Published in final edited form as:

Expert Opin Ther Targets. 2021 March ; 25(3): 167–174. doi:10.1080/14728222.2021.1902991.

KRAS G12C inhibition and innate immune targeting

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Abstract

Introduction—*KRAS* mutations drive tumorigenesis by altering cell signaling and the tumor immune microenvironment. Recent studies have shown promise for KRAS-G12C covalent inhibitors, which are advancing rapidly through clinical trials. The sequencing and combination of these agents with other therapies including immune checkpoint blockade (ICB) will benefit from strategies that also address the immune microenvironment to improve durability of response.

Areas covered—This paper reviews KRAS signaling and discusses downstream effects on cytokine production and the tumor immune microenvironment. RAS targeted therapy is introduced and perspectives on therapeutic targeting of KRAS-G12C and its immunosuppressive tumor microenvironment are offered.

Expert opinion—The availability of KRAS-G12C covalent inhibitors raises hopes for targeting this pervasive oncogene and designing better therapeutic combinations to promote anti-tumor immunity. A comprehensive mechanistic understanding of KRAS immunosuppression is required in order to prioritize agents for clinical trials.

Keywords

IL-1β; KRAS; KRAS-G12C inhibitor; STING; tumorigenesis; oncogene; cancer; targeted therapies

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Declaration of interest

D.A.Barbie is a consultant for Qiagen/N-of-One and Tango Therapeutics, has received research support from Bristol Myers Squibb, Novartis, Lilly, Gilead Sciences, and is a founder and shareholder in Xsphera Biosciences. EH Knelson has a Sponsored Research Agreement with Takeda Pharmaceuticals. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose

1. Introduction

1.1 RAS oncogenes

Following its original discovery from a murine sarcoma virus, decades of study of have firmly established the human *KRAS* oncogene as a key driver of tumorigenesis in non-small cell lung cancer (NSCLC), pancreatic ductal adenocarcinoma (PDAC), colorectal cancer (CRC), and multiple other tumor types (1-3). KRAS has intrinsic GTPase activity and is active when bound to GTP and inactive when bound to GDP, a process that is catalyzed by RAS GTPase activating proteins (GAPs). The three commonly observed missense mutations in *KRAS*: G12, G13, and Q61, impair GAP binding (4), forcing it to rely on its slow intrinsic GTP hydrolysis rate and thus favoring constant downstream signaling (5, 6).

Pharmacologic targeting of KRAS has been hindered by structural characteristics of the KRAS protein along with its high affinity for GTP (7). To overcome the difficulties associated with direct targeting of KRAS, indirect approaches have been devised to target downstream signaling pathways, post-translational modifications, and associated chaperone proteins (5). However, as discussed in greater detail below, these approaches have been laden with difficulty due to achieving pharmacologically effective doses of inhibitors or activation of compensatory signaling pathways.

In this review we focus on recent molecular insights that have enabled covalent targeting of the KRAS-G12C isoform, as well as the increasing recognition that understanding how oncogenic KRAS and its co-mutations shape the immune microenvironment will likely be critical to achieving durable therapeutic responses. While KRAS-G12C inhibitors have entered phase I trials as monotherapy, preclinical efficacy is enhanced in combination with additional pathway inhibitors or with ICB (8, 9). KRAS signaling and associated co-mutations also influence patterns of immune cell infiltration downstream of cytokines such as IL-6, and can promote T cell exclusion (10, 11). Thus, understanding the interplay between these different factors likely holds the key to precision KRAS-directed therapy that ultimately achieves durable response.

1.2 Oncogenic KRAS activation

The RAS gene family includes some of the most common oncogenes including *KRAS, HRAS*, and *NRAS. KRAS* is mutated in 20% of all cancer types, 90% of pancreatic cancers, 45% of colorectal cancers, and 25% of NSCLC (5, 12). While *NRAS* and *HRAS* mutations are less common than *KRAS* mutations, *NRAS* mutations have been found in 29% of melanomas and *HRAS* mutations in 5% and 6% of head and neck squamous and bladder cancers, respectively (12).

