated. Clinical trials (NCT04185883 and NCT03785249) are ongoing to test the combination with pembrolizumab (anti-PDCD1/PD-1 antibody) and adagrasib or sotorasib in *KRAS-G12C*-mutant advanced/metastatic solid tumors.

In 2021, the U.S. Food and Drug Administration (FDA) accelerated the approval of sotorasib as the first KRAS-G12C blocking drug for the treatment of adult patients with NSCLC. The approval is based on a phase 2 trial that included 124 NSCLC patients with *KRAS-G12C* mutations who had previously received other treatments (chemotherapy or immunotherapy) [28]. Sotorasib administered orally at a dose of 960 mg once daily reduced tumor size in 37.1% of participants with a median duration of response of 11.1 months [28]. Later, the FDA also granted breakthrough therapy designation to adagrasib as a potential treatment option for NSCLC patients with *KRAS-G12C* mutations after previous systemic therapy. According to data from a phase 1/2 study of 51 response-evaluable patients with *KRAS-G12C* mutant NSCLC, when participants received adagrasib at a dose of 600 mg twice a day, 45% had a partial response and 51% were in stable condition. Diarrhea, nausea, vomiting, fatigue, and elevated aminotransferase levels are the most common adverse events. In addition to sotorasib and adagrasib [29], the development of other covalent inhibitor of KRAS-G12C (such as ARS-1620, GDC-6036, D-1553, 1_AM, and ARS-853) may also provide unprecedented opportunities for selective targeting of various advanced solid tumors carrying *KRAS-G12C* mutations [18, 21, 22, 30].

Resistance to KRAS-G12C inhibitor

Emerging preclinical and clinical evidence shows that the biggest obstacle to KRAS-G12C inhibitor treatment is the inevitable emergence of drug resistance (Fig. 2) [31]. Although the problem of resistance to therapy is multifaceted, intercellular variability or intratumoral heterogeneity is considered to be the main factor leading to KRAS-G12C inhibitor resistance. Single-cell RNA sequencing analysis of *KRAS-G12C* mutant NSCLC cell line treated with KRAS-G12C inhibitor ARS1620 demonstrated that the subpopulation of cells synthesizing the new KRAS-G12C protein, rather than the wild-type KRAS protein, is the cause of adaptive resistance [10]. Further analysis revealed that the EGFR or aurora kinase A (AURKA) signals can maintain the newly expressed KRAS-G12C protein in the active GTP-bound form, thereby evading KRAS-G12C inhibitor treatment [10]. However, another study suggests that wild-type RAS activation mediated by multiple RTKs, rather than a single RTK, is responsible for the acquired resistance of KRAS-G12C inhibitors (ARS-1620 and sotorasib) in various types of cancer cell lines [32]. Regardless, many independent studies demonstrate the importance of PTPN11/SHP2 as a common downstream of RTKs to activate the wild-type or mutant KRAS protein in mediating acquired drug resistance [10, 32–37]. Clinical trials (NCT04330664) are ongoing to test the combination with TNO155 (SHP2 inhibitor) and adagrasib in patients with advanced solid tumors carrying *KRAS-G12C* mutation. In addition, the activation of the PI3K-AKT-mTOR pathway contributes to the development of sotorasib resistance in human PDAC cell line in vitro and in xenograft mouse models [38]. Gene set enrichment analysis and mass spectrometry-based phosphoproteomics analysis found that

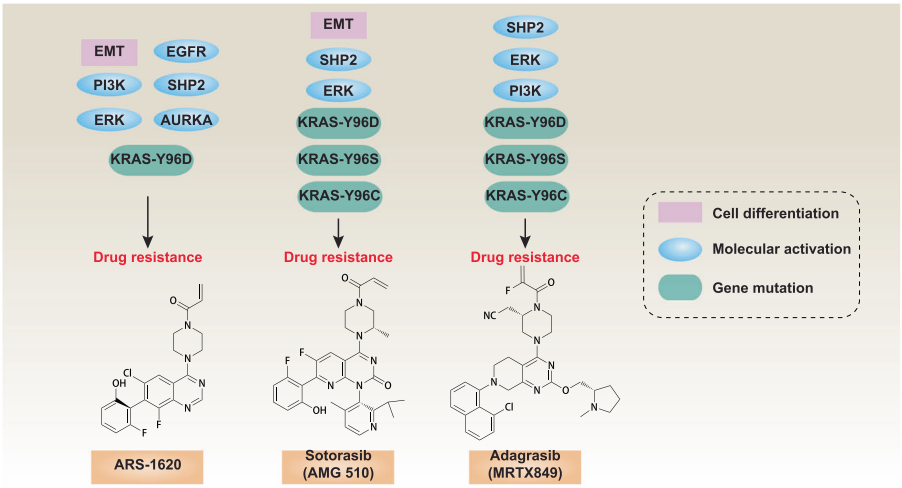

Fig. 2 Mechanisms of resistance to KRAS-G12C inhibitors. Preclinical and clinical studies have shown that cell differentiation, molecular activation, and gene mutations can promote intrinsic or acquired resistance to KRAS-G12C inhibitors, including ARS-1620, sotorasib, and adagrasib.