RAS proteins mediate extracellular signals from receptor tyrosine kinases (RTKs). The main downstream effectors of RAS include the mitogen-activated protein kinase (MAPK), the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR, and RAL signaling pathways. The RAS protein is a single-subunit small GTPase that switches between the GDP-bound state and the GTP-bound state. These two states are regulated by guanine nucleotide exchange factors (GEFs), including son-of-sevenless homologue 1 (SOS1), GRB2, SHP2, in addition to the aforementioned GAPs. GEFs catalyze the exchange of GDP for GTP, and GAPs promote the

hydrolysis of GTP to GDP. The GTP-bound form of RAS activates RAF-MEK-ERK downstream signaling, promoting tumor cell survival and proliferation. The recognition that hotspot mutations in *KRAS* at G12, G13, and Q61 do not lock KRAS in the GTP-bound active state, but rather impair GAP mediated catalysis, forms the basis for the successful inhibition of KRAS-G12C by covalent inhibitors (see below). The frequency of hotspot mutations varies by tumor and isoform. G12 and G13 account for 83% and 14% of *KRAS* mutations, respectively, while Q61 accounts for 63% of *NRAS* mutations (5). Given its association with smoking, *KRAS-G12C* is the most common *KRAS* mutation in lung cancer, occurring in 40-50% of *KRAS*-mutant NSCLC (5, 13). On the other hand, *KRAS-G12D* is the most common mutation in pancreatic ductal adenocarcinoma and colorectal adenocarcinoma (5). While all of these mutations sustain GTP-bound activation, some mutations (excluding *KRAS-G12C*) also differentially affect intrinsic hydrolysis and exchange between GDP and GTP (6, 7).

1.3 Impact of pro-tumorigenic cytokines

KRAS-mutant NSCLC is characterized by evasion of antitumor immunity alongside inflammation that fuels tumor growth and oncogenic mutations, resulting in part from enhanced production of suppressive inflammatory cytokines (Figure 1) (14, 15). In addition to the major KRAS downstream pathways MAPK and PI3K/AKT/mTOR, RAL signaling and IL-1β can activate TBK1 to promote NF-κB and IL-6 mediated autocrine STAT3 pathway activation (16, 17). KRAS signaling and IL-1β pathway activation increases IL-6 secretion and further reinforce a positive feedback autocrine cytokine circuit through STAT3 mediated induction of the TBK1 homologue IKKε (16, 18). These effects are further magnified in the context of LKB1 inactivation as well as therapeutic MEK inhibition (10, 19). In KRAS-LKB1 genetically engineered mouse models, IL-6 neutralizing antibody or JAK/TBK1 inhibitor treatment inhibited tumor growth, though escape occurred due to rapid cellular transcriptional adaptation (10, 19).

Constitutive generation of IL-1β by activation of inflammasomes in the lung can promote chronic inflammation and tumorigenesis. Indeed, depletion of GATA2, a regulator of IL-1β, has been reported to inhibit tumor growth in a mouse model of *KRAS*-mutant NSCLC (20). The inhibition of the NLRP3 pathway, a mediator of the inflammasome and IL-1β release, has also been reported to inhibit cell proliferation and migration in *KRAS*-mutant lung cancer cell lines (18). Canakinumab is a humanized anti-IL-1β monoclonal antibody which antagonizes its activity. In a serendipitous observation, canakinumab treatment strongly reduced the incidence of lung cancer in patients treated for atherosclerosis on the CANTOS trial (21). *KRAS* mutations were not specifically studied in the CANTOS trial, however, the frequency of a smoking history in a population with atherosclerosis was high and it is presumed that these patients have a high frequency of *KRAS* mutations. These protective effects were dose-dependent, strongly supporting that IL-1β is involved in lung cancer carcinogenesis in humans and highlighting the therapeutic potential of its blockade.

KRAS mutations can also enhance pro-tumorigenic immune interactions via metabolic reprogramming, as elegantly shown in models of the pancreatic cancer stroma (22). Blocking the upregulation of cytokine receptors on tumor cells could suppress interactions

with invading Th2 cells in the microenvironment, offering additional therapeutic targets to enhance antitumor immunity in KRAS-driven cancers.

2. RAS Targeted Therapy

2.1 Drugging the undruggable

While therapies targeting KRAS have been tested since the early 2000s, there has yet to be an approved agent. However, the identification of a covalent binding pocket in the KRAS-G12C isoform (7) led to a paradigm shift and emergence of the first direct KRAS inhibitors with promising clinical data and predicted integration into clinical practice. Review of previous strategies for indirect KRAS inhibition, along with recent molecular breakthroughs enabling direct targeting, will inform development of additional KRAS inhibitory strategies and combination with other targeted and immune treatments.

2.2 Farnesyltransferase inhibitors

While directly targeting RAS initially proved difficult, inhibiting post-translational modification of RAS showed early promise. RAS proteins undergo post-translational modification by prenylation, allowing them to translocate to the cell membrane for activation. The number of isoprene units covalently bound to a free thiol of cysteine determines the type of prenylation: While HRAS, NRAS, and KRAS all undergo farnesylation (three isoprenes), NRAS and KRAS can also undergo geranylgeranylation (four isoprenes) (12). Therapies that inhibit these post-translational modifications lock RAS isoforms in an inactive confirmation.

Although farnesyltransferase inhibitors advanced to phase III trials, they failed to meet primary endpoints (23). Preclinical work sheds light on potential mechanisms of resistance, which may have been obscured by over-reliance on *HRAS* mutant models in the development of farnesyltransferase inhibitors. Farnesyltransferase is critical for RAS anchoring to the membrane in *HRAS* mutant tumors, but geranylgeranyl transferase type I governs the process in the absence of farnesyltransferase in *KRAS* and *NRAS* mutant tumors, identifying a potential mechanism of resistance to farnesyltransferase inhibitors (23, 24). These findings raise the possibility of future combination therapies to inhibit these post-translational modifications in *KRAS* and *NRAS* mutant tumors.

2.3 Targeting RAS-activators

The critical cycling from the inactive GDP-bound state to the active GTP-bound confirmation nominated the catalyst of this cycle, the GEF SOS1, as a therapeutic target. In addition to its role as a GEF, SOS1 binds to GTP-coupled KRAS to promote a positive feedback loop via engagement of activating downstream signals. The selective SOS1 inhibitor BI-3406 demonstrated efficacy in xenograft models of *KRAS*-mutant cancers and showed synergy with MEK inhibitors to prevent acquired resistance (25). A phase I clinical trial (NCT04111458) has opened to test the analog BI 1701963 as monotherapy, and in combination with trametinib in advanced *KRAS*-mutant solid tumors.

SHP2 is a phosphatase that mediates activation of KRAS by RTKs. While the precise function of SHP2 has not yet been determined, it appears to bind GRB2 and SOS to mediate downstream activation of RAS (26). Thus, SHP2 inhibition favors the GDP bound state of KRAS by preventing effective GTP loading. SHP2 inhibitors are also being tested in combination with MEK inhibitions to prevent acquired resistance (27). The combination of MEK inhibitors and SHP099 (SHP2 inhibitor) showed efficacy in xenograft and genetically engineered models of *KRAS*-mutant cancers such as pancreatic, lung, and ovarian cancers, as well as KRAS-expressed triple-negative breast cancer (27-29). Inhibition of *KRAS* codon 12 mutant cell proliferation has been observed with the selective SHP2 allosteric inhibitor RMC-4550 (26). Inhibition of codon 13 and 61 mutants, however, was not observed. These results suggest that each *KRAS* mutation conveys a different degree of intrinsic dependence on individual GEFs.

As expected from other studies of RTK vertical pathway inhibition, blocking KRAS effectors can synergize with direct KRAS targeting. In *KRAS*-G12C NSCLC and PDAC cell lines, adding a SHP2 inhibitor to a KRAS covalent inhibitor increased CD8-positive T cells in the TME while decreasing myeloid suppressor cells and enhancing the effect of PD-1 inhibitors (9, 29). These results suggest that SHP2 inhibition can also influence the tumor immune microenvironment.