induction of epithelial-to-mesenchymal transition (EMT) promotes resistance to sotorasib or ARS-1620 through activation of PI3K or ERK pathway in NSCLC cells in a cell type-dependent manner [35, 39]. Nuclear factor, erythroid 2 like 2 (NFE2L2, best known as NRF2) regulated by kelch like ECH associated protein 1 (KEAP1) is a key transcription factor in cellular antioxidant response. *KEAP1* or *NFE2L2* mutations that predict poor response to checkpoint inhibitor immunotherapy [40] may also be related to resistance to adagrasib [24]. These findings provide a kinase- or transcription factor-targeted therapy approach for overcoming resistance to KRAS-G12C inhibitors.

In addition, intrinsic or adaptive resistance may be caused by concurrent genetic changes, such as secondary *KRAS* mutations and other genetic mutations, which are not targeted by KRAS-G12C inhibitors. Indeed, a recent clinical study used next-generation sequencing and deep mutation scanning to characterize genetic variations in tissue samples or circulating tumor DNA from patients resistant to adagrasib [41]. Among 38 patients with *KRAS-G12C* mutation cancer (27 patients with NSCLC, 10 with colorectal cancer, and 1 with appendix cancer) received adagrasib monotherapy, 45% patients are found a putative resistance mechanism to adagrasib [41]. Moreover, 18% of them have multiple overlapping genetic mechanisms: acquired *KRAS* mutations of G12D/R/V/W, G13D, Q61H, R68S, H95D/Q/R, and Y96C; high-level amplification of the *KRAS-G12C* allele; acquired bypass resistance mechanisms including *MET* amplification; activating mutations in *NRAS*, *BRAF*, *MAP2K1*, *RETALK*, *RET*, *RAF1*, *FGFR3*, *NF1*, and *PTEN*; oncogenic fusions involving *ALK*, *RET*, *BRAF*, *RAF1*, and *FGFR3*; and loss-of-function mutations in *NF1* and *PTEN* [41]. This information could finally be synthesized for each tumor cell at any decision point and used to adapt treatment. Similarly, acquired resistance to adagrasib has been reported in an NSCLC patient, which is related to the reactivation of the RAS-MAPK signaling by 10 secondary gene mutations on the RAS-RAF-MEK-ERK pathway [42]. Among them, *KRAS-Y96D* mutation directly affects the binding of adagrasib to the P2 pocket, thereby conferring resistance to sotorasib, adagrasib, or ARS-1620 in multiple cancer cell lines (H358, MIAPaCa2, and BaF3) [42]. In contrast, RM-018, a representative KRAS-G12C-selective inhibitor from Revolution Medicines' new class of RAS(ON) inhibitors, retains potent inhibitory activity against tumor cells harboring dual *KRAS-G12C/Y92D* mutations [42]. In addition to *KRAS-Y96D*, *KRAS-Y96S* and *KRAS-Y96C* also contribute to the resistance to sotorasib or adagrasib in BaF3 cells, and this process can be reversed by the combined use of SOS1 inhibitors (BI-3406) [12, 43]. Altogether, these findings highlight the complexity of the genetic mechanism of KRAS-G12C inhibitor resistance.

Conclusions and perspectives

The KRAS-G12C inhibitor binds to the P2 pocket, trapping the oncoprotein in an inactive GDP-bound state. Combinations of sotorasib or adagrasib with agents that target EGFR, insulin like growth factor 1 receptor (IGF1R), PI3K, mTOR, ERK, ALK, cell cycle, or immune checkpoint demonstrate enhanced response and marked tumor regression in several preclinical tumor models [10, 24, 44, 45]. More trials using KRAS-G12C inhibitor as monotherapy or in combination with various drugs for the treatment of patients with NSCLC or other solid tumors are underway. Despite these exciting clinical benefits, most patients will eventually develop acquired resistance through many underlying mechanisms. These findings raise several important questions about the mechanism and clinical application of KRAS-G12C inhibitors. For example, what fundamentally determines whether the cell adapts or maintains the response to the KRAS-G12C inhibitor in the hypoxia tumor microenvironment? Are genomic mutations or heterogeneities sufficient to drive fully acquired resistance to KRAS-G12C inhibitors in cancer patients? How to use genetic, metabolic and/or immune biomarkers to accurately predict efficacy and toxicity of drug response? What kind of combined treatment strategy can prevent the emergence of clinical drug resistance of different tumor types, but also reduce toxic side effects? Ultimately, a better understanding of the biological basis of drug resistance will provide more opportunities to optimize KRAS-G12C inhibitor regimens and new combinations.

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AUTHOR CONTRIBUTIONS

All authors contributed in the content of, and read the manuscript.

COMPETING INTERESTS

DT is an editorial board member of *Cancer Gene Therapy*.

ADDITIONAL INFORMATION

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