2.4 Targeting RAS effectors: MAPK, PI3K/AKT/mTOR and TBK1/JAK

Efforts to inhibit KRAS activity have focused on the primary downstream signaling pathways for RAS family proteins: MAPK, PI3K/AKT/mTOR and TBK1/JAK. Initial approaches to target the MAPK signaling pathway were carried out using the BRAF V600E inhibitors vemurafenib and dabrafenib, developed to treat melanoma (30). However, BRAF-V600E inhibitors proved unsuccessful in *KRAS*-mutant tumors due to the preponderance of BRAF heterodimers (BRAF and CRAF). Additionally, in *KRAS*-mutant models, BRAF-V600E inhibitors resulted in paradoxical activation of ERK (31, 32). MEK inhibitors were able to overcome this positive feedback loop, suggesting the possibility of single-agent activity to target KRAS effector function. While a number of MEK inhibitors have entered clinical trials for *KRAS*-mutant tumors, none have demonstrated significant efficacy (33, 34). However, MEK inhibitors may prove more effective in combination with other agents. In combination with docetaxel, the selective allosteric MEK1 and MEK2 inhibitor selumetinib showed promise in a phase II trial of second-line treatment in *KRAS*-mutant NSCLC. However, the combination failed to show efficacy as compared to docetaxel monotherapy in a phase III trial (SELECT-1; NCT01933932) (35). Concurrent inhibition of multiple signaling pathways downstream of KRAS was also considered a promising therapeutic strategy. In a preclinical model, the combination of MEK and PI3K inhibitors was found to inhibit tumor growth in *KRAS*-mutant lung cancer (36). Concurrent inhibition of MAPK and TBK1 also showed promising results in preclinical model (19). However, combination treatment MEK inhibitors and PI3K inhibitors, as well as the combination of MEK inhibitors and TBK1 inhibitors, failed in clinical trials because of dose-limiting toxicities from MEK inhibitor effects on normal cells (37, 38) and inadequate dosing to inhibit TBK1, for example (39).

2.5 KRAS-G12C covalent inhibitors

The high affinity of KRAS for GTP prevents the steric hindrance approaches that have proven successful with TKIs. Agents that bind to multiple sites of RAS (40) and inhibit the dimerization of KRAS (41), were tried and failed. A breakthrough came by considering *KRAS* mutations separately, with identification of a previously unknown binding pocket in KRAS-G12C (7). Compounds that covalently bind this pocket trap the enzyme its inactive, GDP-bound state. Viewed more broadly, in contrast with kinase inhibitors that bind the active protein conformation, these drugs can inhibit KRAS activity by binding the nonfunctional state (42). As expected, binding of these agents to GDP-bound KRAS-G12C inhibits activation of downstream signaling such as RAF. Of note, these treatments bind only to GDP-bound KRAS-G12C and not to wild-type KRAS. In addition, although 75% of KRAS-G12C is GTP-bound, this covalent approach is effective due to the fact that KRAS maintains intrinsic GTPase activity (5, 43).

Since the initial observation by Ostrem et al., a number of KRAS-G12C inhibitors have undergone preclinical and clinical development. Targeting this mutation with the covalent binding agent ARS-1620 showed initial promise in animal models (43, 44). AMG 510 was the first agent with reported success in clinical trials for *KRAS*-mutant cancers. In preclinical studies, AMG 510 inhibited cell proliferation in *KRAS-G12C*-carrying cell lines and slowed xenograft tumor growth (45). This study additionally showed synergistic effects with chemotherapy (carboplatin), ICB (PD-1 inhibitor), and vertical pathway inhibition with MEK inhibitors. Phase I trials also showed promising results, in particular with NSCLC patients (46). Among the fifty-nine NSCLC patients receiving AMG 510, 32.2% had a confirmed objective response and 88.1% achieved disease control. Of the forty-two CRC patients, 7.1% had a confirmed objective response while 73.8% achieved disease control (46). The FDA granted a fast-track designation to AMG 510 for patients with previously treated metastatic NSCLC harboring *KRAS-G12C* mutations, with several clinical trials ongoing to assess long-term safety and efficacy, alone or in combination with chemotherapy, targeted or immune therapies, compared with chemotherapy alone (NCT03600883, NCT04303780, NCT04625647, NCT04185883).

MRTX849 is another covalent *KRAS-G12C* inhibitor currently undergoing phase I and II trials. Preclinical studies demonstrated that MRTX849 could suppress proliferation in cell lines and caused tumor regression in 65% of *KRAS-G12C* patient-derived xenograft models (47). MRTX849 treatment led to partial responses in 3/6 NSCLC patients and 1/4 CRC patients, with stable disease in the remaining patients with NSCLC and CRC (47-49). CRISPR screening was used to identify potential combination therapies, with RTKs and components of the mTOR pathway as hits (9). CRISPR/Cas9 screening also identified potential mechanisms of acquired resistance to MRTX849, including alterations in cell cycle genes and loss of *KEAP1* or *NRAS* (9). MRTX849 is being studied in combination with ICB, TKIs, and the SHP2 inhibitor TNO155 in ongoing clinical trials compared with chemotherapy (NCT04613596, NCT04685135, NCT04330664). A similar covalent inhibitor JNJ-74699157 has completed recruitment, with results expected soon (NCT04006301)(5).

3. Immunotherapy in RAS-Mutant Cancers

3.1 Immune checkpoint blockade

ICB has transformed care for patients with non-small cell lung cancers, and colorectal cancers with microsatellite instability (50-52). Checkpoint inhibitors, which bind and inhibit the actions of PD-1, PD-L1, and CTLA-4 inhibitory molecules on tumor and immune cells, unleash cytotoxic T-cells to generate antitumor immunity.

3.2 ICB in RAS-mutant NSCLC

Amongst cancers harboring *KRAS* mutations, NSCLC is the most commonly and successfully treated with ICB. PD-1, PD-L1, and CTLA-4 antibodies are now approved for NSCLC treatment as single agents, in combination, and as a partner to chemotherapy. KEYNOTE-42 showed the efficacy of pembrolizumab monotherapy as first-line treatment in NSCLC with high PD-L1 compared to platinum-doublet chemotherapy, leading to the use of PD-L1 as a predictive biomarker (53). Subsequent trials demonstrated the efficacy of ICB in combination with chemotherapy in patients both with and without PD-L1 expression (54, 55). Nivolumab plus ipilimumab is also FDA-approved for patients with NSCLC whose tumors express PD-L1(≥1%) (56). In addition to PD-L1 expression, tumor mutation burden and tumor infiltrating lymphocytes (TILs) have been reported as predictive factors for ICB (56, 57), but these factors alone are insufficient as predictive biomarkers in current clinical practice.

While *KRAS*-mutant NSCLC responds better to ICB than NSCLC harboring EGFR mutations or ALK fusions, which respond poorly (58-60), the wide variation in response suggests other influences (50, 52). NSCLCs with *KRAS* mutations are more frequently PD-L1 positive and are associated with induced MEK-mediated downstream signaling (61). Co-mutations also influence NSCLC response to ICB (52). *KRAS*-mutant NSCLC can be divided into categories based on co-occurring mutations: *TP53* (KP) and *STK11/LKB-1* (KL). *LKB-1* mutations carry a poor prognosis in NSCLC (62), and KP and KL tumors demonstrate distinct immune response gene signatures (11). KP tumors are more likely to exhibit an interferon-driven inflammatory response, which correlates with improved response to ICB (11). While KP tumors had a 35.7% response rate, KL tumors only exhibited a 7.4% response rate. Another study suggested that progression-free survival and overall survival were also significantly shorter in KL tumors, which demonstrated few PD-L1 positive tumor cells and CD8-positive T-cells (52). Although STK11/LKB1 loss is associated with low PD-L1, response to ICB in PD-L1 positive KL remained inferior to KP. As discussed above, KL tumors produce abundant IL-6, resulting in an immunosuppressive environment (10). TMB is higher in KP as compared to *KRAS* wild-type tumors (with or without *TP53* mutations), which may also influence ICB response (63). These results indicate that other mechanisms in addition to PD-L1 may contribute to the poor response to ICB observed in KL tumors.

4. Combined KRAS G12C Inhibition and Innate Immune Targeting

4.1 Inhibiting the immune suppressive TME

While KRAS-G12C inhibitors have shown promising results, especially in NSCLC, targeted agents often fail to cure patients due to acquired resistance. While ICB combinations are underway, the fact that *KRAS* mutations create an immune TME favorable for tumor growth suggests that other combination therapies with agents capable of reshaping TME may be needed. Early trial data demonstrate that KRAS-G12C inhibitors lack severe side effects compared with MAPK or PI3K inhibition because of their mutation-specific mechanism. Combination of TBK inhibition or IL-1β inhibition may thus be an additional option with KRAS-G12C inhibitors (Figure 1). The low incidence of adverse effects with KRAS-G12C inhibitors may enable sufficient TBK inhibition to have a therapeutic effect. Inhibitors of IL-1β have the potential to break positive feed-forward loops in the TME, as discussed above. IL-1β inhibitors may prove especially effective in early lung cancer because they are likely to affect tumor initiation based on the results of the CANTOS trial. These combinations offer hope of enhancing the direction inhibition of KRAS by reversing the growth promoting TME that likely promotes KRAS-G12C inhibitor escape

4.2 cGAS-STING pathway activation

Cytokines such as IL-6 and IL-1β, which induce chronic inflammation, play an important role in tumorigenesis, while the accumulation of immune cells such as CD8-positive T cells is relevant to the treatment of advanced lung cancer. KL tumors have fewer Tumor Infiltrating Lymphocytes (TILs) compared to KP tumors (64). KRAS-G12C inhibitors have been reported to be effective in combination with ICB and MEK inhibitors (45), and are also expected to be effective in combination with therapies that increase TILs in KL tumors.

We reported that the expression of **St**imulator of **In**terferon **G**enes (STING), which is important for innate immunity, is suppressed in KL tumors (64). Antitumor immunity proceeds in a stepwise fashion starting with innate immune recognition of cancer cells and subsequent activation of cytotoxic T-lymphocytes. The activation of STING results from cytoplasmic dsDNA recognition by the enzyme cGAS, leading to production of the cyclic dinucleotide second messenger 2’3’-cGAMP. During activation, TBK1 and IRF3 undergo cascade phosphorylation (65). Initiation of the STING-TBK1-IRF3 pathway promotes the secretion of type I interferons and cytokines including CXCL10, eliciting T-cell recruitment. Silencing of STING in KL tumors thus prevents IRF3 engagement and is responsible for enhancing pro-tumorigenic IL-6 production downstream of TBK1. Thus, restoring STING expression in KL cells rewires cytokine production towards an anti-tumorigenic interferon response (64).

Activating the STING-TBK1-IRF3 signaling in cancer cells by enhancing cytoplasmic DNA accumulation is being explored from a therapeutic perspective. Indeed, the accumulation of cytoplasmic DNA from radiotherapy and DNA-damaging agents activates the cGAS-STING pathway, leading to antitumor immunity (66, 67). Other strategies for activating the STING pathway include the use of PARP inhibitors against *BRCA*-mutant tumors to promote genomic instability and the accumulation of cytoplasmic DNA (68). Taxanes, such as

paclitaxel, also activate the STING pathway (69). While promising results from preclinical studies show that direct injection of cyclic dinucleotide STING agonists can enhance immunogenicity and restrict tumor growth in mice, results from clinical trials are thus far disappointing, possibly due to delivery and pharmacodynamic issues (65).

Most prior research has focused on activating STING in immune cells, and clinical trials of STING agonists have been conducted in combination with ICB. Yet effective therapeutic combinations may require restoration of tumor cell STING expression, as we have shown for KL tumors. Indeed, we demonstrated that STING expression is silenced in KL NSCLC by epigenetic mechanisms involving EZH2 and DNMT1 (64). Since KRAS-G12C inhibitors are effective in patients with KL tumors (47), they may act in part by increasing interferon-associated cytokine release to promote T cell infiltration (8), Thus priming STING re-expression by treatment with EZH2 and/or DNMT1 inhibitors may also enhance response to KRAS-G12C inhibitors and limit resistance to treatment by restoring immunogenicity, even in advanced stages of disease (Figure 2).

4. Conclusions

For tumors with *KRAS* mutations, future treatments will focus on specific isoforms to build on the recent success of KRAS-G12C inhibitors. ICB monotherapy has proven relatively ineffective for certain tumors harboring *KRAS* mutations, and additional combinations may be necessary to reverse the immunosuppressive KRAS TME.

5. Expert opinion

Current treatments for *KRAS*-mutant tumors depend on the specific isoform and co-mutations. The early success of KRAS-G12C inhibitors, both in suppressing tumor growth and activating antitumor immunity in historically suppressed TMEs, gives hope for therapeutic breakthroughs to help large percentages of patients with NSCLC. The precise role of these new agents in the NSCLC armamentarium remains unclear. In order to gain first-line approval and maximize response, they will likely need to be combined with other targeted and immune therapies. Indeed, as discussed above, trials are underway combining covalent KRAS G12C inhibitors with inhibitors of PD-1, PD-L1, SHP2, MEK, EGFR, CDK, mTOR, and HER2. This panoply of targets, while promising and based on rigorous mechanistic studies, does risk restricting statistical power to identify the most promising combinations and may add years to the development timetable.

Previous trials for SHP2 and MEK inhibitors showed modest activity, suggesting possible benefit in combination with direct KRAS targeting. The known toxicity profile and experience in NSCLC nominates these agents for rapid clinical development in combination with covalent KRAS G12C inhibitors. Toxicity may prove to be a major obstacle, as MAPK signaling is critical for normal cellular function especially in the skin and GI tract, and downstream inhibitors are notoriously unpopular with patients. Furthermore, while dual vertical pathway inhibition has precedent in other oncogene driven lung cancers (EGFR, ALK, BRAF mutations), acquired resistance remains a fundamental barrier. In contrast,

combinations to enhance antitumor immunity could lead to durable long-term responses and even cures by eliminating “persister” cells.

In our view, therapeutic combinations to enhance the observed inflammatory activation from KRAS G12C inhibition represents one of the most promising approaches. Combining KRAS G12C inhibitors with PD-1/PD-L1 checkpoint inhibitors is the most straightforward initial approach and may ease the integration into first line therapy since many patients with KRAS-mutant NSCLC would receive these agents as standard of care. Concerns remain regarding overlapping side effects, including the possibility of pneumonitis, though emerging clinical data for AMG 510 and MRTX849 will allow for a better assessment of this risk. Combinations targeting immune signaling components such as IL-1β or the cGAS-STING pathway, which regulate the suppressed immune response in KL tumors, show potential to enhance response rates from KRAS-G12C inhibitors and prevent acquired resistance. These approaches are earlier in development and would likely apply to select patient subsets. Treatments that generate cytosolic DNA, such as chemotherapy or PARP inhibitors, represent an alternate approach to activate innate immune signaling and may integrate nicely with existing practice for patients scheduled to receive (or already benefiting from) cytotoxic therapy. Epigenetic treatments to restore STING expression, such as EZH2 or DNMT inhibitors, should also be tested in future trials, though their activity and efficacy in NSCLC is currently unproven.

A better understanding of the direct immunosuppressive effects of KRAS, as well as the importance of molecular context in specific tumor types, will allow for combination therapies to reverse KRAS immunosuppression and activate antitumor immunity. Ongoing translational efforts epitomized by the development of AMG 510 and MRTX849 will allow for real-time re-evaluation of therapeutic combinations as they progress through trials. To that end, reliable functional assays that reflect patient clinical responses (i.e. organoids and other ex vivo culture systems), can maximize the knowledge gained from each patient enrolled on trial. As we enter a new era in lung cancer treatment, we hope that the previously parallel development of targeted and immune therapeutics can merge to overcome the weaknesses of each and extend survival for patients with these challenging cancers.

Acknowledgments

Funding

This work was supported by NIH R01CA190294 (DAB), the Parker Institute for Cancer Immunotherapy (DAB), Schaubert Family Funds (DAB), and Gross-Loh Research Fellowship (EHK), Uehara Memorial Foundation Research Fellowship (TT), and Lilly Oncology Fellowship Program (TT).

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Article Highlights

- KRAS downstream pathways enhance production of suppressive inflammatory cytokines such as IL-6 and IL-1β and create an immune TME favorable for tumor growth.
- *KRAS* mutation isoform and co-mutations are critical to designing targeted therapies, as evidenced by the recent clinical success of KRAS-G12C inhibitors.
- KRAS-G12C inhibitors showed promising results in clinical trials for NSCLC and showed synergistic effects with other treatments such as chemotherapy, ICB, and MEK inhibitors in preclinical models.
- KRAS-G12C inhibitors and targeting inflammatory cytokine immune signaling such as IL-1β have the potential to enhance response by altering the TME.
- STING is suppressed in KL NSCLC, and restoring STING could induce T cell infiltration. Combining KRAS-G12C inhibitors and activators of the cGAS-STING pathway may have synergistic effects.

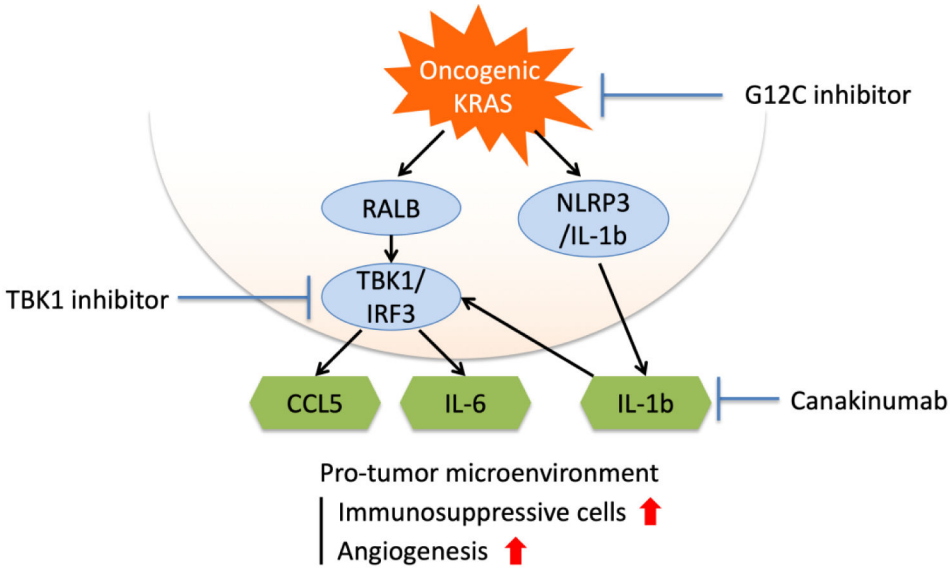

Figure 1.

Enhancing pro-inflammatory signaling in KRAS-driven lung cancer. Immunosuppressive signaling pathways downstream of mutant KRAS and opportunities for pharmacologic inhibition to suppress cytokine signaling.

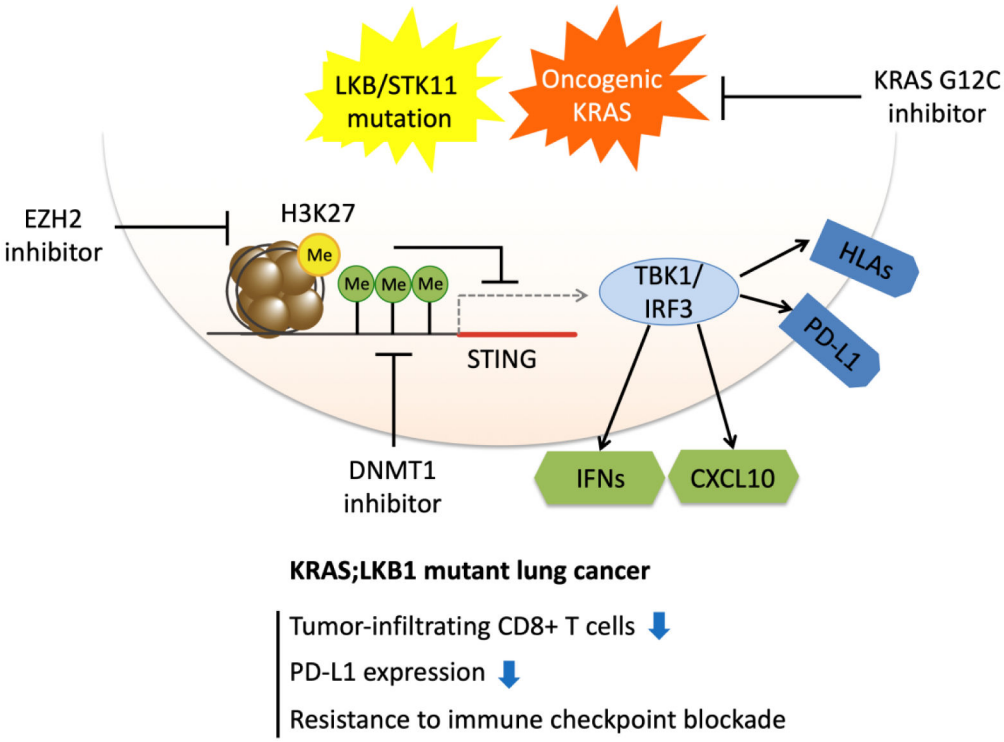

Figure 2.

Activating STING in *KRAS/LKB1*-mutant NSCLC to synergize with KRAS-G12C inhibition. STING re-expression by enhancer of zeste homolog 2 (EZH2) and/or DNA methyltransferase 1 (DNMT1) inhibitors in *KRAS/LKB1*-mutant NSCLC. KRAS-G12C inhibition prevents downstream signaling and may release immunogenic antigens while STING re-expression enhances immunogenicity through TBK1-IRF3 signaling. STING = stimulator of interferon genes; IFN = interferon; HLA = human leukocyte antigen; Me signifies histone methylation to suppress gene transcription.